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- Commentaries
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- Meta-analysis
- Case reports
- Case studies
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Provide a context or background for the study (i.e.,the nature of the problem and its significance). State the specific purpose or research objective, or hypothesis tested the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be made clear and any pre-specified subgroup analysis should be described. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

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Present your results in logical sequence in the text, tables and illustrations, giving the main or most important findings first.

Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. When data are summarized in the results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Table font should be 10 and caption should be below table and figure.

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Table should not be copy pasted or in picture form.

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Discuss your findings by comparing your results with other literature.

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Follow the Pubmed Referencing style.
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Example

Cook NR, Rosner BA, Hankinson SE, Colditz GA. Mammographic screening and risk factors for breast cancer. American Journal of Epidemiology. 2009 Dec;170(11):1422-32. doi: 10.1093/aje/kwp304.

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Conclusion should elucidate how the results communicate to the theory presented as the basis of the study and provide a concise explanation of the allegation of the findings.

ACKNOWLEDGEMENT

Provide the list of individuals who contributed in the work and grant details where applicable.

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ISSN (E) 2790-9352
ISSN (P) 2790-9344

PJHS
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Lahore

VOLUME 05 ISSUE 11

Editorial Team

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CrossLinks International Publishers

VOLUME 05 ISSUE 11

PJHS
Pakistan Journal of Health Sciences
Lahore

ISSN (E) 2790-9352
ISSN (P) 2790-9344

Editorial Board

Published by:
CrossLinks International Publishers

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VOLUME 05 ISSUE 11

Published by:
CrossLinks International Publishers

DOI: https://doi.org/10.54393/pjhs.v5i11.2585

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Strengthening Primary Healthcare in Pakistan: A Foundation for Sustainable Health Reform

OPEN ACCESS

Sami Ullah Mumtaz[1]

[1]King Edward Medical University, Mayo Hospital Lahore, Pakistan
drsumumtaz@gmail.com

ARTICLE INFO

How to Cite:

Mumtaz, S. U. (2024). Strengthening Primary Healthcare in Pakistan: A Foundation for Sustainable Health Reform. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2585

The firsthand health care services and a set of health-improving strategies or interventions, underline the concept of public health care. These are for meeting the health needs of economically compromised groups of people fairly. This concept has been polished since 1978. Public health care does not only comprise the implementation of comprehensive healthcare approaches but also rising economic, environmental, and social concerns that can be useful in optimizing healthcare strategies. According to the Alma-Ata Declaration, PHC underscores the importance of focusing on all the health-improving aspects such as taking precautions for preventing illness to offering treatments, reducing morbidity rates, and improving survival rates [1]. Different regions of the world have different primary health care approaches which are being implemented strategically for the well-being of humankind. There are several challenges faced by the healthcare system in Pakistan such as insufficient funding, low healthcare workforce, and inadequate infrastructure.

According to the World Health Organization (WHO), the health indicators of Pakistan are behind other countries in the continent, and the difference in the healthcare systems in the rural and urban areas is significant. A considerable portion of the population relies on the public sector for health facilities, as the private sector is way too expensive for an average person to afford.

The core issue of the poor health care system in Pakistan is the financing so to strengthen it this must be addressed first. An increase in the spending in this department is imperative, especially in the rural and unprivileged areas where healthcare is not easily accessible.

The difference between the healthcare systems in urban and rural areas can be decreased if there is an equitable distribution of resources. Moreover, training and retaining a skilled healthcare workforce could help resolve this issue. Programs such as Pakistan's Lady Health Worker (LHW) have shown an increase in coverage but all these efforts can be supported by adequate resources and training.

Health equity and primary health care go side by side. PHC ensures that healthcare is accessible not only to the privileged segment of society but also to marginalized populations, women, and children. By providing communities with these facilities Pakistan can take a great step towards achieving health coverage and improving the health of its population.

In conclusion, strengthening PHC is not just an option it's a demand and must be done. It's the base for the achievement of sustainable health reforms. It should be prioritized by the policymakers, ensuring all Pakistanis get quality access to healthcare regardless of economic and geographic differences.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1805

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Occurrence of Hyperkalemia in Patients with Chronic Kidney and Liver Diseases

Farzana Adnan Sheikh[1], Asma Razzak[2*], Mehwish Qamar[3] and Maria Qureshi[4]

[1]Department of Nephrology, Liaquat National Hospital, Karachi, Pakistan
[2]Department of Gastroenterology, Jinnah Medical Dental College(Medicare Cardiac General Hospital), Karachi, Pakistan
[3]Department of Nephrology, Dow University of Health and Sciences, Karachi, Pakistan
[4]Department of Nephrology, Karachi Institute of Kidney Disease, Karachi, Pakistan

ARTICLE INFO

Keywords:
Hyperkalemia, Chronic Kidney Disease, Chronic Liver Disease, Diabetes Mellitus, Hypertension

How to Cite:
Sheikh, F. A., Razzak, A., Qamar, M., & Qureshi, M. (2024). Occurrence of Hyperkalemia in Patients with Chronic Kidney and Liver Diseases: Hyperkalemia in Chronic Kidney and Liver Diseases. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1805

***Corresponding Author:**
Asma Razzak
Department of Gastroenterology, Jinnah Medical Dental College(Medicare Cardiac General Hospital), Karachi, Pakistan
asmarazzak376@gmail.com

Received Date: 31st May, 2024
Acceptance Date: 19th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Hyperkalemia is a common and potentially life-threatening electrolyte imbalance in patients with Chronic Kidney Disease (CKD) and Chronic Liver Disease (CLD), often exacerbated by comorbid conditions such as hypertension and diabetes. **Objective:** To assess the frequency and risk factors associated with hyperkalemia in patients with Chronic Kidney Disease (CKD) and Chronic Liver Disease (CLD) at a tertiary care hospital in Karachi, Pakistan. **Methods:** This cross-sectional study was carried out from March 2024 to May 2024, including 120 adult patients diagnosed with CKD (stage 3 or above) or CLD. Data on demographics, disease duration, comorbidities, previous hyperkalemia episodes, and medication compliance were collected. Serum potassium levels were measured, with hyperkalemia severity classified as mild (K+ 5.0–5.5 mEq/L), moderate (K+ 5.5–6.0 mEq/L), or severe (K+ >6.0 mEq/L). Statistical analysis was performed using SPSS version 24.0, with Spearman correlation and Chi-square tests applied. **Results:** The average age of the patients was 53.33 years, with 55% being male. The mean serum potassium level was 5.42±0.92 mEq/L. Medication compliance was high in 74.2% of patients. Hyperkalemia was present in 70.8% of patients, with 22.5% exhibiting severe hyperkalemia. Significant association was found between severity of hyperkalemia and age ($p<0.01$). Hypertension ($p=0.001$) and diabetes mellitus ($p=0.001$) were significantly associated with severity of potassium levels. **Conclusions:** The study highlighted a high prevalence of hyperkalemia in CKD and CLD patients, significantly associated with age, hypertension, and diabetes mellitus.

INTRODUCTION

Chronic Kidney Disease (CKD) and Chronic Liver Disease (CLD) affect millions worldwide, with significant morbidity and mortality [1-3]. In CKD, the kidney's ability to excrete potassium is diminished, predisposing patients to hyperkalemia. Similarly, in liver diseases, especially in cirrhosis, alterations in potassium handling, due to changes in renal function and the metabolism of medications, also predispose patients to elevated potassium levels [1-3]. Hyperkalemia, an abnormally high potassium level in the blood is one of the most common life-threatening condition that poses a significant clinical challenge [4]. The regulation of potassium is highly relying on hepatic and renal functions, which are greatly compromised in hyperkalemia [4, 5]. Studies have consistently shown medications to be a major contributing factor in hyperkalemia cases. Research suggests that medications are a primary or contributing factor in 35-75% of hospitalized patients with hyperkalemia [6]. The risk of hyperkalemia increases furthermore when patients had pre-existing CKD and liver diseases [7]. Both conditions independently impair the body's capacity to regulate potassium levels, creating a double jeopardy situation. Drugs such as potassium-sparing diuretics, commonly prescribed for hypertension in CKD patients, exacerbate this issue. These diuretics, while effective in eliminating excess fluid, also retain potassium in the body, potentially pushing potassium levels beyond safe limits in CKD patients [6-8]. While liver disease presents a different

DOI: https://doi.org/10.54393/pjhs.v5i11.1805

challenge to potassium balance. Liver damage can indirectly affect potassium homeostasis by diminishing the production of proteins that control the movement of potassium between cells and the bloodstream. Healthy cells maintain a delicate equilibrium of potassium within their walls. However, impaired protein production due to liver disease can disrupt this balance, allowing excessive potassium to accumulate inside cells [9, 10]. Furthermore, some liver diseases can impair blood flow to the kidneys, further hindering their ability to excrete potassium effectively [6, 8]. The combined presence of CKD or CLD significantly increases the risk of hyperkalemia induced by these medications. The impaired excretory capacity in CKD and the altered potassium handling in CLD create a precarious environment where even a modest medication-induced potassium increase can lead to clinically significant hyperkalemia. Despite the recognition of hyperkalemia as a complication in CKD and CLD, the specific risk factors associated with hyperkalemia in these patient populations remain incompletely understood. Existing studies often lack sufficient power or focus primarily on specific medications or disease severities.

Therefore, the objective of current study was to assess the frequency of hyperkalemia in patients with chronic kidney and liver diseases presenting at a tertiary care hospital, Karachi, Pakistan.

METHODS

It was a cross-sectional study conducted at the nephrology and hepatology clinics at Jinnah Medicare hospital, Karachi, Pakistan from March 2024 to May 2024. Sample size of 120 was estimated using Open Epi Sample Size Calculator by taking statistics of hyperkalemia as 35% in CKD, margin of error as 8.5% and 95% confidence level [6]. Adult patients aged 18 years or older diagnosed with CKD (stage 3 or above) or CLD (any stage) were included in the study. Patients with primary hyperparathyroidism or any other endocrine disorder known to directly affect potassium levels, patients who had treatment with bisphosphonates or denosumab within last 6 months and having pregnancy or breastfeeding females were excluded from the study. Patients were selected using non-random convenience sampling method. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the hospital, Ref No. ERC-1436/2024. Informed consents were obtained from all participants after a thorough explanation of the study's purpose, procedures, potential risks, and benefits. Data regarding age, gender, duration of disease, comorbidities, and previous episodes of hyperkalemia was collected. Laboratory test was performed to evaluate the phosphate, and potassium (K+) levels. The severity of hyperkalemia was defined as mild if K+ was >5.0 to <5.5 mEq/L, moderate if K+ was 5.5–6.0 mEq/L, and if severe K+ was >6.0 mEq/L. Compliance with medication was also reported. Data were analyzed using SPSS version 24.0, Descriptive statistics (mean, standard deviation, frequency, and percentage) was used to summarize patient characteristics. Spearmen correlation and Chi-square test was applied to assess the relationship between with hyperkalemia with age, gender, and comorbidities. A p-value<0.05 was considered as statistically significant.

RESULTS

The table 1 provides a summary of the baseline characteristics of the patients in the study. The average age of the patients was 53.33 years, with a standard deviation of 13.77 years. Of 120 patients, most of the patients were male (n=66, 55%). The median duration of disease was 5.23 years, with an interquartile range from 2.82 to 7.05 years. Of 120 patients, 25% were diabetic and 37.5% were hypertensive. About 30.8% of the patients have had previous episodes of potassium disorder, however, 74.2% of the patients showed high medication compliance.

Table 1: Descriptive Statistics of Baseline Characteristics (n=120)

Variables	Descriptive Statistics Mean ± SD / N (%)
Age (Years)	53.33 ± 13.77
Gender	
Male	66 (55.0%)
Female	54 (45.0%)
Duration of Disease (Years)	5.23 (2.82-7.05%)
Comorbidities	
Diabetes	30 (25.0%)
Hypertension	45 (37.5%)
Previous Episodes of Potassium Disorder	
Yes	37 (30.8%)
No	83 (69.2%)
Medication Compliance	
Low	31 (25.8%)
High	89 (74.2%)

The mean K+ of the patients with CLD and CKD was 5.42 ± 0.92 mEq/L. Majority of the patients had hyperkalemia (70.8%), whereas, 29.2% patients had normal K+ levels. Of 85 patients with hyperkalemia, 25% had mild hyperkalemia, 22.5% had moderate hyperkalemia and 23.3% had severe hyperkalemia, respectively (Figure 1).

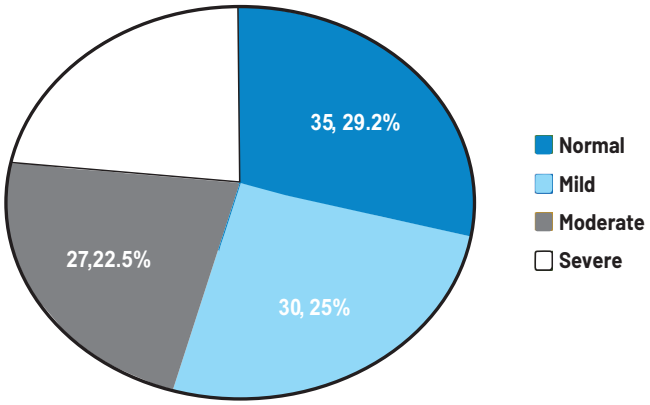

Figure 1: Frequency Distribution of Potassium Status (Hyperkalemia)

DOI: https://doi.org/10.54393/pjhs.v5i11.1805

Patients aged >50 years had a higher proportion of severe hyperkalemia (39.7%) compared to those aged≤50 years (0%). Similarly, proportion of moderate hyperkalemia was higher in age>50 years (38%) as compared to age≤50 years (0%). There was significant association between severity of hyperkalemia and age groups (p<0.01). Females had higher proportion of severe hyperkalemia and males had higher proportion of moderate hyperkalemia. However, there was insignificant association between severity of hyperkalemia and gender (p=0.22) (Table 2).

Table 2: Relationship between Severity of Hyperkalemia and Age Groups

Variables	Severity of Hyperkalemia N (%)				p-Value
	Normal	Mild	Moderate	Severe	
Age Groups					
≤50 Years	35 (71.4%)	14 (28.6%)	0 (0.0%)	0 (0.0%)	<0.01
≤50 Years	0 (0.0%)	16 (22.5%)	27 (38.0%)	28 (39.4%)	
Gender					
Male	16 (29.6%)	16 (29.6%)	14 (25.9%)	8 (14.8%)	0.22
Female	19 (28.8%)	14 (21.2%)	13 (19.7%)	20 (30.3%)	

Individuals with hypertension have a higher percentage of moderate to severe potassium levels compared to those without hypertension. This relationship was statistically significant with a p-value<0.01. Moreover, individuals with diabetes mellitus also have a higher percentage of moderate to severe potassium levels compared to those without diabetes mellitus.This relationship was statistically significant with a p-value<0.01 (Table 3).

Table 3: Relationship between Severities of Hyperkalemia with Comorbidities

Comorbidities		Severity of Hyperkalemia N (%)				p-Value
		Normal	Mild	Moderate	Severe	
HTN	No	29 (38.7%)	12 (16%)	17 (22.7%)	17 (22.7%)	<0.01
	Yes	6 (13.3%)	18 (40%)	10 (22.2%)	11 (24.4%)	
DM	No	31 (34.4%)	15 (16.7%)	19 (21.1%)	25 (27.8%)	<0.01
	Yes	4 (13.3%)	15 (50%)	8 (26.7%)	3 (10%)	

DISCUSSION

The present study investigates the occurrence of hyperkalemia in patients with Chronic Kidney Disease (CKD) and Chronic Liver Disease (CLD) at a tertiary care hospital in Karachi, Pakistan. The study's findings reveal a high prevalence of hyperkalemia among these patients, with significant correlations between hyperkalemia and age, as well as comorbid conditions such as hypertension and diabetes mellitus. Specifically, 70.8% of the studied population exhibited hyperkalemia, with 22.5% experiencing severe hyperkalemia. This study underscores the heightened vulnerability of CKD and CLD patients to hyperkalemia, especially when subjected to certain medications. The detailed analysis of the key outcomes indicates several significant findings. Firstly, the high prevalence of hyperkalemia in the patient cohort aligns with existing literature, which highlights the compromised ability of CKD and CLD patients to regulate potassium levels. Recent studies have consistently demonstrated the increased risk of hyperkalemia in CKD patients due to impaired renal potassium excretion [11, 12]. Furthermore, medications such as potassium-sparing diuretics exacerbate this risk by retaining potassium within the body [13, 14]. Similar mechanisms were at play in CLD patients, where hepatic dysfunction interferes with potassium homeostasis [15, 16]. Secondly, there was significant association between severity of hyperkalemia and age (p=0.001). Older patients (>50 years) exhibited a higher incidence of moderate to severe hyperkalemia, consistent with the notion that aging kidneys have a diminished capacity to excrete potassium efficiently [17, 18]. Moreover, there was statistically significant association between comorbid conditions and severity of potassium levels. This observation aligns with previous research indicating that comorbidities further strain the body's potassium regulatory mechanisms, thereby increasing the likelihood of hyperkalemia [19, 20]. The study's most significant achievement lies in its comprehensive assessment of hyperkalemia in a combined CKD and CLD patient population. Previous research often focused on either condition independently, with limited exploration of their concurrent impact on potassium regulation [20-21]. By addressing this gap, the study provides valuable insights into the compounded risks these patients face, highlighting the critical need for careful medication management and monitoring in this vulnerable group. Additionally, the study's robust methodology, including the use of a cross-sectional design and comprehensive statistical analyses, strengthens the reliability of its findings. The use of non-random convenience sampling may introduce selection bias, potentially limiting the generalizability of the results. Future research should employ randomized sampling methods to validate these findings in broader populations. Further studies should investigate these mechanisms to develop targeted interventions for preventing hyperkalemia in CKD and CLD patients. Lastly, the study's exclusion criteria, such as the exclusion of patients treated with bisphosphonates or denosumab, may overlook other potential contributors to hyperkalemia, necessitating a more inclusive approach in future research.

CONCLUSIONS

Study shows high prevalence of hyperkalemia and significant association of age, hypertension and DM with hyperkalemia in CKD and CLD patients.

Authors Contribution

Conceptualization: FAS, AR
Methodology: FAS, AR
Formal analysis: MQ[1]
Writing, review and editing: FAS, AR, MQ[1], Mq[2]

DOI: https://doi.org/10.54393/pjhs.v5i11.1805

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2068

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Perception of Undergraduate Physiotherapy Students Regarding Clinical Instructors' Behaviour During Clinical Training; A Descriptive Cross-Sectional Study

Abeera Ajmal[1], Moater Iftikhar[2], Iqra Almas[1], Sahreen Anwar[3] and Wajida Perveen[4,5*]

[1]Department of Physical Therapy, University of Sargodha, Sargodha, Pakistan
[2]Department of Physical Therapy, The University of Faisalabad, Faisalabad, Pakistan
[3]University Institute of Physical Therapy, University of Lahore, Lahore, Pakistan
[4]Department of Physical Therapy, Sialkot College of Physical Therapy, Sialkot, Pakistan
[5]Department of Physical Therapy, CMH Lahore Medical College & Institute of Dentistry (NUMS), Lahore, Pakistan

ARTICLE INFO

Keywords:
Undergraduate Physiotherapy Students, Clinical Instructors, Interaction, Clinical Instructor Behaviour Instrument

How to Cite:
Ajmal, A., Iftikhar, M., Almas, I., Anwar, S., & Perveen, W. (2024). Perception of Undergraduate Physiotherapy Students Regarding Clinical Instructors' Behaviour During Clinical Training; A Descriptive Cross-Sectional Study : Undergraduate Physiotherapy Students Regarding Clinical Instructors' Behaviour. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2068

***Corresponding Author:**
Wajida Perveen
Department of Physical Therapy, CMH Lahore Medical College & Institute of Dentistry (NUMS), Lahore, Pakistan
wajida_perveen@cmhlahore.edu.pk

Received Date: 17th August, 2024
Acceptance Date: 17th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Professional therapists must be prepared through clinical training, which forms the foundation of physiotherapy education. The effectiveness of the interactions between students and clinical instructors can help students learn more in the clinical setting. **Objective:** To find out the undergraduate physiotherapy students' perceptions regarding the clinical instructors' behaviours during clinical training. **Methods:** A descriptive cross-sectional study was conducted on 260 undergraduates of Doctor of Physical Therapy from different institutes of Faisalabad and Sialkot after ethical approval from September 2021 to March 2022. Students in 3rd year or 5th semester and above were included. A clinical instructor behaviour instrument was utilized to get the responses and SPSS version 21.0 to extract the results. Mean and standard deviations were computed for individual subsets of the instrument to find the perception. **Results:** Mean age ± standard deviation was 22.79 ± 15.75 years ranging from 21 to 25 years. Among the participants, 226 (86.92%) were female and 34 (13.07%) were male. A total score of all five categories of the clinical instructor behaviour instrument was found 116.17 out of a maximum possible score of 150. **Conclusions:** It was concluded that the perception of students regarding the clinical instructors' behaviours during clinical training was found positive.

INTRODUCTION

Clinical training, which forms the foundation of physiotherapy education, is essential for a qualified physical therapist. The effectiveness of the student-clinical teacher connection might help or hurt the student's ability to learn in the clinical setting. Perception is how a person interprets or makes assumptions about a specific situation, as well as how they think about that specific issue. The way something is viewed, comprehended, or interpreted [1]. The American Physical Therapy Association (APTA) and the American Council of Academic Physical Therapy (ACAPT) are actively concentrating on defining best practices in clinical education [2]. Clinical instructors (CI) in physical therapy are held to professional standards, although the path to becoming a qualified CI has not been well studied in the literature [3]. Furthermore, there is no accepted definition in the literature regarding competency as a CI in the field of physical therapy [3]. Many studies indicated that clinical education is the most important component but still, it is a more challenging area of education for both students and clinical instructors [4].

DOI: https://doi.org/10.54393/pjhs.v5i11.2068

Clinical educators concentrated on the steps in their teaching responsibilities rather than learning support strategies [5]. Clinical physiotherapy students rated the clinical education attributes of their lecturers and supervisors high [6]. Physical therapy students get the chance to apply their classroom knowledge and abilities to patient care experiences in a clinical facility through the clinical training of an entry-level physical therapy (PT) education program. The student applies knowledge and skills under the direction of a professional physical therapist serving as the CI. Students enrolled in the clinical education program must integrate their academic knowledge, professional development, and physical therapy skills to effectively manage patients and clients in difficult situations. CIs have the chance to affect how students are educated by modelling and instructing professional behaviours and abilities that students can learn from and reproduce. Physical therapist (PT) students have the chance to participate in clinical education as part of a professional (entry-level) education programme [5]. When students were assigned to well-run facilities for their clinical rotations, their satisfaction levels increased [7]. About one-third of the teaching is clinical training, the patient and student-centred learning environments are highly valued [8, 9]. The learning process is accelerated by clinical instructors' methods of instruction[10]. In 2018 Clint Newstead et al., studied the confidence, involvement, and training requirements of physical therapists in Australian clinical education (CE). Physiotherapists with different professional backgrounds participated in CE. Even though many participants had taken part in CE-related CPDs, many said that additional training was still needed. Future clinical educator training should be customised for the amount of experience of participants and concentrate on the CE components in which they lack confidence [11]. Students reported being happier with the clinical learning as a result of those instructors' clinical teaching characteristics, according to a 2017 study by Ehsan et al., on undergraduate physical therapy students' evaluations of those instructors' clinical teaching traits [12]. A uniform national curriculum for a five-year Doctor of Physical Therapy (DPT) degree programme was developed and implemented by the Higher Education Commission of Pakistan in 2011, which has been revised periodically. To meet national and international needs and standards a fair proportion of teaching time is dedicated to clinical training in more than 200 bedded hospitals has been made mandatory. The degree programme is offered by public and private degree-awarding institutions and affiliates. National regulatory body being in its infancy is not monitoring the requirements for DPT teaching institutions at present. Clinical training is an aspect that needs regular assessments of whether it is fulfilling the targeted outcomes or not. It is imperative to find out how students feel about the way clinical instructors behave when training DPT undergraduates in clinical settings.

This study aims to find out the undergraduate physiotherapy students' perceptions regarding the clinical instructors' behaviours during clinical training.

METHODS

This multicentre descriptive cross-sectional study was administered among 260 physical therapy undergraduate students of different institutes from two cities of Punjab from September 2021 to March 2022, after ethical approval by the institutional ethics review board of Sialkot College of Physical Therapy wide reference no. IRB-SCPT-DPT-146-2021. The sample size was calculated using G power software, with the formula: n=[Z(1-x/2)]2. P(1-p)/(d)2. Where Z(1-x/2)=1.96 at 95% confidence interval, P=positive perception= 0.70 [13], d=0.056 margin of error and n=258 participants, so 260 participants were included. A convenient sampling technique was used to meet the sample. DPT Undergraduates enrolled in different universities both public and private and affiliated colleges in 3rd year or 5th semester and above, undergoing honorary internships and those carrying out supervised clinical practice as part of their curriculum were included. Students in 1st and 2nd year DPT were excluded. Data were collected using self-structured proforma for demographic and academic information and Clinical Instructor Behaviour Instrument (CIBI), (Cronbach alpha=0.92) after written informed consent from eligible students electronically [14, 15]. CIBI measures behaviours under five subsections including instructional, interpersonal, evaluative, professional and personal behaviours. Each subsection contains six items. The response was recorded on a Likert scale of 1-5, 1 being the least and 5 being the most important. The total score of the instrument ranges from 30-150, the higher the score, the more positive is the behaviour of the instructors [16]. The data were analysed using the statistical software SPSS version 21.0. The descriptive statistical analysis in the form of Mean and Standard deviation was performed.

RESULTS

Of the participants, 34 (13.07%) were male and 226 (86.92%) were females. With a range of 21 to 25 years, the Mean Age ± SD was 22.79 ± 15.75 years (Table 1).

Table 1: Demographic and Academic Information of the Participants

Variables	Results
Mean Age ± SD (Years)	22.79 ± 15.75
Min-Max (Years)	21-25
Gender	
Male	34 (13.07%)
Female	226 (86.92%)
Years of Study	
3rd	80 (30.76%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2068

4th	144 (55.38%)
5th	36 (13.84%)
Institution	
Public	46 (17.69%)
Colleges Affiliated to Public	94 (36.15%)
Private	120 (46.15%)
Cities of Study	
Faisalabad	172 (66.15%)
Sialkot	88 (33.85%)
Supervised Clinical Practice	
Institutional Clinical Training Facility	30 (11.53%)
Public Hospital	90 (34.61%)
Private Hospitals And Clinics	58 (22.30%)
Special Education Rehab Facility	32 (12.30%)
Sports Centres	6 (2.3%)
Others	14 (5.38%)
None	30 (11.53%)

Results indicated that the mean of Explains the Procedure 4.11 ± 0.86, Demonstrates Clinical Skill for Students 4.15 ± 0.74, explains the Basis for Actions and Decisions 3.93± 0.83, Provides Practice Opportunities for Students 3.97 ± 0.86, Stimulates students problem-solving and critical thinking 3.77 ± 0.88, Answers student questions clearly and precisely 3.92 ± 0.89 (Table 2).

Table 2: Summary of Instructional Behavior

Behavioural Description / Instructional	Mean ± S.D
Explains Procedures Clearly	4.11 ± 0.86
Demonstrates Clinical Skills for Students	4.15 ± 0.74
Explains the Basis for Actions and Decisions	3.93 ± 0.83
Provides Practice Opportunities for Students	3.97 ± 0.86
Stimulates Student Problem Solving and Critical Thinking	3.77 ± 0.88
Answers Student Questions Clearly and Precisely	3.92 ± 0.89
Total Mean Score of All Items of Subset	3.97 ± 0.60

Score of Interpersonal Behavior showed that maintains an atmosphere that allows the expression of opinions 3.84 ± 0.85, Encourages students to feel free to ask questions or to ask for help 4.03 ± 0.86, Is available and accessible to students when needed 3.73 ± 0.99, Exhibits a genuine interest in the student 3.76 ± 0.97, Demonstrates confidence in and respect for the student 3.84 ± 0.96, Provides support and encouragement for the student 3.81 ± 0.91 and total mean score of all items of subset 3.83 ± 0.60 (Table 3).

Table 3: Summary of Interpersonal Behavior

Behavioural Description / Interpersonal	Mean ± S.D
Maintains an atmosphere that allows the expression of opinions	3.84 ± 0.85
Encourages students to feel free to ask questions or to ask for help	4.03 ± 0.86
Is available and accessible to students when needed	3.73 ± 0.99
Exhibits a genuine interest in the student	3.76 ± 0.97
Demonstrates confidence in and respect for the student	3.84 ± 0.96
Provides support and encouragement for the student	3.81 ± 0.91
The total mean score of all items of the subset	3.83 ± 0.60

Analysis of evaluation showed that corrects students tactfully without belittling them 3.73 ± 0.93, Provides useful and constructive feedback 3.75 ± 0.936, demonstrates objectivity and fairness in the evaluation of the student 3.91 ± 1.055, Observes and assesses student performance of the student 3.83 ± 0.97, Provides specific suggestions for student improvement 3.80 ± 0.887, Defines clearly the expectations of students 3.72 ± 0.91 and total mean score of all the items of subset was 3.79 ± 0.72 (Table 4).

Table 4: Summary of Evaluative Behavior

Behavioural Description / Evaluative	Mean ± S.D
Corrects students tactfully without belittling them	3.73 ± 0.93
Provides useful and constructive feedback	3.75 ± 0.936
Demonstrates objectivity and fairness in the evaluation of the student	3.91 ± 1.055
Observes and assesses student performance of the student	3.83 ± 0.97
Provides specific suggestions for student improvement	3.80 ± 0.887
Provides support and encouragement for the student	3.72 ± 0.91
The total mean score of all items of the subset	3.79 ± 0.72

The summary of each item of professional behaviour is summarized (Table 5).

Table 5: Summary of Professional Behavior

Behavioural Description / Professional	Mean ± S.D
Facilitates students' awareness of their professional responsibility	3.78 ± 0.98
Demonstrates interest in patients and their care	3.96 ± 0.95
Demonstrates clinical knowledge, competence, and judgment	3.99 ± 0.858
Relates underlying theory to physical therapy clinical practice	3.97 ± 0.88
Accepts responsibility for own actions	3.96 ± 0.94
Acts as a professional role model	3.97 ± 0.846
The total mean score of all items of the subset	3.93 ± 0.70

The summary of each item of personal behaviours is summarized (Table 6).

Table 6: Summary of Personal Behavior

Behavioural Description / Personal	Mean ± S.D
Demonstrates honesty when working with students and patients	3.84 ± 0.849
Displays a sense of humor	3.79 ± 1.027
Demonstrates flexibility when working with students	3.85 ± 0.936
Demonstrates self-control and patience	3.84 ± 1.032
Demonstrates enthusiasm for teaching and clinical training	3.83 ± 1.015
Is friendly and outgoing when working with students	3.79 ± 0.987
The total mean score of all items of the subset	3.82 ± 0.71

The total score of CIBI along with the total of each subset, categorical means, and standard deviation of all five subsets of different behaviours. The categorical means of the behaviours showed us that all the categories have a mean value of less than 4 out of 5 which shows that most of the students' perception lies in the scoring of "important"

DOI: https://doi.org/10.54393/pjhs.v5i11.2068

as mentioned in the questionnaire. CIBI has an overall total score of 116.17 out of 150 which equals 77.45% depicting a positive perception of behaviour (Table 7).

Table 7: Statistical Values of the Total Score of Five Categories of CIBI (n=260)

Categories of CIBI	Total Score Out of 30 Each	Mean ± SD
Instructional	22.94	3.97 ± 0.60
Interpersonal	23.63	3.83 ± 0.60
Evaluative	22.74	3.79 ± 0.72
Professional	23.01	3.93 ± 0.70
Personal	23.85	3.82 ± 0.71
Overall Total Score CIBI	116.17	-

DISCUSSION

The purpose of this study was to evaluate how clinical instructors behaved and how physiotherapy students perceived the qualities of a successful clinical instructor that aided in the learning process. The majority of studies on clinical instructors' efficacy have contrasted faculty and student opinions of these professors. Ismail *et al.*, discovered a direct correlation between nursing students' perceptions of clinical instructor behaviour and their actual usage.The findings of the current study confirmed the results of the previous study and showed a positive association. Aziz *et al.*, performed a study in Karachi in 2018 to learn how physical therapy students felt about the clinical training programme.The participants' responses were good and demonstrated their interest in the study. When participants were questioned about creating a positive learning environment that is approachable, non-threatening, and enthusiastic 70% of them agreed. About 40% of people were hesitant to pursue autonomous learning . Participants of the current study also desired to be trained under the supervision of experienced clinical trainers. Odole *et al.*, in 2017 conducted a study in Southwest Nigeria, aiming to gather feedback on the merits and disadvantages of the clinical education models currently in use there. 53 (71%) of the 74 physiotherapy educators who participated in this cross-sectional population-based survey—45 men and 29 women—had postgraduate degrees. Of the participants, twenty-two (29.7%) reported having received formal training in clinical education before working as clinical trainers. In this qualitative survey, seven themes were identified including the potential to connect theory to practice, growing self-assurance, greater collaboration between academics and clinicians, and improved clinicians. Our study differs in the methodology being a quantitative analysis and involving students only while they targeted the clinical trainers also. While there are advantages, providing practical instruction to physiotherapy students in southwest Nigeria is thought to have numerous advantages. The Nigeria University Commission must develop and execute policies that consider the purported drawbacks. When the students grow into professionals, this will result in a rise in the enhancement of their clinical skills . Safo *et al.*, studied the ratings of physiotherapy students on clinical education attributes of lecturers and clinical supervisors on 81 clinical physiotherapy students using the McGill clinical teachers' evaluation (CTE) tool. They compare the means of students' level of study and ratings regarding the clinical education attributes of clinical supervisors and lecturers. The clinical education attributes of lecturers and supervisors were highly rated '. Rating on clinical education attributes of supervisors (p=0.111) and lecturers (p=0.124) did not differ significantly between the different levels of study. We differ in the study population and in evaluating the class-wise perception feedback of the participants on a different outcome measurement tool. J Quartey *et al.*, studied perceptions of undergraduate allied health students about attributes of clinical trainers and clinical learning environment in Ghana. They utilized the clinical environment learning inventory and McGill clinical teacher evaluation tool on 169 allied health students. They found positive perceptions of AHS students about the environment and the teachers '. The difference of our study is that we only focused on DPT undergraduates using CIBI for data collection although the sample size was comparable in both studies. Fox *et al.*, in their scoping review, reported that health education programs seek to incorporate more inter-professional activities into their respective programs, so it is important to review methods and measures that would best fit their program .Naido *et al.*, during the development of a tool to evaluate a physiotherapy clinical education programme in South Africa, identified the items that could be included.They used focused group discussion for qualitative data gathering. They observed that clinical physiotherapy education is complex and its diversity can be seen in the emerging themes . Current study differs from them as we used a quantitative approach and a validated available tool for data collection. Assessment and analysis of effective clinical attributes was the key element of this study. More focus and improvements are needed highlighting the patient and organization-related factors in the clinical education of physiotherapy students. The results of this study indicate that clinical educators may need to reframe teaching methodologies, especially regarding the behaviour towards the students. More research work is required on this subject with a larger sample size focus group discussions and qualitative analysis at the institutional level in Pakistan.

CONCLUSIONS

It was concluded that clinical practice has a crucial role in undergraduate physiotherapy education assessment and analysis of effective clinical attributes was the key element of this study. So, assessment of clinical instructors' behaviours and physical therapy students' perception towards these characteristics are important in improving physical therapy education to facilitate learning and ultimately the delivery of healthcare services. There is a positive perception of the students about clinical instructors' behaviours.

DOI: https://doi.org/10.54393/pjhs.v5i11.2068

Authors Contribution

Conceptualization: MI, SA, WP
Methodology: MI, IA, SA
Formal analysis: AA, IA, SA
Writing review and editing: MI, SA, WP

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2068

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DOI: https://doi.org/10.54393/pjhs.v5i11.2320

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Prevalence and Histopathological Findings of Endometrioid Carcinoma and Associated Risk Factors: A Cross-Sectional Study

Shagufta Nasir Pervez[1], Muhammad Junaid[2], Shaista Alam[3], Farhan Abbas Baloch[4], Pordil Khan[5] and Noushad Bibi[6*]

[1] Department of Pathology, Khyber Girls Medical College, Hayatabad Medical Complex, Peshawar, Pakistan
[2]Department of Rheumatology, University Hospital Waterford, County Waterford, Ireland
[3]Department of Microbiology and Pathology, Pak International Medical College, Peshawar, Pakistan
[4]Department of Pathology, Pak International Medical College, Peshawar, Pakistan
[5]Department of Histopathology, Khyber Medical College, Peshawar, Pakistan
[6]Department of Gynaecology, District Headquarter Hospital, Swabi, Pakistan

ARTICLE INFO

Keywords:
Endometrioid Carcinoma, Ovarian Cancer, Parity, Menopausal Status

How to Cite:
Pervez, S. N., Junaid, M., Alam, S., Baloch, F. A., Khan, P., & Bibi, N. (2024). Prevalence and Histopathological Findings of Endometrioid Carcinoma and Associated Risk Factors: A Cross-Sectional Study: Prevalence and Histopathology of Endometrioid Carcinoma. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2320

***Corresponding Author:**
Noushad Bibi
Department of Gynaecology, District Headquarter Hospital, Swabi, Pakistan
nash4146@gmail.com

Received Date: 11th September, 2024
Acceptance Date: 17th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Ovarian cancer ranks as the seventh most frequently diagnosed malignancy among women worldwide. Endometrioid carcinoma, a type of proliferative endometrial tumor, accounts for approximately 15% of epithelial ovarian cancers, making it the third most common subtype. **Objective:** To investigate the relationship between Endometrioid Carcinoma and potential risk factors, including demographic, reproductive, and lifestyle factors. **Methods:** A cross-sectional study was conducted at Hayatabad Medical Complex's Department of Pathology from January 1 to December 31, 2023. The study analyzed 139 ovarian tumor specimens confirmed through histopathology. Statistical analysis using SPSS version 26 identified significant associations between variables using Chi-square tests and logistic regression, with a significance level of $p < 0.05$. **Results:** A total of 139 ovarian specimens with the patient's mean age (45.34 years) with the highest prevalence of endometrioid carcinoma observed in women aged 40-49 and 60 years and above. The prevalence of endometrioid carcinoma was about 14.4% (n=20). A significant association was identified between parity and endometrioid carcinoma (p-value = <0.001). Menopausal status also showed a significant association, with postmenopausal women having a higher prevalence of endometrioid carcinoma. Logistic regression analysis indicated that age was a significant predictor of endometrioid carcinoma (p-value = 0.028).**Conclusions:** Significant association between nullipara and premenopausal women with endometrioid carcinoma, emphasizing the importance of considering parity and menopausal status as a risk factor for endometrioid carcinoma.

INTRODUCTION

The second most common gynecologic cancer worldwide, ovarian cancer is the worst in both Europe and the United States [1]. It ranks as the seventh most commonly diagnosed cancer among women worldwide and the tenth in China [2]. In Western and Asian nations, the frequency of ovarian tumors varies; in women of reproductive age, two-thirds of cases occur. Ovarian cancer in children is extremely uncommon, affecting fewer than 5% of cases [3]. Of all ovarian tumors, 75-80% are benign ones, and 55-65% of them are seen in women under 40 years [4]. Most ovarian cancers arise from the epithelial cells of the ovary and are classified by the WHO into five major histological types based on epithelial characteristics. Historically, ovarian tumors have been classified into three categories: benign, borderline (or "carcinoma of low malignant potential"), and malignant, using criteria such as architectural pattern, cytological atypia, and mitotic counts [5]. With a frequency of 15%, endometrioid carcinoma is the third most common epithelial ovarian cancer subtype, after serous and mucinous cystadenocarcinomas, and is characterized by its proliferative growth in the endometrium [6]. Typically

DOI: https://doi.org/10.54393/pjhs.v5i11.2320

appearing a cystic mass with hemorrhagic, serous, or mucinous components, endometrioid carcinoma's ultrasound appearance closely resembles that of an endometrioma, characterized by a low-level echo-filled, thick-walled cystic structure [7]. This carcinoma represents a subset of primary epithelial ovarian tumors, making up approximately 10% to 15% of ovarian malignancies [8]. Patients with endometriosis may develop endometrioid carcinomas, especially if their endometriomas are larger than 10 cm, grow more quickly, or have solid, solid-cystic regions or papillary outgrowths, which are signs of cancer [9, 10]. The prevalence of endometrioid carcinoma varies globally; a study in China reported a prevalence of about 9.5%, while another study found a prevalence of approximately 11% [11, 12]. In Pakistan, the reported prevalence of endometrioid carcinoma varies, with one study documenting a rate of 24.2% and another reporting a prevalence of 7.6% [13, 14]. Women with Endometrioid Carcinoma (EC) may be asymptomatic, while others might experience symptoms related to their pelvic mass [15]. Both endometrioid and clear cell ovarian cancers share similar associations, with increased risks linked to endometriosis, Hormone Replacement Therapy (HRT), and advancing age, and decreased risks associated with tubal ligation [2]. Ovarian cancer often presents with non-specific symptoms, which can lead to late-stage detection. Endometrioid carcinoma has several established risk factors, including advancing age, hormone replacement therapy, high dietary fat intake, family history, genetic predisposition, and nulliparity(never having given birth). Nevertheless, additional research is necessary to ascertain the possible contributions of other risk factors, such as obesity, talc powder use, fertility drugs, infertility, radiation exposure, and in vitro fertilization, to the development of endometrioid carcinoma, as their effects are still unknown [14, 16]. MRI imaging of endometrioid carcinoma identifies two main types: solid and cystic, with cystic types having various subtypes. Endometrial thickening may also be visible in imaging studies [17]. According to their solid development pattern, endometrioid carcinomas are categorized into three categories by the International Federation of Gynecology and Obstetrics (FIGO) system: Grade 1 has less than 5% solid architecture, Grade 2 has 6-50% solid architecture, and Grade 3 has more than 50% solid architecture [18]. The rationale for this study is to address the rising incidence of endometrioid carcinoma in Khyber Pakhtunkhwa, where data on its prevalence and associated risk factors are limited. The objective of the study was to assess the prevalence and risk factors of endometrioid carcinoma in this region to help improve patient outcomes and reduce the burden of ovarian tumors.

METHODS

This one-year descriptive cross-sectional study was conducted from January 1, 2023, to December 31, 2023, at the Department of Pathology, Hayatabad Medical Complex, Peshawar, Pakistan. A non-probability convenience sampling technique was employed, and a sample size of 139 was calculated using OpenEpi, based on an anticipated frequency of endometrioid carcinoma of approximately 10%, a 95% confidence interval, and a 5% margin of error [19]. The study included tumor specimens from patients who underwent surgical procedures such as cystectomy, oophorectomy, salpingo-oophorectomy, and total abdominal hysterectomy with or without salpingo-oophorectomy, with histopathologically confirmed ovarian tumors. Exclusion criteria encompassed patients with two or more synchronous ovarian tumors, incomplete or insufficient histopathological data, and specimens of non-ovarian origin or not meeting the study's diagnostic criteria. Data were collected prospectively from medical records and pathology archives. Tumor specimens obtained from surgical procedures, whether performed at Hayatabad Medical Complex or elsewhere, were processed in the Department of Pathology. Demographic and clinical information including patient age, gender, parity, and presenting symptoms was documented on a pre-designed proforma. Histopathological analysis involved tumor classification following the World Health Organization (WHO) classification system for ovarian tumors [19]. Tumor sections were stained using Hematoxylin and Eosin (H&E) for the assessment of tumor type, presence of necrosis, lymphovascular invasion, and cellular atypia. Ethical approval was obtained from the Institutional Review Board of Hayatabad Medical Complex Peshawar (Ref. No: HMC-QAD-F-00970). Informed consent was obtained in writing from all participants before data collection. To ensure confidentiality, participant data were coded, and access to personal information was restricted to authorized research personnel only. Data analysis was conducted using SPSS version 26.0, with descriptive statistics to summarize baseline data, chi-square tests to examine categorical variable associations, and logistic regression analysis to identify potential correlations between risk factors and endometrioid carcinoma. The chi-square test was chosen to compare categorical variables, while logistic regression was used to analyze relationships between predictor variables and disease occurrence. A significance level of $p < 0.05$ was set for all tests.

RESULTS

The participants were between the ages of 13 and 85, with a mean age of 45.34 ± 17.311 years. The age of the study participants was categorized into six distinct age groups. The majority of participants were either in the 40 to 49 years' age group, representing 25.2% (n=35) of the sample, or in the 60 years and above category, which constituted

DOI: https://doi.org/10.54393/pjhs.v5i11.2320

25.9% (n=36) of the participants. A smaller portion of the participants were under 20 years' old (13.7%, n=19), followed by those in the 30 to 39 years' group (12.9%, n=18). The 50 to 59 years' group accounted for 15.1% (n=21), while the 20 to 29 years' group had about 7.2% (n=10), as shown in figure 1.

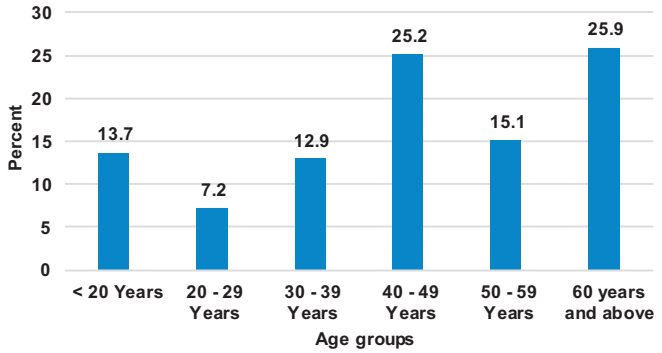

Figure 1: Age Distribution of the study Participants

The specimens analyzed in the study were diverse, with the majority being a uterus with adnexa, accounting for 43.2% (n=60) of the total. This was followed by total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH BSO) specimens, which were about 13.7% (n=19) of the total samples. Ovarian specimens were also significant, with 9.4% (n=13) comprising ovaries alone and 8.6% (n=12) being ovarian cysts. Smaller proportions included pelvic masses (6.5%, n=9), ovaries with fallopian tubes (4.3%, n=6), uterus with adnexa and appendix (3.6%, n=5), and uterus with adnexa and peritoneum (3.6%, n=5). Specimens such as cystectomy (2.9%, n=4), ovary NOS (2.9%, n=4), oophorectomy (0.7%, n=1), and abdominal mass (0.7%, n=1) were also less frequently examined (Figure 2).

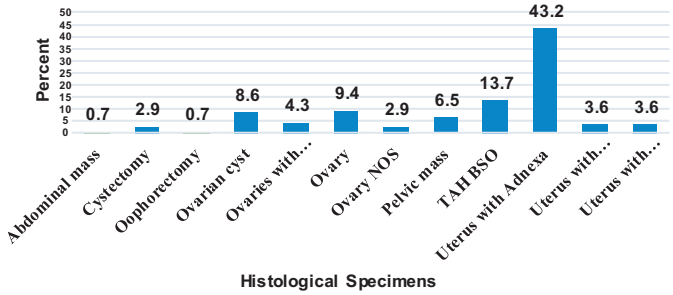

Figure 2: Frequency of Different Histological Specimens

The parity data showed that among the 63 participants with available information, 28.6% (n=18) were nulliparous, while the majority (71.4%, n=45) were multiparous. Regarding menopause status, data was available for 38 participants. Of these, 18.8% (n=6) were in the premenopausal stage, and 81.2% (n=32) were postmenopausal. When examining the prevalence of endometrioid carcinoma, 14.4% (n=20) of the total sample was diagnosed with endometrioid carcinoma, as illustrated in figure 3. The study examined various diagnoses among the participants, with Papillary Serous Adenocarcinoma being the most common, accounting for 20.1% (n=28) of the cases. Serous Carcinoma was also prevalent, accounting for 16.5% (n=23) of the cases. Mucinous Adenocarcinoma was diagnosed in 12.2% (n=17) of the participants, while Clear Cell Carcinoma and Brenner Tumor were identified in 9.4% (n=13) and 7.2% (n=10) of cases, respectively. Other diagnoses included Granulosa Cell Tumor (7.2%, n=10), Sclerosing Stromal Tumor (5.8%, n=8), and Yolk Sac Tumor (2.2%, n=3). Less frequent diagnoses, each representing less than 1% of the cases, included Dysgerminoma (n=1), Low-grade Appendiceal Mucinous Neoplasm (n=1), Malignant Spindle Cell Tumor (n=1), Mixed Mullerian Tumor (n=1), and Mucinous Adenocarcinoma with Omental Implants (n=1) while Mixed Germ Cell Tumor was about 1.4% (n=2)(Figure 3).

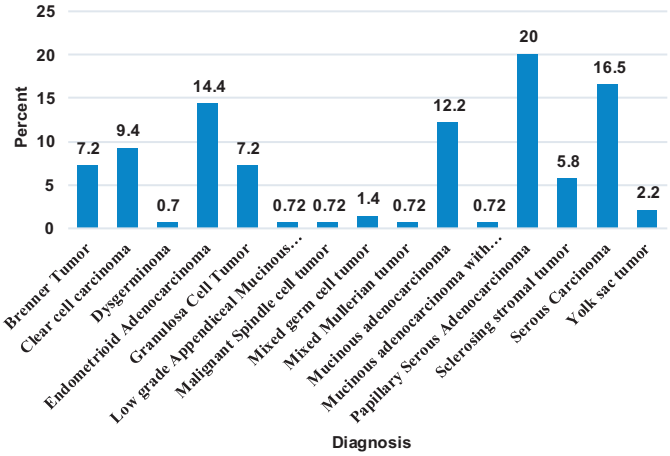

Figure 3: Prevalence of Different Histological Tumors Diagnosed

The histological examination of the endometrioid carcinoma reveals an enlarged uterus with a thickened endometrium on gross examination. Tumors typically present as polypoid or exophytic masses within the uterine cavity. Solid, whitish, and friable ovarian masses were observed in approximately 70% of cases as shown in table 1, indicating a common presentation. Partially cystic and solid tumors were seen in about 55% of patients, with the cystic areas often containing papillary growths in around 35% of cases. Hemorrhagic foci within the tumor were found in approximately 45% of cases. Multiple cysts containing haemorrhagic fluid and necrosis were found in about 25% of patients, while cystic cavities filled with thick, mucoid material were reported in 25% of cases. Additionally, amber-colored fluid within cystic parts was observed in about 15% of specimens, often accompanied by papillary projections. Multiple papillary growths within the uterine cavity were found in approximately 30% of endometrioid carcinoma cases.

Table 1: Histopathological Findings of the Endometroid Carcinoma Cases

Histopathological Findings	Percentage (%)
Ovarian Masses (Solid, Whitish, Friable)	70%
Partially Cystic Solid Tumors	55%
Cystic Areas with Papillary Growth	35%
Hemorrhagic Foci	45%

DOI: https://doi.org/10.54393/pjhs.v5i11.2320

Cysts with Hemorrhagic Fluid and Necrosis	25%
Cysts with Thick Mucoid Material	25%
Cysts with Amber-colored Fluid	15%
Multiple Papillary Growth	30%

The study assessed the association between endometrioid carcinoma and age, parity, and menopause status using Chi-square tests and Logistic Regression analysis. While there was no significant association between age group and endometrioid carcinoma using Pearson Chi-Square ($p = 0.103$). However, the likelihood ratio test showed a significant association ($p = 0.021$), and linear-by-linear association test revealed a significant trend, with increasing likelihood of endometrioid carcinoma with age ($p = 0.009$). The age groups 40—49 years and above 60 years (20% cases each), both showed higher occurrence of endometroid carcinomas as shown in table 2.

Table 2: Correlation of Age, Parity and Menopausal Status with Endometrioid Carcinoma

Variables		Endometrioid Carcinoma N (%)			
		No	Yes	Total	p-Value
Age Groups	<20Years	19 (100%)	0 (0%)	19 (100%)	0.035
	20 - 29 Years	10 (100%)	0 (0%)	10 (100%)	
	30 - 39 Years	17 (94%)	1 (6%)	18 (100%)	
	40 - 49 Years	28 (80%)	7 (20%)	35 (100%)	
	50 - 59 Years	16 (76%)	5 (24%)	21 (100%)	
	60 Years and above	29 (80.5%)	7 (19.5%)	36 (100%)	
Parity	Nulliparity	9 (50%)	9 (50%)	18 (100%)	<0.001
	Multiparity	43 (95.5%)	2 (4.5%)	45 (100%)	
Menopausal Status	Premenopausal Women	2 (33.3%)	4 (66.7%)	6 (100%)	0.009
	Postmenopausal Women	22 (84.6%)	4 (15.4%)	26 (100%)	

The results showed a strong association between nulliparity (having no children) and endometrioid carcinoma, with 9 out of 18 nulliparous individuals diagnosed with the condition (p-value = 0.000), a significantly lower prevalence of endometrioid carcinoma among multiparous individuals (those who have had children), a significant relationship between premenopausal status and endometrioid carcinoma, with 4 out of 6 premenopausal women diagnosed with the condition (p-value = 0.009), and a lower prevalence of endometrioid carcinoma among postmenopausal women, and histopathological changes were also observed (Figure 4).

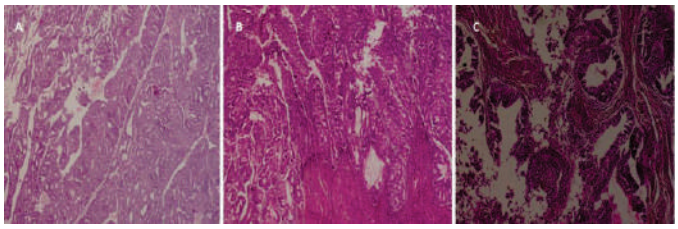

Figure 4: Histologic Features of Endometrioid Carcinoma

A) Confluent back-to-back glands (10x power view of Endometroid Carcinoma)
B) FIGO grade 1 tumor with less than 5% solid component (20x power view of Endometroid Carcinoma)
C) Glands lined by pleomorphic hyper chromatic cells (40x power view of Endometroid Carcinoma)

The multivariate regression analysis was conducted to assess the effects of age group, parity, and menopausal status on the occurrence of Endometrioid Carcinoma (EC). The dependent variable, EC, was observed in two categories: "Yes" (30.8%) and "No" (69.2%). The model fitting criteria indicated a significant improvement over the intercept-only model (Chi-Square=32.097, df=6, $p<0.001$), as presented in Table 3. This suggests that the predictors collectively contribute to distinguishing between the presence and absence of EC. The pseudo-R-square values—Cox and Snell (0.709), Nagelkerke (1.000), and McFadden (1.000)—indicate a strong model fit. Likelihood ratio tests revealed significant effects for parity ($p = 0.006$), age group ($p < 0.001$), and menopausal status ($p = 0.017$).

Table 3: Binary Logistic Regression Analysis of Endometroid Carcinoma with Age

Model Summary: Dependent Variable (EC) Independent Variable (Age) Covariates (Parity and Menopausal Status)					
Model Fit					
Chi-Square	**df**	**p-Value**	**-2 Log Likelihood**	**Cox and Snell R Square**	**Nagelkerke R Square**
32.097	6	0.001	106.088	0.709	1.000
Variables in the Equation					
Predictor	**B**	**S.E.**	**Wald**	**df**	**p-Value**	**Exp (B) (Odds Ratio)**
Age	0.033	0.016	4.429	1	0.001	1.033
Parity	37.894	13324	0.00	1	0.006	1.174
Menopausal Status	-1.749	13626	0.00	1	0.017	1.092

DISCUSSION

This study focused on the prevalence and risk factors associated with endometrioid carcinoma, enrolling 139 ovarian cancer specimens. This study found a prevalence of endometrioid carcinoma of 14.4%, which is consistent with findings from Zhou *et al.* (11%) and Wentzensen et al. (13.2%), although it is somewhat higher than the 9.5% prevalence reported by Mei *et al.* [11, 12, 20]. Mei *et al.* also noted a higher prevalence of 24.2%, while Kanwal *et al.* reported a lower prevalence of 7.6% in a comparable setting [12, 14]. These variations may reflect regional differences and methodological factors, highlighting the importance of locally focused data for accurate assessment. When examining the distribution of ovarian carcinoma subtypes, this study revealed a pattern that diverged from prior research. For instance, Wentzensen *et al.* reported that serous carcinoma constituted 73.7% of cases in their analysis, followed by mucinous (7.2%) and

DOI: https://doi.org/10.54393/pjhs.v5i11.2320

clear cell carcinomas (5.9%) [20]. Similarly, Saeed *et al.* found that serous carcinoma was the most common subtype, at 55.9%, while clear cell carcinoma accounted for 38.9% [21]. In contrast, our study observed a markedly lower prevalence of serous carcinoma (16.5%) but higher occurrences of mucinous adenocarcinoma (12.2%) and clear cell carcinoma (9.4%). Additionally, granulosa cell tumors accounted for 7.2% of cases, close to the 8.1% prevalence found by Ahmad et al. but lower than the 14.4% reported by Kanwal *et al.* [13, 14]. Germ cell tumors, including yolk sac and mixed germ cell tumors, comprised 3.6% of cases in this study, which is lower than the 11% prevalence observed by Kanwal *et al.* [14]. For mucinous carcinoma, Ahmad *et al.* reported a prevalence of 8.1%, aligning with our study's finding of 12.2% [13]. However, the prevalence of clear cell carcinoma in this study was 9.4%, which is higher than Ahmad *et al.* 6.4% and Kanwal *et al.* 3.4% [13, 14]. Such differences in subtype distribution underscore the need for further investigation into potential geographic or genetic factors influencing these rates. The analysis also identified several demographic factors associated with endometrioid carcinoma. Age showed a weak but statistically significant correlation, which aligns with findings from Ali *et al.* [16]. Parity emerged as a significant variable; nulliparous women demonstrated a notably higher risk of developing endometrioid carcinoma than parous women, consistent with findings from Ali *et al.* and Reid *et al.*, who reported that parous women had a 30–60% lower risk of endometrioid carcinoma than nulliparous women [16, 19]. Additionally, this study showed a substantial association between menopausal status and endometrioid carcinoma, with premenopausal women having higher risk, a finding in line with Ali *et al.* report of nulliparity and late menopause as significant risk factors [16]. Our study identified several associations, rather than causal factors, between endometrioid carcinoma and risk factors such as age, parity, and menopausal status, contributing valuable insights to regional ovarian cancer research. Given that these associations are less frequently explored in local literature, further studies are warranted to investigate the impact of these factors in diverse populations and enhance understanding of the disease's etiology. There were a few limitations in this study to consider. The study has limitations that may affect the generalizability and profundity of the findings. Specifically, the cross-sectional methodology and relatively small sample size mean that the data cannot be used to demonstrate a causal relationship between the development of endometrioid carcinoma and the identified risk variables. Larger, multi-center investigations should be conducted in the future to confirm these results and investigate additional possible risk factors.

CONCLUSIONS

This study identified a higher prevalence of endometrioid carcinoma in the region and explored its association with demographic factors such as age, parity, and menopausal status. While age showed a significant association with the condition, nulliparous and premenopausal women were significantly more likely to develop endometrioid carcinoma compared to multiparous and postmenopausal women. These findings underscore the importance of considering parity and menopausal status as potential risk factors. This study highlights associations rather than causative links, given the study's descriptive and cross-sectional design. Further research is needed to explore the underlying mechanisms and causative pathways.

Authors Contribution

Conceptualization: PK
Methodology: PK
Formal analysis: SNP, MJ, SA, FAB, PK
Writing, review and editing: SNP, MJ, SA, FAB, PK, NB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2195

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Evaluation of Platelet Indices and Sepsis Markers in Neonates with Different Types of Sepsis

Hira Arshad[1*], Tanveer Latif[2] and Muhammad Usman[3]

[1]Children's Hospital and University of Child Health Sciences, Lahore, Pakistan
[2]Al-Rehman Hospital, Lahore, Pakistan
[3]Ghurki Trust Teaching Hospital, Lahore, Pakistan

ARTICLE INFO

Keywords:
Neonatal Sepsis, Platelet Indices, C-Reactive Protein, Mean Platelet Volume, Platelet Distribution Width

How to Cite:
Arshad, H., Latif, T., & Usman, M. (2024). Evaluation of Platelet Indices and Sepsis Markers in Neonates with Different Types of Sepsis: Platelet Indices and Sepsis Markers in Neonatal Sepsis . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2195

***Corresponding Author:**
Hira Arshad
Children's Hospital and University of Child Health Sciences, Lahore, Pakistan
hiraarshad218@gmail.com

Received Date: 25th September, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Sepsis in neonates was the main reason for morbidity and mortality globally, primarily in developing countries. The World Health Organization (WHO) approximates that sepsis affects approximately 3 million neonates annually, causing about 750,000 deaths. Platelet indices such as Platelet Crit distribution width (PCT), Platelet Width Volume (PWV), and Mean Platelet Distribution (MPD) were considered major biomarkers for diagnosis. **Objective:** To evaluate the alterations in platelet indices and septic markers (CRP) in neonates with sepsis as compared to established reference values. **Methods:** This cross-sectional study was conducted at the Department of Hematology and Transfusion Medicine in the Children's Hospital and University of Child Health Sciences, Lahore, from November 2023 to February 2024. 57 neonates of the Neonatal Intensive Care Unit (ICU) were sampled. Platelet indices, including PCT, PDW, MPV, and C-reactive protein (CRP), were measured using automated hematology analyzers. Data were analyzed by using SPSS V-23.0. One sample T-test was used to compare the means with the reference value. **Results:** The mean platelet count was significantly lower. MPV and PDW were significantly elevated in neonates with sepsis compared to the reference value, while PCT was considerably lower. CRP levels were significantly elevated in neonates with sepsis. **Conclusions:** This study concluded that platelet indices and CRP levels were valued biomarkers for diagnosing and treating neonatal sepsis. These well-established inflammatory markers suggest a strong systemic inflammatory response typically associated with sepsis.

INTRODUCTION

Sepsis in neonates is one of the main causes of morbidity and mortality globally, particularly in developing and underdeveloped countries, where it causes a quarter of all neonatal deaths [1]. It is estimated by the WHO that around 3 million newborns are affected by sepsis every year, leading to about 750,000 mortalities [2]. Platelets have a very vital role not only in blood clotting but also in the body's immune response to infections [3]. Low platelet count (Thrombocytopenia), is often associated with neonatal sepsis [4, 5]. Studies identify that 20% to 49% of neonates develop thrombocytopenia with sepsis, depending upon the severity of their condition [6]. Low platelet count in neonatal sepsis is a marker of disease seriousness, with exaggerated thrombocytopenia signifying worse results [7]. Despite platelet count, specific markers like mean MPV, PDW, and PCT are used for early diagnosis of neonatal sepsis [8-10]. The average size of platelets, MPV, is increased during infections as more reactive and larger platelets are produced in bone marrow [11]. Literature suggests that septic newborns have increased MPV levels than healthy ones, suggesting it can be a useful marker for predicting sepsis [12]. Current research demonstrated that neonates with sepsis had pointedly higher MPV levels related to healthy controls, signifying its utility as a predictive marker [13]. PDW, which looks at variations in platelet size, has also been explored as a diagnostic tool for neonatal sepsis [10]. An increase in PDW may indicate the production of immature or abnormal platelets, driven by inflammatory responses during sepsis, like those caused by interleukin-6 and tumor necrosis factor-α [11]. Several

DOI: https://doi.org/10.54393/pjhs.v5i11.2195

studies have found a positive link between higher PDW and neonatal sepsis, further emphasizing its potential role in early diagnosis [12]. PCT is another marker that measures the percentage of blood volume made up of platelets. It may help to evaluate the risk of sepsis-associated complications. Although there are limited studies on PCT in neonatal sepsis, early outcomes suggest that low PCT values may indicate high risks of complications. As it states its role in platelet function and turnover, PCT may help evaluate platelet utilization in septic neonates. The availability of advanced laboratory services in tertiary care hospitals allows for complete evaluations of platelet indices, enabling early diagnoses and management of sepsis in tertiary care hospitals [13]. Diagnosis and initial treatment are important, decreasing sepsis-associated problems, yet aggravating due to general clinical indications [14]. This has enforced research into biomarkers that can help in the primary detection and management of neonatal sepsis, with platelet indices and platelet count developing as major parameters [15].

However, despite the availability of such possessions, neonatal sepsis remains an important risk in tertiary care hospitals, mainly in Low and Middle-Income Countries (LMICs). Considering the link between platelet indices, platelet count, and sepsis in such situations is important for refining clinical outcomes. The objective of this research was to evaluate the alterations in platelet indices and septic markers (CRP) in neonates with sepsis compared to established reference values.

METHODS

This cross-sectional study was conducted at the Department of Hematology and Transfusion Medicine in the Children's Hospital and University of Child Health Sciences, Lahore from November 2023 to February 2024. Data were collected from neonates of the neonatal Intensive Care Unit (ICU) of Children's Hospital, Lahore. Patients' guardian consent was taken before sample withdrawal. A consecutive sampling technique was used to collect data from 57 neonates in the neonatal ICU. The sample was calculated as follows:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Confidence Interval = Z = 1.96, Prevalence = p = 28.6% = 0.286, Margin of error = d = 11.7% = 0.117, n = 57 [16]. Postnatal age from birth to 28 days and neonates with signs and symptoms of sepsis, along with either positive culture or other laboratory findings suggestive of bacterial infection without positive culture, were included in the study. At the same time, Neonates with congenital anomalies or congenital and acquired causes of thrombocytopenia other than sepsis were excluded from the study. After approval from the IRB (1256/SAHS), data from neonatal patients admitted to the hospital will be gathered. We extracted roughly 2 milliliters of venous blood from each newborn via peripheral veins into an ethylene diamine tetra acetic acid tube for these assays. Peripheral blood smears were prepared, stained with Leishman's stain, and analyzed to verify thrombocytopenia. An automated device (Sysmex XE 2100, Celltac, and Celltac g) was used to gather platelet indices. Gram staining and blood culture were used to identify bacterial and fungal organisms. Clinical evaluations and a thorough history from the mother were used to assess the newborns. Every infant had peripheral venous blood drawn, which was then sent for testing for platelets, platelet indices, CRP, and blood cultures. Data were entered and analyzed using IBM SPSS version 23.0. Continuous variables such as age, platelet count, MPV, PDW, and PCT were described as mean SD, whereas categorical variables like gender were described as frequencies and percentages. One sample T-test was used to compare the means of controls and cases. P-values less than 0.05 were taken as statistically significant. Ethical clearance was obtained from the ethical committee of the School of Allied Health Sciences, Children's Hospital and Institute of Child Health (ICH), Lahore.

RESULTS

Table 1 showed that 47 neonates were able to tolerate oral feeding with 50-100 ml of milk, while 10 tolerated 100-150 ml. Additionally, 41 neonates were admitted to the NNE Ward, and 16 were admitted to the Special Newborn Intensive Care Unit(NICU).

Table 1: Feeding Tolerance and Ward Distribution of Neonates with Sepsis

Feeding Tolerance (Milk Volume)	Number of Neonates
50–100 ml	47
100–150 ml	10
Ward Locations	**Number of Neonates**
NNE Ward	41
Special Newborn Intensive Care Unit (NICU)	16

The mean platelet count in neonates with sepsis was significantly lower than the reference value ($p < 0.001$). This reduction in platelet count (thrombocytopenia) could be associated with the systemic inflammatory response seen in sepsis. MPV was significantly elevated in neonates with sepsis compared to the reference value ($p < 0.001$). An increased MPV suggests larger platelet size, potentially indicating platelet activation and destruction, which was commonly observed in sepsis. PDW was significantly higher than the reference value ($p < 0.001$). Elevated PDW reflects increased variability in platelet size, indicating platelet activation, which may occur due to the inflammatory process in sepsis. The PCT was significantly lower than the reference value ($p < 0.001$). This reduced platelet crit indicated a lower total platelet mass in the blood, which could be due to decreased platelet production or increased destruction, commonly observed in septic neonates. CRP levels were significantly elevated in

DOI: https://doi.org/10.54393/pjhs.v5i11.2195

neonates with sepsis ($p < 0.001$). CRP was a well-established inflammatory marker, and its marked elevation suggests a strong systemic inflammatory response typically associated with sepsis (Table 2).

Table 2: One-Sample t-Test: Neonatal Sepsis Variables versus Reference Values

Variables	Reference Value	Mean ± SD	p-Value	Mean Difference	95% C.I of Difference (L)	95% C.I of Difference (U)
Platelets (Lac/µL)	3	2.246 ± 1.106	<0.001	-0.754	-1.048	-0.461
MPV (fL)	9	11.074 ± 1.247	<0.001	2.074	1.743	2.405
PDW (%)	13.5	18.337 ± 1.144	<0.001	4.837	4.533	5.14
PCT (%)	0.23	0.113 ± 0.089	<0.001	-0.117	-0.141	-0.093
CRP (mg/L)	6	32.066 ± 14.012	<0.001	26.066	22.348	29.784

Neonatal patients were classified into three groups based on culture: gram-positive culture, gram-negative culture, and fungal sepsis. The test examines several parameters: weight, platelet count, platelet count (MPV), Platelets Distribution Width (PDW), Platelet Crit (PCT), and C-Reactive Protein (CRP). The average number of platelets was slightly higher in gram-negative cultures (2.30) compared to gram-positive cultures (2.11), and fungal sepsis was (2.50). The p-value of 0.803 indicated no statistically significant difference in platelet count. Platelet count alone does not significantly vary with the type of sepsis, indicating that it may not be a strong standalone marker for differentiating between the types of sepsis. MPV was slightly higher in the Gram-positive culture (11.49 fl) compared to the Gram-negative culture (10.86 fl) and fungal sepsis (11.30 fl). The p-value of 0.201 suggests that the differences in MPV across the groups were not statistically significant. MPV does not show a strong correlation with the type of sepsis in neonates. DW was highest in the fungal sepsis group (19.45%), followed by the gram-positive culture (18.82%) and gram-negative culture (18.04%). The p-value of 0.021 indicated a statistically significant difference in PDW among the groups. PDW appears to be a more sensitive marker in differentiating between the types of neonatal sepsis. Higher PDW values might be associated with more severe or different types of infections, such as fungal sepsis. PCT was higher in the Gram-negative culture group (0.13%) compared to the Gram-positive culture (0.08%) and fungal sepsis (0.04%). A p-value of 0.039 indicated a statistically significant difference in PCT between the groups. PCT indicated that there is a significant difference between sepsis types, suggesting that this may be a valuable marker for evaluating severe or characteristic neonatal sepsis. CRP levels were highest in the fungal sepsis group (51.69 mg/l), Gram-positive culture (36.66 mg/l), and Gram-negative culture (28.77 mg/L). A P-value of 0.016 indicated a statistically significant difference in CRP levels. CRP was an important marker in this study, with elevated levels potentially indicative of more serious or specific infections, especially in cases of fungal sepsis. PDW, PCT, and CRP were the main parameters showing statistically significant differences in neonates of different types of sepsis. These findings suggest that these markers might be useful in clinical settings to differentiate between types of neonatal sepsis and potentially to assess the severity of the condition. Platelet count and MPV do not exhibit significant differences across the groups, indicating that they might not be as effective in distinguishing between different types of neonatal sepsis (Table 3).

Table 3: Comparison of Platelet Count, and Platelet Indices across Different Types of Neonatal Sepsis

Characteristics	N	Mean ± SD	p-Value
CRP (mg/L)			
Gram Positive Culture	18	36.66 ± 12.44	0.016
Gram Negative Culture	37	28.77 ± 13.76	
Fungal Sepsis	2	51.69 ± 0.40	
Total	57	32.07 ± 14.01	
Platelets (Lac/µL)			
Gram Positive Culture	18	2.11 ± 0.83	0.803
Gram Negative Culture	37	2.30 ± 1.24	
Fungal Sepsis	2	2.50 ± 0.71	
Total	57	2.25 ± 1.11	
MPV (fL)			
Gram Positive Culture	18	11.49 ± 1.34	0.201
Gram Negative Culture	37	10.86 ± 1.14	
Fungal Sepsis	2	11.30 ± 2.12	
Total	57	11.07 ± 1.25	
PDW (%)			
Gram Positive Culture	18	18.82 ± 0.83	0.021
Gram Negative Culture	37	18.04 ± 1.20	
Fungal Sepsis	2	19.45 ± 0.21	
Total	57	18.34 ± 1.14	
PCT (%)			
Gram Positive Culture	18	0.08 ± 0.05	0.039
Gram Negative Culture	37	0.13 ± 0.10	
Fungal Sepsis	2	0.04 ± 0.03	
Total	57	0.11 ± 0.09	

Platelet count has a weak positive correlation with PCT ($r = 0.242$, $p = 0.070$) and MPV ($r = 0.108$, $p = 0.423$), though these correlations were not statistically substantial. The weak negative association with PDW ($r = -0.247$, $p = 0.064$) suggests that higher platelet counts might be related to lower PDW, but this relationship was also not statistically significant. The correlation between platelet count and CRP was minimal ($r = -0.065$, $p = 0.632$), indicating no meaningful relationship between these two parameters. Overall, the platelet count does not show strong or significant correlations with the other parameters, suggesting that while the platelet count was an important

DOI: https://doi.org/10.54393/pjhs.v5i11.2195

marker, it may not directly correlate with these specific platelet indices or CRP levels in neonatal sepsis (Table 4).

Table 4: Correlation of Platelet Count with Sepsis Markers in Neonates

Variables	Platelets (Lac/µL)	MPV (fL)	PDW (%)	PCT (%)	CRP (mg/L)
Platelets (Lac/µL)					
Pearson Correlation	1.000	0.108	-0.247	0.242	-0.065
Significant (2-Tailed)	-	0.423	0.064	0.070	0.632
MPV (fL)					
Pearson Correlation	0.108	1.000	0.468	-0.546	0.118
Significant (2-Tailed)	0.423	-	0.000	0.000	0.380
PDW (%)					
Pearson Correlation	-0.247	0.468	1.000	-0.546	0.050
Significant (2-Tailed)	0.064	0.000	-	0.000	0.714
PCT (%)					
Pearson Correlation	-0.247	0.468	1.000	-0.546	0.050
Significant (2-Tailed)	0.064	0.000	-	0.000	0.714
CRP (mg/L)					
Pearson Correlation	-0.065	0.118	0.050	-0.164	1.000
Significant (2-Tailed)	0.632	0.380	0.714	0.222	-

DISCUSSION

The present research offers important results on platelet count, such as Platelet Width Volume (PWV), Platelet Crit distribution width (PCT), Mean Platelet Distribution (MPD), and CRP (C-Reactive Protein) in neonates with sepsis. These factors, presentation deviations from the mention values, were reliable with movements detected in current reports, representing their position in the monitoring and diagnosis of neonatal sepsis. The decreased platelet counts in this research (mean: 2.246 lacs/µL) relates to the mean value of 3 lacs/µL, providing the well-standard suggestion between neonatal sepsis and thrombocytopenia. Research such as Toro-Huamanchumo CJ et al., have stated that 20-70% of neonates with sepsis progress to thrombocytopenia reliant on the severity of the infection. Thrombocytopenia happens due to augmented platelet utilization, frequently as a result of disseminated intravascular coagulation (DIC), a general problem of sepsis [17]. The pointedly raised MPV (mean: 11.074 fL) detected in this report was consistent with the results of Kristopher May Pamudji and colleagues, who proved that a rise in MPV showed the issue of greater, more responsive, and early platelets from the bone marrow in response to systemic infection [18]. This rise in MPV proposes augmented platelet yield and a responsive thrombocytosis usually seen during septic situations. Thus, MPV can assist as a marker of infection and inflammation severity in neonates with sepsis. Also, the raised PDW values in the study (mean: 18.337%) align with those stated in Wu J *et al.*, in 2019, where a rise in PDW was related to better variability in platelet size, showing higher platelet destruction and production during sepsis [19]. The important change in PDW among diverse sepsis forms in this report ($p = 0.021$) provides the hypothesis that PDW can help as a sensitive marker in distinguishing between forms of neonatal sepsis, mainly fungal infections. Our study also obtained a momentous decrease in PCT (mean: 0.113%) related to the mentioned value of 0.23%, with a p-value of 0.039, representing statistical importance. Low PCT in neonates with sepsis showed decreased platelet count due to high platelet utilization, mainly in severe infections. The variations in PCT among sepsis emphasize its value in evaluating the severity of the state and the level of platelet demolition in neonatal sepsis [20]. CRP stages in this report (mean: 32.066 mg/L) were markedly increased, particularly in fungal sepsis cases (mean: 51.69 mg/L), aligning with results from Eichberger J et al., who stated that increased CRP points relate with greater infection severity. Raised CRP was a well-recognized marker for fungal and bacterial infections, making it a consistent indicator for monitoring and diagnosing neonatal sepsis [21].

CONCLUSIONS

In conclusion, the study's findings confirm that the platelet indices, such as MPV, PDW, and PCT, along with CRP, were valuable in diagnosing and differentiating between types of neonatal sepsis. These markers provide clinicians with critical insights into the severity and nature of the infection, improving neonatal sepsis management and outcomes.

Authors Contribution

Conceptualization: HA
Methodology: HA, TL, MS
Formal analysis: TL
Writing, review and editing: TL, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2294

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Types of Inherited Hemoglobin Disorders among the Patients Attending a Tertiary Care Hospital

Rehan Anwar[1], Kamran Arzoo[2*], Adnan Riaz[3], Riasat Ali[4], Sumera Saghir[5] and Bilal Habib[2]

[1]Department of Medicine, Sialkot Medical College, Sialkot, Pakistan
[2]Department of Physiology, Rai Medical College, Sargodha, Pakistan
[3]Department of Biochemistry, Islam Medical College, Sialkot, Pakistan
[4]Department of Anatomy, Pak Red Crescent Medical and Dental College, Lahore, Pakistan
[5]Department of Biochemistry, Rashid Latif Medical College, Lahore, Pakistan

ARTICLE INFO

Keywords:
Thalassemia, Hemoglobin, Reticulocyte, Ferritin Level

How to Cite:
Anwar, R., Arzoo, K., Riaz, A., Ali, R., Saghir, S., & Habib, B. Types of Inherited Hemoglobin Disorders among the Patients Attending a Tertiary Care Hospital: Types of Inherited Hemoglobin Disorders among the Patients. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2294

***Corresponding Author:**
Kamran Arzoo
Department of Physiology, Rai Medical College, Sargodha, Pakistan
dr.kamranarzoo@gmail.com

Received Date: 20th September, 2024
Acceptance Date: 17th November, 2024
Published Date: 30th November, 2024

ABSTRACT

The genetic conditions known as hemoglobinopathies, which include thalassemia impact the synthesis and structure of Hemoglobin, the red blood cell protein that carries oxygen. **Objectives:** To investigate the prevalence of different types of thalassemia associated with age, gender and Hematological parameters. **Methods:** The total number of participants was n=139. The cross-sectional study was conducted at Rai Medical College Sargodha. The study was conducted for six months, from July 2023 to Dec 2023. Biochemical parameters investigated such as Hemoglobin, mean corpuscular hemoglobin MCH, reticulocyte and ferritin were done in the Hematology lab. Collected data were analyzed by SPSS version 25.0. **Results:** The gender distribution among the participants included male 50.3% and female 49.6%. The mean age of the patients was approximately 34.8 years. This study of 139 participants found Hb-E Beta Thalassemia (25.4%) to be the most common type, especially among those with a history of cousin marriage. Severe forms like Hb-E Beta Thalassemia and Beta Thalassemia Major had low hemoglobin and MCH levels, indicating severe anemia, while milder forms showed near-normal levels. In mean corpuscular Hemoglobin E Beta Thalassemia (29.7 ± 4.1), p=0.001, mean corpuscular Hemoglobin A levels are considerably lower than Beta Thalassemia Trait. There was no association with age and gender, p>0.005. **Conclusions:** It was concluded that our investigation offered important insights into the biochemical profiles linked to various thalassemia types, even though it did not identify any appreciable variations in thalassemia prevalence by age or gender.

INTRODUCTION

The term "Hemoglobinopathies" refers to a class of hereditary diseases that affect the production of globin chains, which are vital constituents of Hemoglobin (Hb)—the oxygen-transporting protein found in red blood cells. A variety of clinical problems are brought on by genetic changes in these illnesses that change the normal production or structure of Hb [1]. Thalassemia is a disorder marked by diminished synthesis of one or more globin chains, such as beta or alpha chains. Two such instances are the alpha and beta types of thalassemia. Those involve atypical Hb, which is brought about by mutations which alter the globin chains' internal structure. Here are Hb-S, Hb-C, and Hb-E (Hb-E) as examples [2]. About 1,200 different genetic modifications impacting the DNA sequences of the human β-like (Hb-Z, Hb-A2, Hb-A1, and Hb-Q1) and β-like (Hb-E1, Hb-G2, Hb-G1, Hb-D, and Hb-B) globin genes are the primary root cause of the noted clinical variation. These variants have been catalogued in the Hb-Variants database, a locus-specific repository of Hb variants and their associated clinical phenotypes [3]. Accurate DNA diagnosis of thalassemia can be achieved by family research and thorough Hematological tests. For this reason, a variety of methods can accurately, quickly, and affordably identify the underlying genetic abnormality in afflicted individuals [4]. The majority of these are the result of one or more globin chains having a single amino acid

DOI: https://doi.org/10.54393/pjhs.v5i11.2294

substituted. An estimated 320,000 infants are born annually with major Hb disorders: 83% with sickle cell disease and 17% with thalassemia. these births, about 80% take place in poor nations. Five of the most cautious projections indicate that more than 100 million people with a global frequency of 1.5% for beta-thalassemia and at least 5.2% of the world's population (over 360 million) carry a substantial Hb variation [5, 6]. The human body uses Hb for a variety of purposes, including buffering hydrogen ions, metabolizing nitric oxide, carrying carbon dioxide from tissues to the lungs, and transporting oxygen from the lungs to the tissues. Adult blood contains between 11.5 and 18 g/dL of hemoglobin [7]. The two main categories of Hb disorders are hemoglobinopathies, which are caused by abnormalities in the Hb gene structure, and thalassemia, which are caused by mutations that impact the expression and synthesis of the Hb chain. Thalassemia is an inherited hematological disorder categorized by a decrease or absence of one or more of the globin chain synthesis. Beta-thalassemia is caused by one or more mutations in the beta-globin gene. The absence or reduced amount of beta-globin chains causes ineffective erythropoiesis which leads to anemia [8, 9]. A thalassemia phenotype and a functional deficit in the globin chain are the results of some structural Hb variants that are also ineffectively produced or globin chain variants that are so unstable that they cannot form tetramers [10]. The first group, known as thalassemia hemoglobinopathies, comprises the δβ fusion variants (Hb-Lepore) and Hb E, β26 (Glu→Lys). In this case, the substitution at β-codon 26 (GAG→AAG) also results in alternative splicing of the β globin mRNA, which lowers the normally spliced β message encoding the Hb-E variant. Hereditary persistence of fetal haemoglobin (HPFH) is a subset of hemoglobinopathies that cause varying elevations in Hb-F in otherwise healthy individuals [11]. Owing to their simultaneous elevation in Hb-F levels, the δβ- and γδβ-thalassaemias are sometimes categorized as part of the syndrome of elevated Hb Fs, creating a continuous range within the HPFHs. Nonetheless, the differentiation between HPFH and δβ-thalassemia must be maintained for pragmatic and medical purposes [12]. There may be a gap in comparing the research population's Hb problem prevalence and features to those of other genders and ages in Pakistani communities may offer important context and insights.

This study aims to investigate the prevalence of different types of thalassemia associated with age, gender and Hematological parameters.

METHODS

A cross-sectional study was conducted at the Department of Physiology at Rai Medical College Teaching Hospital, Sargodha, from July 2023 to Dec 2023. This study was approved by the institutional review board (IRB) reference number (RMCS/ERC/3/22). The study participants were attending the Physiology and Hematology outpatient department and the sample size was determined to be n=139. The formula for calculating the sample size when estimating a proportion is n= Z2 x P x (1-p) 2/E2, where n=sample size, Z=Z score confidence level (95%), P=prevalence of Hb disorder 10% (p=0.10) and E=margin of error 5% (E=0.05) [13]. Inclusion criteria were participants aged between 15-54 years, male and female gender, and patients suffering from hemoglobinopathies previously diagnosed according to Hb electrophoresis. Exclusion criteria included critically ill patients needing immediate hospitalization, extremes of age, patients already admitted, and those with Hematological malignancy. Informed consent was obtained from all participants or their guardians. The Hematological parameters were examined through blood sampling to diagnose, including Hb, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Red Cell Distribution Width (RDW). The morphological abnormalities, such as microcytosis, hypochromic, and target cells, that are suggestive of thalassemia were investigated in a peripheral smear. Hb Electrophoresis tests were used to detect and quantify abnormal Hb fractions, including Hb-A2 and Hb-F levels. Data were collected through interviews, using a questionnaire including demographic characteristics and relevant information related to Hb disorder [14]. The patient's demographics, clinical state, and laboratory findings were all reported at the time of presentation. Standard deviation, mean, numerical frequencies, and percentages (%) were used to display data. The data were statistically analyzed using descriptive statistics for frequencies of each Hb disorder, One way ANOVA was used for comparing the mean of different groups, and chi-square tests were used for association between categorical data by SPSS version 25. There was statistical significance among the variables (p-value<0.05).

RESULTS

The demographic characteristics of the participants in your study (n=139) reveal important insights into the composition of your sample. The gender distribution among the participants included male 50.3% and female 49.6%. The mean age of the patients is approximately 34.8 years. The majority of the participants 46.7% fell within the age group 15-24 as compared to another age group. The majority of participants included rural area 57.5% and urban area 42.4%. Most participants 56.8% have had their illness for more than 5 years. Of the interviewees, 55 (39.5%) said they were married to a relative. A total of 84 participants, or 60.4%, were not wed to a cousin. Of the participants, 72 (51.7%) were married, and 67 (48.2%) were single. Of the subjects, 84 (60.4%) had no family history of

DOI: https://doi.org/10.54393/pjhs.v5i11.2294

Hb problems and 25 (17.9%) had thalassemia, 30 (21.5%) had sickle cell disease in family history (Table 1).

Table 1: Demographic Characteristics of Participants

Characteristics		Number of Participants (n=139)
Gender	Male	70 (50.3%)
	Female	69 (49.6%)
Age	15-24	65 (46.7%)
	25-34	35 (25.1%)
	35-44	20 (14.3%)
	45-54	19 (13.6%)
Residence	Urban	59 (42.4%)
	Rural	80 (57.5%)
Period of Illness	2 Years	22 (15.8%)
	3 Years	38 (27.3%)
	>5 Years	79 (56.8%)
Cousin Marriage	Yes	55 (39.5%)
	No	84 (60.4%)
Marital Status	Yes	72 (51.7%)
	No	67 (48.2%)
Family History	Thalassemia	25 (17.9%)
	Sickle Cell Disease	30 (21.5%)
	No	84 (60.4%)

The distribution suggests that while milder forms (Hb-E Trait and Beta Thalassemia Trait) are present, they are less common compared to the severe form of Hb-E Beta thalassemia (Figure 1).

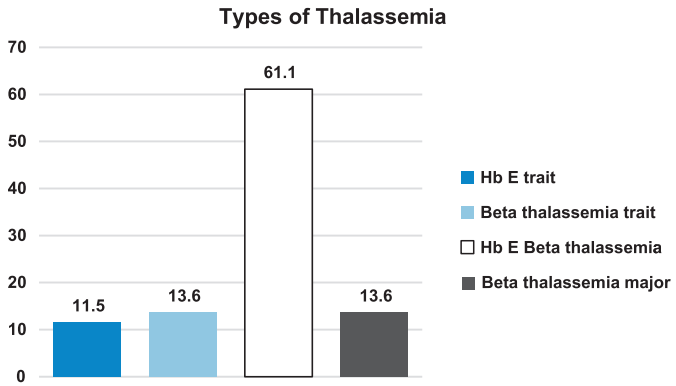

Figure 1: Different Types of Thalassemia in the study Participants

The distribution of inherited hemoglobinopathies among patients with a history of cousin marriage is shown in the table. According to the data, the beta thalassemia trait accounts for 20% of cases, whereas the Hb-E trait is present in 21.8% of cases. Furthermore, the greatest percentage of these conditions—25.4%—are Hb-E Beta thalassemia, a compound illness that involves both Hb-E and Beta thalassemia features. Lastly, 20% of cases are known to have beta thalassemia major, a severe form of thalassemia. With the highest prevalence observed in those with the combined Hb-E Beta thalassemia phenotype, this distribution points to a significant correlation between cousin marriage and several Hb diseases. The possible hereditary hazards are reflected in the comparatively high percentages for all disorders (Figure 2).

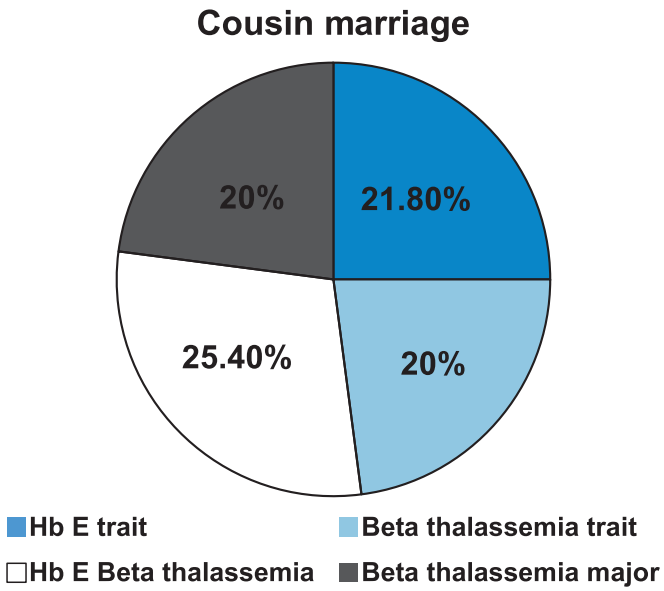

Figure 2: Percentage of Different Types of Thalassemia Associated with Cousin Marriage

Our current study indicates that the various forms of thalassemia differ considerably in terms of electrophoretic profiles and biochemical characteristics. In Hb-E Beta-thalassemia (6.81 ± 1.1 g/dL) and Beta-thalassemia major (5.9 ± 0.4 g/dL), Hemoglobin (Hb) levels were significantly reduced, indicating severe anemia; in contrast, Hb-E trait (14.1 ± 2.2 g/dL) and Beta-thalassemia trait (13.8 ± 0.1 g/dL) showed near-normal levels, suggesting a mild clinical presentation (p=0.001). A similar pattern was seen in the Mean Corpuscular Hemoglobin (MCH), with the lowest values being found in Hb-E Beta-thalassemia (7.7 ± 0.6 pg) and Beta-thalassemia major (5.5 ± 1.3 pg), indicating microcytic hypochromic anemia. MCH readings were lower than normal levels (p=0.001). However, they were greater in the Hb-E trait (15.9 ± 2.9 pg). In Hb-E beta-thalassemia (13.4 ± 4.1%) and beta-thalassemia major (12.8 ± 2.2%), there was a significant rise in the reticulocyte percentage, a measure of red cell formation, suggesting greater hemolysis and red blood cell turnover. The beta-thalassemia trait, on the other hand, had the lowest reticulocyte count (1.5 ± 0.1%), which indicated limited hemolysis (p=0.001). Due to frequent blood transfusions and iron overload, ferritin levels were highest in Hb-E Beta-thalassemia (12.9 ± 2.2 mg/ml) and Beta-thalassemia major (12.5 ± 1.1 mg/ml), while ferritin levels were lowest in Beta-thalassemia trait (2.1 ± 0.2 mg/ml) (p=0.001). Affected by defective beta-globin synthesis, Hb-A levels in the Hb electrophoresis profile were highest in Beta-thalassemia trait (79.4 ± 8.9%) and much lower in Hb-E Beta-thalassemia (22.5 ± 6.2%) and Beta-thalassemia major (29.7 ± 4.1%) (p=0.001). Hb-A2 levels were significantly higher in Hb-E beta-thalassemia (29.3 ± 3.1%) and Hb-E trait (26.9 ± 3.7%), which is consistent with aberrant Hb-E synthesis (p=0.009). As

DOI: https://doi.org/10.54393/pjhs.v5i11.2294

anticipated, the percentage of Hb-E was highest in Hb-E Beta-thalassemia (30.1 ± 5.9%) and lowest in Hb-E trait (17.8 ± 5.2%). Nevertheless, p=0.067 indicates that there was no statistically significant difference in the Hb-E percentages between the groups. Hb-F levels were higher in every group, particularly in Hb-E Beta-thalassemia (19.6 ± 7.3%), which indicates the continued presence of fetal Hb. The groups' differences in Hb-F levels, however, did not reach statistical significance (p-value=1.899) (Table 2).

Table 2: Hematological Parameters and Electrophoretic Profile Associate with Different Types of Thalassemia through Blood Sampling

Parameters	Hb-E trait	Beta Thalassemia Trait	Hb-E Beta Thalassemia	Beta Thalassemia Major	p-value
Hb (g/dL)	14.1 ± 2.2	13.8 ± 0.1	6.81 ± 1.1	5.9 ± 0.4	0.001
MCH (pg)	15.9 ± 2.9	13.5 ± 0.2	7.7 ± 0.6	5.5 ± 1.3	0.001
Reticulocytes %	4.5 ± 3.2	1.5 ± 0.1	13.4 ± 4.1	12.8 ± 2.2	0.001
Ferritin (mg/ml)	4.7 ± 1.4	2.1 ± 0.2	12.9 ± 2.2	12.5 ± 1.1	0.001
Hemoglobin					
Hb-A %	44.8 ± 5.5	79.4 ± 8.9	22.5 ± 6.2	29.7 ± 4.1	0.001
Hb-A 2 %	26.9 ± 3.7	3.0 ± 0.1	29.3 ± 3.1	6.2 ± 0.3	0.009
Hb-E %	17.8 ± 5.2	1.5 ± 0.2	30.1 ± 5.9	10.7 ± 1.1	0.067
Hb-F %	16.3 ± 0.1	15.8 ± 0.4	19.6 ± 7.3	16.9 ± 1.1	1.899

Our study indicates that the Hb-E trait, Beta thalassemia trait, Hb-E beta-thalassemia, and Beta-thalassemia major show that there are no gender differences that are statistically significant in this study sample (0.119, 0.881, 0.055, and 0.121, respectively). These p-values were marginally higher than the 0.05 cutoff (Table 3).

Table 3: Gender based Association with Types of Thalassemia

Types of Thalassemia	Male (n=70)	Female (n=39)	Chi-square (x^2)	p-value
Hb-E Trait	5 (7.1%)	3 (7.69%)	4.1503	0.119
Beta Thalassemia Trait	2 (2.85%)	4 (10.25%)	4.1503	0.881
Hb-E Beta Thalassemia	61 (87.14%)	29 (74.35%)	4.1503	0.055
Beta Thalassemia Major	2 (2.85%)	3 (7.69%)	4.1503	0.121

In this study there are no significant differences between the Hb-E trait, Beta thalassemia trait, Hb-E Beta thalassemia, and Beta thalassemia major, suggesting a potential but non-conclusive age-related difference in prevalence. These p-values were marginally higher than the 0.05 cutoff (Table 4).

Table 4: Age based Association with Types of Thalassemia

Age	15-24	25-34	35-44	45-54	Chi-square (x^2)	df	p-value
Hb-E Trait	6 (37.5%)	3 (18.75%)	4 (25%)	3 (18.75%)	3.364	5	0.009
Beta Thalassemia Trait	5 (26.31%)	6 (31.57%)	3 (15.78%)	5 (26.31%)	3.364	5	0.061
Hb-E Beta Thalassemia	46 (54.11%)	32 (37.64%)	3 (3.5%)	4 (4.7%)	3.364	5	0.006
Beta Thalassemia Major	4 (21.05%)	5 (26.31%)	7 (36.84%)	4 (21.05%)	3.364	5	0.007

Certain types of thalassemia are slightly more common in individuals from cousin marriages. For example, 21.8% of those with the Hb-E trait and 25.4% with H-E beta-thalassemia were born of cousin marriages, compared to 20% for both the beta thalassemia trait and major. These results suggest a modestly increased risk of inheriting thalassemia in consanguineous unions, likely due to a higher chance of recessive gene transmission in genetically similar parents (Table 5).

Table 5: Association of Cousin Marriage with Different Types of Thalassemia

Types of Thalassemia	Cousin Marriage (%)	No Cousin Marriage (%)	Chi-Square Value	p-value
Hb-E Trait	21.8%	78.2%	0.000	1.000
Beta Thalassemia Trait	20.0%	80.0%	0.106	0.744
Hb-E Beta Thalassemia	25.4%	74.5%	0.426	0.514
Beta Thalassemia Major	20.0%	80.0%	0.106	0.744

DISCUSSION

In the present study to found that, the gender distribution is almost equal, with male comprising 50.3% and female 49.6% of the participants. The mean age of the participants is approximately 34.8 years, with the majority (46.7%) falling within the 15-24 age groups. The larger proportion of participants (57.5%) are from rural areas compared to urban areas (42.4%). This indicates that a significant number of patients are living with long-term conditions related to their Hb disorders. The relatively high percentage of participants with a duration of illness exceeding 5 years highlights the chronic nature of these disorders and suggests a need for long-term management strategies. This balanced distribution suggests that both genders and ages are similarly affected or seek medical consultation at a tertiary care hospital for inherited Hb disorders. We agreed that the previous study by Ata *et al.*, and Mairbäurl *et al.*, reported a slightly higher prevalence of male in their sample, with male constituting around 55% of the study population. The balanced gender ratio in this study could suggest that there is increasing awareness and access to healthcare services for female, or it might reflect a true equal prevalence among genders in the region [15, 16]. The current study indicates that severe forms of thalassemia, such as Hb-E Beta Thalassemia and Beta Thalassemia Major, exhibit significantly lower Hb levels (6.81 ± 1.1) and MCH (5.5 ± 1.3) compared to milder forms like Hb-E Trait and Beta Thalassemia Trait. This finding is statistically significant with a p-value of 0.001. Significant differences were observed in biochemical parameters across different types of thalassemia. The patients with Beta Thalassemia Major consistently have lower Hb levels due to ineffective erythropoiesis and increased hemolysis. The low MCH in severe thalassemia reflects microcytic anemia, which is a hallmark of these conditions. These findings emphasize the severe impact of the disease on red

DOI: https://doi.org/10.54393/pjhs.v5i11.2294

blood cell morphology and functionality. Similar results were observed in a study by Wasim *et al.*, and Borai *et al.*, who also reported that patients with Beta Thalassemia Major exhibited significantly lower Hb levels compared to those with Beta Thalassemia Trait, supporting the notion that the severity of hemolytic anemia is a distinguishing factor between these conditions [17, 18]. Significantly elevated ferritin levels (12.9 ± 2.2) and reticulocyte count (13.4 ± 4.1) in severe thalassemia forms, such as Hb-E Beta Thalassemia and Beta Thalassemia Major, indicate higher erythropoietin activity and an excessive amount of iron. This result is also notable with a p-value of 0.001. The results presented here support the hypothesis that in people who suffer from severe thalassemia, the body attempts to combat persistent hemolysis by raising the reticulocyte count. Elevated ferritin levels have been linked with poor erythropoiesis as well as repeated transfusions of blood, which may contribute to iron exhaustion, which is an important concern for patients with chronic thalassemia. Hb-A concentrations in Hb-E beta thalassemia are significantly reduced (29.7 ± 4.1) than in the beta thalassemia trait, with an independent p-value of 0.001. This is suggestive of the abnormal output of Hb caused by the substance's heterozygous status of the Hb-E and beta thalassemia genes. The identical findings have been reported by Ahmad *et al.*, who determined that due to Hb- E being an Hb variant with a structural defect that inhibits the development of normal Hb-A, those with Hb-E beta-thalassemia had significantly decreased Hb-A levels. This outcome emphasizes the complicated Hb makeup in compound heterozygotes and its potential effects on therapy [19]. Understanding the gender disparity in the frequency of these conditions makes it easier to tailor genetic counselling and public health campaigns. While no significant differences were found, it remains important to consider other factors that could impact the occurrence of these disorders, such as cultural background, consanguinity rates, and environmental influences. Extensive research undertaken across diverse populations has revealed significant variations in the gender distribution of thalassemia. For example, an earlier study conducted by Mir *et al.*, did not detect any significant differences in thalassemia prevalence between genders, which is consistent with your findings. However, according to some local studies, there may be a higher frequency in men, possibly due to cultural or genetic reasons [20]. Severe variations of thalassemia, like Beta Thalassemia Major, typically show symptoms in early childhood, although milder versions may go years without symptoms being seen. The lack of notable age-related changes observed in the study sample may be due to the inclusion of individuals at varying stages of the disease progression. According to Shafique *et al.*, some populations may have more thalassemia characteristics in younger age groups due to recent improvements in awareness and diagnosis, whereas more severe variants may appear later as problems occur [21]. A current study showed that hematological indices, such as Hb, MCH, reticulocytes, ferritin, and levels of Hb-A and Hb-A2, are critical indicators for differentiating between different thalassemia syndromes. These markers' noteworthy variations demonstrate their therapeutic value. The non-significant results for Hb-E and Hb-F, however, imply that these metrics might not be enough to distinguish between these circumstances on their own. Programs to raise public awareness about the genetic dangers of consanguineous marriages must be centred in the community.

CONCLUSIONS

It was concluded that even though the analysis did not find any discernible differences in the prevalence of thalassemia by age or gender, it did provide valuable insights into the biochemical profiles associated with different kinds of the disease. Further research is required to fully comprehend the complex links that exist between demographic factors and thalassemia and to enhance the diagnosis, treatment, and management of this inherited illness.

Authors Contribution

Conceptualization: RA
Methodology: KA, AR, RA
Formal analysis: KA, SS
Writing review and editing: SS, BH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2198

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Fetuin-A as A Marker of Vascular Calcification in Chronic Kidney Disease

Raisa Shaikh[1], Sama Ul Haque[2], Javed Mahmood[3], Imran Mehboob Baig[4], Ghazala Panhwar[5] and Adeel Zafar[3*]

[1]Department of Biochemistry, Shahida Islam Medical and Dental College, Lodhran, Pakistan
[2]Department of Anatomy, Fazaia Ruth Pfau Medical College, Karachi, Pakistan
[3]Department of Pathology, Shahida Islam Medical and Dental College, Lodhran, Pakistan
[4]Department of Physiology, Shahida Islam Medical and Dental College, Lodhran, Pakistan
[5]Department of Biochemistry, Shahida Islam Medical and Dental College, Lodhran, Pakistan

ARTICLE INFO

Keywords:
Chronic Kidney Disease, Human Fetuin A, Vascular Calcifications, Association

How to Cite:
Shaikh, R., Haque, S. U., Mahmood, J., Baig, I. M., Panhwar, G., & Zafar, A. (2024). Fetuin-A as A Marker of Vascular Calcification in Chronic Kidney Disease: Fetuin-A Marker of Vascular Calcification in Chronic Kidney Disease. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2198

***Corresponding Author:**
Adeel Zafar
Department of Pathology, Shahida Islam Medical and Dental College, Lodhran, Pakistan
aznagra@hotmail.com

Received Date: 25th September, 2024
Acceptance Date: 20th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Multiple factors contribute to vascular calcification in chronic kidney disease. Fetuin-A is known for its potent inhibitory effects on ectopic calcification **Objectives:** To determine the association between fetuin-A levels and vascular calcification in chronic kidney disease patients. **Methods:** 90 samples were collected from patients admitted to the Nephrology ward of Shahida Islam Medical Complex, Lodhran due to renal disease, and 90 samples were collected from normal healthy subjects. Patients with congestive heart failure, use of hormonal contraceptives or hormone replacement therapy, malignancy, pregnancy and with a history of trauma or surgery within a month were excluded. Mann-Whitney was applied to test Serum Fetuin A between cases and controls keeping $p<0.05$ as statistically significant. **Results:** Of 90 cases and 90 controls, 63 male (70%) and 27 female (30%) were in cases and 45 (50%) male and female were in the control group. the cases exhibited lower levels of Fetuin-A (0.4416 ± 0.17 g/L) compared to the controls (0.752 ± 0.176 g/L). The clustering revealed a possible association between the severity of chronic kidney disease and decreased Fetuin-A levels. The values ranged from as low as 0.034 to a peak at 2.132 g/L, with several outliers distributed across the chronic kidney disease stage. **Conclusions:** It was concluded that comparing fetuin-A levels in chronic kidney disease patients to controls revealed a significant correlation. Patients had lower levels of fetuin-A compared to controls.

INTRODUCTION

Chronic kidney disease (CKD) is a significant healthcare burden the world over, affecting millions [1]. CKD is characteristically denoted by progressive loss of kidney function, posing substantial challenges, such as being associated with multiple complications, like cardiovascular disease (CVD) [2]. Amongst the most concerning cardiovascular complications is vascular calcification, which is marked by the deposition of calcium phosphate crystals in vascular tissues [3]. The pathological calcification leads to an increase in arterial stiffness, elevation of pulse pressure, and heightened risk of adverse cardiovascular events, which are leading causes of mortality and morbidity among CKD patients [4]. In CKD, Vascular calcification is multifactorial which involves complex interactions in-between mineral imbalances, inflammatory processes, and metabolic disturbances. One of the key biomarkers in CKD pathophysiology is fetuin-A, a glycoprotein predominantly synthesized in the liver [5]. Fetuin-A is recognized for its potent inhibitory effects on ectopic calcification. The function of Fetuin-A acts via binding to calcium and phosphate ions and prevents their precipitation and subsequent deposition in vascular tissues. This resultantly causes fetuin-A to serve as a crucial regulator of mineral metabolism and thus a potential marker for vascular calcification [6]. According to published research, CKD is associated with lower levels of fetuin-A, which are correlated with the degree of arterial calcification and can result in severe cardiovascular events

DOI: https://doi.org/10.54393/pjhs.v5i11.2198

[7]. This progressive decline in renal function observed in CKD disrupts the homeostasis of calcium and phosphate, and so promotes an environment conducive to vascular calcification [8]. The concomitant reduction in fetuin-A exacerbates this process, underscoring its significance as both a protective factor and a biomarker [9]. Researchers have shown that lower serum fetuin-A levels are linked with increased calcification scores and arterial stiffness in CKD patients, especially. This inverse relationship suggests that monitoring fetuin-A levels could offer valuable insights into the extent of vascular calcification and overall cardiovascular health in this population, especially in hypertension [10]. Moreover, fetuin-A's role extends beyond a mere biomarker; it also represents a potential therapeutic target [11]. Enhancing fetuin-A levels or mimicking its inhibitory effects on calcification could pave the way for novel interventions aimed at mitigating vascular calcification and improving cardiovascular outcomes in CKD [12]. Despite the promising implications, the precise mechanisms by which fetuin-A modulates vascular calcification in CKD remain incompletely understood [13]. Ongoing research aims to elucidate the pathways involved, with a focus on the interplay between fetuin-A, mineral metabolism, and inflammatory mediators. Understanding these mechanisms is crucial for developing targeted therapies and refining clinical strategies to manage vascular calcification in CKD patients [14]. Fetuin-A emerges as a pivotal marker of vascular calcification in chronic kidney disease, reflecting its broader role in mineral metabolism and cardiovascular health. As CKD continues to pose significant health challenges, leveraging biomarkers like fetuin-A for early detection, risk stratification, and therapeutic intervention holds promise for improving patient outcomes [15]. Since the burden of CKD is high in the local population along with its associated complications, investigating the potential biomarker (Feutin-A) for early detection of vascular calcification in CKD is vital for Pakistani patients.

This study aims to determine the association between fetuin-A levels and vascular calcification in CKD patients.

METHODS

This case-control study was done at Shahida Islam Medical Complex, Lodhran for six months after approval of the research proposal from the Institutional Review Board Committee (IRB) letter no. SIMC/ET.C/10012/23. The study was done from February 2023 to July 2023. The sample size for the study was calculated using open epi online software for sample size calculation. Keeping the prevalence of chronic kidney disease in Pakistan at 12.5% as reported in local research and a 95% confidence level, with precision at 5% the sample size came out to be 169. However, 180 samples were taken from patients (accounting for loss to follow-up and a 5 % margin of error). admitted to the Nephrology Department of Shahida Islam Teaching Hospital due to any renal illness, and 90 samples were collected from otherwise healthy people as controls. Informed consent was taken from all subjects. Out of 180 samples, 90 were cases of renal disease between 18 and 75 years of age, whilst 90 were standard demographically compared to healthy controls. Patients with congestive heart failure, use of hormonal contraceptives or hormone replacement therapy, malignancy, pregnancy, and a history of trauma or surgery within a month were excluded from the study. The sampling method used was non-probability convenience sampling. The demographical data included age, weight, and status of diabetes while laboratory data included Feutin-A, fasting glucose, urea, creatinine, and creatinine clearance; serum calcium and phosphorus were assessed after a 12-hour fast wherein serum was obtained after centrifugation of blood at 3000 rpm. For Fetuin A, an ELISA kit was used for testing in blood serum. This kit is for Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated using human FETU-A antibodies. The FETU-A from the sample was added, and it interacted with the antibodies on the boreholes by binding to them. The subsequent addition of biotin-conjugated human FETU-A antibody causes it to adhere to the sample's FETU-A. Streptavidin-HRP is then added, which binds the biotinylated FETU-A antibody. Post incubation, unattached Streptavidin-HRP was eliminated through washing. After that, a substrate mixture was introduced. As additional Human FETU-A is included, the color gradually changes. When an acidic stop solution was introduced to stop the reaction, absorbance at 450 nm was measured. For data analysis, SPSS version 23.0 was used. Mean and standard deviation were reported for numerical variables while frequency and percentage for categorical variables. Stratification of data was performed according to age. Mann-Whitney was applied to test Serum Fetuin A between cases and controls keeping $p<0.05$ as statistically significant.

RESULTS

The key variables from the 90 cases and 90 controls are contrasted. The mean age of the cases was 44.55 ± 15.95 years, while the controls had a similar mean age of 45.5 years ± 15.95 years. BMI was slightly higher among cases ($27.33 \pm 5.31\ kg/m^2$) compared to controls ($25.5 \pm 5.13\ kg/m^2$). The distribution of gender among the participants was notably skewed in the cases group, with 63 male (70%) and 27 female (30%). In contrast, the control group had an equal gender distribution, with 50% male and 50% female. Regarding comorbidities, diabetes was present in 30 % of the cases compared to 7.8% of the controls. Hypertension was also more prevalent among the cases (38.9%) compared to the controls (10%). Biochemically, the patients had lower Fetuin-A levels (0.4416 ± 0.17 g/L) than the controls (0.752 ± 0.176 g/L). Furthermore, the cases showed altered glucose levels (104.67 ± 23.01 mg/dL) compared to the controls (92.05 ± 97.57 mg/dL). Renal function indicators, including urea and creatinine, were highly elevated in the cases, with urea levels at 100.95 ± 28.73 mg/dL and creatinine at 2.07 ± 3.15 mg/dL, compared

DOI: https://doi.org/10.54393/pjhs.v5i11.2198

to controls who had urea levels at 23.92 ± 3.44 mg/dL and creatinine at 0.94 ± 0.01 mg/dL. The mean Glomerular Filtration Rate (GFR) (mL/min/1.73 m2) in cases was 42.47 ± 16.72 mL/min/1.73 m2 while in controls was 98.39 ± 11.29 mL/min/1.73 m2. Serum calcium in cases was 12.65 ± 0.72 mg/dl while in controls was 9.81 ± 0.5 mg/dl. Serum cholesterol in cases was 237 ± 37.22 mg/dl while in controls was 173.34 ± 23.95 mg/dl (Table 1).

Table 1: Demographics of Patients Included in the Study (n=180)

Variables		Cases n=90	Controls n=90
Age (Years)		44.55 ± 15.95	45.5 ± 15.95
BMI (kg/m^2)		27.33 ± 5.31	25.5 ± 5.13
Gender	Male	63 (70 %)	45 (50 %)
	Female	27 (30 %)	45 (50 %)
Co-morbidities	Diabetes	27 (30 %)	07 (7.8 %)
	Hypertension	35 (38.9 %)	09 (10 %)
Fetuin-A (g/l)		0.4416 ± 0.17	0.752 ± 0.176
Glucose (mg/dl)		104.67 ± 23.01	92.05 ± 97.57
Urea (mg/dl)		100.95 ± 28.73	23.92 ± 3.44
Creatinine (mg/dl)		2.07 ± 3.15	0.94 ± 0.01
Creatinine Clearance (ml/min)		33.99 ± 22.24	97.48 ± 8.51
Glomerular Filtration Rate (mL/min/1.73 m^2)		42.47 ± 16.72	98.39 ± 11.29
Calcium (mg/dl)		12.65 ± 0.72	9.81 ± 0.5
Phosphorus (mg/dl)		5.54 ± 1.1	4.41 ± 0.37
Serum Cholesterol (mg/dl)		237 ± 37.22	173.34 ± 23.95

A graphical representation of the stages of kidney disease among the cases (n=90) was analyzed. The distribution indicates a progression of the disease, with a significant proportion of cases (54%) in Stage V, which represents end-stage kidney disease. The earlier stages of kidney disease, such as Stage 0, were less prevalent, comprising only 13% of the cases, while intermediate stages show a gradual increase in prevalence, with 20% in Stage IV, 8% in Stage III, 3% in Stage II, and 2% in Stage I (Figure 1).

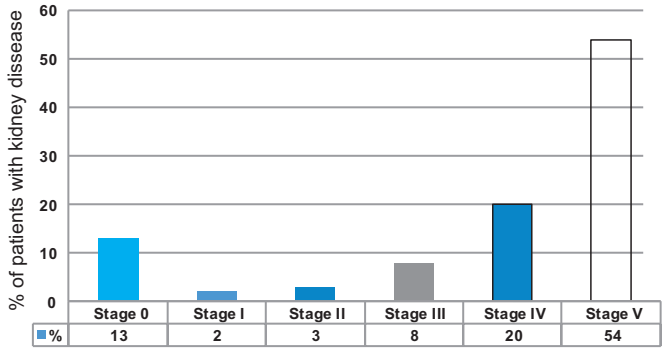

Figure 1: Graphical Representation of Stages of Kidney Disease in Cases (n=90)

The relationship between serum Fetuin-A levels and age in both patients and controls is examined. Serum Fetuin-A levels showed a notable age-related decrease in cases across all age categories. The mean Fetuin-A level in subjects aged 18 to 30 was 0.7390 ± 0.22111 g/L for controls and 0.6440 ± 0.11871 g/L for cases, with a significant p-value of 0.007. In all age categories, there was a consistent pattern of reduced Fetuin-A levels in cases relative to controls, which became more noticeable as people aged. For instance, in the 51-60 years age group, cases had a mean Fetuin-A level of 0.3936 ± 0.11879 g/L compared to 0.7598 ± 0.18164 g/L in controls, with a highly significant p-value of 0.0001. The oldest age group (61-75 years) showed the lowest mean Fetuin-A levels, with cases at 0.3667 ± 0.15254 g/L versus controls at 0.6916 ± 0.16181 g/L, again with a significant p-value of 0.0001 (Table 2).

Table 2: Association of Serum Fetuin-A Levels According to Age among Cases Vs Controls (n=180)

Year	Serum Fetuin-A (g/L)		p-value
	Cases	Control	
18-30 Years	0.6440 ± 0.11871	0.7390 ± 0.22111	p=0.007*
31-40 Years	0.4648 ± 0.15180	0.7532 ± 0.19389	p=0.0001**
41-50 Years	0.4893 ± 0.18718	0.7932 ± 0.16947	p=0.0001**
51-60 Years	0.3936 ± 0.11879	0.7598 ± 0.18164	p=0.0001**
61-75 Years	0.3667 ± 0.15254	0.6916 ± 0.16181	p=0.0001**

A scatter plot illustrating the distribution of Fetuin-A levels among cases with different stages of kidney disease (n=90). The plot displays a wide range of Fetuin-A levels, with a notable clustering at lower levels, particularly in advanced stages of kidney disease. This clustering suggested a potential correlation between lower Fetuin-A levels and the severity of kidney disease. The values range from as low as 0.034 to a peak at 2.132 g/L, with several outliers distributed across the stages. There was variability between Fetuin-A levels and kidney disease progression (Figure 2).

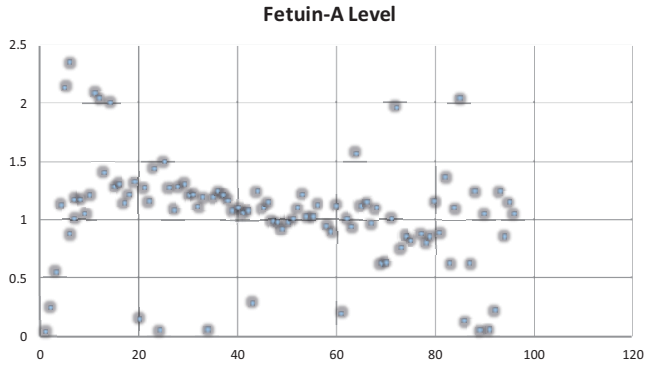

Figure 2: Scattered Diagram of Different Fetuin-A Levels in Kidney Disease Cases (n=90)

DISCUSSION

The relationship between fetuin-A levels and vascular calcification in patients with chronic kidney disease was investigated in this study. Fetuin-A was noted to be a biomarker for the progression of renal illness for the assessment of baseline kidney failure. It was seen that even in subjects with slight to severe kidney weakening, fetuin-A had a significant diagnostic value. Also, we found that serum concentrations of creatinine at baseline were

DOI: https://doi.org/10.54393/pjhs.v5i11.2198

excellent indicators of CKD disease progression. This is consistent with previous studies findings [16-18]. Serum fetuin-A concentrations were considerably lower in patients with renal disease (Mean=0.452 0.16 g/L) compared to the control group (mean=0.765 0.17 g/L; p=0.001). Additionally, it was shown that fetuin-A levels decreased gradually from stage 2 renal failure (CrCl=60-90 ml/min) to stage 5 renal failures (CrCl=15 ml/min). This demonstrates that decreases in serum fetuin-A quantity occur rather early in the course of renal illness. These results are comparable to a study done by Caglar *et al.*, which exposed all levels of CKD but Stage 1 had a decline in serum fetuin-A levels [19]. Another study by Makulska *et al.*, reported lesser levels of serum fetuin-A in children having vascular calcifications in CKD [20]. Serum Calcium and Serum cholesterol levels have been attributed to vascular calcification. In the current study, both serum calcium and cholesterol were found to be within normal limits in the control group (having higher fetuin-A levels while the cases showed higher than normal levels of serum calcium and cholesterol with low fetuin-A levels, denoting vascular calcification. The mean serum fetuin-A level in CKD cases in this study was 0.45 0.16 g/L. These findings are consistent with research by Cottone *et al.*, who discovered that CKD patients had an average fetuin-A level of 0.53 0.17 g/L. Furthermore, as compared to controls, this study discovered that the amount of serum fetuin-A was significantly lower in both sexes and at all ages, indicating that serum fetuin-A levels are unaffected by age or sex. Synthesis of fetuin-A was down-regulated in the chronic inflammatory state of CKD [21].

CONCLUSIONS

It was concluded that when compared to controls, this study showed a strong correlation between fetuin-A levels and CKD. Lower levels of fetuin-A were observed in cases as compared with controls. Estimating these levels may help with early intervention in CKD for managing vascular calcification. The advancement of cardiovascular disease in CKD may be slowed down by early and quick control of the pro-inflammatory factors and the use of fetuin-A.

Authors Contribution

Conceptualization: RS
Methodology: SUH, AZ
Formal analysis: JM, IMB
Writing review and editing: SUH, JM, IMB, GP, AZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2310

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Fetomaternal Outcomes of Obstructed Labour in Tertiary Care Hospital Dera Ismail Khan

Najma Bibi[1,2], Sadia Anwar[3*], Maria Ghafoor[1], Umm-e-Aimen Saleem[1], Uzma Zaman[1], Nayar Latif[1] and Shumaila Noreen Malik[1]

[1]Department of Gynecology and Obstetrics, Women and Children Hospital, Dera Ismail Khan, Pakistan
[2]Department of Gynecology and Obstetrics, ZHQ Hospital, Gomal Medical College, Dera Ismail Khan, Pakistan
[3]Department of Gynecology and Obstetrics, Mufti Mehmood Hospital, Dera Ismail Khan, Pakistan

ARTICLE INFO

Keywords:
Obstructed Labour, Morbidity, Mortality, Bladder Trauma, Uterine Rupture, Hysterectomy, Sepsis, Postpartum Hemorrhage

How to Cite:
Bibi, N., Anwar, S., Ghafoor, M., Saleem, U.- e-A., Zaman, U., Latif, N., & Malik, S. N. (2024). Fetomaternal Outcomes of Obstructed Labour in Tertiary Care Hospital Dera Ismail Khan: Fetomaternal Outcomes of Obstructed Labour . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2310

Corresponding Author:
Sadia Anwar
Department of Gynecology and Obstetrics, Mufti Mehmood Hospital, Dera Ismail Khan, Pakistan
sasajjaddr@gmail.com

Received Date: 27th September, 2024
Acceptance Date: 20th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Strong contractions that prevent the fetus from moving through the birth canal, known as obstructed labour, were often due to a mismatch between the size of the fetal head and the pelvis. Despite being preventable, this condition significantly contributes to maternal and neonatal morbidity and mortality and is a leading cause of hospitalization. **Objective:** To assess the frequency and types of adverse maternal and fetal outcomes associated with obstructed labour in Tertiary Care Hospital, Dera Ismail Khan. **Methods:** This cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Gomal Medical College, Dera Ismail Khan, from December 1, 2021 to June 1, 2022. The sample size was 193 calculated using WHO sample size software by convenient sampling technique. Adverse fetomaternal outcomes such as bladder trauma, uterine rupture, hysterectomy, sepsis, Postpartum Hemorrhage (PPH), birth asphyxia, and stillbirth were the outcomes of the study. All the data were entered on a pre-designed proforma and analyzed by SPSS version 25.0. **Results:** The age range for pregnant women was Participants between 18 to 40 years with a mean age of 28.689±3.05 years, the average gestational age was 37.492±2.24 weeks and the average parity was 1.507±1.51. Bladder trauma was observed in 8.3% of patients, ruptured uterus 15.5%, hysterectomy 7.8%, sepsis 19.2%, PPH 6.2%, birth asphyxia 56.5%, and stillbirth was 33.2% **Conclusions:** This obstetrical emergency affects relatively younger women with a mean age of 28.69 years, with a mean gestational age of 37.49 weeks. Birth asphyxia and stillbirth were the common outcomes while maternal bladder trauma uterine rupture, hysterectomy sepsis, and postpartum hemorrhage were significant.

INTRODUCTION

Obstructed labour is the ultimate consequence of cephalopelvic disproportion when a fetus is unable to enter the birth canal despite strong contractions [1]. This can result in significant maternal and perinatal complications. The cephalopelvic disproportion could be either due to a contracted pelvis in a labouring mother where a normal-sized fetus cannot enter the pelvic inlet or due to fetal malpresentation and malpositioning of the fetal presenting part. The pelvis is contracted pelvis due to malnutrition, infection, muscular and bony disorders like poliomyelitis, sickle cell disease, or osteomyelitis in mothers [2]. The malpresentation includes brow and compound presentations, the persistent occiput-posterior position of the fetal head, mento-posterior face presentation, congenital anomalies like gross hydrocephalus, fetal ascites, etc [2]. Some pelvic causes include space-occupying tumors like fibroids in a lower uterine segment or ovarian tumors impacted in the pelvis below the presenting part and undiagnosed multiple gestations [1]. The fetal complications of obstructed labour are intracranial hemorrhage due to severe molding of the fetal head, severe caput formation, and acidosis due to fetal hypoxia and distress. This will lead to neonatal sepsis and increased perinatal mortality [3]. In case of prolonged obstructed labour, excessive pressure on the placenta and umbilical cord compression can lead to fetal distress poor neonatal outcome, or fetal death. Maternal complications like uterine rupture, PPH, septic shock, and maternal

DOI: https://doi.org/10.54393/pjhs.v5i11.2310

mortality are threatening. In contrast, long-term complications, like fistula, cervical stenosis, and infertility due to hysterectomy, uterine rupture, or Sheehan's syndrome significantly affect the quality of life of mothers [4, 5]. A study by Wonde TE et al., conducted in Ethiopia in 2015 about obstructed labour outcomes in 91 mothers revealed the frequency of bladder trauma as 8.8%, ruptured uterus 16.5%, hysterectomy 11%, sepsis 25.3%, PPH 11%, birth asphyxia 52.1%, and stillbirth was 36.2% [6]. Maternal mortality due to complications of pregnancy and childbirth like obstructed labour is on the rise globally [7]. In Southeast Asia, there is a paucity of data available on this subject at local levels. Despite its critical nature, there remains a notable gap in the existing literature about specific adverse outcomes and long-term complications of obstructed labour. In our local community, no such study was conducted previously. This study will provide insight into maternal and fetal complications in patients with obstructed labour.

The objective of this study was to determine the frequency and types of adverse maternal and fetal outcomes associated with obstructed labour in Tertiary Care Hospital, Dera Ismail Khan.

METHODS

This cross-sectional study was carried out in the Department of Obstetrics and Gynecology at Gomal Medical College, Dera Ismail Khan, from December 1, 2021, to June 1, 2022, after approval from the ethical board (Reference Letter No.258/GJMS/JC). The sample size of 193 was calculated using WHO sample size software with a 95% confidence interval, a 4% margin of error, and an expected frequency of bladder trauma of 8.8% in cases of obstructed labour by a convenient sampling technique [6]. The inclusion criteria were pregnant women with a single fetus confirmed on ultrasound with gestational age > 28 weeks calculated by last menstrual period, of any parity and obstructed labour as per operational definition while women with H/o placenta previa, uterine fibroids, and previous C-section were excluded from the study. Obstructed labour is diagnosed as per the following criteria. Vulva: oedematous. Vagina: dry and hot. Cervix: fully or partially dilated, oedematous, and not well applied to the head. The presenting part: high and not engaged or impacted in the pelvis. If head it showed excessive molding and caput formation. The demographics like age, gestational age, and parity were noted on a pre-designed proforma. Basic demographics (age, gestational age, and parity) were noted and Informed consent was taken from patients/caregivers, ensuring confidentiality and the fact that there was no risk involved to the patient while taking part in this study. Bladder trauma was diagnosed when indigo carmine dye was injected into the ureter or a portion of the kidney, it showed a blue-tinged urine leaking out of the bladder. Sepsis was diagnosed as the presence of at least two of the following four criteria, central temperature >38.5 C or <36.0 C, Tachycardia or bradycardia, respiration rate exceeding 2 square deviations from the age norm or the need for a ventilator, the number of white blood cells increased or decreased in comparison with the age norm. Postpartum hemorrhage was diagnosed when estimated blood loss was≥ 1000 ml postpartum after cesarean section and ≥ 500 ml after vaginal delivery within 24 hours. Birth asphyxia was diagnosed when the newborn not breathing(> 90 seconds) and the chest not rising symmetrically with a frequency of>30/minute on physical examination and an umbilical artery blood test showed a pH of <7.1 laboratory test. Stillbirth was diagnosed when a fetal loss as the fetus's heart stopped beating and it was diagnosed by ultrasonography after 28 weeks on LMP. Adverse fetomaternal outcomes were managed as per unit protocols and recorded on specially designed proforma. Data were analyzed with a statistical analysis program (IBM-SPSS version 25.0). Frequencies and percentages were computed for categorical variables like bladder trauma, ruptured uterus, hysterectomy, sepsis, PPH, birth asphyxia, and stillbirth. Mean ± SD was presented for quantitative variables like age, gestational age, and parity. Adverse fetomaternal outcomes were stratified about age, gestational age, and parity. Post-stratification using the chi-square test was applied, and p ≤0.05 was considered statistically significant.

RESULTS

The mean age was 28.68 ± 3.05 years with mean gestational age 37.49 ± 2.24 weeks and mean parity was 1.50 ± 1.51 (Table 1).

Table 1: Mean of Patients According to Age, Gestational Age and Parity(n=193)

S. No.	Demographics	Mean ± SD
1.	Age (Years)	28.68 ± 3.05
2.	Gestational Age (Weeks)	37.49 ± 2.24
3.	Parity	1.50 ± 1.51

Table 2 illustrates the feto-maternal outcomes associated with obstructed labor. Among the fetal outcomes, sepsis was noted in 19.2% of cases (37 out of 193), while stillbirth occurred in 33.2% (64 out of 193). For maternal outcomes, uterine rupture was reported in 15.5% of cases (30 out of 193). Postpartum Hemorrhage (PPH) was observed in 6.2% (12 out of 193), hysterectomy was required in 7.8% (15 out of 193), and bladder trauma was seen in 8.3% (16 out of 193) of cases.

Table 2: Feto-Maternal Outcomes Obstructed Labour

Variables	Yes N (%)	No N (%)
Fetal Outcomes		
Sepsis	37 (19.2%)	156 (80.8%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2310

Still Birth	64 (33.2%)	129 (66.8%)
Maternal Outcomes		
Raptured Uterus	30 (15.5%)	163 (84.5%)
PPH	12 (6.2%)	181 (93.8%)
Hysterectomy	15 (7.8%)	178 (92.2%)
Bladder Trauma	16 (8.3%)	177 (91.7%)

Among women with 0-2 pregnancies, 14.7% experienced a ruptured uterus, while 85.3% did not. In the group with more than 2 pregnancies, 17.5% experienced a ruptured uterus, and 82.5% did not. There was no statistically significant difference in the occurrence of ruptured uterus based on parity. In the group with 0-2 pregnancies, 19.1% of women developed sepsis, while 80.9% did not. Among women with more than 2 pregnancies, 19.3% developed sepsis, and 80.7% did not. There was no statistically significant difference in the incidence of sepsis between the two parity groups (P-value>0.05) (Table 3).

Table 3: Comparison of Parity with Ruptured Uterus and Sepsis

S. No.	Parity	Ruptured Uterus			Sepsis		
		Yes N (%)	No N (%)	p-Value	Yes N (%)	No N (%)	p-Value
1.	0-2	20 (14.7%)	116 (85.3%)	0.620	26 (19.1%)	110 (80.9%)	0.977
2.	>2	10 (17.5%)	47 (82.5%)		11 (19.3%)	46 (80.7%)	
Total		30 (15.5%)	163 (84.5%)		37 (19.2%)	156 (80.8%)	

In the 28th to 39th week gestational age group, 34.2% of pregnancies resulted in stillbirth, while 65.8% did not. For pregnancies beyond 39 weeks, 28.1% resulted in stillbirth, and 71.9% did not. There was no statistically significant difference in the occurrence of stillbirth between these gestational age groups (Table 4).

Table 4: Comparison of Gestational Age with Still Birth

Gestational Age (Weeks)		Still Birth		p-Value
		Yes N (%)	No N (%)	
1	28-39	55 (34.2%)	106 (65.8%)	0.508
2	>39	9 (28.1%)	23 (71.9%)	
Total		64 (33.2%)	129 (66.8%)	

The data were categorized into two age groups: 18-30 years and over 30 years. In the 18-30-year group, 7.7% of women experienced PPH, while 92.3% did not. In the group over 30 years of age, 2% experienced PPH, and 98% did not. There was no statistically significant difference in the incidence of postpartum hemorrhage between the two age groups. In the 18-30 years' group, 9.1% of women underwent a hysterectomy, while 90.9% did not. In the group over 30 years of age, 4% of women underwent a hysterectomy, and 96% did not. The p-value for this comparison was 0.247, indicating no statistically significant difference in the incidence of hysterectomy between the two age groups. In the 18-30-year group, 8.4% of women experienced bladder trauma, while 91.6% did not. In the group over 30 years of age, 8% experienced bladder trauma, and 92% did not. The p-value for this comparison was 0.931, indicating no statistically significant difference in the incidence of bladder trauma between the two age groups (Table 5).

Table 5: Comparison of Age with Post-Partum Hemorrhage (PPH), Hysterectomy, and Bladder Trauma

Age (Years)	PPH			Hysterectomy			Bladder Trauma		
	Yes N (%)	N N (%)	p-Value	Yes N (%)	N N (%)	p-Value	Yes N (%)	N N (%)	p-Value
18-30	11 (7.7%)	132 (92.3%)	0.151	13 (9.1%)	130 (90.9%)	0.247	12 (8.4%)	131 (91.6%)	0.931
>30	1 (2%)	49 (98%)		2 (4%)	48 (96.0%)		4 (8%)	46 (92.0%)	
Total	12 (6.2%)	181 (93.8%)		15 (7.8%)	178 (92.2%)		16 (8.3%)	177 (91.7%)	

DISCUSSION

The prevalence of obstructed labour varies all over the world depending on factors like socioeconomic circumstances, health care access, etc. as reported in the current study obstructed labour was more prevalent in rural areas. The study conducted by Maged AM had the same result with patient turnover from rural areas presenting with obstructed labour. (65.3%) [8]. One of the major risk factors for obstructed labour was poor antenatal visits or poor access to health facilities. In our study, 73.6% of pregnant women had irregular antenatal checkups. These findings were consistent with research showing that mothers referred from health facilities have a higher risk of unfavorable maternal outcomes. This was consistent with a study where a large number of mothers resided in rural areas, making it difficult for them to access health facilities and delaying their access to care when problems arose [9]. Additionally, mothers who attempted labour at health centers or home experienced worse maternal outcomes compared to those who delivered in hospitals. This supports findings from a study in India and Halaba, which indicates that hospital-based deliveries benefit from better access to comprehensive emergency obstetric and newborn care compared to those at health centers or home [10-12]. In the current study, outcome of obstructed labor like PPH, sepsis and hysterectomy were a bit more common in younger age group. These findings were similar to studies conducted by Hofmeyr and Yifru where most of the cases were primiparas, young and presented with obstructed labour [13, 14]. Sepsis emerged as the most common maternal complication in cases of obstructed labour, occurring in 19.2% of patients. This finding aligns with research conducted by Tura and Abera in Ethiopia and Gafoor M in Pakistan, all of which identified sepsis as a significant complication associated with obstructed labour [15-17]. Sepsis often arises from infections related to prolonged labour or interventions, highlighting the importance of prompt and effective management. Additionally, Postpartum Hemorrhage (PPH) was seen in 6.2% of obstructed labour cases. This finding was supported by studies from Norway and Ethiopia, which

DOI: https://doi.org/10.54393/pjhs.v5i11.2310

similarly identify PPH as a significant complication in obstructed labour [18-20]. PPH can result from uterine atony, retained placenta, or delivery trauma, emphasizing the need for careful monitoring and timely intervention to manage bleeding effectively. This difference may be due to variations in labour duration, with prolonged labour leading to more complications. Other adverse outcomes included birth asphyxia and birth injuries. Maternal complications such as uterine rupture, sepsis, anemia, postpartum hemorrhage, bladder injury, and fistula were noted. There were many limitations to this study which was conducted in a remote area like ours. Although the sample size was small it may not represent the overall population and the impacts of such alarming obstetrical issues. Similarly, a short study period can cause long-term complications. Confounding factors like maternal age, socioeconomic status, and access to health care may influence outcomes. Health professionals need to educate pregnant women about the risks of obstructed labour to reduce trauma and improve outcomes.

CONCLUSIONS

This study has highlighted several important maternal and perinatal outcomes related to obstructed labour. This obstetrical emergency affects relatively younger women with a mean age of 28.69 years, with a mean gestational age of 37.49 weeks. Birth asphyxia and stillbirth were the common outcomes while maternal bladder trauma, uterine rupture, hysterectomy sepsis, and postpartum hemorrhage were significantly seen in all age groups.

Authors Contribution

Conceptualization: NB
Methodology: NB, SA, MG, SNM
Formal analysis: MG, UZ, UA
Writing, review and editing: NB, SA, MG, NL

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2409

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Role of Uroflowmetry in Patients of Benign Prostatic Hyperplasia Presenting with Lower Urinary Tract Symptoms

Aijaz Hussain Memon[1*], Mumtaz Ali Chandio[1], Zahoor Hussain Bhellar[2], Hameed-Ur-Rehman[1], Suhail Akhtar[1] and Asadullah Bhurt[1]

[1]Department of Urology, People's University of Medical and Health Sciences for Women, People's Medical College Hospital, Nawabshah, Pakistan
[2]Department of General Surgery, Khairpur Medical College Hospital, Khairpur, Pakistan

ARTICLE INFO

Keywords:
Benign Prostatic Hyperplasia, Lower Urinary Tract, Uroflowmetry, International Prostate Symptom Score

How to Cite:
Memon, A. H., Chandio, M. A., Bhellar, Z. H., Rehman, H. U., Akhtar, S., & Bhurt, A. (2024). Role of Uroflowmetry in Patients of Benign Prostatic Hyperplasia Presenting with Lower Urinary Tract Symptoms: Uroflowmetry in Benign Prostatic Hyperplasia . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2409

***Corresponding Author:**
Aijaz Hussain Memon
Department of Urology, People's University of Medical and Health Sciences for Women, People's Medical College Hospital, Nawabshah, Pakistan
draijaz77@gmail.com

Received Date: 14th October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Benign Prostatic Hyperplasia (BPH) is prevalent among aging men, causing Lower Urinary Tract Symptoms (LUTS) that can impact quality of life. **Objective:** To assess the role of uroflowmetry in determining Lower Urinary Tract Symptom (LUTS) severity in Benign Prostatic Hyperplasia (BPH) patients by examining correlations between symptom scores and uroflowmetric parameters (Qmax, Qavg, PVR, and voiding time). **Methods:** This cross-sectional study was conducted on sixty BPH male patients presenting with a spectrum of symptom scores based on IPSS. With a standard uroflowmeter, uroflowmetric parameters were determined and correlation coefficients and t-tests between parameters about most severe complaints yielded statistical analyses. **Results:** Uroflowmetric parameters were significantly different among severity groups of symptoms. Mean Qmax values decreased successively from 12.5 mL/s in mild to severe symptoms of 6.5 mL/s ($p < 0.001$). The same results were evident for average flow rates, as mean flows at mild were 8.0 mL/s vs severe of 4.0 mL/s ($p < 0.001$) Residual urine increased from 25 mL to 110 mL ($p < 0.001$ and voiding times from 15 seconds up to 40 seconds ($p < 0.001$). Correlation analysis revealed moderate positive and negative correlations between residual urine and IPSS ($r = 0.60$), Qmax ($r = -0.54$), and Qavg ($r = -0.50$) with IPSS scores ($p < 0.001$). **Conclusion:** The importance of uroflowmetry in clinical assessments and management methods was shown by the substantial correlation found between uroflowmetric parameters and the severity of BPH symptoms.

INTRODUCTION

One disorder that causes the prostate gland to expand non-canceratically is called benign prostatic hyperplasia, or BPH. As it expands, it can impede bladder outflow and constrict the urethra, among other lower urinary tract symptoms. Dihydrotestosterone (DHT) and other androgens are necessary for the prostate gland to mature normally [1]. Both bladders may become obstructed and disturbed as a result of the prostate's ability to compress the urethra and reduce urine flow. The pathogenesis of BPH is complex and multifaceted, combining hormonal, molecular, and also structural changes in the prostate as well as surrounding structures [2]. According to a report, the overall incidence rate was 15 per 1000 man-years. The incidence increased linearly with age from three cases per 1000 man-years at the age of 45-49 years to a maximum of 38 cases per 1000 man-years at the age of 75-79 years. After the age of 80 years, the incidence rate remained constant. For a symptom-free man of 46 years, the risk of developing Lower Urinary Tract Syndrome (LUTS)/BPH over the coming 30 years, if he survives, is 45%. The overall prevalence of LUTS/BPH was 10.3%. The prevalence rate was lowest among males 45-49 years of age (2.7%) and increased with age until a maximum at the age of 80 years (24%). Pakistan with as many as 50% of the 2 million men

DOI: https://doi.org/10.54393/pjhs.v5i11.2409

older than 65 years are at risk of bladder outlet obstruction from BPH [3]. The enzyme 5-alpha reductase present in the prostate converts the most potent male hormone generated by the testes, which is then turned from testosterone to Dihydrotestosterone (DHT) [4]. DHT is a stronger androgen than testosterone and is responsible for prostatic development. It binds to androgen receptors in prostate cells, stimulating cell growth and inhibiting apoptosis. In men, a small quantity of estrogens was produced (mainly estradiol), but the levels increased with age due to androgen aromatization in adipose tissue. Estrogens could not only increase the local effects of androgens in prostate cells by increasing AR activity but might also improve it. Many adults, especially older men, suffer from Lower Urinary Tract Symptoms (LUTS), which are among the most common presentations in urology clinics. LUTS can be extremely detrimental to a patient's quality of life and are often associated with Benign Prostatic Hyperplasia (BPH), though they can also result from several different conditions [5]. The relationship between lower urinary tract symptoms (LUTS) and the storage and voiding cycle determines their classification. This association shows if there is an issue during the bladder's storage, during its emptying, or immediately after. Although the LUTS are categorized in this manner, there is a wide range of possible underlying mechanisms, and the balance of symptoms may point to contributing variables. Importantly, nocturia and higher frequency during the day are two symptoms of LUTS, but they can also result from processes completely unrelated to the lower urinary tract [6]. Urgency, with or without urgency incontinence, is typically accompanied by frequency and nocturia. Urinary tract infections can produce LUTS, including frequency, urgency, and dysuria (painful urination). The scar tissue narrows the urethra, causing obstructive voiding symptoms. Inflammation of the prostate gland can induce both LUTS and pelvic discomfort. Bladder stones can cause LUTS, which can manifest as frequency, urgency, and hematuria [7]. Bladder dysfunction is a symptom of neurological disorders such as multiple sclerosis and spinal cord damage. Usually, a combination of clinical surveys, questionnaires, and diagnostic tests is used to examine LUTS. BPH causes the balance between cell death and proliferation to be upset, allowing the prostate to grow longer and with more cells surviving. Increase cell survival rates via decreasing apoptosis. In response to increased resistance the bladder muscle (detrusor) hypertrophies, and generates higher pressures at voiding. As time passes, this may eventually lead to partial detrusor decompensation and reduced contractility. This leads to detrusor overactivity due to bladder outlet obstruction and incomplete emptying of urea symptoms of urgency, frequency, and nocturia [8]. The pathogenesis of Benign Prostatic Hyperplasia (BPH) is multifactorial and may have a hormonal cellular structural genetic basis. Androgens, especially DHT, are important in promoting prostatic growth, while alterations in apoptosis and proliferation induce hyperplasia. Subsequent nodular hyperplasia of the prostate GRAINS down on the urethra, resulting in bladder OUTLET obstruction and contributing to the diagnosis of BPH SYMPTOMS. Identification of such pathways is pivotal in the development of effective treatment regimens and disease control [9]. Lower Urinary Tract Symptoms (LUTS) caused by Benign Prostatic Hyperplasia (BPH) require prompt diagnosis and treatment. Various grading systems have been created to assess symptom severity and its impact on quality of life, including the Danish Prostatic Symptom Score (DAN-PSS), the Boyarsky score, the Madsen-Iversen score, and the International Prostate Symptom Score (IPSS). The American Urological Association (AUA) developed and validated the IPSS questionnaire. Which is frequently used to assess LUTS [10, 11]. Ultrasound of the prostate is a common diagnostic imaging method that permits direct visualization of the organ. It can be done both superpubic (through the abdominal wall) and transrectal. Lower Urinary Tract Symptoms (LUTS) are frequently caused by the common condition known as Benign Prostatic Hyperplasia (BPH), which has a major negative influence on the quality of life for older men. Uroflowmetry is a useful, non-invasive diagnostic technique that can objectively evaluate urine flow patterns, which helps with the diagnosis and treatment of LUTS in individuals with BPH.

The present study aimed to investigate the influence of the symptom severity on uroflowmetric parameters (Qmax, Qavg, post-void residual urine volume, and voiding time) in patients with LUTS BPH.

METHODS

It was a cross-sectional study carried out at Department of Urology of PMC Hospital Nawabshah from June 2024 to October 2024. There were sixty male participants in this study. Inclusion criteria were all these patients detailed history, age range above 50 years, physical examination, International prostatic symptom score (IPSS), and digital rectal examination. Exclusion criteria were prior urinary tract or pelvic surgeries, carcinoma, prostatic, ureteral stricture, and neurogenic bladder. For the sample size calculation, the formula was used: n=Z2×p×(1−p) d2. Confidence level (Z= 95%), Prevalence estimating (p=0.5 or 50%), and margin of error (d=0.125) [12]. The prevalence ratio was assumed as 50% due to the unavailability of the country-specific estimates of LUTS in BPH patients and the estimated sample size was N=60 participants. A convenience sampling technique was used for selecting participants. Uroflowmetry was a simple approach for calculating urine flow rate over time. Peak flow rate (Q max), flow time, and voided volume were computed using the apparatus. The device determined the time to peak flow, voiding volume, voiding duration, and peak flow rate. Patients experienced no discomfort throughout the test

DOI: https://doi.org/10.54393/pjhs.v5i11.2409

because it involved normal urine. The patients' data was analyzed and categorized according to IPSS-determined symptom severity. At the time of presentation, details regarding the patient's clinical status, demographics, and test findings were recorded. These patients' uroflowmetry data were compared using statistical methods. 26 SPSS was used to analyze the data statically. The relationship between uroflowmetric parameters and IPSS scores was the main result. "The IPSS includes eight items, seven of which were regarding urinary symptoms and one about quality of life. Each urinary symptom question has six choices that indicate increasing symptom severity, with a score ranging from 0 to 5. The overall score goes from 0 to 35. Higher scores indicate more severe symptoms. Clinical recommendations from the American Urological Association (AUA) and the European Association of Urology (EAU) serve as the foundation for the cut-off points used in the International Prostate Symptom Score (IPSS) to classify the severity of symptoms. This was how the severity was categorized: IPSS scores between 0 and 7 indicate mild symptoms, whereas scores between 8 and 19 indicate moderate problems. IPSS score of 20 to 35 indicates severe symptoms. To effectively evaluate, monitor, and treat patients with Benign Prostatic Hyperplasia (BPH), these cut-off points enable systematic assessment of Lower Urinary Tract Symptoms (LUTS). Calculating descriptive statistics and utilizing Pearson's correlation coefficient, the association between uroflowmetry findings and the intensity of symptoms was evaluated. Statistical tests ANOVA was applied to compare these parameters in different severity groups (i.e. mild, moderate, and severe symptoms). Further post-hoc test (Tukey's HSD) was applied for pairwise comparisons. The p-value of less than 0.05 showed that the variables were highly significant. This study was approved by the Institutional Review Board (IRB) under reference number [PUMHSW/SBA/PVC//ERC/41/2024]. Written informed consent was obtained from all participants before their inclusion in the study, ensuring that they were fully aware of the study's purpose, procedures, potential risks, and benefits.

RESULTS

There was a total of 60 males. The patient's average age was 55.2 years see table 1.

Table 1: Demographic Variables of study participants (n=60)

Variables	Total Number of Patients N (%)
Male	60 (100%)
Age	
50-60	32 (53.3%)
61-70	28 (46.6%)

The study comprised 60 male patients aged range 50 to 70 years, divided equally into two age groups: (53.3%) patients aged 50-60 years and (46.6%) patients aged 61-70 years. The younger group had a mean prostate size of 42 ± 5 mm, with 10 patients (33.3%) reporting mild symptoms, 15 (50.0%) experiencing moderate symptoms, and 5 (16.7%) exhibiting severe symptoms. In contrast, the older group had a mean prostate size of 48 ± 6 mm, where 5 patients (16.7%) had mild symptoms, 15 (50.0%) had moderate symptoms, and 10 (33.3%) had severe symptoms. Overall, 25% of patients experienced mild symptoms, 50% had moderate symptoms, and 25% exhibited severe symptoms, indicating a notable prevalence of moderate to severe lower urinary tract symptoms, particularly in the older age group, which underscores the need for effective management of Benign Prostatic Hyperplasia (BPH) in this population see table 2.

Table 2: IPSS Score Results and Clinical Status of Patients

Demographic Variables		N (%)	Prostate Size (Mean ± SD)	Mild Symptoms (0-7) N (%)	Moderate Symptoms (8-19) N (%)	Severe Symptoms (20-35) N (%)
Age Group	50-60 Years	32 (53.3%)	42 ± 5 mm	10 (33.3%)	15 (50.0%)	5 (16.7%)
Age Group	61-70 Years	28 (46.6%)	48 ± 6 mm	5 (16.7%)	15 (50.0%)	10 (33.3%)
Total		60 (100%)	45 ± 5.5 mm	15 (25%)	30 (50%)	15 (25%)

Table 3 demonstrated the correlation between the International Prostate Symptom Score (IPSS) and various uroflowmetric parameters in sixty patients (n=60) with Benign Prostatic Hyperplasia (BPH). There was an average amount of remaining urine 70.3 ± 25.4 (mL) and the p-value was less than 0.001 this showed that there exists a significant difference between IPSS scores, correlation coefficient = 0.60 with a positive moderate relationship frequently the EQ-5D and its dimension's table 3. The mean peak flow rate was 10.2 ± 3.1 mL/s there was a moderate negative correlation between IPSS scores and it with a correlation coefficient of -0.54. The mean flow rate was 6.5 ± 2.2 mL/s The correlation coefficient of -0.50 depicts a moderate negative association with IPSS scores ($p < 0.001$).

Table 3: Correlation between Uroflowmetric Variables and IPSS Scores (n=60)

Variables	(Mean ± SD)	Correlation Coefficient (r)	p-Value	Interpretation
Residual Urine (mL)	70.3 ± 25.4	0.60	<0.001	Moderate Positive Correlation
Peak Flow Rate (Qmax) (mL/s)	10.2 ± 3.1	-0.54	<0.001	Moderate Negative Correlation
Average Flow Rate (Qavg) (mL/s)	6.5 ± 2.2	-0.50	<0.001	Moderate Negative Correlation

The mean peak flow rate was 12.5 ± 2.0 mL/s, so this seems like a fairly decent urinary stream organization up to now. Qmax decreases substantially to 9.0 ± 2.0 mL/s with the increase in symptoms, indicative of an impairment in urinary function. The Qmax was still significantly reduced to a mean of 6.5 ± 2.1 mL/s suggesting very poor urinary

DOI: https://doi.org/10.54393/pjhs.v5i11.2409

flow. This demonstrated a statistically significant decline in peak flow rates with higher symptom severity, indicating that urinary flow was proportionally more restricted with increasing burden of symptoms in table 4.

Table 4: Uroflowmetric Variables by IPSS Symptom Severity (n=60)

Variables	Mild Symptoms (Mean ± SD)	Moderate Symptoms (Mean ± SD)	Severe Symptoms (Mean ± SD)	p-Value	Post-Hoc Test	Post-Hoc P-value
Peak Flow Rate (Qmax) (mL/s)	12.5 ± 2.0	9.0 ± 2.0	6.5 ± 2.1	<0.001	Mild > Moderate > Severe	<0.05 (Significant)
Average Flow Rate (Qavg) (mL/s)	8.0 ± 1.5	5.5 ± 1.5	4.0 ± 1.0	<0.001	Mild > Moderate > Severe	<0.05 (Significant)
Residual Urine (mL)	25.0 ± 10.0	65.0 ± 15.0	110.0 ± 20.0	<0.001	Mild > Moderate > Severe	<0.05 (Significant)
Voiding Time (Seconds)	15.0 ± 3.0	25.0 ± 5.0	40.0 ± 8.0	<0.001	Mild > Moderate > Severe	<0.05 (Significant)

DISCUSSION

This study was conducted to evaluate the correlation of uroflowmetric parameters with urinary symptom severity in Benign Prostatic Hyperplasia (BPH) patients. Further evidence of the severity of symptoms related to urine function was obtained by comparing these characteristics with the International Prostate Symptom Score (IPSS) in a significantly negative correlation. The analysis showed that the peak flow rate (Qmax) and average flow rate (Qavg) decreased significantly, and post-void residual urine volume as well as voiding time increased with an increase in the severity of urinary symptoms. These changes were important because they provide quantifiable markers of urinary function that closely track how patients feel [13]. The mean Qmax of patients with mild symptoms was 12.5 mL/s, suggesting normal urinary function. Those with mild symptoms had mean Qmax values of 9.2 mL/s, and those with moderate and severe symptoms had respective average Qmax values of 9.0 mL/s and 6.5 mL/s. Reduced Qmax indicates an obstruction the urine outflow was blocked [14]. In this regard, it was in line with previous studies by Mevcha and Napier-Hemy, in 2021 which show that reduced flow usually occurs in patients with more symptoms of urinary outlet obstruction and prostatic obstruction. In the same way, the peak flow rate also showed a similar trending by symptom severity (4.0 mL/s in severe urinary symptoms), and the rate of flow was significantly worse amongst more severely symptomatic patients [15]. Mean residual urine volume was significantly increased with worsening of symptoms such that, it rose from 25 mL in patients with mild symptoms to 110 mL in severe symptoms. Large residual volumes were problematic because they may cause UTIs and bladder dysfunction [16, 17]. Going on to say that this finding supports the previous study by Lopategui in 2024 touching off post-void residual urine in clinical practice, especially when patients present with moderate to severe symptoms. The correlation of increased residual volume with increased symptom scores reinforces the notion that these patients may need to be treated for urinary retention. The bladder ultrasonography was effective in measuring urinary volume after removal of the indwelling urinary catheter and and may contribute to the detection of urinary retention [18]. The average time of voiding was also correspondingly prolonged; the time being 15 s in mild, and 40 s in severe cases. Bladder outlet obstruction results not only impaired urological efficacy of urination but also can lead to patient discomfort and anxiety about the urinary function because voiding times were prolonged. The longer voiding times in patients with these symptoms, indicative of the enlarged effort exerted to start and finally stop urination, would lead to a significant drop in quality of life [19, 20]. Current findings underline the need for uroflowmetric parameters to be taken into account in a comprehensive management strategy for men with BPH. These associations were clinically relevant to the purpose of uroflowmetry in voiding function because data generated by uroflowmetry help to score the IPSS and aid diagnostic evaluation. Additionally, patients with pathological uroflowmetric findings may be identified, and the decision concerning further treatment or necessity of surgery made in clinical examination [21]. This study was also a reminder that healthcare providers should be monitoring changes in urinary symptoms, particularly in patients who report an increasing incidence of them. These early warning signs in patients of increased residual volume or decreased flow rate may allow urologists to intervene before downstream catastrophic complications from BPH, including acute urinary retention or irreversible bladder damage.

CONCLUSIONS

This study concluded that uroflowmetric parameters were significantly related to urinary symptom severity in patients with BPH. The prostate grows in an aging man, it manifests with irritative and obstructive symptoms in the form of reduced flow rates along with prolonged voiding time and an increase in post-voidal volume. Our results

DOI: https://doi.org/10.54393/pjhs.v5i11.2409

supported the structuring of uroflowmetry in everyday clinical practice thus improving the quality of life and managing patients with BPH.

Authors Contribution

Conceptualization: AHM
Methodology: HUR, AB
Formal analysis: MAC
Writing, review and editing: ZHB, HUR, SA, AB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research,

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DOI: https://doi.org/10.54393/pjhs.v5i11.2409

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DOI: https://doi.org/10.54393/pjhs.v5i11.1927

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance and Prospects for Targeted Therapy

Sarah Rabbani[1], Aman-Ur-Rehman[2], Rabia Anjum[1], Nauman Rauf Khan[1] and Saima Chudhary[3*]

[1]Department of Oral Pathology, University of Health Sciences, Lahore, Pakistan
[2]Department of Oral Pathology, Shaikh Zayed Postgraduate Medical Institute, Lahore, Pakistan
[3]Department of Oral Pathology, The University of Lahore, Lahore, Pakistan

ARTICLE INFO

Keywords:
Platelet-derived Growth Factor Receptor Beta, Squamous Cell Carcinoma, Immunohistochemistry, Clinical Significance

How to Cite:
Rabbani, S., Rehman, A. ur, Anjum, R., Khan, N. R., & Chudhary, S. (2024). Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance and Prospects for Targeted Therapy: Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1927

***Corresponding Author:**
Saima Chudhary
Department of Oral Pathology, The University of Lahore, Lahore, Pakistan
drsaimach@outlook.com

Received Date: 25th September, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

The most prominent and key cells in cancer development are fibroblasts, known as cancer-associated fibroblasts. Limited data available on Head and Neck Cancer showed the presence of platelet-derived growth factor receptor beta as the most prevalent marker. Furthermore, therapies can be targeted against this receptor for the treatment of cancer. **Objectives:** To evaluate the expression of Platelet-derived growth factor receptor beta as a specific marker of cancer-associated fibroblasts in different grades of oral squamous cell carcinoma through immunohistochemistry. **Methods:** This descriptive study included 51 cases of squamous cell carcinoma of the head and neck region. Platelet-derived growth factor receptor beta expression was assessed based on the extent and intensity of immune-labelling in a tumor. SPSS was used to determine the association between the grade of tumor and Platelet-derived growth factor receptor beta expression. **Results:** Mean age was found as 53.65 + 17.15 years and there were 30 (58.8%) male and 21 (41.2%) female. The most commonly affected sites were glottis and supra-glottis areas accounting for 18.9% of total cases followed by the tongue which accounts for 13.2% of cases. The majority of the patients 34 (66.7%) patients had an intermediate grade of squamous cell carcinoma. In most cases, the degree of staining was strongest, with intermediate-grade tumors exhibiting the highest platelet-derived growth factor receptor beta staining. **Conclusions:** It was concluded that platelet-derived growth factor receptor beta emerges as a promising tumor marker in head and neck squamous cell carcinoma, with its expression levels increasing proportionately with the tumor grade.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common cancer oral cavity cancer, with 177,000 deaths yearly worldwide [1]. It is the sixth most common cancer globally. The incidence of OSCC is highest in South and Southeast Asia and is increasing in developed countries [2]. Pakistan is a major Centre for this disease and, alongside China and India, is among the top three countries with the highest incidence of oral cancer [3]. The tongue, the floor of the mouth, and buccal mucosa are the most common sites of OSCC. Male is affected more than females with a ratio of 3:1 and have a mean age of 61±12 years. The most common risk factors for OSCC include tobacco, alcohol, and certain viruses including human papillomavirus (HPV) infection [4].

Platelet-derived growth factor beta (PDGFRβ) is a sub-type of receptors that are a part of the class III receptor tyrosine kinase family. PDGFRβ is an important biomarker of cancer-associated fibroblasts (CAFs) that play a crucial role in the tumor invasion and growth. It is a critical regulator of various cellular processes such as proliferation, differentiation, and survival. It becomes activated upon binding with its ligand, Platelet-Derived Growth Factor (PDGF), which triggers downstream signalling pathways that drive cell growth and angiogenesis. While PDGFRβ normally plays an essential role in tissue repair and development, its abnormal activation has been linked to the development of several

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

cancers, including OSCC [5]. A variable expression of PDGFRβ has been observed across various tumors, including breast cancer, colon cancer, and lung tumors. However, it is most commonly found in colon and lung tumors where PDGFRβ is involved in promoting tumor growth and metastasis. Its role in remodeling the tumor stroma and facilitating angiogenesis makes it a promising target for therapy. Studies have shown that PDGFRβ expression is frequently elevated in cancerous tissues compared to normal tissues, which is associated with more aggressive disease and a worse prognosis. In OSCC, PDGFRβ is recognized as a significant factor in the tumor microenvironment, affecting both tumor cell behaviour and the surrounding stromal components [6]. PDGFRβ expression is upregulated and associated with worse survival in squamous cell carcinoma [5, 7]. However, Valle et al in 2023, found a low PDGFRβ expression in advanced stages of OSCC [8]. Targeting PDGFRβ has become a focal point in cancer therapy due to its involvement in tumor progression. PDGFRβ inhibitors, such as Imatinib and Sunitinib, have proven effective against various other cancers and are now being investigated for treating OSCC. Targeting PDGFRβ in OSCC holds the potential for therapeutic benefits, including reduced tumor growth, lower rates of metastasis, and improved patient survival [9].

This study aimed to evaluate the expression of PDGFRβ as a specific marker of CAFs in different grades of OSCC through immunohistochemistry. The aggressiveness of the tumor and its spread can be estimated and thus the prognosis. Furthermore, therapies can be targeted against this marker if PDGFRβ is found to be sensitive to OSCC.

METHODS

This cross-sectional study was conducted in the Department of Oral Pathology, UHS, and Pathology Department of Sheikh Zaid Hospital, Lahore after getting approval from the Ethical Review Committee of UHS vide letter no UHS/REG-18/ERC/469. The duration of the study was one year from April 2018 to May 2019. Paraffin-embedded blocks of 51 cases were recruited including both males and females of all age groups. A written informed consent was taken by the patients for the use of the blocks. However, the blocks of the patients who underwent chemotherapy or radiotherapy were excluded from the study. The demographic data consisting of age, gender, and tumor site was noted. The tumor was graded using Byrne's grading system based on the degree of keratinization, polymorphism, mitotic activity, and pattern of invasion [10]. The paraffin-embedded tissue blocks of all samples were cut into 4 µm sections and immunohistochemistry was performed with rabbit polyclonal anti- PDGFRβ antibody. Tissue sections along with positive control (human breast cancer) were taken. PDGFRβ expression was evaluated by using two different quantification systems. According to Kwon et al., PDGFRβ expression was determined based on proportion and staining intensity [11]. The total score (Score 0 – Negative; Score 1-2 - weak positive +1; Score 3-4 - moderate positive +2; Score 5-6 - strong positive +3) for each case was calculated by adding the proportion score (PS)(0 - less than 5% immune-reactive; 1 - less than 33% immune-reactive; 2 - 33%-66% immune-reactive; 3 - greater than 66% immune-reactive) and intensity score (IS)(0 - no staining; 1 – mild; 2 – moderate; 3 – Intense) of that particular case. The scoring system proposed by Shinohara et al. in 2007 was also used for PDGFRβ staining [12]. The labelling score (Low degree – 0 to 199; High degree – 200 to 300) of PDGFRβ was calculated by multiplying the intensity score (1 – Weak; 2 – Moderate; 3 – Intense) by percent area. SPSS version 20.0 was used for data analysis, including demographic data like age and gender. The grade of the tumor was analyzed along with its morphological parameters. PDGFRβ staining was analyzed according to its presence or absence, and the total score of PDGFRβ staining was seen using two scoring systems. The relationship between tumor grade, PDGFRβ staining scores, and gender was examined through bivariate analysis. The chi-square test of independence was applied, and ≤ 0.05 was taken as a significant p-value at a confidence level of 95%.

RESULTS

A total of 51 cases were enrolled in this study. Out of these, 17 were younger than 45 (32.1%), and 34 were 45 or older (67.9%). The mean age was 53.65 years, with the standard deviation of 17.152. The study included patients aged 16 to 87 years. Male was 30 (58.8%) and female was 21 (41.2%). This revealed a greater prevalence of SCC in men than in women, with a male-to-female ratio of 1.4:1. The highest examined sites were glottis and supra-glottis areas accounting for 18.9% (10) of total cases. Tongue was the next most frequent area of involvement, i.e., 7(13.2%). The least involved areas were the alveolus, cheek, and lip, accounting for one patient of each site. Out of 51 cases, most of the cases 34 (66.6%) were of grade 2 followed by 13 (25.4%) cases of grade 3 and 4 (7.8%) cases of grade 1 respectively. Intense PDGFRβ staining in 29(57%) cases among fifty-one cases of OSCC was analyzed (Table 1).

Table 1: Degree of Distribution PDGFRβ Expression

Degree of Staining	Frequency (n%)
Mild	2 (3.9%)
Moderate	20 (39.2%)
Intense	29 (56.9%)
Total	51 (100%)
Degree of PDGFRβ Staining	
Low Degree	23 (45.1%)
High Degree	28 (54.9%)
Total	51 (100%)

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

A strong membranous expression of PDGFβ was seen in moderately- differentiated squamous cell carcinoma while moderate expression was observed in well-differentiated squamous cell carcinoma(Grade 1)(10X)(Figure 1).

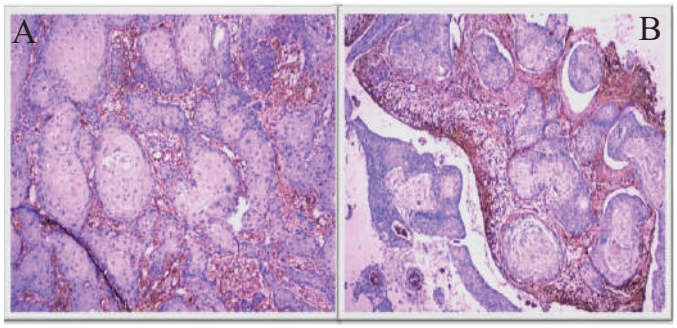

Figure 1: (A) Strong membranous expression in moderately- differentiated squamous cell carcinoma. (B) Moderate membranous expression in well-differentiated squamous cell carcinoma(Grade 1)(10X)

A statistically significant positive correlation was noted between PDGFβ expression and tumor grade(Table 2).

Table 2: PDGFRβ Expression in Different Grades of Tumor

Variable	Grade of Tumor (n=51)					
	Intensity	Low Grade n(%)	Intermediate Grade n(%)	High Grade n(%)	Total n(%)	p-value
PDGFRβ Expression	Mild	2 (100%)	0(0%)	0(0%)	2 (100%)	<0.005
	Moderate	2 (10%)	17(85%)	1(5%)	20 (100%)	
	Intense	0(0%)	17(58.62%)	12 (41.38%)	29 (100%)	

Chi-Square was applied to determine the p-value

Likewise, PDGFRβ expression showed a signification association in different grades of tumors(Table 3).

Table 3: Signification Association in Different Grades of Tumor

Variable	Grade of Tumor (n=51)					
	Intensity	Low n(%)	Intermediate n(%)	High n(%)	Total n(%)	p-value
PDGFRβ Expression	Low Degree	4 (17.4%)	18 (78.26%)	1 (4.35%)	23 (100%)	<0.005
	High Degree	0(0%)	16(58.6%)	12(41.4%)	28 (100%)	

Chi-Square was applied to determine the p-value

Weak, moderate, and strong positive results showed varied and non-significant distribution among male and female (Table 4).

Table 4: Association of PDGFRβ Expression with Gender

Variables	PDGFRβ Expression in Both Genders				
Gender	Mild n(%)	Moderate n(%)	Intense n(%)	Total n(%)	p-value
Male	2(6.7%)	13(43.3%)	15(50%)	30(100%)	0.314
	-	16(53.3%)	14(46.7%)	30(100%)	0.158
Female	0(0%)	7(33.3%)	14(66.7%)	21(100%)	0.314
	-	7(33.3%)	14(66.7%)	21(100%)	0.158

Chi-Square was applied to determine the p-value

DISCUSSION

The tumor microenvironment, composed of stromal cells and extracellular matrix components, plays a crucial role in cancer cell growth, invasion, and metastasis. Cancer-associated fibroblasts (CAFs), an important part of tumor microenvironment, facilitate tumor growth and invasion through elevated matrix metalloproteinase (MMPs), CCL-2 and Il-6, and activate the STAT-3 pathway [12]. Additionally, CAFs induce angiogenesis directly through vascular endothelial growth factor (VEGF) and indirectly by PDGF receptors, recruiting more CAFs that further increase VEGF levels [13]. In cancer treatment, PDGF and other tyrosine kinase molecules contribute to drug resistance by elevating intracellular pressure, and hindering drug penetration [14]. Notably, PDGFRβ serves as a reliable marker for detecting CAFs, identified through various techniques like immunoassays and immunohistochemistry. Early identification and targeting of these interactions are essential for effective cancer management [15]. Little research has focused on the immune-histochemical expression of PDGFRβ and the relation of expression on different grades of squamous cell carcinoma of the head and neck area. In the present study, Byrne's grading system was used to grade the tumor as a low, intermediate, and high-grade tumor. Most of the patients were diagnosed with an intermediate grade of squamous cell carcinoma found in 34 of the patients. High-grade tumors were seen in 13 patients. Only 4 patients had low-grade tumors. For the expression of PDGFRβ, two scoring systems were used. We labelled tumors as low and high degrees by multiplying the intensity score with percent area that was positively stained as indicated by Shinohara *et al.*, [12]. We also categorized the PDGFRβ expression as weak, moderate, and strong positive by calculating intensity and proportion score as done by Kwon *et al.*,[11]. There was no case of negative staining in our study. We found the intensity of staining was maximum in patients with an intermediate grade of tumor according to Shinohara *et al.*, system [12]. Intermediate grades had more low-degree cases (52.9%) compared to high-degree cases (47.1%). High-grade tumors had 92.3% cases of high-degree cases compared to only 7.7% of low-degree cases. Low-grade tumors showed only a low degree of staining in all cases while there was no case of a high degree in low-grade tumors. The results showed a significant association between the degree of PDGFRβ expression in different grades of tumor (p-value=0.001). As the grade increases, the expression of PDGFRβ also increases. This approach can be applied in reverse to identify the grade of the tumor. We found that the staining intensity was maximum in patients with intermediate grade of tumor. Intermediate

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

grade had the same number of severe and moderate staining 17 (50.0%). While high-grade tumors showed 12 (92.3%) strong positive results compared to only 1 (7.7%) moderate positive case. Mild staining was seen in only 2 (100%) cases, and both were of low grade. We found some significant results according to this grading system (p-value=0.000). The current study did not find a significant association between PDGFRβ expression and different age groups and gender distribution. Our results were consistent with Zhang *et al.*, 2016, who concluded that the expression of PDGF-D and PDGFRβ levels are upregulated in tongue squamous cell carcinoma and correlate positively with the grade of the tumor [7]. Cierpikowski, Lis-Nawara, and Bar 2023 observed that the expression of PDGFRβ was upregulated in 70% of cases of OSCC, and this high expression was associated with shorter overall survival [7]. Lin *et al.*, in 2020 observed the upregulated expression of PDGFRβ in OSCC in association with metastatic lymph nodes and poor overall survival [16]. Wang *et al.*,also reported a significant association of PDGFRβ with the clinical stage (p=0.036), lymph node metastasis (p=0.013) and tumor histological grade (p=0.037)[17]. A 5-year follow-up showed a shorter overall survival of the patients with high expression of PDGFRβ[4]. Kartha *et al.*, in 2016 found high expression of PDGFRβ in oral squamous cell carcinoma in only 12 cases, and they found that this marker was present in the perivascular stroma and is absent in tumor epithelium.They concluded that PDGFRβ expression is high in the case of OSCC [18]. Our findings were in contrast to the findings of Valle *et al.*, in 2023,who reported that the advanced-stage tumors showed a low expression of PDGFRβ (p=0.020). According to their findings,a low expression of PDGFRβ was associated with a shorter disease-free survival (p=0.036). They also concurred that a reduction in expression is associated with a 209.874-fold increase in recurrence (p=0.006) [7]. Different studies have been conducted on the expression of PDGFRβ in different body cancers. Paulsson *et al.*, in 2009, determined PDGFRβ expression in different tumors. They found that 80% of colon carcinoma showed PDGFRβ in the perivascular region, while only 31% of prostate cancer were positive for this marker. They also noted a significant correlation between the expression of PDGFR and the grade of breast tumor in which they found PDGFRβ only in the perivascular area in pericytes and is not present in the tumor itself [19]. However, some studies negate this concept. Shinohara *et al.*, published their study on PDGFRβ expression in small cell lung carcinoma. They found that there is no significant difference in marker staining in different age groups, gender, or tumor grade. They also mentioned that the degree of marker staining does not affect the 5-year survival rate [12]. Following a tissue injury, as in the case of cancer, platelets get activated, which not only activates the coagulation cascade but also results in the release of PDGF. PDGF attaches to its specific receptors present on CAFs, pericytes, and other cells, leading to their stimulation. In the same way, binding of these molecules on their specific receptors on different cells causes an increase in endothelial growth factor (EGF), resulting in fibroblast migration, proliferation, and remodeling. PDGF not only influences the levels of tumor growth factor (TGF) and fibroblast growth factor (FGF) but also contributes to the chemotaxis of inflammatory cells and mitogenesis of mesenchymal stem cells. PDFG also influences the levels of VEGF and connective tissue growth factor (CTGF), both of which are responsible for angiogenesis and an increase in the levels of collagen [20]. By blocking the PDGFRβ on CAF cells, the respective pathways can be blocked, thus inhibiting tumor growth, invasion, and metastasis. PDGFR pathway antagonists like Ezetimibe work by inducing G1 blockade in tumor cells thus inhibiting cancer cell proliferation [21]. Agents or antibodies that block PDGF receptors have more specific targets. Imatinib, Sorafenib, Nilotinib, Sunitinib and Pazopanib are some of the PDGFR kinase inhibitors [22]. The present study shows that PDGFRβ is also found in OSCC and increases by increased tumor grade and can be a potential therapeutic target. No study has been conducted regarding the therapeutic role of targeting PDGF/PDGFR in OSCC. The current study did not determine the effect of the expression of PDGFRβ on local invasion, distant metastasis of tumor, prognosis, and patient survival. Further studies are suggested to check the effect of the expression of tumor markers on overall patient management. Furthermore, studies should be done to check the therapeutic role of PDGFRβ.

CONCLUSIONS

It was concluded that head and neck cancer is one of the leading causes of morbidity and mortality around the globe. Early diagnosis and prompt treatment may reduce the morbid effects of this devastating condition. Identification of specific tumor markers may prove a milestone in achieving this goal. Platelet-derived growth factor receptor β is a promising tumor marker. Based on this study, it is concluded that PDGFRβ increases proportionately to the increasing grade of tumor. PDGFRβ may prove a beneficial target for not just the early diagnosis but also for the treatment of OSCC.68196.

Authors Contribution

Conceptualization: SR
Methodology: SR, SC
Formal analysis: SR, AUR, RA, SC
Writing review and editing: AUR, RA, NRK, SC

All authors have read and agreed to the published version of

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2380

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Frequency of Abnormal Electroencephalography in Cases with Ischemic Stroke

Ammar Yasir[1], Qudsum Yousaf[2*], Madiha Malik[3], Mamoona Tanwir Rana[4], Muhammad Imran[1] and Rashid Imran[1]

[1]Department of Neurology, Punjab Institute of Neurosciences, Lahore General Hospital, Lahore, Pakistan
[2]Department of Neurology, Central Park Teaching Hospital, Lahore, Pakistan
[3]Department of Neurology, Rashid Latif Khan University Medical College, Hameed Latif Teaching Hospital, Lahore, Pakistan
[4]Akhtar Saeed Medical and Dental College, Lahore, Pakistan

ARTICLE INFO

Keywords:
Ischemic Stroke, Electroencephalography, Acute Stroke Outcomes, Neurological Biomarkers

How to Cite:
Yasir, A., Yousaf, Q., Malik, M., Rana, M. T., Imran, M., & Imran, R. (2024). Frequency of Abnormal Electroencephalography in Cases with Ischemic Stroke: Abnormal Electroencephalography in Ischemic Stroke . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2380

***Corresponding Author:**
Qudsum Yousaf
Department of Neurology, Central Park Teaching Hospital, Lahore, Pakistan
qudsumyousaf@gmail.com

Received Date: 2nd October, 2024
Acceptance Date: 20th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Stroke was a common global condition, with low-income countries bearing the highest burden. It leads to reduced cerebral blood flow, limiting oxygen and glucose, and causing cerebral infarction. Electroencephalography has been used as a biomarker to predict outcomes in ischemic stroke during its acute and subacute phases. **Objective:** To determine the frequency of abnormal EEG in cases with ischemic stroke. **Methods:** After obtaining approval from the CPSP research evaluation unit, this cross-sectional study was conducted at the Department of Neurology, Punjab Institute of Neurosciences, Lahore, from January 2019 to June 2019 on 96 ischemic stroke patients. Written informed consent was taken from patients/attendants, and demographic details were noted. Using a CT scan, all cases were diagnosed as ischemic stroke. The EEG was done in all cases within 24 hours of admission. All data were entered and analyzed using SPSS version 26.0. **Results:** In the current study, 57.3% of patients with ischemic stroke were found to have abnormal EEG. Data stratification was found to be significant concerning gender and duration of stroke, p- value = 0.01 and 0.000, respectively. However, abnormal EEG frequency was noted more among 45-60-year-old male patients of normal weight and those who presented within 1-2 days of stroke. **Conclusions:** According to current study findings, more than half of the ischemic stroke cohort was found to have abnormal EEG. The high frequency of aberrant EEG results highlights the importance of EEG as a useful diagnostic tool when evaluating individuals who have had acute ischemic stroke.

INTRODUCTION

Stroke is prevalent disease globally, with the highest burden on low-income countries. In 2016, an estimated 13.7 million people had a stroke, with 87% of cases being ischemic [1]. Stroke often causes severe motor and sensory deficits. Prognosis depends on the brain area affected and the underlying cause [2]. Stroke causes sudden changes in the brain, decreasing cerebral blood flow and reducing oxygen and glucose supply, which results in cerebral infarction [3]. Clinical examination, along with neuroimaging, is essential for diagnosing ischemic stroke and assessing eligibility for reperfusion treatment. CT and MRI were commonly used to evaluate brain injury, but neither is ideal for tracking the progression of brain ischemia in the acute phase [4]. New approach, Electroencephalography (EEG), have recently emerged to address this limitation [5]. EEG offers rapid, non-invasive bedside monitoring, providing real-time brain activity assessment with high temporal resolution. It can detect sudden changes in brain metabolism and cerebral blood flow [6]. Acute ischemic stroke often disrupts neurovascular coupling, leading to changes in brain oscillatory activity that reflect neurophysiological responses to reduced blood flow, depicted by increased delta power and decreased alpha power [7]. Researchers have explored quantitative EEG (qEEG) as a potential biomarker for predicting outcomes in ischemic stroke [8]. Its capability to detect lesion size makes it valuable tool for diagnosis and clinical decision-making [9]. Recent developments in qEEG analysis, including the Brain Symmetry Index and portable systems with minimal electrode requirements, enhance its feasibility in pre-hospital and emergency settings [10, 11]. While studies

DOI: https://doi.org/10.54393/pjhs.v5i11.2380

highlight strong links between EEG biomarkers and stroke, further technological advancements and rigorously designed, adequately powered studies were crucial before qEEG can be recommended for routine acute stroke assessment [12]. Despite these advancements, there is limited data on the frequency of abnormal EEG patterns in ischemic stroke, particularly in this locality.

The objective of this study was to determine the frequency of abnormal EEG findings in ischemic stroke cases. By achieving this, the study aimed to contribute to improved stroke management, particularly in resource-limited settings, where timely intervention is critical for better patient outcomes.

METHODS

This cross sectional study was conducted at Department of Neurology, Punjab Institute of Neurosciences, Lahore, from 1st Jan 2019 to 30th June 2019, after approval of synopsis from CPSP (CPSP/REU/NEU-2017-069-441). 96 cases were estimated by 95% confidence level with 10% margin of error and using percentages of abnormal EEG in 53.7% cases [13]. Non-Probability Consecutive sampling technique was used. Patients with acute ischemic stroke (history of weakness of one or more part of body, and CT scan on which focal cerebral ischemic lasting more than 24 hours), aged 18-60 years of either gender were included. However, those with history of ischemic heart disease or atrial fibrillation (as determined on ECG findings), or those with previous ischemic or hemorrhagic CVA (on available record) were excluded. All cases were enrolled after taking informed written consent from patients/ attendants. Data were recorded by using proforma. Detailed demographic information like name, age, gender and contact details was taken. Risk factors including diabetes (HbA1c >6.5%), hypertension, and active smoking status was noted. Using CT scan, all cases were diagnosed as ischemic stroke cases as per operational definition. EEG was performed on all cases within 24 hours of admission to capture cerebral electrical activity across the scalp, reflecting the firing of neurons within the cerebral cortex. EEG recordings were obtained using a standardized 10-20 electrode placement system, ensuring consistent electrode positioning for optimal data reliability. The sampling rate was set at [specific sampling rate, e.g., 256 Hz], allowing high-resolution recordings of cortical activity. EEG recordings captured excitatory and inhibitory postsynaptic potentials in neuronal dendrites, particularly within the superficial regions of the cerebral cortex. Abnormal EEG findings were defined based on specific Cerebral Blood Flow (CBF) thresholds; (a) At a CBF of 25-35 ml/100g/min, the EEG may show a decrease in amplitude of faster frequencies. (b) As CBF decreases to 18-25 ml/100g/min, theta frequencies become apparent, and marked suppression of faster frequencies may appear with a further CBF drop to 12-18 ml/100g/min. (c) Suppression of all frequencies is seen when CBF drops below 8-10 ml/100g/min. All EEGs were interpreted by a single consultant with over five years of experience to minimize inter-observer variability and avoid potential bias. Data were analyzed using SPSS version 26.0. Mean ± SD was computed for quantitative data and frequency and percentage for qualitative data. Data were stratified for age, gender, BMI and duration of stroke to address the effect modifiers. Post-stratification, chi-square test was applied, p-value ≤0.05 was taken as significant.

RESULTS

In table 1, mean age of study population calculated was 52 ± 6.63 years, among them 32 (33.3%) patients belong to age group < 45 years and 64 (66.7%) belong to age ≥45 years. There were more male patient's 64% as compared to 36% females. According to BMI 46 (47.9%) patients had normal weight, 39 (40.6%) patients were overweight and 11 (11.5%) were obese. 59 (61.5%) patients presented within 1-2 days of clinical symptoms, while 37 (55%) patients presented after 2 days of symptoms. Risk factors were studied among study participants; DM was noted in 36%, HTN in 42%, and 29% patients were found to be active smokers.

Table 1: Socio-demographic Characteristics of Study Groups (n=96)

Age	N (%) / (Mean ± SD)
<45 Years	32 (33.3%)
≥45 Years	64 (66.7%)
Age (Years)	52.00 ± 6.63
Gender	
Male	61 (64%)
Female	35 (36%)
BMI	
Normal	46 (47.9%)
Overweight	39 (40.6%)
Obese	11 (11.5%)
Duration Of Stroke	
1-2 Days	59 (61.5%)
>2 Days	37 (55%)
Risk Factors	
DM	35 (36%)
HTN	40 (42%)
Active Smoking	2 (29%)

Table 2 showed that, out of 96 study participants presented with ischemic stroke 55 (57.3%) patients found to have abnormal EEG.

Table 2: Frequency of Abnormal EEG

Abnormal	EEG N (%)
Yes	55 (57.3%)
No	41 (42.7%)
Total	96 (100%)

Data stratification was done, as shown in table 3, found to be significant for gender and duration of stroke p- Value 0.01 and 0.000, respectively. However abnormal EEG was noted more among patients with age 45-60 years, male

DOI: https://doi.org/10.54393/pjhs.v5i11.2380

gender, among normal weight patients, and those who presented with 1-2 days of symptoms onset.

Table 3: Data Stratification with Respect to effect Modifiers

Variables	Abnormal EEG N (%)		Total N (%)	p-value
Age Groups	**Yes**	**No**		
<45 Years	20 (36.4%)	12 (29.3%)	32 (33.3%)	0.46
45-60 Years	35 (63.6%)	29 (70.7%)	64 (66.7%)	
Total	55 (100%)	41 (100%)	96 (100%)	
Gender	**Abnormal EEG N (%)**		**Total N (%)**	0.01
	Yes	**No**		
Male	29 (52.7%)	32 (78%)	61 (63.5%)	
Female	26 (47.3%)	9 (22%)	35 (36.5%)	
Total	55 (100%)	41 (100%)	96 (100%)	
BMI	**Abnormal EEG N (%)**		**Total N (%)**	0.28
	Yes	**No**		
Normal Weight	28 (50.9%)	18(43.9%)	46(47.9%)	
Overweight	19 (34.5%)	20 (48.8%)	39 (40.6%)	
Obese	81 (4.5%)	3 (7.3%)	11 (11.5%)	
Total	55 (100%)	41 (100%)	96 (100%)	
Duration	**Abnormal EEG N (%)**		**Total N (%)**	0.00
	Yes	**No**		
1-2 Days	53 (96.4%)	6 (14.6%)	59 (61.5%)	
>2 Days	2 (3.6%)	35 (85.4%)	37 (38.5%)	
Total	55 (100%)	41 (100%)	96 (100%)	

DISCUSSION

In the current study, the mean age of patients with ischemic stroke was calculated to be 52 ± 6.63 years, with a predominance of male patients. Most patients, based on BMI, were of normal weight (47.9%), followed by overweight (40.6%), and only 11.5% were classified as obese. Studies have documented age variations among stroke patients. Previous research shows that younger stroke patients typically have a mean age between 36.4 and 36.9 years, while older patients have a mean age between 60.9 and 70.3 years [14-16]. Unlike these studies, which focused on specific age groups, this study included a broader age range of 20-60 years. In line with these findings, one study reported also male predominance in ischemic stroke patients, reported 59.9% males and 40.1% females [17]. Additionally, a large cohort study on acute ischemic stroke found that only 12.6% of patients were obese, consistent with these results [18]. Another study further supports this, reporting a mean BMI within the normal range among stroke patients [19]. In this study, 57.3% of ischemic stroke patients showed abnormal EEG findings. Similarly, Ag Lamat MS *et al.*, in (2023) reported that 51.5% of acute ischemic stroke patients had abnormal EEGs, most often with localized slowing (28.2%), followed by generalized slowing (18.9%) and epileptiform changes (4.4%) [20]. Unlike their study, we did not further classify EEG abnormalities. A strong correlation was found between seizures and abnormal EEG results, with EEG abnormalities predicting post-stroke seizures [21]. EEG was useful in Acute Ischemic Stroke (AIS), but its sensitivity varies. Some patients may show normal EEG results despite significant ischemic changes, underscoring the need for a comprehensive diagnostic approach, as noted by Wijaya SK *et al.*, in 2015 [22]. In contrast, one study reported lower percentage of EEG abnormalities (37.9%), in ischemic stroke patients [23]. Recent research on focal cerebral ischemia outcomes has identified EEG suppression as part of malignant EEG patterns, marking it as a poor indicator for diffuse cerebral ischemia. This feature has also been shown to independently predict functional outcomes one year after stroke [24]. The potential for improving diagnosis, treatment, and patient outcomes in ischemic stroke patients presents serious global health challenges. Although conventional neuroimaging methods offer vital information, they might not be able to keep up with the quick development of acute cerebral ischemia. Results from abnormal EEGs can be useful biomarkers for early diagnosis and prognosis, allowing for prompt interventions and well-informed therapy choices. Knowing the patterns and frequency of these EEG alterations might help develop better management techniques, particularly in environments with limited resources, which will ultimately enhance patient outcomes and quality of life for stroke survivors. This study has certain limitation that needs to be addressed in future work. Firstly, this study was done on broader age range have not classified according to age related stroke patterns, neither we have studied brain volume effected, and we have not followed patients for short and long term outcomes. Furthermore, we not further classified EEG. In future more studies will be needed to cover these limitations.

CONCLUSIONS

According to current study findings, more than half of ischemic stroke cohort found to have abnormal EEG. The high frequency of aberrant EEG results highlights the importance of EEG as useful diagnostic tool when evaluating individuals who have had acute ischemic stroke.

Authors Contribution

Conceptualization: AY
Methodology: MM, MTR, MI, RI
Formal analysis: MM
Writing, review and editing: AY, QY, MTR, MI, RI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research,

DOI: https://doi.org/10.54393/pjhs.v5i11.2380

authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1919

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Efficacy of Artesunate versus a Combination of Artesunate and Quinine Di-Hydrochloride Given Intravenously for the Treatment of Malaria; A Comparative Study

Asma Akbar[1], Irum Jabeen[1*], Kiran Kanwal[1], Sonia Ilyas[1] and Shakeel Ahmad[1]

[1]Department of Pediatric Medicine, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan

ARTICLE INFO

Keywords:
Artesunate, Efficacy, Malaria, Quinine Di-Hydrochloride, Treatment

How to Cite:
Akbar, A., Jabeen, I., Kanwal, K., Ilyas, S., & Ahmad, S. (2024). Efficacy of Artesunate versus a Combination of Artesunate and Quinine Di-Hydrochloride Given Intravenously for the Treatment of Malaria; A Comparative Study: Efficacy of Artesunate and Quinine Di-Hydrochloride for the Treatment of Malaria. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1919

***Corresponding Author:**
Irum Jabeen
Department of Pediatric Medicine, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan
irumjabeen2020@gmail.com

Received Date: 29th August, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

In developing countries, malaria is still one of the leading causes of morbidity and mortality. **Objectives:** To evaluate the efficacy of intravenous artesunate alone versus intravenous combination of artesunate and quinine. **Methods:** This randomized control trial was conducted in the Pediatric Medicine Unit-2, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan. The inclusion criteria were children of either gender, aged 2-14 years and admitted to the emergency department with the diagnosis of severe malaria. Children were randomly allocated to two treatment groups of equal size. The intravenous artesunate group received artesunate administered intravenously for a maximum of 7 days. The intravenous combination of artesunate and quinine group received artesunate intravenously combined with quinine di-hydrochloride intravenously for a maximum of 7 days. they were employing the lottery method. The outcome was measured as the number of hours elapsed for an individual to become fever-free (temperature below 36.8°C). **Results:** In a total of 104 children with severe malaria. the mean duration required to become fever-free was 28.3 ± 5.4 hours in intravenous artesunate alone versus 26.5 ± 6.4 hours in intravenous combination of artesunate and quinine groups (p=0.1242). The most frequent treatment-related side effects were nausea, loss of appetite, hypoglycemia, diarrhea, and rash, noted in 21 (20.2%), 13 (12.5%), 11 (10.6%), 5 (4.8%), and 2 (1.9%) patients, respectively. **Conclusions:** It was concluded that intravenous artesunate and quinine together did not provide any additional benefit or synergistic effect over intravenous artesunate alone in treating severe malaria in children.

INTRODUCTION

In developing countries, malaria is still one of the leading causes of morbidity and mortality. According to the WHO, there were 247 million cases of malaria worldwide in 2021, resulting in 619,000 deaths [1]. Although many zones of the world have been declared malaria-free, countries like Pakistan, India, Sri Lanka, Afghanistan, and many countries in Africa are still struggling against the crippling disease and continue to be endemic malaria [2]. All age groups are indiscriminately affected, but children, like any other disease, lie among the most vulnerable owing to their low immunity, dependency on caretakers for preventive measures, and repeated exposure. About three out of every four malaria victims happen to be children [3]. In a systematic review by Khan *et al.*, pooled malaria prevalence in Pakistan was estimated to be 23.0%. Severe malaria can be caused by any of the plasmodium species, but most commonly by vivax and falciparum species, as these species abundantly exist in the Indo-Pak region [4]. Classic clinical presentation, a high index of suspicion, and rapidly available diagnostic techniques rarely impart a diagnostic challenge in malaria but effective and time management are the real areas of concern. Regarding management, where supportive treatment plays a crucial role in immediate resuscitation and resolution of vitals, specific treatment remains the cornerstone for limiting morbidity and mortality [5]. The treatment of severe malaria varies according to age, immunity status, and local susceptibility patterns. Currently, the WHO recommends artesunate as the drug of choice for the treatment of severe malaria [6]. A study done by Botta *et al.*, from Italy, reported that the

DOI: https://doi.org/10.54393/pjhs.v5i11.1919

efficacy of IV Artesunate (IVA) alone or in combination with IV quinine (IVQ) was 83.3% versus 47.0% (p=0.002) respectively, favouring IV artesunate alone [7]. The efficacy of this single drug as compared to the combined drug regimen in severe malaria remains questionable. Therefore, we intended to evaluate the efficacy of only IVA versus IVA+IVQ in the treatment of severe malaria in children. The findings of the study were thought to help know whether the two drugs, when given together, have considerable benefits over single-drug therapy when given for the same. This is the first research comparing two treatment regimens in severe malaria in Pakistan so the findings of this study may bring very important insights about the treatment and outcome-related aspects of severe malaria in children.

This study aims to evaluate the efficacy of IVA alone versus IVA in combination with IVQ in the treatment of severe malaria in children.

METHODS

This randomized controlled trial was conducted in the indoor settings of the Pediatric Medicine Unit-2, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan, from 16th May 2024 to 25th June 2024. Approval from the institute's ethical committee was obtained (Letter number: PM.U-II/0011/58). Considering the efficacy of IVA at 83.3% versus IVA plus IVQ at 47% in severe malaria [7], with a 95% confidence level and 97% power of the study, the sample size was calculated to be 104 (52 in each group). A simple random sampling technique was adopted. The inclusion criteria were children of either gender, aged 2-14 years and admitted to the emergency department with the diagnosis of severe malaria as defined by the WHO [6]. The exclusion criteria were patients with chronic kidney disease, chronic liver disease, immunosuppressive disorders, hematological disorders, malignancies, and congenital heart disease (as per medical history). Before taking informed and written consent from the parents or caregivers, the study objective and safety aspects related to this study were explained. This clinical trial (NCT06472258) was registered. At the time of enrollment, gender, age, residential address, and maternal educational status were noted. Mothers who could read and write, and went to any form of formal education were labelled as literate, or illiterate otherwise. Laboratory evaluation of the involvement of plasmodium species was performed using an immune-chromatographic test (ICT) malarial parasite antigen. Patients were randomly allocated to two treatment groups employing the lottery method. The IVA group (n=52) received IVA with a weight-appropriate dosage at 0, 12, 24, and 48 hours and continued 12 hours for a maximum duration of seven days, with each dose diluted in normal saline and given as an infusion. The IVA+IVQ group (n=52) received IVA with a weight-appropriate dose at 0, 12, 24, and 48 hours, combined with IVQ by weight, with a loading dose of 20mg/kg in a 10% dextrose infusion, followed by a 10mg/kg infusion every 8 hours for 2 days and every 12 hours onwards for a maximum of 7 days. All the patients were provided symptomatic supportive therapy as needed, along with the mentioned specific drugs. All the patients were followed for the resolution of fever. The primary outcome was measured as the number of hours elapsed for an individual to become fever-free (temperature below 36.8°C). During their stay, children were monitored and their parents/caregivers inquired about the common treatment-related side effects. All the study data were recorded on a pre-designed proforma. The data were analyzed through IBM SPSS Statistics, version 26.0. Qualitative data like gender, age groups, residence, maternal education, plasmodium species, and treatment-related side effects were represented as frequency and percentages. Quantitative data like age and time to get fever-free were described as mean and standard deviation (SD). Comparison of categorical data in between study groups was done employing the chi-square test. Independent sample t-test was applied to compare quantitative data between study groups. For all statistical analyses, $p<0.05$ was taken as significant.

RESULTS

In a total of 104 children with severe malaria, 58 (55.8%) children were male. The mean age was 6.35 ± 3.61 years, ranging between 2-14 years. Plasmodium vivax was the most common plasmodium species, noted in 65 (62.5%) children. A comparison of characteristics of children is shown between both study groups and no significant differences was observed in terms of gender (p=0.6929), age (p=0.2748), residence (p=0.4201), maternal education (p=0.6759), and plasmodium species (p=0.5268).

Table 1: Comparison of Characteristics of Patients in Both Study Groups (n=104)

Characteristics		Groups		p-value
		IVA (n=52)	IVA + IVQ (n=52)	
Gender	Male	28 (53.8%)	30 (57.7%)	0.6929
	Female	24 (46.2%)	22 (42.3%)	
Age Groups (Years)	2-5	27 (51.9%)	21 (40.4%)	0.2748
	6-14	25 (48.1%)	31 (59.6%)	
Plasmodium Species	Vivax	32 (61.5%)	33 (63.5%)	0.5268
	Falciparum	14 (26.9%)	10 (19.2%)	
	Vivax and Falciparum	6 (11.5%)	9 (17.3%)	

The outcome was measured in the number of hours elapsed for an individual to become fever-free. The mean duration required to become fever-free was 28.3±5.4 hours versus 26.5±6.4 hours in IVA alone versus IVA plus IVQ groups, respectively, and the difference was found to be statistically insignificant (p=0.1242) (Figure 1).

DOI: https://doi.org/10.54393/pjhs.v5i11.1919

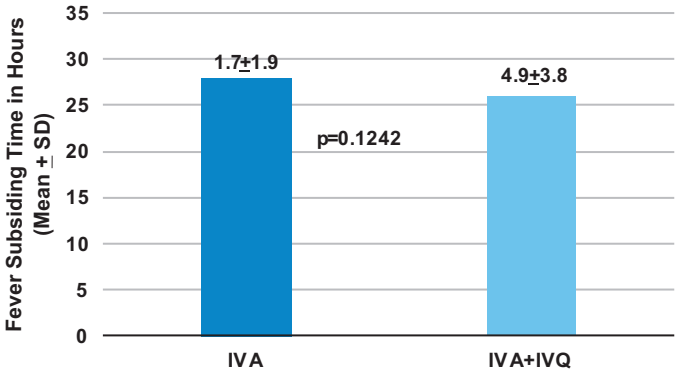

Figure 1: Fever Subsiding Time in Both Study Groups

The most frequent treatment-related side effects were nausea 21(20.2%), loss of appetite 13(12.5%), hypoglycemia 11(10.6%), diarrhea 5 (4.8%), and rash 2 (1.9%). Nausea was significantly associated with IVA alone group (p<0.01). Hypoglycemia was reported in 10.6%, and all these belonged to the combination group (p=0.01). Diarrhea was significantly associated with the combination group as all 4.8% who had diarrhea belonged to the combination group (p=0.0219). Frequency and comparison of treatment-related side effects in both study groups are shown. All 104 patients, whether receiving a single or combined drug regime, were successfully treated and discharged (Table 2).

Table 2: Frequency and Comparison of Treatment-Related Side Effects in Both Study Groups

Side effects	IVA	IVA + IVQ	p-value
Nausea (n=21)	19 (36.5%)	2 (3.8%)	2 (3.8%)
Loss of Appetite (n=21)	7 (13.5%)	6 (11.5%)	0.7668
Hypoglycemia (n=11)	-	11 (21.2%)	<0.01
Diarrhea (n=5)	-	5 (9.6%)	0.0219
Rash (n=2)	2 (3.8%)	-	<0.01

DISCUSSION

Malaria remains one of the leading causes of illness and death in Pakistan, while intense transmission occurs mainly in districts located in regions bordering Iran and Afghanistan, as well as the coastal belt in Sindh and Baluchistan provinces [8]. In the current study, 85.6% of children with severe malaria had involvement of either plasmodium vivax or falciparum and these findings are consistent with the recent trends as plasmodium vivax or falciparum are considered to be the most common-causing species of malaria in this region [9]. The ideal drug for the treatment of severe malaria remains a topic of interest, especially in endemic countries like Pakistan, where the susceptibility patterns continue to vary rapidly owing to emerging resistance due to multiple factors. Severe malaria in the pediatric age group remains one of the most commonly dealt with emergencies. Currently, WHO recommends intravenous artesunate for the treatment of severe malaria followed by artemether and quinine, respectively [10, 11]. However, the synergistic effect of giving combination drugs together in severe malaria is often questioned [12]. The present study fulfilled the desired purpose by answering the question. The outcome was measured in the number of hours elapsed for an individual to become fever-free. The mean duration required to become fever-free was 28.3 ± 5.4 hours versus 26.5 ± 6.4 hours in the intravenous artesunate group versus intravenous artesunate plus intravenous quinine group, respectively, and the difference was found to be statistically insignificant (p=0.1242). A similar study was conducted by Newton *et al.*, comparing parenteral artesunate alone with combined intravenous artesunate and intravenous quinine in the treatment of severe malaria. However, the study only enrolled the disease caused by plasmodium falciparum, while our study included both falciparum and vivax species leading to the disease. Nevertheless, the results of both studies supported each other and proved that there was no additional benefit to combining the two drugs and no synergistic effect was noted [13]. The combination of intravenous artesunate and intravenous quinine has been administered to severe malaria patients along the Thai-Myanmar border, where P. falciparum showed widespread resistance to artemisinin derivatives [14]. The authors suggested that adding intravenous quinine empirically to intravenous artesunate could be a precautionary measure in these cases. The WHO's latest malaria guidelines of July 2021 recommend the combined use of parenteral artesunate and quinine in full doses for treating severe malaria in regions with established artemisinin resistance [15]. Although combination therapy with intravenous artesunate plus intravenous quinine could be a last-resort option for patients from areas at risk of artemisinin resistance, further data on the combined use of these drugs would be valuable [16, 17]. In the present study, hypoglycemia was a dominant treatment-related side effect among children treated with intravenous artesunate plus intravenous quinine. Contemporary literature has highlighted a relatively higher incidence of hypoglycemia among cases treated with intravenous quinine when compared to those administered intravenous artesunate so caution is advised for regular monitoring among this set of children [18-20]. The current study had some limitations. Due to a lack of appropriate microscopy facilities, species confirmation was possible only through ICT malarial parasite antigen. Treatment-related side effects reported in this study were subjective complaints other than hypoglycemia which was confirmed through blood glucose level monitoring.

DOI: https://doi.org/10.54393/pjhs.v5i11.1919

CONCLUSIONS

It was concluded that intravenous artesunate and quinine together did not provide any additional benefit or synergistic effect over intravenous artesunate alone in the treatment of severe malaria in children. Being rapid in action and safe and cost-effective, intravenous artesunate alone outweighs the benefit of giving an intravenous combination of artesunate and quinine di-hydrochloride.

Authors Contribution

Conceptualization: AA
Methodology: AA, IJ, KK, SI, SA
Formal analysis: AA, IJ, KK, SI, SA
Writing review and editing: AA, IJ, KK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2335

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Compliance and Barriers among Nurses Regarding Surgical Site Infection Prevention Guidelines at Public Tertiary Care Hospitals of Islamabad

Rubina Afsar[1*], Rehana Khadim[2], Samina Yasmeen[3], Shagufta Parveen[1] and Mehreen Aslam[1]

[1]College of Nursing, Armed Forces Post Graduate Medical Institute, National University of Medical Sciences, Rawalpindi, Pakistan
[2]Pakistan Armed Forces Medical Journal, Army Medical College, Rawalpindi, Pakistan
[3]College of Nursing, Rawalpindi, Pakistan

ARTICLE INFO

Keywords:
Surgical Site Infections, Nurses Compliance, Prevention Guidelines, Barriers, Healthcare-Associated Infections

How to Cite:
Afsar, R., Khadim, R., Yasmeen, S., Parveen, S., & Aslam, M. (2024). Compliance and Barriers among Nurses Regarding Surgical Site Infection Prevention Guidelines at Public Tertiary Care Hospitals of Islamabad: Nurses Compliance in Surgical Site Infection Prevention. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2335

Corresponding Author:
Rubina Afsar
College of Nursing, Armed Forces Post Graduate Medical Institute, National University of Medical Sciences, Rawalpindi, Pakistan
rubinaafsar72@gmail.com

Received Date: 28th September, 2024
Acceptance Date: 22nd November, 2024
Published Date: 30th November, 2024

ABSTRACT

Surgical Site Infections (SSI) are a common healthcare-related issue, occurring within 30 days to a year after surgery or prosthesis implantation. **Objective:** To assess nurses' compliance and identify barriers related to SSI prevention guidelines. **Methods:** A cross-sectional study conducted from February to July 2024 involved 270 participants from four hospitals in Islamabad, using convenience sampling. A validated questionnaire, based on WHO guidelines (2016), was adopted, comprising three sections: demographic information, compliance (before surgery, during surgery, and after surgery), and barriers to compliance. **Results:** The study revealed that while most participants had over five years of experience, only 43.7% adhered to SSI prevention standards. Significant barriers included insufficient surgical supplies, lack of formal training, limited hospital oversight, and poor communication within healthcare teams. **Conclusions:** Nurses exhibited limited awareness and adherence to SSI prevention guidelines, with key barriers hindering effective prevention. Addressing these challenges is essential to improving SSI control and patient outcomes.

INTRODUCTION

Surgical Site Infection (SSI) is an infection that develops within 30 days of a surgical operation or a year of prosthetic installation. SSI occurs in up to 30% of surgical procedures and accounts for up to 14% of hospital-acquired infection HAIs [1]. SSIs have been linked to a significant increase in patient morbidity and mortality, as well as healthcare expenses worldwide. Every year, over 234 million surgical patients are operated on worldwide, with 3%–16% of them having complications and other preventable surgical errors [1]. Several studies have examined the global prevalence and risk factors for SSIs. In Pakistan, there is a lack of nationally representative data to support evidence-based guidance [2]. Numerous studies have been conducted worldwide to evaluate nurses' knowledge, and practices related to SSI prevention. However, the literature review revealed that research on nurses' compliance with SSI prevention guidelines and the difficulties they encounter in Pakistan was lacking. Similarly, few studies have been conducted to assess nurses' knowledge, attitude, and practice regarding SSI prevention in Pakistan [3]. The identified gaps in the literature can therefore be addressed with great benefit from this study. Surgical Site Infection

DOI: https://doi.org/10.54393/pjhs.v5i11.2335

(SSI) rates in low- and middle-income countries (LMICs) range from 8% to 30%, making them the most frequent healthcare-associated infection (HAI) with substantial morbidity, mortality, and economic impacts [4]. Surgical Site Infections (SSIs) represent a significant public health concern in Pakistan, with prevalence rates varying widely across different studies and settings. Research indicates that the incidence of SSIs in Pakistan ranges from 9.3% to 33.6%, depending on various factors such as the type of surgery and patient demographics [2]. Nurses played a critical role in following and implementing SSI prevention recommendations in hospital settings, including preoperative, intraoperative, and postoperative phases. According to the CDC and WHO, SSI prevention guidelines can limit the spread of SSIs and provide occupational safety for healthcare professionals [5]. Guidelines apply to all healthcare settings and patients, regardless of their diagnosis. The guidelines cover various infection control topics, including preoperative showering, dietary assessment, antibiotic administration, surgical site preparation, hand washing, Personal Protective Equipment (PPE) use, and sharps disposal, aiming to reduce hospital-acquired infectious diseases [5]. However, current barriers to nurses' compliance with infection prevention guidelines are inadequate knowledge, leadership engagement, lack of resources, time constraints, and insufficient training [6]. The lack of local standard operating protocols and implementation manuals further exacerbates the situation, hindering effective practice and patient outcomes. Despite detailed infection control guidelines, SSI rates in Pakistan remain high, with low nurse practice levels, particularly in public-sector hospitals [7]. Nurses play a crucial role in preventing SSI by adhering to key practices such as consistent hand hygiene, aseptic techniques, skin antisepsis, timely prophylactic antibiotics, postoperative wound care, patient education, proper use of PPE, and effective communication with the surgical team. These practices help maintain a safe environment and reduce infection risks [8].

This study proposed to assess nurses' compliance with SSI prevention guidelines and identify the barriers they face in implementing these guidelines.

METHODS

A cross-sectional study was conducted to assess nurses' compliance with and identify barriers regarding Surgical Site Infection (SSI) prevention guidelines. The sample size was calculated using the Rao Soft Sample Size Calculator, with a 95% confidence level, a 5% margin of error, and an accessible population size of 800, yielding an initial sample size of 260. After accounting for a 10% attrition rate, the adjusted sample size was 286. Data collection involved 286 participants; however, 16 incomplete questionnaires were discarded, leaving 270 participants for analysis. In Inclusion criteria, registered nurses working in surgical settings, with at least 6 months of experience in the field of surgery, were included in the study. While in exclusion criteria, nurses who were on leave during the data collection period or those with less than 6 months of surgical experience were excluded. Written informed consent was obtained from all participants before data collection. Participants were informed about the study's purpose, procedures, potential risks, and benefits, ensuring their voluntary participation. Convenience sampling was employed due to time, resource, and access constraints. Ethical approval for the study was obtained from the IRB/ERC Committee (Reference No. 461-AAA-ERC-AFPGMI). Two validated questionnaires, developed based on the WHO SSI Prevention Guidelines (2016), were utilized to measure nurses' compliance and barriers. Content Validity Index (CVI) was assessed by a panel of five experts, and the tool's reliability was calculated using Cronbach's alpha (0.86 for compliance and 0.87 for barriers). A pilot test was conducted on 27 nurses (10% of the sample) in a nearby hospital. The questionnaire consisted of three sections: (a) Socio-demographic Information (7 items); (b) Compliance: Nurses' adherence to SSI prevention protocols before, during, and after surgery was assessed using a 5-point Likert scale ranging from Never to Always. The compliance level for each stage (before, during, and after surgery) was categorized as follows: (a) Low Compliance: Before Surgery: 21-26, During Surgery: 47-50, After Surgery: 48-51, (b) Moderate Compliance: Before Surgery: 27-30, During Surgery: 51-55, After Surgery: 52-54, (c), High Compliance: Before Surgery: 31-34, During Surgery: 56-59 After Surgery: 55-58. These categories were established by dividing the scale range for each stage by the number of categories (low, moderate, and high) as used in previous studies. (d) Barriers: A 15-item Likert scale assessed the barriers nurses face when complying with SSI prevention guidelines. The responses were recorded on a 5-point Likert scale, ranging from strongly disagree to strongly agree [8, 9]. This section aimed to identify the factors preventing nurses' adherence, such as lack of resources, inadequate training, or poor communication within healthcare teams. Data analysis was performed using SPSS version 27.0. Descriptive statistics were applied to calculate frequencies and percentages. The compliance categories (low, moderate, and high) were analyzed to determine the distribution of nurses' adherence across the different stages of surgery (before, during, and after surgery).

RESULTS

According to the statistics in table 1, most respondents were aged between 41 and 50 years, with 60.7% being women and 39.3% men. A significant proportion of nurses (46.7%) held a post-RN degree, while only 3% had obtained a master's degree. Nearly half of the respondents (45.9%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2335

reported having 1 to 5 years of experience in surgical wards. However, 63.7% of the nurses did not receive training in SSI prevention, which may have affected compliance and put patient safety at risk. The study recommends enhancing adherence to SSI prevention guidelines by developing comprehensive training programs for the 63.7% of nurses who lack this training.

Table 1: Demographic Information of the Respondents (n = 270)

Variables	Categories	N (%)
Age of Respondents	20-30	54 (20.0%)
	31-40	88 (32.6%)
	41-50	107 (39.6%)
	51-60	21 (7.8%)
Gender of Respondents	Male	106 (39.3%)
	Female	164 (60.7%)
Level of Professional Education	Diploma	92 (34.1%)
	Post R.N	126 (46.7%)
	GBSN	44 (16.3%)
	MSN	08 (3.0%)
Work Experience in Surgical Ward	1 Year	66 (24.4%)
	5 Years	124 (45.9%)
	10+ Years	80 (29.6%)
Attended SSI Prevention Guidelines Training Program	No	172 (63.7%)
	Yes	98 (6.3%)
Clinical Placement Area	General Surgery	70 (25.9%)
	Neurosurgery	20 (7.4%)
	Post Cardiac	29 (10.7%)
	Orthopedics	29 (10.7%)
	Urology	25 (9.3%)
	O.T	27 (10.0%)
	E.N.T/Eye	13 (4.8%)
	Gynecology	24 (8.9%)
	Pediatrics	15 (5.6%)
	Surgical ICU	18 (6.7%)
Marital Status of the Respondent	Single	90 (33.3%)
	Married	175 (64.8%)

Table 2 presented the compliance levels of nurses with SSI prevention guidelines at three critical time points: before surgery, during surgery, and after surgery (n=270). Prior to surgery, a significant majority of nurses (53.3%) demonstrated moderate compliance, while 24.4% exhibited low compliance and 22.2% showed high compliance. During surgery, compliance significantly improved; only 0.7% of nurses had low compliance, 49.3% had moderate compliance, and 50% had high compliance. However, after surgery, compliance levels declined, with 33.3% of nurses returning to low compliance. Moderate compliance remained constant at 53.3%, while only 13.3% maintained high compliance. These data indicate a significant decrease in postoperative compliance with SSI prevention practices, highlighting the need for ongoing education and support for nurses.

Table 2: Participants' Responses to the Compliance with SSI Prevention Guidelines, Before, During and, After Surgery (n=270)

A score of the Nurse's Compliance with SSI Prevention Guideline	Time Line		
	Before Surgery N (%)	During Surgery N (%)	After Surgery N (%)
Low	66 (24.4%)	2 (0.7%)	90 (33.3%)
Moderate	144 (53.3%)	133 (49.3%)	144 (53.3%)
High	60 (22.2%)	135 (50.0%)	36 (13.3%)

In table 3, regarding the barriers to compliance with Surgical Site Infection (SSI) prevention guidelines, about 53% of nurses strongly agreed that several factors hindered their adherence. These included insufficient supplies of surgical consumables, an inappropriate nurse-to-patient ratio (95.5%), lack of time (56.7%), and the absence of a professional model (62.2%). Additionally, 51.1% of nurses believed that some measures for preventing SSI were not their responsibility. These factors collectively represented the major barriers nurses faced in following SSI prevention guidelines.

Table 3: Response of the participants of facing Barriers to Compliance with SSI Prevention Guidelines

S. No.	Barriers to Compliance with Surgical Site infection Prevention Guidelines	Strongly Disagree N (%)	Disagree N (%)	Undecided N (%)	Agree N (%)	Strongly Agree N (%)
01	Inadequate Supply of Surgical Consumables (cap, mask, scrub, antiseptic solution)	0 (0.0%)	0 (0.0%)	17 (6.3%)	110 (40.7%)	143 (53.0%)
02	Lack of Supervision by the Hospital Infection Control Committee	1 (0.4%)	28 (10.4%)	95 (35.2%)	146 (54.1%)	0 (0.0%)
03	Inadequate knowledge about disinfection and Sterilization Techniques	48 (17.8%)	94 (34.8%)	0 (0.0%)	118 (43.7%)	10 (3.7%)
04	Lack of Training on Measures for the Prevention of Surgical Site Infections in the Hospital	0 (0.0%)	0 (0.0%)	24 (8.8%)	128 (47.4%)	118 (43.7%)
05	Lack of Evidence-based Recommendations for Preventing Surgical Site Infections	0 (0.0%)	0 (0.0%)	39 (14.9%)	190 (70.4%)	41 (15.2%)
06	Inappropriate Nurse-to-Patient Ratio	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (4.1%)	259 (95.9%)
07	Lack of a Role Model or Mentor in SSI Prevention	0 (0.0%)	3 (1.1%)	24 (8.9%)	168 (62.2%)	75 (27.8%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2335

08	Poor Integration of Research findings into Practice	0 (0.0%)	76 (28.1%)	94 (34.8%)	96 (35.6%)	4 (1.50%)
09	Lack of time makes it Hard for Nurses to Follow SSI Prevention Guidelines	0 (0.0%)	0 (0.0%)	10 (3.7%)	107 (39.6%)	153 (56.7%)
10	Nurses do not have the Required Skills for Effective SSI Prevention	0 (0.0%)	0 (0.0%)	108 (40.0%)	144 (53.3%)	18 (6.7%)
11	Some Measures for SSI Prevention may not be Clearly defined as Nurses' Responsibilities	0 (0.0%)	0 (0.0%)	4 (1.5%)	138 (51.1%)	128 (47.4%)
12	Lack of Awareness about SSI Prevention guidelines	2 (0.7%)	8 (3.0%)	0 (0.0%)	109 (40.4%)	151 (55.9%)
13	Communication Gaps Hinder the Effective Implementation of SSI Prevention Guidelines	0 (0.0%)	10 (3.7%)	19 (7.0%)	107 (39.6%)	134 (49.6%)
Prevention Guidelines						
14	Nurses may Resist Adopting new Guidelines due to Established Routines	0 (0.0%)	77 (28.5%)	147 (54.5%)	46 (17.0%)	0 (0.0%)
15	Without Regular feedback, Nurses May not identify Areasfor Improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)	75 (27.8%)	195 (72.2%)

DISCUSSION

This study assessed nurses' compliance and identified barriers to adhering to surgical site infection prevention guidelines. The study indicated that participating nurses had various levels of compliance with SSI prevention guidelines. For example, 43.9% of nurses reported frequently ensuring that patients bathe or shower before surgery, whereas 54.8% rarely used chlorhexidine for skin preparation, showing inconsistent adherence. These findings are consistent with those of those who observed similar compliance rates in preoperative hygiene routines [10]. The inconsistent compliance is challenging, given the evidence that showed that preoperative bathing reduces microbial load and SSI risk [11]. The study also found that more than 90% of nurses were given antibiotics before surgery, which is consistent with an 83% compliance rate [12]. In this study, more than half of the participants did not utilize alcohol-based treatments for skin preparation before surgery, in contrast to a Bangladeshi study in which over 70% of nurses did so. This study's nurses demonstrated high compliance (over 90%) with handwashing after surgery, which is comparable with the findings of [13]. This devotion indicates a recognition that hand hygiene plays a crucial role in SSI prevention. However, awareness of other SSI requirements, such as preoperative hair removal techniques, was low, with just 43.3% correctly recognizing clipping as the best approach, in contrast to the study, which had 100% inaccurate answers [13]. Due to a lack of resources, many institutions continue to use razors instead of clippers [14]. The study highlighted various challenges to SSI guideline compliance, including 93% of nurses believing that certain SSI prevention practices were beyond their purview. These findings are consistent with those of, those who reported that nurses faced constraints such as a lack of professional role models, insufficient time, and limited education [15]. Inadequate availability of surgical materials, such as caps, masks, and antiseptic solutions, was a widespread issue, as reported by those who also mentioned a shortage of personal protective gear [16]. The study identified a lack of training on SSI guidelines as a major hurdle, with 93% of nurses reporting no formal instruction in this area. This is similar to the findings of, those who discovered that educational gaps impede compliance [17, 18]. Furthermore, high nurse-to-patient ratios were regarded as a major issue, with 99% of nurses reporting staffing shortages. This finding is consistent with, those who exposed that high staffing levels can contribute to negative outcomes such as burnout and SSIs [19]. Another significant hurdle was the lack of a feedback system, which was reported by more than 95% of nurses as limiting their capacity to identify areas for development and reported similar conclusions, finding that inefficient feedback mechanisms impeded hospital performance improvement [20].

CONCLUSIONS

The study found moderate adherence to Surgical Site Infection (SSI) prevention guidelines among nurses, despite significant barriers like resource limitations, inadequate training, and staffing issues. Addressing these issues is crucial for improving patient outcomes and reducing infection rates. Regular training programs, stronger infection control protocols, and collaboration with the Pakistan Nursing Council are recommended.

Authors Contribution

Conceptualization: RA
Methodology: RA
Formal analysis: RA, SP, SY, MA
Writing, review and editing: RK, SY

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v5i11.2335

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2368

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

ABO and Rh Blood Group Distribution and Its Association with Hemoglobin Levels in Pregnant Women: A Study from Peshawar District

Nadra Jamil[1], Nayab Sarwar[2], Shaista Alam[3], Maida Khalid[4], Sara Jamil Khan[5] and Saira Nasr Malik[6*]

[1]Department of Obstetrics and Gynaecology, Mardan Medical Complex, Mardan, Pakistan
[2]Department of Pathology, Pak International Medical College, Peshawar, Pakistan
[3]Department of Microbiology/Pathology, Pak International Medical College, Peshawar, Pakistan
[4]Department of Pathology, Hayatabad Medical Complex, Peshawar, Pakistan
[5]Department of Obstetrics and Gynecology, Frontier Medical and Dental College, Abbottabad, Pakistan
[6]Department of Hematology, Khyber Medical College, Khyber Teaching Hospital, Peshawar, Pakistan

ARTICLE INFO

Keywords:
Anemia, Blood Group Distribution, ABO Blood Group, Rh Factor, Hemoglobin Levels

How to Cite:
Jamil, N., Sarwar, N., Alam, S., Khalid, M., Khan, S. J., & Malik, S. N. (2024). ABO and Rh Blood Group Distribution and Its Association with Hemoglobin Levels in Pregnant Women: A Study from Peshawar District: Blood Group Distribution in Pregnant Women. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2368

Corresponding Author:
Saira Nasr Malik
Department of Hematology, Khyber Medical College, Khyber Teaching Hospital, Peshawar, Pakistan
sairamalik87@gmail.com

Received Date: 27th September, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Anemia was a significant global health issue, leading to preterm birth, low weight at birth, and fetal malformations in pregnancy. Determination of blood group distribution and their relationship with anemia was essential for improving anemia management in pregnancy. **Objective:** To assess the distribution of the ABO blood group and Rh type of pregnant women and its relationship with the concentration of hemoglobin. **Methods:** A descriptive cross-sectional design study was conducted at a primary healthcare center in Peshawar from 1st January 2023 to 31st December 2023, enrolling 1049 pregnant women attending antenatal care. ABO and Rh typing were determined, and Hb levels were assayed to assess the presence of anemia in the participants. The data were analyzed using SPSS version 26.0. To examine the relationship between various blood group types and anemia, ANOVA and correlation analysis were employed. **Results:** B-type was the most prevalent blood group among the participants, about 358 (34.1%), followed by O 295 (28.1%), A 279 (26.6%), and AB about 117 (11.2%). The majority of participants, 972 (92.7%), were Rh-positive. Anemia was prevalent in 878 (83.7%) of participants, with 639 (60.9%) having mild anemia. Linear regression analysis indicated no significant impact of ABO blood group or Rh factor on hemoglobin levels ($p > 0.05$). **Conclusions:** In the current study, B-type was the most prevalent blood group among pregnant women, differing from previous reports of blood group O. However, no significant association was observed between blood group types and anemia, suggesting that other factors might play a more significant role in the prevalence of anemia.

INTRODUCTION

Anemia during pregnancy is a major public health concern that can lead to severe complications and negative outcomes for both the mother and the baby [1]. In pregnancy, anemia can result in serious maternal and fetal complications, potentially elevating the risk of maternal mortality [1, 2]. The main causes of anemia during pregnancy include nutritional deficiencies, parasitic infections, and acute blood loss [2]. Among the blood group systems, ABO and rhesus (Rh) antigen systems are fundamental in hematology and transfusion therapeutics [3]. Among the blood grouping systems, ABO and Rhesus are the most prominent and well-known in humans [4]. Approximately 1.93 billion people worldwide are currently affected by anemia [5]. Blood Group Distribution: Research in different populations indicated a predominance of blood group O, followed by groups A, B, and AB. In one study, group O was observed in about 59.1% of pregnant women, with group A at 19.1%, group B at 17.1%, and group AB at 4.8 [6]. The highest prevalence of anemia among pregnant women is observed in sub-Saharan Africa, with rates ranging from 38.9% to 48.7% [7]. The majority of pregnant women are Rh-positive (around 97.1%), while Rh-negative individuals

DOI: https://doi.org/10.54393/pjhs.v5i11.2368

constitute a smaller percentage (2.9%) [8]. Another study reported that type O was the most prevalent at 47.7% [4]. In Jordan, another study found that O-type was the commonest, about 38.9%, with 90.2% of the population being Rh positive and 9.8% Rh negative [9]. The ABO system plays a crucial role in blood therapeutics and transplantation, and studies have highlighted its involvement in various disorders, including DM, malignancy, and GI ulcers [3, 10]. The incidence of HDN varies widely, affecting 3–80/100,000 newborns annually, with rates differing across populations and ethnic groups, ranging from 7.2–14.3 per 10,000 births [11, 12]. A comprehensive understanding of blood type patterns is crucial for preventing and managing hemolytic disease of the newborn (HDN), ensuring adequate blood supplies in banks, and reducing neonatal and maternal morbidity and mortality associated with transfusions [11, 12]. Monitoring hemoglobin levels is equally essential, as anemia during pregnancy can lead to adverse maternal and fetal outcomes [5]. Despite the importance, there is a lack of data on blood type prevalence and hemoglobin concentrations in women attending antenatal care centers in the region. This knowledge gap can hinder effective maternal health interventions and blood management strategies.

Therefore, this present study was conducted to assess the prevalence of ABO and RhD typing and hemoglobin concentrations among women seeking antenatal care at a primary healthcare center in Peshawar.

METHODS

This descriptive cross-sectional study was conducted at a Primary Healthcare Center in District Peshawar, from 1st January to 31st December 2023. About 1,049 sample size was determined with a 99.9% confidence interval and a margin of error at 1%. This substantial sample size was determined based on expected outcome factor frequency of 41.1% and a population of 6,000,000 [12]. A non-probability convenient sampling technique was employed for the selection of study participants. The inclusion criteria for this present study consisted of pregnant women aged 18 years or older who provided written informed consent to participate. Participants were required to be attending the primary healthcare center in Peshawar during the study period and to have no history of blood transfusion within the past six months. Women were excluded from the study if they refused to give consent, had known blood disorders such as thalassemia, sickle cell disease, or other hematological conditions, or had received a blood transfusion within the last six months. All the participants meeting this current study inclusion criteria were enrolled in the study after approval from the Hospital Ethics Committee (Ref. No: 1042/HEC/B&PSC/2022). The confidentiality of the collected data was thoroughly maintained during the study. Blood samples were collected from all patients by antecubital venipuncture and transferred into EDTA anticoagulant tube. The blood samples were thoroughly mixed by placing on the rolling mixer. ABO and Rh blood typing were performed by forward agglutination methods with anti-A, anti-B, and anti-Rh antisera. Agglutination was observed when erythrocyte antigens reacted with the corresponding antibodies in the serum or plasma sample, then Reverse blood typing was done to confirm the blood type. A full blood count was conducted on the blood samples using the Ruby Cell-dyn Hematology Analyzer, and hemoglobin (Hb) levels were recorded for all participants. Anemia was identified in females with Hb levels below 12.5g/dL. Anemia was classified according to the National Cancer Institute's grading system as follows: hemoglobin levels between 10.0g/dL and the lower limit of normal were classified as having mild anemia. Those with hemoglobin levels between 8.0-10.0g/dL were categorized as having moderate anemia, and individuals with hemoglobin levels between 6.5-7.9g/dL were classified as having severe anemia [13]. The statistical analysis of the collected data, including the demographic and blood groups distribution, was performed using SPSS version 26.0. The distribution of blood group types was expressed as frequencies and percentages. Quantitative variables such as Hemoglobin concentration was summarized using Mean and SD. Tables and figures were used to illustrate the findings. ANOVA, Linear regression and Chi-square tests were employed to assess any relation between blood group types and prevalence of anemia.

RESULTS

The analysis of the ABO and Rh blood typing of the 1049 participants revealed that B-type was most common, observed in 358 (34.1%) of the participants, followed by blood group O, which was present in 295 (28.1%) of the women. Blood group A accounted for 279 (26.6%) of the sample, while the least common was blood group AB, found in 117 (11.2%) of the participants. Regarding the Rh factor, a significant majority of 972 (92.7%) were Rh-positive, with only 77 (7.3%) being Rh-negative (Figure 1).

DOI: https://doi.org/10.54393/pjhs.v5i11.2368

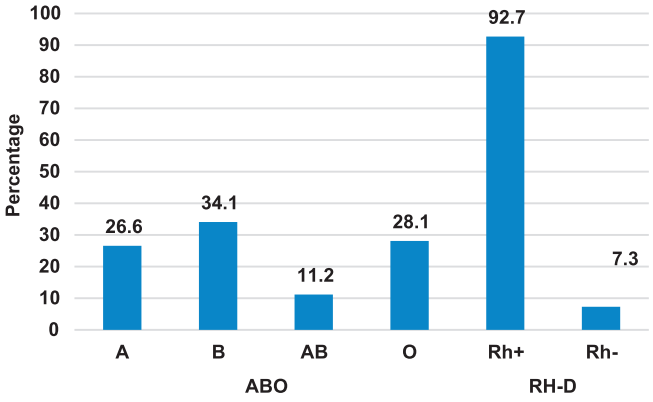

Figure 1: Prevalence of Different Blood Group Systems

The statistical analysis of the presence of RhD-Ag in each ABO blood groups distribution among the pregnant women reveals that the most prevalent was B+ about 322 (30.7%) of the participants. Blood groups O+ and A+ were equally prevalent, each accounting for 269 (25.6%). AB+ constituted 112 (10.7%) of the sample, and AB- was the least common, observed in only 5 (0.5%), as illustrated in figure 2.

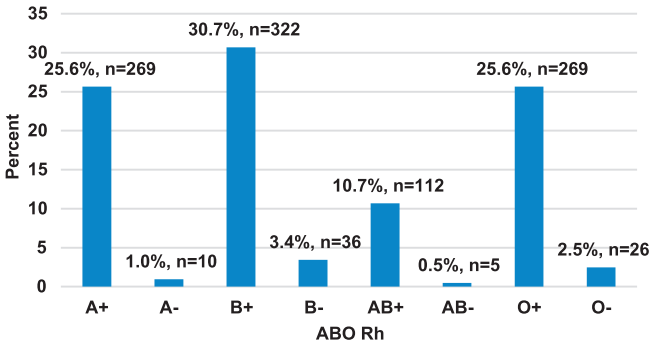

Figure 2: Prevalence of Rh-D Antigen in ABO Blood System

The mean Hgb level was 11.19 ± 1.61g/dL ranging from 6.0-16.6 g/dL. About 878 (83.7%) of the participants were found to be anemic, while 171 (16.3%) were non-anemic, as illustrated in figure 3. Within the anemic population, 639 (60.9%) had mild anemia. Moderate anemia was observed in 219 (20.9%) of the participants. While severe anemia was present in 20 (1.9%) of the women.

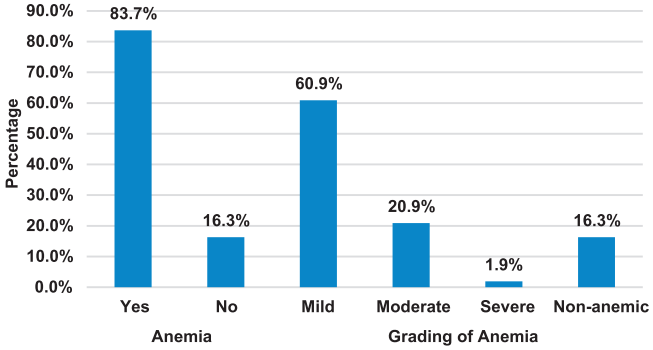

Figure 3: Prevalence and Grading of Anemia among Study Participants

To assess the impact of ABO blood group and Rh factor on hemoglobin (Hb) levels among participants, the linear regression analysis was performed. The model yielded an R-value of 0.052 and an R-squared value of 0.003, which indicated a very weak correlation and minimal explanatory power. The results of ANOVA showed an F-value of 1.396 with a p-value of 0.248, suggesting that the model was not statistically significant. Among the predictors, ABO had a coefficient of 0.071 (p=0.098), reflecting a marginal and non-significant effect, while Rh had a coefficient of -0.027 (p=0.889), indicating no significant impact on Hb levels. The overall analysis showed that ABO and Rh-D antigen did not significantly affect the hemoglobin levels in the study participants, as illustrated in figure 4.

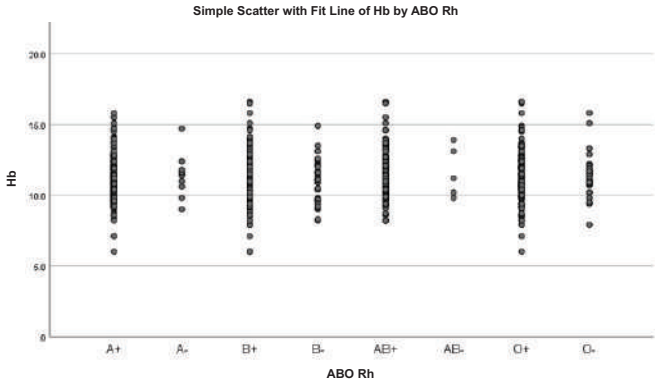

Figure 4: Scatterplot of Hb Levels by ABO and Rh Blood Groups

The crosstab analysis examined the link between ABO blood groups and Rh type with the prevalence of anemia, as shown in Table 1. The Chi-square test for ABO blood groups yielded a Pearson Chi-Square value of 9.743 with a p-value of 0.372, indicating no significant association between ABO blood group and anemia severity. The Chi-square test for Rh factor resulted in a Pearson Chi-Square value of 0.245 with a p-value of 0.970, suggesting no significant association between Rh status and anemia severity.

Table 1: Correlation of Anemia with Different Blood Group Systems

Blood Group System		N	Prevalence of Anemia					
			Mild	Moderate	Severe	Non-Anemic	Total	p-Values
ABO	A	279	176	61	4	38	279	0.372
	B	358	206	82	10	60	358	
	AB	117	71	22	0	24	117	
	O	295	186	54	6	49	295	
	Total		639	219	20	171	1049	
Rh	Negative	77	47	17	1	12	77	0.970
	Positive	972	592	202	19	159	972	
	Total		639	219	20	171	1049	

The crosstab analysis assessed the association between Rh-D antigen in each ABO blood groups with the severity of anemia among the participants, as presented in table 2. Evaluating the relationship between ABO and Rh type and

DOI: https://doi.org/10.54393/pjhs.v5i11.2368

anemia severity yielded a Pearson Chi-Square value of 15.934 with a p-value of 0.773. This result suggests that there was no relationship between the ABO and Rh type and the severity of anemia, as many cells had expected counts of less than 5.

Table 2: Association of Rh-D Antigen in ABO Blood type with Anemia

ABO	N	Rh type	Severity of Anemia					
			Mild	Moderate	Severe	Non-Anemic	Total	p-Values
A	279	Rh+	169	59	4	37	269	0.992
		Rh-	7	2	0	1	10	
B	358	Rh+	186	71	10	55	322	0.500
		Rh-	20	11	0	5	36	
AB	117	Rh+	69	21	0	22	112	0.512
		Rh-	2	1	0	2	5	
O	295	Rh+	168	51	5	45	269	0.712
		Rh-	18	3	1	4	26	

DISCUSSION

Current study findings explored the association of ABO and Rh blood types and Hb concentrations among participants. The statistical analysis showed that group B was the most common type (34.1%), followed by group O (28.1%), and AB was the least common (11.2%). A significant majority of the participants were Rh-positive, with 92.7% exhibiting the Rh-D antigen. Karami M *et al.*, reported a 36.8% anemia prevalence among pregnant women, classifying 70.8% of these cases as mild anemia. In contrast, the present study found a substantially higher anemia prevalence of 83.7%. Of these, 60.9% had mild anemia, 20.9% had moderate anemia and 1.9% had severe anemia [1]. In comparison, Nwauche CA *et al.*, reported an anemia prevalence of 93.1% among 1,000 pregnant women in Pakistan. This prevalence was notably higher than the present finding of 83.7% [14]. Liyew AM *et al.*, reported an occurrence of anemia of about 41.85% in pregnant women. Current study findings highlight a moderate level of anemia in their study population, which was much lower than the 83.7% observed in the current study [2]. Group B was reported in 35.96% of the population by Barot T *et al.*, and group AB was the least common at about 8.43%. Previous studies also found that 93.45% of individuals were Rh-positive, which was consistent with the high Rh-positive prevalence observed in the present study (92.7%) [15]. Akogu SP *et al.*, reported a higher prevalence of blood group B at 27.97% compared to other blood types, whereas the current study found an even greater prevalence of 34.1% [16]. Blood group O was reported at about 41.1% and 37.44% by Al-Kuran O *et al.*, and Chanko KP *et al.*, respectively [8, 12]. While present findings underscore a notable regional variation, with blood group B being the most common in the current study sample, contrasting with the predominance of blood group O in other studies. In comparison with Alemu M *et al.*, the current study observed a lower prevalence of blood group O at 28.1% compared to 41.5% reported by Megbaru. Conversely, the present study found a higher prevalence of blood group B at 34.1%, compared to 25% in Alemu M *et al.*, and a higher prevalence of blood group AB at 11.2%, compared to 5.5%. The prevalence of blood group A in the present study was 26.6%, which was similar to the 28% reported by Megbaru. Both studies reported similar frequencies for the Rh-D antigen, with 92.7% of women being RhD positive and 7.3% RhD negative [17]. About 28.0% of the anemic individuals in the current study belonged to blood group O, while Nwabuko O *et al.*, reported that 61.2% of individuals of O blood type were anemic, indicating a significantly higher incidence of anemia in this group compared to other ABO blood groups. Additionally, it was reported that O positive blood group was particularly prone to anemia by Nwabuko O *et al.* In contrast, the present study did not find a significant association between ABO blood types and anemia severity (p-value = 0.372). While a substantial percentage of the anemic population had blood group O, the anemic individuals with blood group O (28.0%) in the present study were notably lower than the 61.2% reported by Nwabuko O *et al.* This discrepancy suggests that while blood group O was more prevalent among the anemic in the study, it does not exhibit the same heightened susceptibility to anemia as observed by Nwabuko O *et al.* [18]. The individuals of group O had lower Hgb thresholds reported by Alemu M *et al.*, compared to other group types, suggesting that blood group O individuals might experience anemia at lower Hb levels. In contrast, the linear regression analysis in the present study showed no significant impact of the ABO blood group on hemoglobin concentrations [17]. Magtooph MG *et al.*, found no difference in Hgb levels between blood groups A, B, and AB, with p-values >0.05 [19]. However, they observed group O in women had much lower Hgb concentrations than other ABO groups (p-values of <0.029). While the linear regression analysis in the present study showed no significant relationship between ABO types and Hgb levels (R-squared = 0.003 and p-value = 0.248). Similarly, the current study found no significant variance in hemoglobin concentrations between ABO blood groups, in contrast to Kumar BA *et al.*, findings, which associated blood group O with lower hemoglobin thresholds [20]. Among thalassemia major patients, the B+ (positive) blood group was found more common in the district of Peshawar [20]. Biologically, blood group O has been associated with lower hemoglobin concentrations in previous studies, potentially due to increased susceptibility to gastrointestinal blood loss and iron deficiency [17]. However, the present findings did not support this association, as no significant relationship between ABO types and hemoglobin levels was observed in the current study (R-squared=0.003, p-

DOI: https://doi.org/10.54393/pjhs.v5i11.2368

value=0.248). This discrepancy could be due to differences in genetic background or environmental factors, such as nutritional status or access to healthcare. There were a few limitations to the present study: cross-sectional design and data from a single center, which cannot make causal inferences about the association between the prevalence of anemia and different blood types. Potential confounding factors such as age, dietary habits, and socioeconomic status were not accounted for, which could have influenced the observed associations. Selection bias may also have affected present results, as women attending antenatal care at the healthcare center may not represent the broader population of pregnant women in the region. Furthermore, data collection methods relied on self-reported information, which may introduce recall bias. Future studies should address these limitations by including multiple centers, controlling for confounding factors, and using longitudinal designs to clarify the relationship between blood groups and anemia. This would allow for more robust conclusions about the clinical and biological factors influencing anemia risk in pregnant women.

CONCLUSIONS

Present study provides valuable insights into the distribution of blood groups and their correlation with anemia among pregnant women attending antenatal care at a primary healthcare center in Peshawar. Present study found that blood group B was the most prevalent, differing from previous studies where group O was more common. While present findings were consistent with other studies regarding the high prevalence of Rh positivity, no significant association was observed between ABO/Rh blood groups and anemia prevalence. This suggests that blood group systems may not play a significant role in determining anemia risk. Instead, other factors such as nutritional status, genetic predisposition, and socioeconomic conditions may be more influential.

Authors Contribution

Conceptualization: NJ
Methodology: SJK
Formal analysis: NJ, NS, SA, MK
Writing, review and editing: NJ, NS, SA, MK, SJK, SNM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research,

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DOI: https://doi.org/10.54393/pjhs.v5i11.2139

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Clinical and Demographic Factors Associated with Preterm Labor in Twin Pregnancies at Mardan Medical Complex

Sumaira[1], Sumera Qayyum[2], Aimen Adil[3], Sadaf Sarwar[4*], Noushad Bibi[5] and Sara Jamil Khan[6]

[1]Department of Gynaecology, Mardan Medical Complex, Mardan, Pakistan
[2]Department of Gynaecology, Hayat Medical Complex, Mardan, Pakistan
[3]Department of Obstetrics and Gynaecology, Mercy Teaching Hospital, Peshawar Medical College, Peshawar, Pakistan
[4]Department of Gynaecology, Main Rashid Hussain Shaheed Memorial Hospital Pabbi, Nowshera, Pakistan
[5]Department of Gynaecology, District Headquarter Hospital, Swabi, Pakistan
[6]Department of Obstetrics and Gynaecology, Frontier Medical and Dental College, Abbottabad, Pakistan

ARTICLE INFO

Keywords:
Twin Pregnancies, Preterm Labor, Maternal Weight, Antenatal Care

How to Cite:
Sumaira, ., Qayyum, S., Adil, A., Sarwar, S., Bibi, N., & Khan, S. J. (2024). Clinical and Demographic Factors Associated with Preterm Labor in Twin Pregnancies at Mardan Medical Complex: Preterm Labor in Twin Pregnancies. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2139

***Corresponding Author:**
Sadaf Sarwar
Department of Gynaecology, Main Rashid Hussain Shaheed Memorial Hospital Pabbi, Nowshera, Pakistan
sadafturangzai@gmail.com

Received Date: 2nd October, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Twin pregnancies (TP) were often associated with preterm labor due to excessive dilation of the endometrium. Most twin pregnancies result in delivery before 37 weeks of gestation. In this study, which did not focus on cervical selection, the average pregnancy duration was 35.83 ± 8.7 weeks, with 50% of the babies delivered before 37 weeks. **Objective:** To figure out how frequently twin pregnancies that present at Mardan Medical Complex, Mardan, result in preterm labor. **Methods:** This descriptive case series was conducted over six months, from January 1st, 2022, to June 30th, 2022, in the Obstetrics and Gynaecology Department of Mardan Medical Complex. The study included 98 women pregnant with twins, and each was followed up until 36 weeks of pregnancy. Data analysis was performed using SPSS version 23.0. **Results:** There was a significant association between preterm labor and maternal weight. Women weighing 70 kg or less had a higher rate of preterm labor (55.7%) compared to those weighing more than 70 kg (35.1%) with a p-value of 0.048. Preterm labor occurred in 49.2% of women aged 18-30 years and 45.5% of those over 30 years (p=0.724). **Conclusions:** Maternal weight appears to be a key factor in the risk of preterm labor. Future studies should investigate the impact of weight on preterm labor and explore weight management interventions as part of antenatal care.

INTRODUCTION

During the past few years, the frequency of twin pregnancies has risen significantly due to the increasing incidence of older mothers and the widespread use of technologies for assisted reproduction [1, 2]. Twin gestations are becoming more common, which is a major medical and social issue that baffles doctors and patients alike. Preterm deliveries before 37 weeks were 8.13% for singles and 59.43% for twins, respectively [3]. This resulted in significant rates of perinatal illness and death in twins [4, 5]. Furthermore, compared to women carrying one child, women carrying twins are three times more likely to experience serious problems [6]. Since the majority of patients are conscious of the risks involved in having twins, they choose to increase their chances of having singles [7]. Although just 2% of conceptions end in multiples, twin pregnancies account for 15% of extremely preterm births (≤32 weeks). As a result, preventative strategies for preterm delivery are crucial to the administration of healthcare systems everywhere [8]. Because of excessive uterine dilation, twin pregnancies are linked to preterm; typically, twins deliver before the 37th week of gestation. In those who were not chosen by the cervix, the average duration of a pregnancy with twins was 35.83 ± 8.7 weeks, and 50% of the babies were delivered before 37 weeks [9].

DOI: https://doi.org/10.54393/pjhs.v5i11.2139

In addition to spontaneous preterm delivery, medical and obstetric conditions that cause preterm birth frequently compromise having multiple babies [10]. The risk of restricted intrauterine growth, fetal anomalies, hypertension, placental abruption, and fetal compromise increased with the total number of fetuses in a pregnancy [10]. According to an investigation by Gashi AM and colleagues, 47% of twin pregnancies resulted in preterm labor [11]. According to a study by Wagura P and colleagues, 6.8% of twin pregnancies resulted in preterm labor [12]. Like the majority of developing nations, Pakistan does not have adequate statistics on the prevalence of preterm delivery in twin pregnancies. International research findings vary, making it impossible to extrapolate findings to the broader community. For example, one study reported a 47% prevalence of preterm labor in twin pregnancies, while another found a 6.8% frequency [11, 12]. The precursor for this study arises from the realization of gaps in the knowledge of the cause of preterm labor, which is one of the leading causes of morbidity and mortality among neonates. Despite the studies, the significance of the demographic factors, including age, gestational age, parity, and weight, in preterm labor has not been established. Through analyzing these factors, this paper seeks to identify the extent of their contribution to the occurrence of preterm labor. Estimating influential variables like weight can help in the development of specific preventions and enhance patient care approaches. Consequently, this research aims to fill existing gaps in the available literature and inform the development of evidence-based interventions to prevent/pre-treat preterm labor and improve the well-being of mothers and newborns. Determining the prevalence of preterm labor in twin pregnancies was, thus, the goal of this research.

The study's findings will be useful in determining the true cost of this morbidity to the broader public.

METHODS

The outcomes of 98 women with multiple pregnancies were assessed in this comprehensive case series study, conducted at the Department of Obstetrics and Gynecology, Mardan Medical Complex, in Mardan from January 1st, to June 30th, 2022. The sample size of 98 was calculated by WHO sample calculator software using 95% confidence interval, 5% margin of error and anticipated frequency of preterm labor about 6.8% [13]. The sample size deemed sufficient to ensure the statistical power of the study and to capture significant associations between maternal characteristics and preterm labor. Participants were selected using non-probability sequential sampling based on the study's inclusion and exclusion criteria. Women between 18 to 40 years of age with a diagnosed twin pregnancy and a gestational age of less than 24 weeks based on their last menstrual period were included in the study. Eligible participants were recruited irrespective of their parity status. The exclusion criteria includes women with a history of smoking, those with pre-existing hypertension or pregnancy-related hypertensive disorders, women with a history of previous pregnancy loss, and participants who were lost to follow-up during the study period were also excluded. Written informed consent was obtained from all participants, who were fully briefed on the study's objectives, potential risks, and benefits. The consent form detailed the voluntary nature of participation, the right to withdraw at any time without repercussions, and assurances of confidentiality and data protection. Ethical approval was obtained from the ethics committee (No. 165/BKMC). Baseline demographic data, including weight, parity, age, and gestational age, were recorded. Clinical features relevant to preterm labor, such as uterine contractions, cervical dilatation, and effacement, were systematically monitored and documented throughout the study. A specifically designed proforma was used for recording these clinical features and instances of preterm labor, adhering to a predefined operational definition. Participants were followed up until they reached 36 weeks of gestation. Data analysis was performed using IBM SPSS software version 23.0. Quantitative variables like age, gestational age, parity, and weight were summarized using means and standard deviations, while categorical variables, such as age groups and cases of preterm labor, were presented as frequencies and percentages. The chi-square test was employed to assess the statistical significance of the association between preterm labor and variables like age, gestational age, parity, and weight. A p-value of < 0.05 considered statistically significant.

RESULTS

In a study involving 98 patients, the age range was between 18 and 40 years, with a mean age of 29.510 ± 2.40 years. The mean gestational age among these patients was 19.153 ± 2.26 weeks, and the mean parity was 1.632 ± 1.35. The average weight recorded was 68.581 ± 4.76 kg. Among the participants about 66.3% were within the 18-30 years' age group, while 33.7% were above 30 years. Preterm labor was observed in 48% of the patients, while 52% did not experience preterm labor (Table 1).

Table 1: Demographic Characteristics, Age Distribution, and Preterm Labor Frequency Among Patients (n=98)

Histopathological Findings		Mean ± SD
Continuous	Age (Years)	29.510 ± 2.40
	Gestational Age (Weeks)	19.153 ± 2.26
	Parity	1.632 ± 1.35
	Weight (Kg)	68.581 ± 4.76
Categorical		**N (%)**
Age Groups (Years)	18-30	65 (66.3%)
	>30	33 (33.7%)
	Total	98 (100%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2139

Preterm Labor	Yes	47(48%)
	No	51(52%)
	Total	98(100%)

Stratification of preterm labor was further analyzed concerning various demographic factors. When examining the relationship between age and preterm labor, it was found that 49.2% of patients aged 18-30 years and 45.5% of patients above 30 years experienced preterm labor. However, the difference was not statistically significant (p=0.724). Regarding gestational age, preterm labor was slightly more common in patients with a gestational age of less than 20 weeks (47.5%) compared to those with a gestational age of 20 weeks or more (48.7%). This difference was also not statistically significant (p=0.903) (Table 2).

Table 2: Stratification of Preterm Labor Concerning Age and Gestational Age(n=98)

Variables	Preterm Labor Yes N (%)	Preterm Labor No N (%)	p-Value
Age (Years)			
18-30	32(49.2%)	33(50.8%)	0.724
>30	15(45.5%)	18(54.5%)	
Total (Age)	47(48%)	51(52%)	-
Gestational Age (Weeks)			
<20	28(47.5%)	31(52.5%)	0.903
≥20	19(48.7%)	20(51.3%)	
Total (Gestational Age)	47(48%)	51(52%)	-

When stratified by parity, 50% of patients with parity between 0 and 2 experienced preterm labor, compared to 43.8% of those with parity greater than 2. This difference was not statistically significant (p=0.561). Finally, stratification by weight revealed a statistically significant relationship between weight and preterm labor. Patients weighing 70 kg or less had a higher incidence of preterm labor (55.7%) compared to those weighing more than 70 kg (35.1%), with a p-value of 0.048 (Table 3).

Table 3: Stratification of Preterm Labor Concerning Parity and Weight(n=98

Variables	Preterm Labor Yes N (%)	Preterm Labor No N (%)	p-Value
Age (Years)			
0-2	33(50%)	33(50%)	0.561
>2	14(43.8%)	18(56.2%)	
Total (Parity)	47(48%)	51(52%)	-
Gestational Age (Weeks)			
≤70	34(55.7%)	27(44.3%)	0.048
>70	13(35.1%)	24(64.9%)	
Total (Weight)	47(48%)	51(52%)	-

DISCUSSION

The findings of this study provide valuable insights into the prevalence of preterm labor in twin pregnancies in Pakistan. In this cohort, 48% of the women experienced preterm labor, a rate comparable to that found by Gashi AM *et al.*, where 47% of twin pregnancies led to preterm delivery [11]. This high incidence can be attributed to the unique physiological demands of twin gestations, which were often linked to premature births. This finding was higher than what Ngambwa T *et al.*, reported in their study, where only 6% of twin pregnancies resulted in preterm labor [12]. This discrepancy could stem from differences in study populations, healthcare systems, or research design. One of the significant findings in this study was the association between maternal weight and preterm labor. We found that women weighing 70 kg or less had a higher rate of preterm labor (55.7%) compared to those weighing over 70 kg (35.1%), with a statistically significant p-value of 0.048. This supports the hypothesis that maternal weight plays an important role in pregnancy outcomes, specifically in twin gestations. Future studies should explore weight management interventions as part of antenatal care to mitigate the risks of preterm labor. The findings regarding maternal weight and preterm labor were in line with previous studies. Similar associations have been documented in research focused on singleton pregnancies, where low maternal weight has been linked to a higher risk of preterm birth [13]. However, limited research exists on twin pregnancies, indicating a gap that needs further exploration. Regarding other factors like maternal age, this study did not find a statistically significant relationship between age and preterm labor (p = 0.724), a finding consistent with prior studies [14]. Besides preterm labor, this work also identified other severe pregnancy-related risks. We found that all the women in this study had hypertension during pregnancy, while a global percentage estimate of 8% to 10% was given by Beketie ED *et al.*, in 2021 study [14]. These consistencies show that these findings were relevant to the current state of affairs in the international maternal health study. Further, gestational diabetes was identified in 12 patients. We found a higher prevalence of gestational diabetes in women compared to 2% to 10% in the Zhu and colleagues study of 2022, among both singletons and multiple pregnancies [15]. The observed differences in study findings may be attributed to variations in diet, age, sex, and methodology, highlighting the need for further research. In the present study, most patients with a parity between 0 and 2 experienced preterm labor compared to those with a parity greater than 2. These findings align with the study by Kashani-Ligumsky L *et al.*, 2024, which found that women with high parity (more than 2 pregnancies) had a reduced risk of preterm birth compared to women with first-time pregnancies [16]. In our study, there was a significant association between weight and preterm labour. Our findings are consistent with a study conducted

DOI: https://doi.org/10.54393/pjhs.v5i11.2139

by Özçil MD., 2021 from Turkey who found that higher maternal weight increases the risk of preterm labor [17]. They also reported that the rate of preterm delivery is slightly higher in the primiparae and multiparae who have a history of ART (Assisted Reproductive Technology) pregnancies because of maternal complications and medical intervention. A study conducted in Nepal by Gurung *et al.*, 2020 also found that the rate of preterm birth was higher in women with primary pregnancies than in multiple pregnancies [18]. Another study by Szyszka M, *et al.*, 2023 from Poland also reported that over 50% of preterm deliveries were observed in primiparous women [19]. In contrast to our study findings, studies by Alhainiah *et al.*, 2018 from Saudi Arabia, Luo *et al.*, 2020 from China reported preterm birth to be more prevalent in multiparous women [20]. The high rate of preterm labor in twin pregnancies observed in this study has significant implications for maternal and neonatal health in Pakistan. The findings suggest that weight management and close monitoring of ART pregnancies should be integral parts of antenatal care in twin pregnancies. Moreover, this study emphasized the need for targeted interventions to prevent preterm labor, particularly in lower-weight women carrying twins. Despite the strengths of this study, several limitations must be considered. Future longitudinal studies with larger sample sizes were needed to confirm these associations and provide more generalizable results. Further research was necessary to explore these relationships in greater depth, especially in resource-limited settings where healthcare access may differ significantly from urban and developed areas.

CONCLUSIONS

The study revealed an exceptionally high frequency of preterm deliveries (48%) among twin pregnancies. These findings not only highlight the urgent need for targeted strategies to prevent and manage preterm labor in twin gestations but also serve as a critical foundation for further research on this subject in Pakistan. The data gathered from this investigation could contribute to the development of a population-based database for multiple pregnancies, which would be invaluable for both research and clinical applications. Such a resource could aid in the identification of risk factors and improve healthcare outcomes for women with twin pregnancies.

Authors Contribution

Conceptualization: NB
Methodology: NB, SS, S
Formal analysis: S, NB
Writing, review and editing: S, SQ, AA, SS, NB, SJK
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2201

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

The Association Between High Cholesterol Levels and Severity of Periodontitis

Rashid Javaid[1*], Sana Mukhtar[2], Ambreen Nawaz[3], Anila Errum[4], Bakhtawar Arslan[5] and Anum Fatima[6]

[1]Department of Oral Biology, De' Montmorency College of Dentistry, Lahore, Pakistan
[2]Department of Periodontology, Foundation University College, Lahore, Pakistan
[3]Department of General Pathology and Microbiology, Azra Naheed Dental College, Lahore, Pakistan
[4]Department of Pharmacology, Azra Naheed Dental College, Lahore, Pakistan
[5]Department of Prosthodontics, Liaquat Institute of Medical and Health Sciences, Thatta, Pakistan
[6]Department of Dentistry Surgeon, Islamabad Medical and Dental College, Islamabad, Pakistan

ARTICLE INFO

Keywords:
Periodontitis, Dyslipidemia, Triglycerides, Cardiovascular Disease

How to Cite:
Javaid, R., Mukhtar, S., Nawaz, A., Errum, A., Arslan, B., & Fatima, A. (2024). The Association Between High Cholesterol Levels and Severity of Periodontitis: High Cholesterol Levels and Severity of Periodontitis. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.201

Corresponding Author:
Rashid Javaid
Department of Oral Biology, De' Montmorency College of Dentistry, Lahore, Pakistan
rashidjavaid282@gmail.com

Received Date: 27th September, 2024
Acceptance Date: 24th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Periodontitis is a common inflammatory condition affecting tooth-supporting structures, leading to tooth loss and is linked to systemic diseases, including cardiovascular disease. **Objectives:** To examine the association between high cholesterol levels and periodontitis severity in a sample from Lahore, Pakistan. **Methods:** A cross-sectional study was conducted at De' Montmorency College of Dentistry, Lahore, over six months. A total of 154 participants aged ≥40 years with periodontitis symptoms and without any systemic diseases were included. Participants were grouped based on the severity of periodontal disease status into no periodontitis group, mild disease group, moderate disease group, and severe periodontitis. Blood samples were collected and analyzed for lipid profile parameters. Multivariable regression analyses were performed, adjusting for age, gender, BMI, smoking, alcohol use, and exercise, to evaluate associations between lipid levels and periodontitis severity. **Results:** Severe periodontitis was found in 58 participants (37.7%). Multivariable regression indicated an inversely associated link between high-density lipoprotein cholesterol in blood and disease severity ($p<0.05$). Lower total cholesterol and higher triglyceride levels were associated with severe periodontitis ($p<0.05$). Logistic regression showed that participants with severe periodontitis had significantly higher values of the odds ratio of decreased high-density lipoprotein cholesterol (OR 1.34, 95% CI 1.05–1.72), total cholesterol (OR 1.26, 95% CI 1.02–1.55), and triglyceride levels (OR 1.48, 95% CI 1.12–1.96). **Conclusions:** It was concluded that severe periodontitis is greatly linked with lower high-density lipoprotein cholesterol and elevated triglyceride and total cholesterol levels, suggesting that periodontal health may influence lipid profile and increase cardiovascular disease risk.

INTRODUCTION

Periodontitis is a localized inflammatory condition which may affect the structures that support the tooth, resulting in tooth loss by affecting the gingiva, bone, and periodontal ligament that support the teeth [1]. About 45–50% of adults have mild types of periodontitis, and that number rises to over 60% in those over 65 [2]. Severe periodontitis affects 11.2% of people worldwide and is reported to be the 6th most frequent disease in humans globally [3]. The prevalence of periodontitis in Pakistan has been estimated to vary across different provinces, with 37% reported in Punjab, 40% in Sindh, 20% in Khyber Pakhtunkhwa, and 3% in Baluchistan, based on a 95% confidence interval [4]. Research suggests that bacteria isolated from the subgingival swab of a periodontitis patient may enter the bloodstream and stimulate host cells, leading to the production of inflammatory mediators in distant body parts [5]. Periodontitis raises the chance of developing other systemic disorders [6, 7], including cardiovascular diseases (CVD) [8, 9]. CVD accounts for approximately one-third of all deaths worldwide, with around 17.8 million fatalities annually [10]. Since atherosclerosis is a major factor in CVD pathophysiology, high-density lipoprotein

DOI: https://doi.org/10.54393/pjhs.v5i11.2201

cholesterol (HDL-C) has been reported to be associated inversely with CVD development [11]. Its activity in increasing cholesterol outflow, endothelium restoration, angiogenesis, and preventing oxidative alteration of LDLs, inflammation of the vessels, and thrombosis has been linked to its potent anti-atherosclerotic actions [12]. Epidemiological studies on humans [13] and animals [14] indicate that elevated lipid levels contribute to periodontitis, though the exact mechanism linking periodontitis to atherosclerosis is unknown. Few studies from published literature have examined the correlation between lipid profiles and periodontitis after controlling for variables including health-related behaviours and demographic factors that may skew the results. Comprehensive investigations are necessary since there is a close link between HDL-C with periodontitis and variables such as BMI, alcohol consumption, and smoking habits [15]. Furthermore, many population studies have divided participants based on the condition that periodontitis exists or not, often ignoring disease severity, making it difficult to determine the full impact [16].

This study aims to assess if there is any association between elevated cholesterol levels with the severity of periodontitis in a sample population from the dental clinic at de' Montmorency College of Dentistry, Lahore, Pakistan.

METHODS

The research took place at De' Montmorency College of Dentistry, Lahore, over six months starting from October 2023 to March 2024, after approval from the institutional review board (Ref # 8105/DCD). Participants in this study were selected from the outpatient department for routine dental check-ups. A simple random sampling technique was used to recruit participants. The inclusion criteria required participants to be 40 years or older, with at least 10 remaining natural teeth and no systemic diseases (diabetes, cardiovascular disease, cancer, nephrosis, or hepatopathy). Additionally, participants must not have undergone systemic antibiotic treatment or periodontal treatment within the last three months. Exclusion criteria included individuals not following the inclusion criteria and/or unable or unwilling to complete the necessary examinations and provide blood samples. The number of samples was considered using the equation for comparing means among three groups, considering the expected differences in cholesterol levels between these groups. An expected mean difference of 0.5 mmol/L was estimated to ensure the accuracy of the sample size calculation. The sample size calculation aimed to detect a significant association with a significance value at ≤0.05 and 80% power. Based on this calculation, 42 participants per group were required. Accounting for a 20% dropout rate, the final sample size was increased to 51 participants per group, making a total sample size of 154. Periodontal examinations were conducted by experienced periodontists at de' Montmorency College of Dentistry, Lahore. The examinations involved assessing probing depth (PD) and clinical attachment loss (CAL) at multiple sites per tooth. The severity of periodontitis was categorized into no periodontitis, mild, moderate, and severe disease. The criteria for periodontitis severity were based on the American Academy of Periodontology (AAP) and Centers for Disease Control (CDC) guidelines [17] (Table 1).

Table 1: Criteria for Severity of Periodontitis

Periodontitis Severity	CAL	PD	Criteria
Severe Periodontitis	≥6 mm at ≥1 Interproximal Site	≥5 Mm at the Same Site with CAL ≥6 Mm Or Distinct Site(S)	Must Meet Both CAL and PD Criteria
Moderate Periodontitis	≥4 mm at ≥1 Interproximal Site	≥5 Mm at the Same Site Or Distinct Site(S)	Must Meet Either CAL Or PD Criteria
Mild Periodontitis	≥3 mm at ≥1 Interproximal Site	≥4 Mm at the Same Spot With CAL ≥3 Mm Or Distinct Site(S)	Must Meet Both CAL and PD Criteria
No Periodontitis	No Sites Meeting the Criteria for Mild, Moderate, Or Severe Periodontitis	-	Absence of Any of the Above Criteria

All the participants were informed about the study and written consent was taken. After collecting blood samples from eight-hour-fasted participants, biochemical analyses were performed. The serum lipid profile parameters included total cholesterol (TC), HDL-C, Low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). To account for potential confounding variables, additional covariates were evaluated alongside periodontal and biochemical tests. Participants completed questionnaires to provide information on age, gender, weight, height, alcohol consumption, exercise frequency, and smoking behaviour. BMI was calculated as weight (kg)/height (m^2). Alcohol consumption was categorized as never, rarely, frequently, or every day, exercise regularity as never, 1 to 3 times a week, 4 to 6 times a week, once per day, and more than once per day, and smoking habits as current smoker, former smoker, and non-smoker. Former smokers were those who had quit smoking for at least six months. Data were analyzed statistically with SPSS-25.0. The categorical type of data was presented as percentages, while continuous variables were expressed as means ± standard error. ANOVA was done for the continuous type of variables, while, chi-square was used to analyze categorical variables for the comparison of various factors across groups. The multivariate analysis between different parameters of lipid profile and periodontitis severity was determined using multiple linear regression models adjusted for gender, age, BMI, alcohol consumption,

DOI: https://doi.org/10.54393/pjhs.v5i11.2201

exercise frequency, and smoking behaviours. Logistic regression tests were conducted to investigate the relationship between abnormal lipid profile parameters and periodontitis severity. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were applied for the quantification of the strength of these correlations.

RESULTS

The analysis of the ABO and Rh blood typing of the 1049 participants revealed that B-type was most common, observed in 358 (34.1%) of the participants, followed by blood group O, which was present in 295 (28.1%) of the women. Blood group A accounted for 279 (26.6%) of the sample, while the least common was blood group AB, found in 117 (11.2%) of the participants. Regarding the Rh factor, a significant majority of 972 (92.7%) were Rh-positive, with only 77 (7.3%) being Rh-negative (Figure 1).

Table 2: Demographic Features and Covariates of Patients

Characteristic	No Periodontitis (n=20)	Mild/Moderate (n=76)	Severe. (n=58)	Overall. (n=154)	p-Value
Male Participants	8 (40.0%)	38 (50.0%)	29 (50.0%)	75 (48.7%)	0.344
Age (Years)	67.2 ± 4.1	68.9 ± 5.0	69.1 ± 5.2	68.5 ± 4.8	0.260
BMI (kg/m^2)	23.9 ± 3.1	24.5 ± 2.9	24.3 ± 3.2	24.3 ± 3.1	0.694
Exercise Frequency					
- Never	4 (20.0%)	24 (31.6%)	16 (27.6%)	44 (28.6%)	<0.001*
- 1–3 Times Per Week	1 (5.0%)	3 (3.9%)	3 (5.2%)	7 (4.5%)	
- 4–6 Times Per Week	1 (5.0%)	1 (1.3%)	0 (0.0%)	2 (1.3%)	
- Once Per Day	10 (50.0%)	38 (50.0%)	31 (53.4%)	79 (51.3%)	
- >1 Time Per Day	4 (20.0%)	10 (13.2%)	8 (13.8%)	22 (14.3%)	
Alcohol Use					
- Never	14 (70.0%)	52 (68.4%)	39 (67.2%)	105 (68.2%)	0.177
- Seldom	3 (15.0%)	5 (6.6%)	4 (6.9%)	12 (7.8%)	
- Often	0 (0.0%)	3 (3.9%)	3 (5.2%)	6 (3.9%)	
- Every day	3 (15.0%)	16 (21.1%)	12 (20.7%)	31 (20.1%)	
Smoking Habits					
- Current Smoker	2 (10.0%)	10 (13.2%)	8 (13.8%)	20 (13.0%)	0.287
- Former Smoker	1 (5.0%)	4 (5.3%)	3 (5.2%)	8 (5.2%)	
- Nonsmoker	17 (85.0%)	62 (81.6%)	47 (81.0%)	126 (81.8%)	

The unadjusted correlations between blood lipid markers and periodontitis severity are displayed. In individuals without the disease, mild or moderate disease condition, and severe disease, the mean value of HDL-C levels was 1.45 ± 0.35 mmol/L, 1.42 ± 0.340 mmol/L, and 1.38 ± 0.32 mmol/L, respectively. Significantly decreased HDL-C values were seen in participants with severe periodontitis ($p<0.05$). Additionally, compared to individuals with minimal or mild-to-moderate periodontitis, those with severe periodontitis had significantly higher levels of triglycerides (TG) and total cholesterol (TC) ($p<0.05$). There were no discernible variations in LDL-C values between the groups (Table 3).

Table 3: Serum Lipid Parameters by Periodontitis Severity

Lipid Parameter	No Periodontitis (n=20)	Mild/Moderate (n=76)	Severe (n=58)	p-Value
HDL-C (mmol/L)	1.45 ± 0.35	1.42 ± 0.340	1.38 ± 0.32	0.042*
Low-HDL-C (%)	4 (20.0%)	16 (21.1%)	13 (22.4%)	0.434
TC (mmol/L)	5.15 ± 1.30	5.45 ± 1.05	5.55 ± 1.03	0.038*
High-TC (%)	11 (55.0%)	37 (48.7%)	25 (43.1%)	0.297
TG (mmol/L)	1.59 ± 1.05	1.67 ± 0.90	1.69 ± 0.92	0.049*
High-TG (%)	7 (35.0%)	18 (31.0%)	22 (28.9%)	0.195

Higher total cholesterol and triglyceride levels were associated with increased severity of periodontitis, while HDL-C levels were inversely correlated. Specifically, each step, in periodontitis severity was linked to a significant rise in the value of total cholesterol ($p<0.05$) and triglyceride levels ($p<0.05$), and a reduction in the levels of HDL-C ($p<0.05$). LDL-C levels did not show any significant correlation. The multivariable linear regression analysis revealed the adjusted means and 95% confidence intervals for the lipid parameters stratified by periodontitis severity (Table 4).

Table 4: Multiple Linear Regression Analysis of HDL-C, TC, and TG Levels

Variable	HDL-C (p-Value)	TC (p-Value)	TG (p-Value)
Periodontitis	0.040*	0.034*	0.048*
Age	0.213	0.015*	0.022*
Gender	<0.01*	<0.01*	0.03*
BMI.	<0.01*	0.197	0.162
Alcohol usage	<0.01*	0.072	0.054
Exercise Regularity	0.459	0.947	0.634
Smoking Behaviors	0.124	0.121	0.145

To examine the odds ratios between clinically aberrant

DOI: https://doi.org/10.54393/pjhs.v5i11.2201

HDL-C, TC, and TG levels and the severity of periodontitis, a multivariate logistic regression model was built. Participants having severe periodontitis have substantially more chances to have aberrant TG levels (adjusted OR 1.48, 95% CI 1.12–1.96, p<0.05) and abnormal HDL-C levels (adjusted OR 1.34, 95% CI 1.05–1.72, p<0.05) after controlling for all other variables. A statistically significant result was also observed in the relationship between aberrant TC levels and severe periodontitis (adjusted OR 1.26, 95% CI 1.02–1.55; p<0.05) (Table 5).

Table 5: Regression Analysis of Clinically Abnormal Lipid Profile Levels and Severity of Periodontitis

Lipid Parameter	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)	p-Value
HDL-C	1.34 (1.05–1.72)	1.30 (1.03–1.68)	0.043*
Total Cholesterol	1.26 (1.02–1.55)	1.22 (1.01–1.52)	0.048*
Triglycerides	1.48 (1.12–1.96)	1.42 (1.08–1.90)	0.037*

Age, gender and BMI have been adjusted in model 1; BMI, alcohol consumption, age, exercise frequency, gender and smoking habits have been adjusted in the results shown for model 2; results are considered significant at ≤0.05

DISCUSSION

This study characterizes one of the first comprehensive investigations into the link between the severity level of periodontitis and various parameters of lipid profiles, specifically HDL-C, total cholesterol, and triglycerides, in a population-based study. Previous research has consistently linked aging with adverse lipid profiles, suggesting that changes in lipoprotein cholesterol absorption, synthesis, and metabolism occur through complex mechanisms as individuals age [18]. These changes predispose older adults to dyslipidemia, thereby increasing their susceptibility to cardiovascular disease (CVD) [19]. The findings of current research also indicated that severe periodontitis was linked significantly with the levels of various parameters of lipid profile. This verifies the clinical importance of monitoring lipid profiles in patients with periodontitis. Routine monitoring of lipid profiles in these patients may allow for timely management to alleviate the risk of systemic complications associated with both dyslipidemia and periodontitis. Some of the published studies have identified lower HDL-C levels among individuals with periodontitis [20] while some others have shown links between periodontitis and higher HDL-C levels [21]. These inconsistencies could be due to variations in research design, sampling technique and size, or the demographic features of the study population [22]. Moreover, the link between periodontitis and lipid profile parameters may be influenced by confounding factors such as gender, age, and genetic predispositions [21]. Several studies report a bidirectional relationship between periodontitis and lipid profile. The presence of periodontitis may inversely influence serum lipid profile, contributing to dyslipidemia [23]. Conversely, low HDL-C levels may increase periodontitis and vice versa [24]. The protective effects of hyperlipidemia treatment of periodontal health further support this bidirectional relationship [25]. Using full-mouth periodontal examinations (FMPE), the "gold standard" for assessing periodontal health, is one of our study's strengths [26]. However, the resource-intensive nature of FMPEs and their potential to cause fatigue for both participants and clinicians should be considered when designing such studies. Despite these challenges, FMPEs offer high accuracy and thoroughness, enhancing the validity of findings related to the link between periodontitis and lipid profiles [27]. We acknowledge some limitations to our study. Being cross-sectional, it limits the ability to establish a causal relationship between periodontitis severity and abnormal lipid levels. Additionally, as the study was carried out on a specific population, the findings might not be generalized to other population groups. Future large-scale, longitudinal studies with a detailed examination of confounding factors are needed to explore the underlying mechanisms of the association between periodontal disease and lipid profile more deeply.

CONCLUSIONS

It was concluded that the results of this research show a significant relationship between severe periodontitis with dyslipidemia. This justifies the clinical inferences for managing lipid profiles in patients with periodontitis and highlights the need for more research to investigate possible therapeutic interventions.

Authors Contribution

Conceptualization: RJ
Methodology: RJ, SM, AN, AE, BA
Formal analysis: SM, AF
Writing review and editing: RJ, AE, AF

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research,

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DOI: https://doi.org/10.54393/pjhs.v5i11.2181

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Frequency of Malignancy in Retrosternal Multinodular Goiter

Faridullah Khan Ismail[1], Abdul Baseer[1*], Muhammad Abid Khan[1], Asif Ahmad[1] and Muhammad Imran[1]

[1]Department of Thoracic Surgery, Medical Teaching Institute, Lady Reading Hospital, Peshawar, Pakistan

ARTICLE INFO

Keywords:
Retrosternal Multinodular Goiter, Thyroidectomy, Thyroid Malignancy, Carcinoma Thyroid

How to Cite:
Ismail, F. K., Baseer, A., Khan, M. A., Ahmad, A., & Imran, M. (2024). Frequency of Malignancy in Retrosternal Multinodular Goiter: Malignancy in Multinodular Goiter. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2181

***Corresponding Author:**
Abdul Baseer
Department of Thoracic Surgery, Medical Teaching Institute, Lady Reading Hospital, Peshawar, Pakistan
drbaseer782@gmail.com

Received Date: 26th September, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Retrosternal Multinodular Goiter (MNG) was a condition often associated with benign thyroid disease, but it may harbor undetected malignancies. Accurate diagnosis was essential to avoid complications during and after surgery. **Objective:** To determine the frequency of malignancy in patients undergoing total thyroidectomy for retrosternal multinodular goiter. **Methods:** This retrospective observational study included data of 80 patients, aged 40 years or more who underwent total thyroidectomy for retrosternal multinodular goiter. Data of patients with smoking history, recurrent goiter, previous neck surgeries, solitary nodules, metastatic lymphadenopathy, Graves' disease, known carcinoma thyroid, or associated carcinoma of other organs were excluded. Thyroidectomy was performed via cervical incision, with or without sternotomy. Histopathological examination of the excised thyroid tissue was conducted. Data were analyzed using SPSS version 25.0. The quantitative variables were shown in tables as mean ± standard error, and qualitative data as frequency (percentage); N (%). **Results:** According to the results, 14 (17.5%) patients were aged 40-50 years, 47 (58.75%) were aged 51-60 years, and 19 (23.75%) were aged 61-70 years. Histopathological examination revealed thyroid malignancy in 10% of the cases. **Conclusion:** A notable percentage of patients with retrosternal multinodular goiter were found to have malignancy that was not detected in preoperative investigations.

INTRODUCTION

Thyroid enlargement is a slow process with gradual development of symptoms of secondary hormonal dysfunction, obvious neck swelling, and pressure symptoms. The most common symptoms are shortness of breath, discomfort during sleep, swallowing difficulty, and hoarseness of voice, which are caused by esophageal and tracheal compression [1]. Worldwide, about 500 to 600 million people are affected by multinodular goitre, which is one of the most common endocrine diseases [2]. Retrosternal goiter is defined as an enlargement of the thyroid gland that extends below the sternal notch [3]. Clinically, a goiter is considered retrosternal if the lower border of the thyroid is not palpable when the neck is fully extended [4]. Approximately 20% of patients undergoing thyroidectomy have retrosternal extension. It is slowly progressive and commonly presents after the fifth decade of life [5]. The reported rate of retrosternal goiter varies between 5% to 22% due to differences in the definition of retrosternal goiter [6]. These are typically found in the anterior mediastinum, with rare cases occurring in the posterior mediastinum, which is an important consideration for surgical planning [7]. Due to its slow growth, it often remains asymptomatic and is frequently an incidental finding on radiological investigations [8, 9]. Relevant clinical history, physical examination, and radiological investigations are used as diagnostic tools for retrosternal goiter [10, 11]. Retrosternal and primary intrathoracic goiter are considered two separate entities based on their blood supply. Primary intrathoracic goiters receive their blood supply directly from thoracic vessels and the aorta, with no connection to the thyroid gland in the neck [12]. Recent studies indicate that malignant transformation may occur in long-standing multinodular goiter, with rates varying from 3% to 35% [13]. The mainstay treatment of retrosternal multinodular goiter is surgery through Kocher's neck incision, with sternotomy

DOI: https://doi.org/10.54393/pjhs.v5i11.2181

required in only 1-11% of cases [14]. It is widely acknowledged that a key environmental factor for an increase in thyroid nodules is iodine deficiency. Thyroid enlargement was discovered in 15.0% and 22.6% of the ultrasonographic exams in Denmark's mildly and moderately iodine-deficient regions, respectively. In 30% of the examinations in both locations, thyroid nodules were observed; however, in areas with significant iodine deficiency, nodules were larger and more frequently palpable. In a study, 9.8% of people with mild iodine deficiency and 14.6% of those with significant iodine deficiency had palpable goiters[15].

Previous research on Multinodular Goiter (MNG) suggests that malignancies in these goiters may often be overlooked during preoperative evaluations [8]. Despite advancements in diagnostic imaging techniques, identifying malignant transformations within retrosternal MNG remains a challenge, potentially leading to inadequate surgical planning and outcomes [11]. Given the prevalence of retrosternal MNG and its association with thyroid malignancies, particularly in various populations, it is essential to examine the incidence of malignancy in this condition.

The current study aimed to fill a gap in the literature by providing updated and region-specific data on the frequency of malignancy in patients undergoing total thyroidectomy for retrosternal MNG in Peshawar, Pakistan and to compare the clinical and pathological features between benign and malignant type of retrosternal MNG in these patients.

METHODS

This retrospective study was conducted using hospital medical records from 1st July 2022 to 30th June 2023 at the Medical Teaching Institution Lady Reading Hospital, Peshawar. A non-probability consecutive sampling technique was employed to select patients. Data of 80 patients aged 40 to 70 years were included in the study, as retrosternal goiter commonly presents in later decades of life. The study was approved by the Institutional Review Board (IRB) of Medical Teaching Institution Lady Reading Hospital, Peshawar (288/LRH/MTI). Patients were excluded if their records indicated a history of neck irradiation, recurrent goiter, a family history of thyroid cancer, evidence of malignancy, or suspicion of malignancy based on preoperative Fine-Needle Aspiration Cytology (FNAC). Records with incomplete medical histories or missing laboratory data were also excluded. Data from medical records were analyzed, including preoperative and postoperative clinical, biochemical, radiological, and pathological findings. Information retrieved from the records included surgical procedures performed, early postoperative complications, thyroid scintigraphy results, thyroid hormone profiles, thyroid Ultrasonography (US) findings, FNAC results, and histological diagnoses. Based on the final histological analysis of the surgical specimens, participants were categorized into two groups: Group A included patients with benign diagnoses, and Group B consisted of those with malignant diagnoses. Statistical analysis was performed using Version 25.0 of the Statistical Package for Social Sciences (SPSS). Descriptive statistics such as percentages and frequencies were used for categorical variables. Fisher's exact test was employed to assess associations between qualitative variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

This study consisted of 80 patients who underwent thyroidectomy for retrosternal multinodular goiter without known malignancy. All patients underwent comprehensive preoperative and postoperative evaluations, which included clinical, biochemical, radiological and histopathological studies. The mean age of the patients was 56.11 ± 7.53 years, with an age range of 40 to 70 years. The majority of the patients were females (60%, 48 patients), while 32(40%) patients were males. Age distribution analysis revealed that 14(17.5%) patients were in the 40-50 years age range, 47(58.75%) patients were in the 51-60 years age range, and 19(23.75%) patients were in the 61-70 years age range. The mean BMI of the patients was 26.13 kg/m^2, (Table 1).

Table 1: Demographic characteristics of study participants

Gender	N (%)/(Mean ± SD)
Men	32 (40%)
Female	48 (60%)
Age (Years)	
40-50	149 (17.5%)
51-60	47 (58.75%)
61-70	19 (23.75%)
Age	56.11 ± 7.53
BMI (Kg/m^2)	26.13 ± 2.02

All patients came with a complaint of thyroid swelling. Among them, 50(66.6%) patients had dyspnea, 14.4 % (15 patients) were asymptomatic, 10(12.5%) patients had painful swelling and 5(6.3%) patients experienced dysphagia. Six patients required median sternotomy, while 74 patients were operated through a cervical neck incision. The duration of stay for these patients was 3 ± 1 days, and follow-up was conducted for up to 6 ± 3 months (Table 2).

Table 2: Symptoms, Signs, and Surgical Details of study participants

Abnormal	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
Swelling	80 (100.0%)	72 (100.0%)	8 (100.0%)	1.000
Swelling with Dyspnea	50 (66.6%)	45 (62.5%)	5 (62.5%)	1.000
Swelling with No Symptoms	15 (18.8%)	15 (20.8%)	0 (0.0%)	0.332
Swelling with Pain	10 (12.5%)	8 (11.1%)	2 (25.0%)	0.286

DOI: https://doi.org/10.54393/pjhs.v5i11.2181

Swelling with Dysphagia	5 (6.3%)	4 (5.5%)	1 (12.5%)	0.415
Median Sternotomy	6 (7.5%)	4 (5.5%)	2 (25.0%)	0.048*
Cervical Neck Incision	74 (92.5%)	68 (94.4%)	6 (75.0%)	0.048*
Hospital Stay (Mean ± SD)	3 ± 1 Days	3 ± 1 Days	4 ± 1 Days	0.031*
Follow-up Duration (Mean ± SD)	6 ± 3 Months	6 ± 3 Months	6 ± 2 Months	0.715

(*P < 0.05 indicates statistical significance).

Figure 1 presented frequency of malignancy.

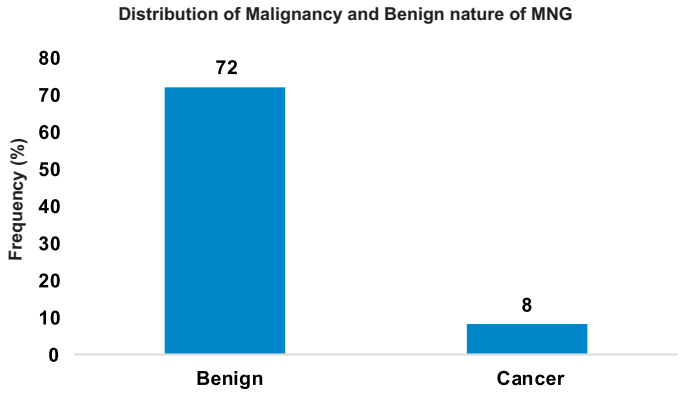

Figure 1: Frequency of Malignancy among Study Participants

Histopathological examination revealed that 10% (8 patients) had thyroid malignancy, while 90% (72 patients) were diagnosed with benign thyroid disease. Among the malignancy, 6.25% was papillary, 2.5% Follicular and 1.25% was undifferentiated thyroid malignancy (Table 3).

Table 3: Post-Operative Diagnosis Based On Histopathology

Diagnosis	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
Colloid Goiter	72 (90.0%)	72 (100.0%)	0 (0.0%)	<0.001*
Papillary Carcinoma	5 (6.25%)	0 (0.0%)	5 (62.5%)	<0.001*
Follicular Carcinoma	2 (2.5%)	0 (0.0%)	2 (25.0%)	<0.001*
Undifferentiated Thyroid Malignancy	2 (2.5%)	0 (0.0%)	2 (25.0%)	<0.001*

(*P < 0.05 indicates statistical significance).

Regarding postoperative complications, only 1 patient (1.25%) developed postoperative hoarseness, which resolved by the second postoperative month, with normal vocal cord movements observed on a laryngoscopy examination. Two patients (2.5%) experienced secondary hemorrhage, and 3 patients (3.75%) developed a surgical site infection, which was treated with antibiotics (Table 4).

Table 4: Post-Operative Complications

Complications	Total (N = 80)	Benign (Group A, N = 72)	Malignant (Group B, N = 8)	p-Value
No Complications	73 (91.2%)	69 (95.8%)	4 (50.0%)	<0.001*
Hemorrhage	2 (2.5%)	1 (1.4%)	1 (12.5%)	0.126
Infection	3 (3.75%)	2 (2.8%)	1 (12.5%)	0.214
Recurrent Laryngeal Nerve Injury	1 (1.25%)	0 (0.0%)	1 (12.5%)	0.048*
Recurrence	1 (1.25%)	0 (0.0%)	1 (12.5%)	0.214

(*P < 0.05 indicates statistical significance).

There were 12.5% of the males and 87.5% of the females in the thyroid cancer group, whereas benign group had16.7% of the males and 83.3% of the females. In this comparison, the P-value was 1.00, meaning that there was no discernible change in the distribution of sexes between the two groups. Age distribution analysis showed that the highest incidence of thyroid cancer occurred in patients aged 40-50 years (37.5%), while the highest incidence in the benign group was among those aged 51-60 years (50%) (Table 5).

Table 5: Comparison of Sex and Age in Patients with and without Thyroid Malignancy (n=80)

Variables	Benign Group N (%)	Cancer Group N (%)	p-Value
Sex			
Male	12 (16.7%)	1 (12.5%)	1.00
Female	60 (83.3%)	7 (87.5%)	
Age (Years)			
40-50	11 (15.28%)	3 (37.5%)	0.368
51-60	36 (50%)	3 (37.5%)	
61-70	25 (34.72%)	2 (25.0%)	

All patients with thyroid malignancy presented with neck swelling, with some cases showing additional symptoms such as dyspnea (37.5%) or dysphagia (12.5%). Notably, swelling without any additional symptoms was significantly more common in the benign group (P=0.012). Multinodular goiter was predominantly seen in the benign group (94.4%), whereas solitary thyroid nodules were equally distributed between benign (5.6%) and cancer groups (50%) (P=0.001), highlighting a potential diagnostic marker. Post-operative complications were more in thyroid malignant cases as compared to benign cases (Table 6).

Table 6: Comparing the Signs/Symptoms, Diagnosis and Postoperative Complications of Patients with and without Thyroid Malignancy (n=80)

Symptom/Sign	Benign Group N (%)	Cancer Group N (%)	p-Value
Swelling with No Symptoms	25 (34.72%)	0 (0%)	0.012
Swelling with Dyspnea	33 (45.8%)	3 (37.5%)	
Swelling with Pain	10 (13.9%)	0 (0%)	
Swelling with Dysphagia	4 (5.6%)	5 (62.5%)	
Diagnosis			
Multinodular Goiter	68 (94.4%)	4 (50%)	0.001
Solitary Thyroid Nodule	4 (5.6%)	4 (50%)	

DOI: https://doi.org/10.54393/pjhs.v5i11.2181

Postoperative Complications			
Recurrent Laryngeal Nerve	0 (0%)	1 (14.29%)	0.02
Hemorrhage	0 (0%)	2 (28.57%)	
Recurrence	0 (0%)	1 (14.29%)	
Infection	1 (14.29%)	2 (28.57%)	

DISCUSSION

Enlargement of the thyroid gland evident as neck swelling was defined as goiter, which in most cases was multinodular [15]. Goiter can extend through the thoracic inlet and pass into the mediastinum, known as substernal or retrosternal thyroid gland extension. Substernal goiter may be primary or secondary [16]. The secondary type of substernal goiter originates from the cervical region and descends into the mediastinum due to the effects of negative intrathoracic pressure and gravity [17]. Primary STG, which was extremely rare, accounting for approximately 1% of all cases, arises from aberrant thyroid tissue within the mediastinum and receives its blood supply from the mediastinal vessels, as opposed to the normal superior and inferior thyroid arteries [18, 19]. The incidence of retrosternal goiter varies from 2% to 20%, largely due to the lack of a standardized definition of retrosternal goiter [20]. Surgery was the mainstay treatment in most cases of retrosternal goiter, particularly due to symptoms of airway compression. In the majority of retrosternal goiter cases, total thyroidectomy was performed. Some of the postoperative complications include transient symptomatic hypoparathyroidism, hematoma, wound infection, pneumonia, and transient laryngeal nerve paresis [21]. Thyroid cancer accounts for approximately 1% of all human cancers and was the most common endocrine malignancy. Risk factors for thyroid malignancy include female sex, exposure to ionizing radiation, and a family history of endocrine malignancy [22]. The primary objective of this study was to evaluate the postoperative outcomes and incidence of thyroid malignancy in patients undergoing thyroidectomy for retrosternal multinodular goiter. This results revealed that 10% of patients had thyroid malignancy, while 90% were diagnosed with benign thyroid disease. These findings highlight the importance of histopathological examination in retrosternal goiter cases, especially given the limitations of Fine-Needle Aspiration (FNA) in obtaining accurate samples from substernal tissue. In line with previous studies, this study demonstrated a higher prevalence of retrosternal goiter among females, with 60% of the total cases being female patients. This gender distribution was consistent with the known increased risk of thyroid diseases in females [21]. The mean age of 56.11 years in this cohort was also comparable to other studies, which report a mean age of around 50 to 60 years for patients with retrosternal goiter [23]. The results of this study show that dyspnea was present in 66.6% of patients, which reflects findings in other studies where respiratory symptoms were the most common clinical presentation of retrosternal goiter [21]. Previous research by Abdelrahman H *et al.*, who reported a malignancy rate of 10% in patients undergoing thyroid surgery for benign disease [24]. The malignancy rate in this cohort (10%) supports the concept that retrosternal goiters may have malignancies that were not easily detectable preoperatively through FNA. Thyroid cancer incidence ranged from 3 to 23% in a systematic evaluation of individuals with retrosternal goiter having thyroidectomy [25]. Patients with a single nodule and those with several nodules had similar rates of malignancy. Of the 90 patients with numerous nodules, 8 had cancer (8.9%), while 4 of the 60 patients with solitary nodules (6.7%) had cancer [26]. According to Di Crescenzo V *et al.*, cancer was found in 7 out of 97 cases of retrosternal goiter (7.6%) [27]. Another study found that there were no significant differences in the frequencies of malignancy across the groups, however papillary carcinoma was diagnosed in 76 out of 390 patients (19%) with retrosternal goiter and 200 out of 880 patients (22%, control group) with benign multinodular goiter [28]. Regarding postoperative complications, we observed a low incidence of recurrent laryngeal nerve injury (1.25%) and transient hypocalcemia (8.3%), with these complications being more frequent in the malignancy group (P=0.04 and P=0.03, respectively). This was consistent with existing literature, which indicates that more complex surgeries, such as those for malignant goiters, were linked with an increased risk of complications [21]. Additionally, the rate of wound infection (3.75%) and secondary hemorrhage (2.5%) was low, similar to the complication rates described in previous literature [23]. The higher incidence of solitary thyroid nodules in cancer patients (50% vs. 5.6% in the benign group) could be a useful diagnostic marker, as the presence of a solitary nodule was more commonly associated with malignancy [21].

CONCLUSIONS

There was a risk of malignancy in longstanding multinodular retrosternal goiter, which requires proper and timely workup, in order to devise appropriate management strategies for these patients and to prevent complications secondary to carcinoma. Further studies with larger sample size were required to further strengthen the findings of this study and to know about the actual burden of disease.

DOI: https://doi.org/10.54393/pjhs.v5i11.2181

Authors Contribution

Conceptualization: FKI
Methodology: FKI, AA
Formal analysis: MAK, MI
Writing, review and editing: AB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2233

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Comparative Evaluation of Lipid Profile and C-Reactive Protein in Chronic Periodontitis and Coronary Heart Disease

Afsheen Zehra[1*], Farzeen Tanwir[2], Sana Barkat Ali[3], Hasan Ali[1], Ali Nawaz Khan[4] and Allah Bakhsh[5]

[1]Department of Biochemistry, Bahria University Health Sciences, Karachi, Pakistan
[2]Department of Periodontology, Bahria University Health Sciences, Karachi, Pakistan
[3]Department of Physiology, Bahria University Health Sciences, Karachi, Pakistan
[4]Department of Cardiology, Armed Forces Post Graduate Medical Institute, Rawalpindi, Pakistan
[5]Department of Health, Tehsil Headquater Hospital Usta Mohammad, Balochistan, Pakistan

ARTICLE INFO

Keywords:
Chronic Periodontitis, Coronary Heart Disease, C-Reactive Protein, Lipid Profile, Systemic Inflammation

How to Cite:
Zehra, A., Tanwir, F., Ali, S. B., Ali, H., Khan, A. N., & Bakhsh, A. (2024). Comparative Evaluation of Lipid Profile and C-Reactive Protein in Chronic Periodontitis and Coronary Heart Disease: Lipid Profile and C-Reactive Protein in Periodontitis and Heart Disease. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2233

***Corresponding Author:**
Afsheen Zehra
Department of Biochemistry, Bahria University Health Sciences, Karachi, Pakistan
afsheenzehra.bumdc@bahria.edu.pk

Received Date: 26th September, 2024
Acceptance Date: 24th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Epidemiological studies suggest local infections may elevate systemic inflammatory mediators and lipid levels, potentially promoting atherosclerosis. **Objective:** To investigate the correlation between Chronic Periodontitis (CP) and Coronary Heart Disease (CHD), assessing C-Reactive Protein (CRP) and lipid profile alterations in affected patients. **Methods:** This case-control study included 88 participants, divided into four groups: 22 with Chronic Periodontitis (CP), 22 with Coronary Heart Disease (CHD), 22 with both CP and CHD and 22 systemically healthy controls, aged 30-60 years, selected through consecutive sampling. Conducted at Bahria University Health Sciences and PNS Shifa Hospital from December 2022 to May 2023, the study assessed clinical and periodontal parameters, including probing depth and clinical attachment level. Fasting blood samples were analyzed for lipid profiles and C-Reactive Protein Levels. Statistical analysis included the Pearson Chi-square test for baseline demographics, the Kruskal-Wallis test for comparing biochemical and periodontal parameters, and the Spearman Rank Correlation. **Results:** Serum HsCRP levels were twice higher in participants with CP and CHD than in healthy individuals and three times higher in subjects with combined disorder (CP + CHD). Patients with both CP and CHD (CP + CHD) have the highest median CRP levels. C-reactive protein was negatively correlated with TC, LDL-C, HDL-C, and number of teeth, while positive correlations were demonstrated with PD, CAL, BoP%, and PI scores. **Conclusion:** Coronary heart disease and other inflammation driven atherosclerotic processes may be exacerbated by chronic infections, such as periodontitis, which can alter systemic levels of TC, HDL, LDL, and CRP.

INTRODUCTION

Periodontitis is a persistent inflammatory condition caused by complex interactions among the oral dysregulated microbes, the host's immunological-inflammatory mechanisms, and a wide range of genetic, behavioural and environmental risk indicators [1]. These interactions lead to permanent damage to the structures of periodontium and loss of tooth. The incidence of periodontitis, particularly its moderate and mild variants, is far higher in adult populations worldwide, with rates of occurrence about 50% [2]. According to the outcomes of the Global Burden of Disease Study carried out in 2019, the worldwide count of periodontal disease cases reached more than one billion, with roughly 91.5 million new occurrences and 7.1 million DALYs recorded in 2019 [3]. Nationally, periodontal disease is estimated to affect approximately 58.4% of Pakistan's population [4]. Coronary Heart Disease (CHD), commonly referred to as Coronary Artery Disease (CAD), is a condition characterized by obstruction of blood vessels (coronary arteries), leading to decreased blood circulation to the heart. It is a gradual disorder that can develop over many years and frequently results from atherosclerosis, a process whereby fatty deposits (plaque) are formed in the coronary arteries [5]. According to the Global Burden of Diseases study, there were 523 million cases of CVDs around the world in 2019. CVD fatalities have risen steadily from 12.1 million individuals in 1990 to an estimated 18.6 million in 2019 [6]. Pakistan has a higher prevalence rate of Coronary Artery

DOI: https://doi.org/10.54393/pjhs.v5i11.2233

Disease (CAD) which represents more than 30% of the national population (above 45 years old) being affected by the disease [7]. Epidemiological studies have investigated the correlation between periodontal health and cardiovascular disease. Numerous theories exist about the impact of periodontitis on atherosclerotic plaque development. The influence of pathogenic microbes from biofilm pockets can be categorized into three distinct pathways: bacteremia, dispersion of locally generated inflammatory mediators, and the beginning of an autoimmune response. Periodontitis is a persistent, chronic source of inflammatory mediators, including cytokines and lipopolysaccharides, which might give rise to atherosclerosis. Moreover, the pathogens responsible for periodontitis can breach the periodontal epithelium and infiltrate the bloodstream, resulting in localized atherogenic consequences [8, 9]. There is growing interest in the probable connection between periodontitis and coronary heart disease as measured by C-Reactive Protein (CRP), a widely recognized systemic inflammation indicator. CRP is an inflammatory marker and potential mediator in the pathophysiology of atherosclerosis; it has a long history of association with an increased likelihood of cardiovascular incidents [10]. Another key factor in the development of plaques characterized by atherosclerosis is dyslipidemia, which is defined by dysregulated lipid profiles which include elevated levels of Low-Density Lipoprotein (LDL) cholesterol and reduced levels of High-Density Lipoprotein (HDL) cholesterol [11]. Foam cells filled with lipids and cholesterol form in the endothelium lumen as a consequence of the disruption of Low-Density Lipoprotein (LDL) distribution brought about by the enhanced oxidation seen in CHD and periodontitis. Atherosclerosis and endothelial dysfunction are the ensuing consequences of this mechanism. This may represent the most likely pathway connecting the two diseases [12]. The investigation of the association between periodontitis and cardiovascular disease has underscored the significance of inflammatory mediators generated by oral microorganisms. These mediators infiltrate the endothelium, eliciting inflammatory responses that augment cardiovascular risk. The relationship between inflammatory indicators and lipid molecules in chronic periodontitis, as well as their combined influence on the onset of cardiovascular disease, is not sufficiently comprehended.

The present study aimed to clarify the relationship between these two pathways, enhancing the knowledge regarding how inflammatory processes and dyslipidemia in periodontitis may lead to cardiovascular disease.

METHODS

This case-control research comprised 88 men and women aged 30–60 years. Sixty-six individuals had periodontal and coronary heart disease, while twenty-two were healthy individuals. 22 patients were allocated to the CP, CHD, CP + CHD, and control groups (clinically healthy individuals). The individuals were recruited using a consecutive sampling technique. Before participating in the investigation, each participant executed a written informed consent form. In the Chronic Periodontitis (CP) group, inclusion criteria specified a minimum of 16 natural teeth, with at least 35% of sites exhibiting a clinical attachment level (CAL) of 3 millimeters or greater, a probing depth (PD) of 4 mm or greater, and 40% of sites showing bleeding on probing. The Coronary Heart Disease (CHD) cohort included 30-60-year-olds with ACS, or stable ischemic disease. Participants were confirmed to have stenosis of a minimum of one coronary artery (≥50%) confirmed through coronary angiogram, CABG, or PCI. Patients were also asked about cardiovascular risk elements, medications, underlying medical disorders, previous echocardiography, electrocardiography, and coronary angiography. Similar criteria were used to define the inclusion criteria for the chronic periodontitis and coronary heart disease (CP + CHD) group. Patients in the control group were systemically healthy and did not present with any locations with PD or CAL beyond 4 mm. Radiographs showed no alveolar bone loss and ≤10% BOP locations. All individuals were excluded for diabetes, insulin resistance, chronic renal disease, and SLE. Patients taking hormonal contraceptives, antibiotics, anti-inflammatory drugs, or immunosuppressive drugs for three months before enrolling in the research were excluded. Also, women who were pregnant or nursing, along with individuals who smoked or drank, were exempt. Patients who had periodontal therapy within three months of the study or patients receiving Cyclosporin A, Hydantoin, Nifedipine, and other gingival hyperplasia-causing drugs were not enrolled in the study. In collaboration with the Periodontology outpatient department of Bahria University Dental College Hospital, the Cardiac Care Unit (CCU) of PNS Shifa Hospital, and the Multidisciplinary Research Laboratory, the study was executed in the Biochemistry department of BUHSCK. The Bahria University Health Sciences Campus and Dental College Faculty Review Committee (FRC) (FRC-BUHS-50/2022-508) and Ethical Review Committee (ERC) (ERC 04/2023) approved the six-month study starting from December 2022 to May 2023. The sample size was estimated using ADMA levels as the major outcome variable. G Power version 3.1.9.2 (mean of F test, one-way ANOVA with fixed effects) calculated that 88 subjects divided into four groups were needed, assuming an effect size of 0.379, an a priori power of 0.80, an alpha level probability, and four groups. Twenty-two people per cohort were recruited [14]. Data were stored and analyzed using IBM-SPSS version 23.0. The normality of the data was evaluated using the Shapiro-Wilk test. Counts with percentages were reported on baseline demographics across the four studied groups. Median with interquartile range (75^{th} percentile-25^{th} percentile) was reported for CRP, lipid profile, and periodontal parameters. The association of baseline characteristics was tested using the Pearson Chi-Square

DOI: https://doi.org/10.54393/pjhs.v5i11.2233

test. To report the correlations between biochemical and periodontal parameters, Spearman rank correlation analysis was implemented. All p-values less than 0.05 were considered statistically significant.

RESULTS

In the current study there were four study groups, each contained twenty-two samples. In Control group there were 59.1% individuals who were aged less than or equal to 40 years old among which 40.9% were females. In CP group there were 59.1% were aged 41-50 years old among which 18.2% were female gender. In CHD group there were 54.5% were aged more than 50-years old, 4.5% were female gender, whereas in CP + CHD groups there were 68.2% individuals who were aged more than 50-years old, none was female gender. The Pearson Chi Square test provided a significant association of age group and gender with studied groups (p<0.05)(Figure 1).

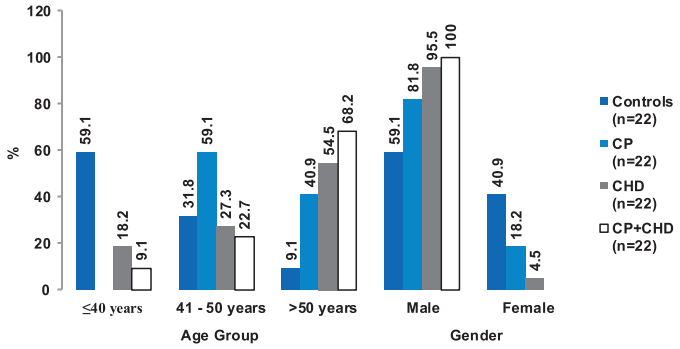

Figure 1: Distribution of Study Participants According to Age and Gender

Lipid profile demonstrated that total cholesterol was significantly higher for CP group compared to CHD and CP + CHD groups. The difference between the tested groups was not significant for triglycerides. HDL was significantly low in CHD group compared to both groups CP and CP + CHD. LDL levels between groups were significantly different depicting low concentrations for CP + CHD group while higher values for CP, CHD and controls (p<0.01)(Table 1). Patients with CP and CP + CHD presented with a higher median values of PD and CAL compared with CHD and healthy individuals (p < 0.01)(Table 1).

Table 1: Comparison of CRP, Lipid Profile and Periodontal Parameters across the Studied Groups

Variables	Controls	CP	CHD	CP + CHD	p-Value
	Median (Q3 – Q1)	Median (Q3 – Q1)	Median (Q3 – Q1)	Median (Q3 – Q1)	
CRP mg/L	1.05 (1.5-0.7)	3.55 (4.4-2.9)	3.6 (7.15-0.82)	6.85 (9.2-4.36)	<0.01*
TC (mg/dL)	185 (195-180)	185.85 (190 -182.35)	160.61 (205.11 -127.32)	147.45 (172.67 -135.45)	<0.01*
TG (mg/dL)	131 (140-122)	116.1(137.8 -109.4)	140.36 (170.7 -100.32)	135.45 (158.4 -110.88)	0.38
HDL-C (mg/dL)	50 (55-45)	37.6 (41.9-35.6)	34.64 (42.96-29.41)	37.75 (48.02-30.19)	<0.01*
LDL-C (mg/dL)	120 (125-110)	104.6 (108.2 -101.2)	116.49 (144.35-81.27)	85.95 (95.2-77.4)	<0.01*
PD (mm)	1.5 (2-1)	4.5 (5-4)	2 (2.5-1)	5.5 (6-5)	<0.01*
CAL (mm)	2.25 (2.5-2)	7 (8-6)	2.75 (3.5-2.5)	7.75 (9-7)	<0.01*

Group CP= Chronic Periodontitis, Group CHD= Coronary Heart Disease, Group CP + CHD= Chronic Periodontitis and Coronary Heart Disease, TC= Total Cholesterol, TG= Triglycerides, HDL-C= High Density Lipoprotein Cholesterol, LDL-C= Low Density Lipoprotein Cholesterol, PD= Probing Depth, CAL= Clinical Attachment Loss, Test applied: Kruskal Wallis Test, *p<0.05 considered statistically significant. CRP has a negative correlation with Total Cholesterol (31.3%), LDL cholesterol (46.5%), HDL cholesterol (21.8%), number of teeth (63.1%) and a positive correlation with probing depth (55.3%), clinical attachment loss (51.9%), bleeding on probing (61.9%) and plaque index score (43.6%). Total cholesterol has a negative correlation with probing depth (50.3%), clinical attachment loss (31.7%) and bleeding on probing (32.5%) and a positive correlation with LDL cholesterol (70.2%) and number of teeth (37.3%). LDL cholesterol has a negative correlation with probing depth (64.6), clinical attachment loss (56%), bleeding on probing (48.9%) and plaque index score (35.3%) and a positive correlation with number of teeth (46.8%). HDL cholesterol has a negative correlation with bleeding on probing (25.2%) and plaque index score (34.4%) and a positive correlation with number of teeth (28.8%)(Table 2).

Table 2: Correlation between Lipid Profile and Periodontal Parameters (Spearman Rank Correlation)

Variables	CRP (mg/L)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)
CRP mg/L	1	-	-	-	-
Total Cholesterol (mg/dL)	-0.313**	1	-	-	-
Trigly -cerides (mg/dL)	0.09	0.085	1	-	-
LDL Cholesterol (mg/dL)	-0.465**	0.702**	0.106	1	-
HDL Cholesterol (mg/dL)	-0.218*	0.16	-0.016	0.125	1
Number of Teeth	-0.631**	0.373**	-0.017	0.468**	0.288**
PD (mm)	0.553**	-0.503**	-0.097	-0.646**	-0.181
CAL (mm)	0.519**	-0.317**	-0.072	-0.560**	-0.141
BoP %	0.619**	-0.325**	0.041	-0.489**	-0.252*
PI Score	0.436**	-0.086	-0.098	-0.353**	-0.344**
** Correlation is Significant at the 0.01 Level (2-Tailed)					
* Correlation is Significant at the 0.05 Level (2-Tailed)					

DISCUSSION

Inflammation in the development of Cardiovascular Diseases (CVD) has received considerable focus in recent times, with chronic periodontitis being identified as a possible causative element. Among the indicators of inflamed tissues, C-Reactive Protein (CRP) was especially

DOI: https://doi.org/10.54393/pjhs.v5i11.2233

significant because of its well-established link with endothelial dysfunction, which was a precursor to atherosclerosis. C-Reactive Protein (CRP) serves as both an indicator of inflammation and an active contributor to the inflammatory pathways, establishing a connection between periodontal disease and cardiovascular disorders. Endothelial dysfunction, demonstrated by the compromised capacity of blood vessels to expand, was a pivotal occurrence in the initial phases of atherosclerosis. The blood lipid profile, characterized by increased concentrations of LDL and diminished concentrations of HDL, was essential in the progression of endothelial dysfunction. The presence of dyslipidemia, in conjunction with increased CRP levels, intensifies the inflammatory reaction, therefore facilitating the development of atherosclerosis. In the present study, 59.1% of individuals were aged between 41 and 50 in the CP group. Among the CHD and CP + CHD groups, 54.5% and 68.2% were aged above 50 years. Males outnumbered females in all four groups (59.1%, 81.8%, 95.5%, 100%). This may be because male dental hygiene and periodontal health did not meet enrollment standards for a healthy periodontium [13-15]. In this study, CP patients had considerably higher median CRP readings than controls. Aoyama N *et al.*, found similar hsCRP results in CP and healthy people [16]. In CHD patients, C-reactive protein was much higher than in controls. Some of the participants had just experienced an angina episode, which may have boosted their levels. Similarly, Esteves-Lima RP *et al.*, found that hs-CRP was strongly linked to CHD [17]. Compared to controls and CP groups, CP + CHD patients showed significantly higher C-reactive protein values. These results lined up with literature reported in previous studies [18–20]. CVD was exacerbated by inflammation [21]. The synthesis of CRP in hepatocytes was enhanced by pro-inflammatory cytokines generated locally at infection or inflammation sites, which were known to increase the risk of atherosclerotic implications. CRP may stimulate human endothelial cell adhesion molecule expression and atherosclerotic lesion development [21, 22]. Thus, severe periodontal disease may be linked to atherosclerotic lesions. Based on the findings of the investigation, it was found that CHD and CP + CHD patients had lower cholesterol levels compared to CP individuals and controls. It was attributed to the fact that these individuals were on cholesterol-lowering therapy. HDL has an atheroprotective effect that is mediated by reverse cholesterol transport. This study found that patients who had both chronic periodontitis and Coronary Heart Disease (CHD) consistently exhibited lower levels of High-Density Lipoprotein (HDL), which was consistent with the well-established association between reduced HDL and increased cardiovascular risk. The decrease in HDL levels can be ascribed to the persistent inflammatory state present in both disorders, which was recognized to adversely affect lipid metabolism. This result highlights the possible influence of systemic inflammation in worsening lipid abnormalities, hence contributing to the advancement of cardiovascular disease in these individuals. The highest median values for parameters PD and CAL were recorded in individuals having combined disease (CP + CHD). 23.Gupta S *et al.*, conducted a study on periostin levels to evaluate the correlation between CHD and persistent periodontal disease [23]. They found out that the highest mean values were found in the group CHD-CP for periodontal parameters.Furthermore, these findings were by the literature documented by Kumar KR *et al.*, which demonstrated the highest mean values for PD and CAL in CP + CHD patients [25]. Clinical periodontal parameters and lipid profiles have substantial correlations, highlighting the complicated link between systemic inflammation, lipid metabolism, and periodontal health. Inflammatory markers, such as CRP, were negatively correlated with total cholesterol, LDL, HDL, and tooth count, while positive correlations were found for probing depth, CAL, BoP, and PI score ($p<0.01$). This suggested that inflammation may autonomously affect periodontal and cardiovascular health. These findings were aligned with the literature reported by Kumar KR *et al* [24, 25]. However, total cholesterol and LDL were positively associated with periodontal parameters, including tooth count, demonstrating a complex relationship between lipid status and oral health. According to research by Katz J *et al.*, males suffering from periodontitis had far greater levels of LDL and total cholesterol in their blood compared to those with healthy periodontal tissue or gingivitis [26, 27]. One of the study's key drawbacks was its limited sample size, which may limit the findings' applicability to a larger population. A limited sample size can reduce statistical power, making it difficult to identify subtle but clinically significant variations between groups. Another restriction was the potential bias imposed by the exclusion criteria, which were particularly relevant to lifestyle factors such as smoking, alcohol consumption, and poor eating habits. While these eliminations were essential to control for confounding variables, they may limit the study's application to real-world groups that exhibit such behaviours. By omitting people with these lifestyle characteristics, the study may not accurately represent the average periodontitis patient group, which frequently has complicated connections between oral health, lifestyle, and cardiovascular disease. This may result in an underestimation of the cumulative influence of these factors on interest-related outcomes. The clinical implications of the correlation between dyslipidemia, C-Reactive Protein (CRP), Coronary Heart Disease (CHD), and Chronic Periodontitis (CP) were significant. CP patients

DOI: https://doi.org/10.54393/pjhs.v5i11.2233

may be at an increased risk for cardiovascular events due to high levels of CRP and dyslipidemia, which were established risk factors for CHD. Additionally, the results indicate that specific measures, such as lipid-lowering compounds or anti-inflammatory therapies, may be beneficial for CP patients in reducing cardiovascular morbidity.

CONCLUSIONS

There was a complex relationship between dyslipidemia, inflammation, and periodontal health, as evidenced by the strong correlations between systemic indicators of inflammation, lipid profiles, and periodontal parameters. The potentially detrimental impact of inflammation on both cardiovascular and periodontal diseases was underscored by the negative associations between CRP and lipid levels and the positive associations between CRP and periodontal parameters. The role of inflammation in modulating lipid metabolism and periodontal disease was supported by these insights, necessitating additional research to investigate such relationships and the consequences for treatment strategies in both cardiovascular and periodontal health.

Authors Contribution

Conceptualization: AZ
Methodology: AZ
Formal analysis: AZ, AB
Writing, review and editing: FT, SBA, HA, ANK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2119

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Medicinal Plants Used by Nursing Mothers for the Treatment of Children Diseases (Diarrhea and Malaria) in Bichi Northern Nigeria

ADAMU Shehu Usman[1*], Maryam Adamu Bappah[2], Lois C. Dickson[3] and Salima Adamu Sada[4]

[1]Department of Public Health, Faculty of Health Sciences, National Open University of Nigeria, Abuja, Nigeria
[2]Department of Medical Microbiology, College of Medical Sciences, Abubakar Tafawa Balewa University, Bauchi, Nigeria
[3]Department of Laboratory Services, Bichi Specialist Hospital, Bichi, Nigeria
[4]Department of Environmental Health, Faculty of Health Sciences, National Open University of Nigeria, Abuja, Nigeria

ARTICLE INFO

Keywords:
Medicinal Plants, Complementary Medicine, Alternative Medicine, Paediatric Disease Treatment, Nursing Mothers

How to Cite:
Adamu, S. U., Bappah, M. A., Dickson, L. C., & Sada, S. A. (2024). Medicinal Plants Used by Nursing Mothers for the Treatment of Children Diseases (Diarrhea and Malaria) in Bichi Northern Nigeria: Medicinal Plants for Children Diseases in Bichi. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2119

***Corresponding Author:**
ADAMU Shehu Usman
Department of Public Health, Faculty of Health Sciences, National Open University of Nigeria, Abuja, Nigeria
suadamu@noun.edu.ng

Received Date: 15th August, 2024
Acceptance Date: 16th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Medicinal plants as means of complementary and alternative medical practices. This study examines the use of plant materials as a means of complementary and alternative medicine in treating children's diseases (Diarrhea and Malaria) by nursing mothers in Bichi LGA. **Objective:** To evaluate the use of plant materials by nursing mothers in treating diarrheal and Malaria disease in Bichi LGA, to assess the percentage of nursing mothers that prefer using traditional medicine alone and those that use traditional medicine with orthodox paediatric drugs, to determine common plants in use and their sources used in the treatment of paediatric condition like malaria and diarrhea. **Methods:** Three research questions were formulated and data was collected using both focused group discussion and structured questionnaires. Based on the analysis of the data, the following findings were discovered. **Results:** Ninety-eight (98%) of Bichi's nursing mothers know Medicinal Plants. 74% of which utilize medicinal plants and 47% use medicinal plants exclusively, while 26% use it in addition to orthodox medication. The primary causes of this high medicinal plant use among these women were: socioeconomic status (45%) of Nursing mothers were unemployed 30% of them lack a formal education) the beliefs that medicinal plants were more effective than orthodox medicine and the availability or easy accessibility of these plants. **Conclusion:** The sources of the plants used by these women were 100% natural and organic from their farmland

INTRODUCTION

The use of Medicinal Plants is a form of Complementary and alternative medicine (the general word for a wide range of treatments that originate from around the world and employ several techniques. "Complementary" refers to a non-mainstream approach that is used in addition to conventional medicine, while "alternative" refers to a non-mainstream practice that is utilized in place of conventional medicine, according to the National Center for Complementary and Integrative Health (NCCIH, 2020) [1]. Globally, almost 80% of people use natural products; in developing nations, that percentage jumps to 95% [2]. Furthermore, studies in Africa and other developing countries have high use of medicinal plants with Nigeria having 20-80% of the Population practicing it openly or the other, and many of the medicinal plants were proven to have some level of efficacy [3, 4]. Studies connected women's use of medicinal plants as a way of complementary and alternative medicine to their perception of medicinal plants as a secure replacement for conventional/orthodox medicine due to its cheapness and availability and its use by Nursing Mothers to treat children diseases had also been reported [5-8]. Other reasons leading to the wide usage of medicinal plants by women include lack of access to orthodox medical facilities, cultural beliefs, and affordability. Diarrhea and malaria are major childhood diseases in Africa, and Nigeria in general,

DOI: https://doi.org/10.54393/pjhs.v5i11.2119

and are usually treated using medicinal plants the world over, particularly with herbs using different plants in various form of concoction [9, 10]. The information gathered from this study on the extent to which nursing mothers in Bichi LGA are treating paediatric conditions with complementary and alternative medicine (medicinal plants) has the potential to improve knowledge of regional healthcare practices, guide initiatives to increase healthcare equity and access, strengthen safety and efficacy considerations, ease integration with traditional medicine, raise public awareness and education, and have an impact on healthcare laws and regulation.

The purpose of this study was to evaluate the use of complementary and alternative medicine in treating child diseases (Diarrhea and Malaria) by nursing mothers in Bichi LGA by answering the research question to, evaluate the use of complementary and alternative medicine in treating child diseases diarrhea and malaria by nursing mothers in Bichi LGA. Assess the percentage of nursing mothers who prefer using medicinal plants alone and those that use medicinal plants with orthodox paediatric drugs in Bichi LGA. Determine common medicinal plants in use, their sources, and the method of preparation used in the treatment of paediatric conditions like malaria and diarrheal in Bichi LGA.

METHODS

An investigative cross-sectional study design was used for this study because it was a population-based survey that investigated the use of medicinal plants in treating malaria and diarrhea among infants within a specified group of people within the population which were nursing mothers. All nursing mothers residing in Bichi LGA who attend medical services at B.E.S.H, Badume PHC, or Bichi Excellent Hospital were included while the excluded were non-nursing mothers residing in Bichi LGA. A total of 300 nursing mothers, 170 from Bichi emirates specialist Hospital, 80 from PHC Badume, and 50 from Excellence Hospital Bichi were enrolled for these studies from the different sample areas and simple random sampling was used in selecting sample subjects for 12 weeks. The qualitative sample was arrived at based on data saturation of the Interview while the quantitative data of 300 was arrived at by using Krejcie and Morgan's table of sample size determination with a 95% confidence level with a 5% margin of error. Data were collected through structured questionnaires categorized into; 1-demographic background; 2-the knowledge and use of complementary and alternative medicine. The type of plant material used for the treatment of infant diarrhea and malaria, preparation, co-administration, and frequency of use. In Sections three and four, research questions one and two were discussed respectively. The questionnaires were open-ended and the mothers who couldn't read, the questions were discussed with them in the form of a group discussion to have a better understanding of their views and medicinal plant use. SPSS version 25.0 was used to analyze the quantitative data regarding demographic parameters and the number of respondents with knowledge of using plants for the treatment while the saturation method was used for the qualitative data of the method of preparation of the plants used for the treatment of the diseases by nursing mothers and the results were then displayed using straightforward proportions and percentages. Ethical clearance and approval to conduct this research were obtained from the Chief Medical Director's office for Bichi Zone, ethical committee National Open University of Nigeria (ETC/2024/04/NOU222077423), and verbal consent from each participant and ethical clearance from NOUN Ethics Department were also obtained for this study.

RESULTS

A total of 300 nursing mothers were used for these studies from 3 health facilities in Bichi LGA, the following were the major findings: From these studies, 242 (80.6%) of nursing mothers in Bichi LGA happened to be Indigenes of Bichi LGA whereas the other 58 (19.4%) were either settlers for business or civil servants. About 205 (70%) of the nursing mothers in Bbichi LGA have at least completed secondary education while 95 (30%) were either not educated or have only completed primary school. In terms of number of children, 49% of these nursing mothers have 3 or more children. From these studies, it was discovered that 269 (88.7%), of nursing mothers in Bichi LGA were full-time housewives (Table 1).

Table 1: Quantitative Variable of Demographic Information of Respondents (n=600)

Variables	B.E.S.H	Badume P.H.C	Excellence Hospital	Percentage (%)
Age				
<20 Years	67	25	8	32.6%
21-35 Years	83	43	30	52.7%
36-55 Years	20	12	12	14.6%
>56 Years	0	0	0	0%
Tribe				
Bichi LGA Indigene	150	60	32	80.6%
Just Residing in Bichi LGA	20	20	18	19.4%
Marital Status				
Married	155	72	42	88.7%
Single	0	0	0	0%
Widow	3	5	2	4.3%
Separated/Divorce	12	3	6	7%
Level of Education				
Not Educated	12	20	5	12.3%
Primary School	20	25	8	17.6%
Secondary School	95	20	24	46%
Tertiary and Above	43	15	13	24.1%
Number of Children				
1-2	57	10	22	30.4%

DOI: https://doi.org/10.54393/pjhs.v5i11.2119

3-5	83	37	20	48.7%
>5	30	18	8	20.4%

From table 2 below, 298 (98%) of nursing mothers in Bichi LGA have heard of medicinal plants, 207 (68%) of them got their information from family and friends especially their mothers, grandmothers and aunts. Basically 223 (74%) of nursing mothers in Bichi LGA have used medicinal plants to treat paediatric diseases like malaria and diarrhea at least once. In addition, 249 (83%)of the women had moderate to high satisfaction from their use of medicinal plants on their children with 143 (47%) nursing mothers in Bichi LGA said when they use herbs (medicinal plants) to treat pediatric disease they use it exclusively, they also recommend this practice to other women. A total of 80 (26%) of the nursing mothers in Bichi LGA use complementary medicine with orthodox medicine and also recommend this practice to other women.

Table 2: Quantitative Variable Showing Perception and Attitude of Respondents on use of Medicinal Plants (n=600)

Variables	B.E.S.H	Badume P.H.C	Excellence Hospital	Percentage (%)
Knowledge of Medicinal Plants				
Yes	170	80	48	99%
No	0	0	2	2%
Source of Knowledge				
Medical Professionals	28	8	8	15%
Family and Friends	122	55	30	69%
Religious Institutions	12	17	10	13%
Others (Please Specify)	122	55	30	69%
Is Medicinal Plants Effective in Treating Malaria and Diarrhea				
Yes	148	63	38	83%
No	22	17	12	18%
Have You Ever Used Medicinal Plants to Treat Your Child's Diarrhea or Malaria				
Yes	128	65	30	74%
No	52	15	20	26%
Do You Manage Your Children's Paediatric Illnesses like Malaria or Diarrheal only with Traditional Herbs?				
Yes	80	40	23	47%
No	90	40	27	53%
Do You Treat Your Children for Malaria or Diarrheal Using Complementary Medicine in Addition to Orthodox Medicines?				
Yes	48	25	7	26%
No	122	55	43	74%

Table 3 provided a summary of the major plants identified by nursing mothers in Bichi LGA as treatments for childhood diarrhea. Each plant is listed with its local name, botanical name, part(s) of the plant used, preparation method, and reported effectiveness. Additional columns may include the source of the plant (e.g., wild or cultivated), administration method (e.g., oral, topical), and any noted side effects or limitations reported by the mothers. This qualitative data highlights the diversity and cultural significance of plant-based remedies in managing pediatric diarrhea within the community.

Table 3: Qualitative Variable of Major Plants Reported to be used by Nursing Mothers to Treat Diarrhea

Plants Name	Family Name	Vernacular Name	Percentage of Nursing Mothers Using the Plants N (%)
Momordica balsamina (Leaves)	Cucurbitaceae	*Garafuni*	135 (45%)
Mangifera indica (Stem)	Anacardiaceae	*Mangwaro*	42 (14%)
Guiera Senegalensis (Leaves)	Combretaceae	*Sabara*	57 (19%)
Guiera Senegalensis (Roots)	Combretaceae	*Sabara*	42 (14%)

Nursing mothers in Bichi commonly use these three plants *Detarium senegalense*, *Cassia occidentalis*, and *Azadirachta indica* for treating malaria in infants. The preparation involves boiling the leaves to extract the juice, which is used in a steam treatment with the mother and infant, followed by bathing the baby in the herb infused water (Table 4).

Table 4: Qualitative Variable Showing Major Plants used by Nursing others to Treat Malaria

Plants Name	Family Name	Vernacular Name	Percentage of Nursing Mothers Using the Plants N (%)
Detarium senegalense	*Fabaceae*	Taura	68 (22.6%)
Cassia occidentalis	*Fabaceae*	Rai-Dore	83 (27.3%)
Azadirachta indica	*Meliaceae*	Dogon Yaro	122 (40%)

DISCUSSION

Out of the 300 nursing mothers that were utilized in these investigations, 170 of the ladies were affiliated with B.E.S.H., 80 with Badume Primary Health Facility, and the remaining 50 with Bichi Excellence Hospital. 156 (52.7%) of these women were under the age of 35, while just 44 (14.6%) were over the age of 36. 242 (80.6%) of these women were Bichi LGA indigenes, and the remaining 58 (19.4%) were either commercial settlers or civil servants. About 269 (88.7%) of the women were married, 21 (7%) were separated or divorced, 10 (4.3%) were widows, and none was single. Of these women, 121 (46%) had finished secondary school, 71 (24.1%) had either completed or were enrolled in university education, and 53 (17.6%) had only completed basic school or had no education at all. This was supported by other studies where age, socioeconomic status, and level of education have been linked to higher prevalence of medicinal plants use [11, 12]. However, there was no link between age and use of medicinal plants in this study. This finding was similar to reports from other developing countries where age had no relationship with medicinal plants use [13]. Of these women, 89 (31%) had one or two children, 196 (69%) had three or more this finding was in

DOI: https://doi.org/10.54393/pjhs.v5i11.2119

conformity with a 2023 study [14]. Of the 300 women included in the study, 298 (99%) admitted to knowing about complementary and alternative medicine (medicinal plants) this was in agreement with a work does in Sokoto Nigeria, while 2 claimed to know nothing about it [15]. Of these women, 207 (68%) obtained their information from friends and family, primarily from their moms; 44 (15%) obtained it from medical professionals; and 39 (13%) obtained it from places of worship. Ten (4%) of the ladies had unclear sources of information. Mangifera indica bark (sassaken mangwaro) which was dried and boiled, the use of which was also reported in kastina, Nigeria and Zimbabwe [16-18]. Guiera senegalensis Leaves or Roots (Ganyen sabara) also referred to by the study community as "Sabara" in Hausa, was another plant that nursing women in Bichi LGA primarily used during the study period. Another study reported same in Sudan and Laboratory experiment also confirmed [19, 20]. Momordica balsamina Leaves (Ganyen Garafuni) also known as African Pumpkin or Garafuni in Hausa. Earlier on, in-vitro studies have demonstrated its antidiarrheal properties by [21-23]. When questioned about plants used as anti-malaria, Detarium microcarpum known locally as "Taura" was brought up during the focused group talks. This study complements of its use in additional research findings on its activity [24, 25]. Cassia occidentalis Leaves (Ganyen Rai-Dore) also referred to as Rai-Dore in Hausa, possesses potent anti-malaria and anti-fever properties as reported by a study and confirmed by another study. Azadirachta indica Leaves (Gayen Dogon Yaro) was discovered to be one of the widely regarded Anti-malaria plant used in Bichi LG A. was Azadirachta indica, commonly referred to as neem or "Dogon Yaro" in Hausa. These findings were very similar to a report of its use in Benue state Nigeria (north western and south western part of Nigeria) and it's used in North eastern part of Nigeria for the treatment of enteric fever.

CONCLUSIONS

A study was conducted in Bichi LGA, Kano State Nigeria, it was discovered that, 298 (98%) of Bichi's nursing mothers had knowledge of medicinal plants, 223 (74%) of which were using medicinal plants. It was discovered that the common medicinal plants practices and their sources used in the treatment of paediatric condition like malaria and diarrheal in Bichi LGA were 100% natural and organic, medicinal plants from farmlands such as Garafuni *(Momordica balsamina),* Raidore *(Cassia occidentalis),* or wild bushes Sabara *(Guiera senegalensis).* Other medicinal plants sources that these women use were found around the house, such as Mango *(Magifera indica)* and neem/dogon yaro *(Azadirachta indica),* but neither the herbal nor medication processes used to make them were optimal.

Authors Contribution

Conceptualization: ASU
Methodology: ASU, LCD
Formal analysis: MAB, LCD, SAS
Writing, review and editing: MAB, LCD, SAS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2236

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Frequency of Neonatal Respiratory Distress among Newborns of Mothers with Preterm Premature Rupture of Membranes in Tertiary Care Hospital

Maryam Nazir[1], Sadaf Saifullah[1], Sadia Anwar[2*], Kosar Inayat[1], Saima Umar[2] and Najma Bibi[3]

[1]Department of Obstetrics and Gynecology, Women and Children Hospital, Abbottabad, Pakistan
[2]Department of Obstetrics and Gynecology, Mufti Mehmood Hospital, Dera Ismail Khan, Pakistan
[3]Department of Obstetrics and Gynecology, Women and Children Hospital, Dera Ismail Khan, Pakistan

ARTICLE INFO

Keywords:
Preterm Premature Rupture of Membranes, Respiratory Distress, Frequency, Newborns

How to Cite:
Nazir, M., Saifullah, S., Anwar, S., Inayat, K., Umar, S., & Bibi, N. (2024). Frequency of Neonatal Respiratory Distress among Newborns of Mothers with Preterm Premature Rupture of Membranes in Tertiary Care Hospital: Neonatal Respiratory Distress among Newborns of Mothers with Preterm Premature Rupture of Membranes . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2236

***Corresponding Author:**
Sadia Anwar
Department of Obstetrics and Gynecology, Mufti Mehmood Hospital, Dera Ismail Khan, Pakistan
sasajjaddr@gmail.com

Received Date: 5th October, 2024
Acceptance Date: 24th September, 2024
Published Date: 30th November, 2024

ABSTRACT

Respiratory distress leads to neonatal morbidity and mortality. The premature rupture of membranes before labor at less than 37 weeks. **Objectives:** To determine the frequency of neonatal respiratory distress in newborns delivered with preterm premature rupture of membranes. **Methods:** Cross-sectional study conducted in the Gynecology unit at Ayub Teaching Hospital Abbottabad from 1-4-2018 to 1-9-2018. Sample size 244 was calculated using WHO software by non-probability consecutive sampling using a convenience sampling technique. Pregnant women with singleton pregnancy, gestation 34-36 weeks, parity 0-4 with preterm rupture of membranes were included. After birth, an examination of the newborn for features of respiratory distress was done by a neonatologist. Data were analyzed with SPSS version 22.0. Mean ± SD was presented for quantitative variables and frequency percentage was computed for qualitative variables like respiratory distress. **Results:** The mean age was 28.733 ± 2.71, the mean gestational age was 34.750 ± 0.65 and the mean parity was 1.028 ± 1.11. Respiratory distress was observed in 40.2% of newborns. Stratification of Respiratory Distress concerning maternal age, parity, and gestation done. This was 87.9 % in newborns of women aged 18-27 and 25.3% in women aged 28-35 years. 43% of newborns developed respiratory distress at gestation less than 35 weeks and 20% at gestation more than 35 weeks. **Conclusions:** It was concluded that the frequency of neonatal respiratory depression was 40% in newborns with premature rupture of membranes. It was more common in younger ages and at less than 35 weeks of gestation.

INTRODUCTION

Respiratory depression is a major devastating and challenging problem in premature newborns. A significant number of newborns are admitted to NICU with respiratory distress [1]. According to every Newborn Action Plan (ENAP), complications associated with preterm birth contribute to a significant number of neonatal deaths which need to be addressed promptly [2]. Respiratory distress syndrome (RDS) contributes to 45 % of neonatal deaths in premature newborns in low and middle-income countries [3]. Several obstetrical risk factors are identified for this morbidity which include prematurity, meconium-stained liquor, operative delivery, gestational diabetes, pre-labour rupture of membranes, or neonatal congenital lung anomalies [4]. Other factors like antepartum bleeding, parity, antenatal steroid use and Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at birth are predictors of neonatal respiratory depression. Many fetal pulmonary congenital malformations like tracheoesophageal fistula, bronchopulmonary dysplasia, bronchogenic cysts lung parenchymal diseases, or pulmonary hypoplasia also contribute to respiratory diseases and undiagnosed respiratory depression in preterm infants [5]. The term PPROM is defined as premature rupture of amniotic membranes leading to per vaginal leaking of liquor before labour at gestation less than 37 completed weeks [6]. It is the ultimate cause of pulmonary depression in the majority of premature births leading to increased mortality. The management of PPROM is challenging for obstetricians concerning sepsis prevention and in-utero referral. The WHO recommends

DOI: https://doi.org/10.54393/pjhs.v5i11.2236

the use of corticosteroids for fetal lung maturity for women at risk of preterm labour. Other strategies like Kangroo mother care and enhancing training and skill in newborn resuscitation can also reduce the burden of the problem [7]. Sims demonstrated frequency of respiratory distress in 39% of newborns with rupture of membranes at less than 35 weeks of gestation [8]. Diriba et al., reported respiratory distress in 49% of neonates born with ruptured membranes [9]. Neonatal pulmonary depression can end up with serious respiratory compromise cardiac sequel and neonatal demise. It not only contributes to the sufferings of neonates but puts an economic expenditure burden on health provider services in low- and middle-income countries (LMIC) like Pakistan. Very few studies were available in the local population.

This study aimed to determine the frequency of respiratory distress in premature neonates born with ruptured membranes. This will help obstetricians and pediatricians to plan structured evaluation and early management of respiratory distress associated with PPROM.

METHODS

This cross-sectional study was carried out in the obstetrics and gynecology unit of Ayub Teaching Hospital, Abbottabad from 1-4-2018 to 1-9-2018. The sample size was 244, calculated using WHO software for sample size calculations with the following assumptions: Confidence level=95% and anticipated proportion of respiratory distress=2.6% [9]. Absolute precisions=2% by non-probability consecutive sampling using a connivance sampling technique. Pregnant women 18-35 years old with singleton pregnancy on ultrasound and gestational age 34-36 weeks by Last Menstrual Period (LMP), parity 0-4, and preterm premature rupture of membranes were included in the study. Preterm premature rupture of membranes was diagnosed when the following conditions were observed at the period of gestation less than 37 weeks of pregnancy. (1) Amniotic fluid leaking from the vagina observed as soaking seen on pad or clothes. (2) A speculum examination reveals liquor pooling in the upper vagina or trickling through the cervical canal which will further increase by coughing or straining (Valsalva manoeuvres). Women with meconium aspiration syndrome (Infant's chest X-ray show asymmetric, patchy pulmonary opacities with pleural effusions), antepartum hemorrhage, and history of ABO/Rh hemolytic disease on medical record were excluded from the study. After ethical approval (letter no CPSP/REU/OBG-2016-010-7988), patients fulfilling the inclusion criteria were recruited from the indoor department. Basic demographics like age, parity, gestational age, etc. were recorded and Informed consent was taken. After delivery complete clinical examination of the newborn for the features suggestive of respiratory depression was done by an expert neonatologist. Respiratory distress was diagnosed as an infant showing all of the following: Tachypnea defined as a respiratory rate greater than 60 breaths per minute, nasal flaring, and chest grunting by physical examination. Respiratory distress data were entered on specially designed proforma. Data analysis was done with SPSS version 22.0. Mean ± SD was presented for quantitative variables like age, gestational age, and parity. Frequency and percentage were computed for qualitative variables like respiratory distress. Effect modifiers like age, gestational age, and parity were controlled by stratification. Post-stratification chi-square test was applied and p-value ≤0.05 was considered statistically significant.

RESULTS

The mean age of patients was 28.733 ± 2.71, with a mean period of gestation of 34.750 ± 0.65 weeks and a mean parity of 1.028 ± 1.11 (Table 1).

Table 1: Mean ± SD of Age, Gestational Age, and parity (n=244)

Demographic Variables	Mean ± S.D
Age (Days)	28.733 ± 2.71
Gestational Age (Weeks)	34.750 ± 0.65
Parity	1.028 ± 1.11

Respiratory distress was observed in 40.2% of newborns (Table 2).

Table 2: Frequency, %Age of Patients with Respiratory Distress

Respiratory Distress	Frequency Percentage
Yes	98 (40.2%)
No	146 (59.8%)
Total	244 (100%)

Stratification of Respiratory Distress concerning maternal age indicated that 87.9% of women between the age group 18- 27 and 25.3% of women between the age group 28-35 years old newborns developed respiratory distress. (p-value significant) (Table 3).

Table 3: Stratification of Respiratory Distress with Age

Age (Years)	Respiratory Distress		p-value
	Yes (Frequency %)	No (Frequency %)	
18-27	51 (87.9%)	7 (12.1%)	0.000
28-35	47 (25.3%)	139 (74.7%)	
Total	98 (40.2%)	146 (59.8%)	

Gestational age less than 34-35 weeks was associated with respiratory distress of 43% while gestation of more than 35 weeks was associated with respiratory distress of 20% (Table 4).

Table 4: Stratification of Respiratory Distress Concerning Gestational Age

Variables	Respiratory Distress		p-value
Gestational Age (weeks)	Yes (Frequency %)	No (Frequency %)	
Less than 34-35	92 (43%)	122 (57%)	0.016
>35	6 (20%)	24 (80%)	
Total	98 (40.2%)	146 (59.8%)	

Maternal Parity of 0-2 and 3-4 was associated with 41% and

DOI: https://doi.org/10.54393/pjhs.v5i11.2236

35.95% respiratory distress in newborns respectively (Table 5).

Table 5: Stratification of Respiratory Distress Concerning Parity

Parity	Respiratory Distress		p-value
	Yes (Frequency %)	No (Frequency %)	
0-2	84(41%)	121(59%)	0.553
3-4	14(35.9%)	25(64.1%)	
Total	98(40.2%)	146 (59.8%)	

DISCUSSION

Respiratory depression is one of the major causes of neonatal death worldwide. Prematurity is a major contributing factor. The overall prevalence of preterm labour with ruptured membranes occurs in 7-10% of births [10]. The frequency of respiratory depression has an inverse association with gestational age [11]. The current study was carried out in a tertiary care facility situated in a remote area of the province of KPK Pakistan. The frequency of respiratory distress was found to be 40.2% in newborns of mothers with preterm ruptured membranes. This higher frequency correlates well with a study conducted by Niesłuchowska-Hoxha et al., who reported 52.29% of RDS in PPROM cases [12]. Another study conducted by Aslamzai et al., in Kabul Afghanistan reported 52% respiratory distress in premature newborns. In their study, the highest rates were observed in very premature and low birthweight babies [13]. This high prevalence of respiratory depression in premature newborns well explains the burden of disease across the world particularly in LMIC and emphasizes the significance of addressing risk factors leading to this morbidity. In our study, the frequency of respiratory depression was more common in pregnant women between the age of 18-27 years (87.9%) while it was less commonly observed in the age group 28-35 years (25.3%). This shows that younger women particularly with teenage pregnancies are more at risk of developing PPROM and the birth of newborns with higher percentages of respiratory depression. However, a study conducted by Bibi et al., in Abbottabad categorized the women in 18-23 years and 24-29 years' age groups for acute and chronic respiratory disease in pregnancies with preterm rupture of membranes and found more acute and chronic conditions in the age group 24-29 years. Very few studies in the literature address maternal age as a risk factor for PPROM because they pair PPROM cases with age-match controls [14]. Our results indicate that neonatal respiratory depression was more frequent at the gestational age of less than 35 weeks (43%) than at gestation of more than 35 weeks (20%). The better respiratory function and secretions of alveolar surfactants after 34 weeks of gestation are well documented and a known prognostic factor. The study conducted by Wang L in China compared respiratory depression at various gestation and found that newborns at lesser than 34 weeks' gestational age are in increased demand for surfactants [15]. Another research conducted by Lemyre et al., found similar results in very preterm newborns [16]. Maternal parity and neonatal respiratory depression share an association. In our study, the frequency of neonatal respiratory depression was more commonly observed in pregnant women having a parity of 0-2 (41%) as compared to a parity of 3-4 (35%). These results are comparable to other studies that show that PPROM is more common in prim gravidas or those having previous miscarriages [17, 18]. The assessment of respiratory depression could vary based on observer, equipment, and definition criteria [19, 20]. These limitations were part of our study. The confounding factors like maternal infections, antenatal corticosteroid use, and mode of delivery can impact respiratory outcomes. It is challenging to control all these variables. Increasing the sample size, conducting a study across multiple tertiary care hospitals, controlling confounding factors, including a control group, and extending follow-up beyond the neonatal period can provide a more comprehensive view of the study.

CONCLUSIONS

It was concluded that a significant proportion of respiratory depression occurs in neonates born with preterm premature membrane rupture. It was 40% in a current research study, more commonly seen in younger ages (18-27 years) and at less than 35 weeks of gestation.

Authors Contribution

Conceptualization: MN
Methodology: MN, SS, KI
Formal analysis: SS, SU
Writing review and editing: SA, NB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1957

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Markers of Systemic Inflammation in Smoker and Non-Smoker Chronic Obstructive Pulmonary Diseases

Snehanshu Debabrata Malla[1], Amit Kumar Verma[2*], Shiva Narang[1], Mohit Mehndiratta[3] and Edelbert Anthonio Almeida[3]

[1]Department of Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India
[2]Department of Respiratory Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India
[3]Department of Biochemistry, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India

ARTICLE INFO

Keywords:
Obstructive Pulmonary Disease, Inflammatory Markers, Erythrocyte Sedimentation Rate, C-Reactive Protein, Fibrinogen, Interleukin

How to Cite:
Malla, S. D., Verma, A. K., Narang, S., Mehndiratta, M., & Almeida, E. A. (2024). Markers of Systemic Inflammation in Smoker and Non-Smoker Chronic Obstructive Pulmonary Diseases: Systemic Inflammation in Smokers and Non-Smokers. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1957

***Corresponding Author:**
Amit Kumar Verma
Department of Respiratory Medicine, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India
dramitkverma@hotmail.com

Received Date: 7th September, 2024
Acceptance Date: 28th October, 2024
Published Date: 30th November, 2024

ABSTRACT

Non-smoker and tobacco smoker also have different inflammatory and proteolytic effects in the lung in experimental studies. **Objectives:** To compare the clinical, investigational profile and inflammatory markers e.g. ESR, CRP, Fibrinogen, IL-5 and IL-6 between smoker and non-smoker COPD patients.2. To compare the CAT score, mMRC score and various spirometry parameters between smoker and non-smoker COPD patients3. To calculate the diagnostic performance, sensitivity and specificity of inflammatory markers e.g. ESR, CRP, Fibrinogen, IL-5 and IL-6 between smoker and non-smoker COPD patients. **Methods:** In this cross-sectional study 80 subjects between age group of 40 to 65 years participated. This study included category A, B and C patients of COPD included and category D of COPD patients were excluded and those who were exposed to occupational exposure to smoke. Serum levels of inflammatory markers including ESR, CRP, IL-5, IL-6, and Fibrinogen measured. **Results:** This study showed that there was statistically significant difference in ESR, CRP and fibrinogen levels between smoker and non-smoker COPD. There was also significant statistical difference between smoker and non-smoker COPD with respect to gender, old TB, haemoglobin, and the spirometry parameters. **Conclusions:** Therefore, this phenotypical categorization of patients with COPD may result in better understanding of the varied pathophysiology and help as screening tool for diagnosis of non-smoker COPD patients. ESR, CRP and fibrinogen may be used as a screening tool between smoker and non-smoker COPD patients, for a focused approach to treatment.

INTRODUCTION

As per the GOLD guidelines, COPD is a preventable, and treatable disease. Airflow limitation which is characteristic feature in COPD, is not fully reversible [1]. This airflow limitation is progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. Currently, COPD becomes the public health challenge as mortality related to COPD is on number 4th in the world [2]. Tobacco smoking in past or current is most important risk factor for COPD development. However, not all patients with COPD have a history of smoking. As per available literature 10% to 12% of individuals with COPD have never smoked and only 50 % worldwide COPD cases are related to smoking [3, 4]. This suggests that other environmental factors are also involved, including biomass fuel exposure (outdoor and indoor air pollution), occupational hazards, passive smoking and smoking in mother during early pregnancy, childhood respiratory infections [5, 6]. OPD is a complex chronic disease, involving several types of inflammatory cells and variety of inflammatory mediators. Its pathogenesis entails complex interactions among multiple factors, including oxidative stress, extracellular matrix destruction, alterations of cell growth and repair, cellular apoptosis on exposure to air pollutants including tobacco smoke [7]. IL-1 is mainly

DOI: https://doi.org/10.54393/pjhs.v5i11.1957

produced by the airway epithelium and macrophages, and it is released along with IL-6, IL-8 and TNFα. It causes neutrophilia, macrophage activation and responses by T cells [8, 9]. Various clinical studies reported elevated levels of inflammatory cytokines in respiratory tract and/or peripheral blood of COPD patients in comparison to healthy controls [10, 11]. The major inflammatory cell in the process is the neutrophil. It has been seen that number of neutrophils in small airways is related to severity of COPD [12]. The number of circulating leukocytes, together with blood levels of markers of systemic inflammation like CRP, IL-6, TNF-alpha and fibrinogen, is regarded as an associated with lung function impairment over time [13]. The number of macrophages is increased in the Airways in COPD and these cells seem to be of direct importance of development of emphysema. Eosinophils as a marker of airway inflammation have attracted some interest in COPD. There are studies indicating the number of sputum eosinophils increases in COPD in association with acute exacerbations [14]. Only a few studies have been done globally as well as in India, which have attempted to evaluate and compare the clinical, inflammatory marker's patterns between smoker and non-smoker COPD patients. Therefore, it was planned to do this study to demonstrate any significant difference in systemic inflammatory biomarker levels between smoker and non-smoker COPD.

METHODS

This cross-sectional observational study was conducted from January 2021 to April 2022 at University College of Medical Sciences and GTB Hospital, New Delhi. 80 subjects were included in this study. Sample size of current study was calculated by Rincon M *et al.*, in 2017 t α = 5% and power = 80% [10]. This study included category A, B and C patients of COPD between ages of 40 to 65 years. We excluded patients of category D of COPD and those who were exposed to occupational exposure to smoke and patients with recent episode of febrile illness, autoimmune disorders and taking systemic corticosteroids were also excluded from study. Institutional Ethics Committee-Human Research (IEC-HR) of University College of Medical Sciences, University of Delhi, India, Reference number of ethics committee – IECHR /2020/PG/46/46 had given ethical clearance and written informed consent was taken from each study subject. Complete history and examination were done for each patient. Basic routine sampling of each patient was done by taking venous blood sample.10 mL of peripheral venous blood was collected in all patients. 2 mL of blood was collected in plain vacutainer for biochemical investigations like LFT, KFT. 4 mL of blood was collected in plain vacutainer for inflammatory biomarkers (IL-5, IL-6, CRP). 2 mL of blood was collected in EDTA vacutainer for hemogram and ESR. 2 mL of blood was collected in Sodium citrate vacutainer for plasma Fibrinogen. ESR was estimated using Westergren principle in a ROLLER 20LC Autoanalyzer (ALIFAX, ITALY). CRP was estimated using RANDOX RX Imola Autoanalyzer, (RANDOX, UK) using company reagent packs. Serum IL-6 was estimated using commercially available IL-6 ELISA kit (Diaclone, France) following manufacturer's protocol. Serum IL-5 was estimated using commercially available IL-5 ELISA kit (FineTest, China) following manufacturer's protocol. Plasma fibrinogen was estimated using commercially available Fibrinogen ELISA kit (FineTest, China) following manufacturer's protocol. Flow Sensing Spirometer was used to assess PFT on basis of FEV1, FEV1 as percent predicted, FVC, FVC as percent predicted, FEV1/FVC. Biochemical investigations like Hemogram, LFT, KFT and inflammatory markers ESR, CRP, Fibrinogen, IL-5 and IL-6 levels were measured. PFT, CAT (COPD Assessment test) score and mMRC (Modified Medical Research Council (mMRC)) score were also assessed and compared in between smoker and non-smoker COPD patients. Data were analysed using SPSS version 20.0 software. For comparing the clinical and investigational profile and inflammatory markers, unpaired t-test/Wilcoxon-Mann-Whitney U test was used, depending upon the nature of the data. All tests were two tailed. P-value of <0.05 was statistically significant. ROC curve was used to measure diagnostic performance, sensitivity and specificity of each inflammatory marker.

RESULTS

In current study (Table 1) mean age of the patients was 56.69 ± 6.78 years. The mean age of patients categorized under smoker COPD was 57.58 ± 6.53 years, while in other non-smoker COPD group it was 55.80 ± 7.00 years. Of the 40 patients categorized under smoker COPD, 38 (95%) were male and 2 (5%) were female. While 28 (70%) of the patients categorized under non-smoker COPD were male and 12 (30%) were female. Significant difference between the two groups in terms of distribution of Gender (p = 0.003) was observed. Out of all the comorbidities, the association between the two groups in terms of distribution of Old TB was significant (p = <0.001). Out of the routine blood investigations, there was significant difference between the two groups in terms of haemoglobin level (mg %) (p = 0.031), with the mean haemoglobin (mg %) being highest in the smoker COPD group. In the inflammatory markers p-value were significant for ESR, CRP and Fibrinogen. Difference between groups for IL5 and IL-6 were not significant.

DOI: https://doi.org/10.54393/pjhs.v5i11.1957

Table 1: Distribution of Age, Comorbidity, Routine Investigations and Inflammatory Biomarkers

Gender	Smokers COPD Mean ± SD / N (%)	Non-Smokers COPD Mean ± SD / N (%)	p-Value
Male	38 (95.0%)	28 (70.0%)	0.003
Female	2 (5.0%)	12 (30.0%)	
Mean Age	57.58 (6.53%)	55.80 (7.00%)	0.215
Comorbidity	**Present**	**Absent**	
HTN	6 (7.5%)	74 (92.5%)	-
T2DM	9 (11.2%)	71 (88.8%)	
Thyroid Disease	2 (2.5%)	78 (97.5%)	
CAD	5 (6.2%)	75 (93.8%)	
CVA	3 (3.8%)	77 (96.2%)	
CKD	4 (5.0%)	76 (95.0%)	
Old TB	25 (31.2%)	55 (68.8%)	
Asthma	2 (2.5%)	78 (97.5%)	
Investigations			**p-Value**
Hemoglobin (mg%)	12.40 ± 2.03	11.30 ± 2.43	0.031
TLC (mL)	8142.75 ± 2972.73	8577.25 ± 3090.02	0.427
Platelets Counts (mL)	230395.00 ± 89757.88	229800.00 ± 71762.50	0.946
Eosinophil Count (%)	4.10 ± 2.35	3.42 ±1.74	0.240
Absolute Eosinophil Count (mL)	335.58 ± 203.82	298.58 ± 188.95	0.303
Neutrophil Count (%)	69.00 ± 6.62	66.95 ± 7.08	0.138
Absolute Neutrophil Count (mL)	5790.65 ± 2483.31	5875.68 ± 2646.40	0.866
Urea (mg/dL)	43.38 ±18.28	44.67 ± 22.99	0.950
Creatinine (mg/dL)	0.98 ± 0.66	1.14 ± 1.26	0.706
Total Bilirubin (mg/dL)	0.94 ± 0.33	0.94 ± 0.56	0.395
Direct Bilirubin (mg/dL)	0.41 ± 0.25	0.42 ± 0.31	0.911
SGOT (U/L)	68.03 ± 95.95	50.23 ± 33.43	0.450
SGPT (U/L)	48.27 ± 28.32	44.83 ± 25.60	0.433
ALP (IU/L)	90.35 ± 26.28	87.03 ± 19.93	0.513
Inflammatory Biomarkers			**p-Value**
ESR (mm/Hr)	24.50 ± 7.04	19.10 ± 7.09	0.001
CRP (mg/L)	43.76 ± 24.62	28.31 ± 27.22	<0.001
Fibrinogen (ng/mL)	349.61 ± 126.53	416.85 ± 88.06	0.006
Il-5 (pg/mL)	50.60 ± 35.95	50.67 ± 31.04	0.847
Il-6 (pg/mL)	56.23 ± 50.38	40.07 ± 34.99	0.204

The mean of ESR in smoker COPD group was 24.50 ± 7.04) and non-smoker COPD group was 19.10 ± 7.09). Between the 2 groups in terms of ESR p- value was 0.001 which was statistically significant, with the median ESR being highest in the smoker COPD group. The area under the ROC curve (AUROC) for ESR showing smoker versus non-smoker COPD was 0.723 (95% CI: 0.609 - 0.836), thus explaining fair diagnostic performance and this difference was statistically significant (p = 0.001). At a cut-off of ESR (mm/Hr) ≥18, it predicts smoker COPD with a sensitivity of 85%, and a specificity of 50%.

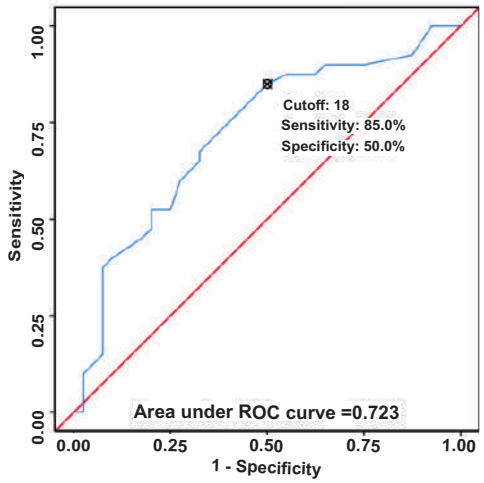

Figure 1: ROC Curve Analysis Depicting Diagnostic Performance of ESR (mm/Hr) in Predicting Smoker versus Non-Smoker COPD

CRP: The mean of CRP in smoker COPD group was 43.76 (± 24.62) and in non-smoker COPD group was 28.31 ± 27.22); this difference in CRP was significant. Median CRP being highest in the smoker COPD group. The area under the ROC curve (AUROC) for CRP predicting smoker versus non-smoker COPD was 0.762 (95% CI: 0.649 - 0.876), thus demonstrating fair diagnostic performance. Difference between two groups for CRP was statistically significant (p0.001). At a cut-off of CRP (mg/L) ≥24.3, it predicts patients with smoker COPD with a sensitivity of 90%, and a specificity of 67.5%.

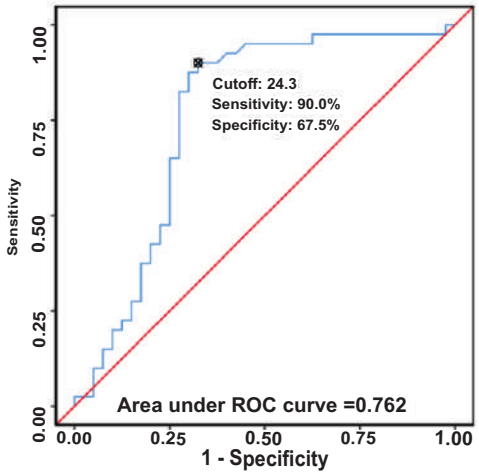

Figure 2: ROC Curve Analysis Depicting Diagnostic Performance of CRP (mg/L) in Predicting Smoker versus Non-Smoker COPD

The mean fibrinogen (ng/mL) were 349.61 ± 126.53 and 416.85 ± 88.06 in smoker and non-smoker COPD groups respectively; p – value between groups were significant (p= 0.006). The area under the ROC curve (AUROC) for Fibrinogen predicting smoker versus non-smoker COPD

DOI: https://doi.org/10.54393/pjhs.v5i11.1957

was 0.68 (95% CI: 0.559 - 0.801), hence depicting poor diagnostic performance. Difference between two groups were statistically significant (p = 0.006). At a cut-off of fibrinogen (ng/mL) ≤396, it predicts patients with smoker COPD with a sensitivity of 62.5%, and a specificity of 72.5%.

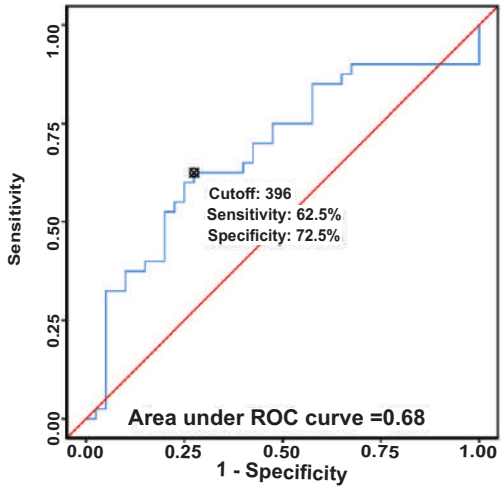

Figure 3: ROC Curve Analysis Showing Diagnostic Performance of Fibrinogen (ng/mL) in Predicting Smoker versus Non-Smoker COPD

The mean of Il-5 (pg/mL) in smoker COPD group was 50.60 ± 35.95, in nonsmoker COPD group was 50.67 (± 31.04). The AUROC for Il-5 (pg/mL) predicting smoker versus non-smoker was 0.513 (95% CI: 0.382 - 0.643), hence its diagnostic value was not good. It was not statistically significant (p = 0.847). At a cut-off of Il-5 (pg/mL) ≥50, it predicts smoker COPD with a sensitivity of 62%, and a specificity of 60%. The mean of Il-6 (pg/mL) in smoker COPD group was 56.23 (± 50.38), in non-smoker COPD group was 40.07 (± 34.99). AUROC for Il-6 predicting smoker versus non-smoker COPD was 0.583 (95% CI: 0.455 - 0.71), thus diagnostic performance of Il-6 was not good. Difference between groups were statistically not significant (p = 0.204). At a cut-off of Il-6 (pg/mL) ≥47.69, it predicts smoker COPD with a sensitivity of 50%, and a specificity of 75%.

Table 2 below depicted the mean of various spirometric test parameters among patients under smoker COPD and non-smoker COPD. There was significant difference between the two groups regarding all the spirometric test parameters, with all the parameters being greater in the patients categorized under smoker COPD group.

Table 2: Comparison of Mean of Spirometric Parameters between Smoker and Non-Smoker COPD

Variables	Smoker COPD (Mean ± SD)	Non-smoker COPD (Mean ± SD)	p-Value
FEV_1 (Liter)	1.75 ± 0.62	1.31 ± 0.52	0.001
FEV_1 (%)	67.80 ± 16.24	57.25 ± 18.33	0.010
FVC (Liter)	3.60 ± 0.71	3.09 ± 0.67	0.001
FVC (%)	106.60 ± 15.06	98.70 ± 15.93	0.0019
FEV_1/FVC	62.91 ± 9.37	57.03 ± 12.88	0.012

In table 3 variables between three sub-groups of COPD according to Refined ABCD Assessment Tool was described. The mean of mMRC Score was 1.20 ± 0.91 and 1.20 ± 0.82 in smoker COPD versus non-smoker COPD respectively. However, this difference between groups were not significant. (p = 0.946) Out of the patients under smoker COPD, 22.5% had mMRC-0, 45.0% had mMRC-1, 22.5% had mMRC-2 and 10% had mMRC-3. Out of patients under non-smoker COPD, 20.0% had mMRC-0, 48.8% had mMRC-1, 22.5% had mMRC-2 and 8.8% had mMRC-3. The mean of CAT score in smoker COPD group was 18.00 (± 8.48) non-smoker COPD group was 18.65 (± 6.76). There was no significant difference between the groups in terms of total CAT score, or in any individual component of CAT score. Out of all the patients recruited for the study, it was found that 9 patients belonged to category A (6 in smoker COPD, 3 in non-smoker COPD), 66 patients belonged to category B (30 in smoker COPD, 36 in non-smoker COPD), and 5 patients belonged to category C subgroup (4 in smoker COPD, 1 in non-smoker COPD), according to the Refined ABCD Assessment Tool. Category D patients were not included in this study. The parameters which had significant difference (p-value<0.05) between various subgroups of COPD were Eosinophil Count (%), mMRC Score, CAT Score: Cough, CAT Score: Phlegm, CAT Score: Chest Tightness, CAT Score: Breathlessness, CAT Score: Activities, CAT Score: Confidence, CAT Score: Energy, CAT Score: Total, FEV1 (%), FVC (Litre), FVC (%), FEV1/FVC. Rest other parameters were not statistically significant.

Table 2 : Comparison of Parameters with significant difference between three Sub-groups of COPD according to Refined ABCD Assessment Tool

Variables	Category A Mean ± SD / Frequency (%)	Category B Mean ± SD / Frequency (%)	Category C Mean ± SD / Frequency (%)	p-Value
Eosinophil Count	2.78 ± 1.92	4.00 ± 2.05	2.40 ± 2.19	0.045
mMRC Score	0.56 ± 0.53	1.33 ± 0.87	0.60 ± 0.55	0.008
mMRC Score				0.122
0	4 (44.4%)	10 (15.2%)	2 (40.0%)	-
1	5 (55.6%)	31 (47.0%)	3 (60.0%)	
2	0 (0.0%)	18 (27.3%)	0 (0.0%)	
3	0 (0.0%)	7 (10.6%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
CAT Score: Cough	0.78 ± 0.83	2.98 ± 1.48	2.40 ± 0.55	<0.001
CAT Score: Phlegm	1.00 ± 0.87	2.88 ± 1.57	1.60 ± 1.52	0.002
CAT Score: Chest Tightness	1.89 ± 1.17	3.15 ± 1.32	1.40 ± 0.89	0.002

DOI: https://doi.org/10.54393/pjhs.v5i11.1957

CAT Score: Breath lessness	1.56 ± 1.24	3.08 ± 1.52	1.40 ± 1.52	0.005
CAT Score: Activities	1.00 ± 0.87	2.45 ± 1.38	0.80 ± 0.84	0.012
CAT Score: Confidence	0.78 ± 1.09	2.03 ± 1.40	1.00 ± 0.71	0.012
CAT Score: Energy	0.78 ± 0.83	1.92 ± 1.44	0.40 ± 0.55	0.004
CAT Score: Total	8.67 ± 1.50	20.30 ± 6.90	9.60 ± 0.55	<0.001
FEV_1 (%)	73.00 ± 19.33	60.59 ± 17.05	69.20 ± 23.88	0.044
FVC (Liter)	3.82 ± 0.56	3.25 ± 0.71	3.65 ± 0.94	0.042
FVC (%)	113.56 ± 13.45	100.59 ± 15.38	110.20 ± 19.56	0.041
FEV_1/ FVC (%)	63.53 ± 13.91	59.38 ± 11.09	61.24 ± 15.00	0.043

DISCUSSION

Multiple studies have been done in the past to compare the phenotypic difference as well as the systemic inflammation profile between the patients of smoker and non-smoker COPD. One such study was done by Rincon M *et al.* in 2017, significant difference was not observed between the two groups for age, body mass index, dyspnea, or oxygen saturation. Pulmonary function tests were also similar in both groups. Almost all inflammatory biomarkers were significantly higher in both COPD groups than in controls. Differences between tobacco COPD and biomass COPD were only significant in IL-6, IL-8 and IL-5, which were higher in the former group [10]. This was in contrary to this study, which established a significant difference between the two groups regarding ESR, CRP level and fibrinogen level. However, there was no significant statistical difference in terms of IL-5 and IL-6 in this study. Similar to this observations Garth J *et al.*, in 2024 from Lucknow (India) reported that males predominated in S-COPD (80.3%), while females predominated in NS-COPD (60.54%) because of more biomass fuel exposure in females during cooking. They also found 19% of non-smokers had TB. Contrary to this, we found 68.8% old TB cases in Nonsmoker group. This might be because in this hospital we get more patients from various states [15]. Pandey AK *et al.*, in 2020 observed higher levels of IL-8 and TNF-α in patients with COPD and higher smoking rate in the COPD group was considered to have contributed to these findings [16]. In another study by Yazici O *et al.*, in 2020, it was concluded that the mean age of the non-smoker COPD (NS-COPD) subjects was significantly less. The smoker COPD (S-COPD) patients were all male; whereas 53% of NS-COPD were male and 47% were female. NS-COPD subjects had lower FVC values than S-COPD, but no differences were observed for other spirometric parameters. NS-COPD subjects had similar CAT score to S-COPD subjects. Further, NS-COPD subjects had significantly greater serum CRP levels than healthy subjects and no difference from S-COPD subjects. Also, S-COPD subjects had higher blood hemoglobin, RBC counts, PCV and MCV compared to NS-COPD subjects [17]. This was in part similar to this study, where it was shown that smoker COPD patients were predominantly males, had higher hemoglobin, greater spirometric parameters. While, on the contrary, we had established significant difference in CRP levels between the two groups. Studied by Salvi SS *et al.*, in 2020 on an Egyptian population, they estimated IL-6 levels and correlated with severity and frequency of COPD. They observed that decrease in smoking index will associate the increased in IL-6 levels, this negative correlation was significant. But this was contrary to this study results. Moreover, they found significant positive correlation with between the level of IL-6 and each CAT score and MMRC among cases with COPD [18]. Reported by Huhang H that levels of IL-6 was a better predictor of the frequency of acute exacerbation of COPD rather than in stable COPD cases; hence in this study we could not find significant difference between these groups as they were stable cases as we have excluded Group D patients [19]. IL-5 was a homodimer cytokine involved in eosinophil differentiation, recruitment, maturation, activation and degranulation. Stated by Narendra DK *et al.*, that airway eosinophilia has been shown to predict an increased risk of exacerbations and lung tissue and airway remodelling as well as an increased expression of interleukin (IL)-5. In current study differences between eosinophil level and IL-5 were not significant, this might be due to only stable COPD cases were taken in this study [20]. Strengths of this study was that it has a good sample size of 80 patients thus giving a more accurate prediction of prevalence and association of smoking with inflammatory biomarkers.This study also had certain limitations. Patients were from single center only. So, the results of this study cannot be applied to a larger population or to a different geographical region. In current study healthy controls were not enrolled; so unable to know the baseline values of studied inflammatory markers in healthy control group.

CONCLUSIONS

This study found significant difference between smoker versus nonsmoker COPD patients, hence these inflammatory biomarkers can be used as a screening tool between smoker and non-smoker COPD patients, for a more focused approach to treatment. This also recommended large multi-centric studies to identify cut off for inflammatory biomarkers for bedside screening of non-smoker COPD patients.

DOI: https://doi.org/10.54393/pjhs.v5i11.1957

Authors Contribution

Conceptualization: SDM, AKV
Methodology: AKV, MM
Formal analysis: MM, EAA
Writing, review and editing: SDM, SN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2290

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Knowledge and Preparedness Regarding Chemical, Biological, Radiological and Nuclear (CBRN) Warfare among Doctors and Medical Students at Combined Military Hospital (CMH) Lahore Medical College

Fariha Rahman[1*], Fatima Shakoor[1], Tahira Raza[2], Gull Sher[1] and Bushra Aziz[1]

[1]Combined Military Hospital, Lahore Medical College, Lahore, Pakistan
[2]Department of Community Medicine, Combined Military Hospital, Lahore Medical College, Lahore, Pakistan

ARTICLE INFO

Keywords:
Chemical, Biological, Radiological, Nuclear

How to Cite:
Rahman, F., Shakoor, F., Raza, T., Sher, G., & Aziz, B. (2024). Knowledge and Preparedness Regarding Chemical, Biological, Radiological and Nuclear (CBRN) Warfare among Doctors and Medical Students at Combined Military Hospital (CMH) Lahore Medical College: Chemical, Biological, Radiological and Nuclear (CBRN) Warfare among Doctors and Medical Students . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.290

***Corresponding Author:**
Fariha Rahman
Combined Military Hospital, Lahore Medical College, Lahore, Pakistan
fariharahman250@gmail.com

Received Date: 30th September, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Chemical, biological, radiological and nuclear-related disasters have become increasingly common all around the world. **Objectives:** To assess the knowledge and preparedness regarding chemical, biological, radiological and nuclear Warfare among Doctors and Medical students at Combined Military Hospital Lahore Medical College. **Methods:** In this descriptive cross-sectional study, 311 respondents participated from November 2022 to May 2023. Non-probability convenience sampling technique was used. Data were analyzed on SPSS version 26.0. **Results:** The study revealed a significant knowledge gap regarding chemical, biological, radiological and nuclear warfare. Almost 290 participants had never encountered the term 'chemical, biological, radiological and nuclear' signifying a substantial lack of awareness. Furthermore, a slightly higher knowledge gap was observed among female participants, although this difference did not reach statistical significance (p-value=0.07). Additionally, students in their 3rd, 4th, and final years of medical college demonstrated a more comprehensive understanding of chemical, biological, radiological and nuclear compared to those in their initial years of study (p-value=0.008). **Conclusions:** It was concluded that there is a significant knowledge gap about chemical, biological, radiological and nuclear Warfare and its management among medical professionals. A very low percentage of professionals were properly trained in chemical, biological, radiological and nuclear emergency management. Respondents stressed the inclusion of chemical, biological, radiological and nuclear emergency management training in the curriculum. These findings suggest that proper provision of knowledge, and training related to these disasters is inevitable for timely management and future risk reduction from such events.

INTRODUCTION

Chemical, biological, radiological and nuclear (CBRN) weapons have the potential to cause significant mass destruction and pose a threat to public health and safety. Although CBRN events are rare, they have been consistently seen in the past. Technological advancement can potentiate their use. The effects of CBRN agents depend on a multitude of factors such as the type of agent, the dose and the concentration of the agent. There have been 565 individual CBRN incidents around the world from 1990-2020, causing a significant number of morbidities and mortalities [1]. Basic and prompt actions taken effectively by the first responders are of utmost importance in the CBRN chain of survival. Competent healthcare providers are inevitable for the prompt response, and management of these incidents, in terms of reduction in CBRN-related morbidities & mortalities but also their protection [2]. Over time many events have put the risk of CBRN terrorism on the rise; the 1995 Tokyo subway sarin (nerve gas) attack was done in peacetime as a weapon of mass destruction [3]. Intentional distribution of Bacillus anthracis spores through the postal system in 2001 caused 22 cases of Anthrax, and five mortalities in America and changed the domain of public health [4]. Nuclear & radiological emergencies are among the highest priority

DOI: https://doi.org/10.54393/pjhs.v5i11.2290

risks. Education about protective behaviour is essential to combat mortality associated with these incidents. Lack of preparedness is significantly associated with fatalism [5]. Unfortunately, there is a concerning lack of preparedness internationally. Healthcare providers need to enhance their knowledge so that they can respond adequately to CBRN emergencies. Their willingness to respond, knowledge & competence are the main prerequisites for prompt management and risk reduction [6]. After World War II many countries have embarked on nuclear arms and by the end of 2022, 1300 nuclear warheads were possessed by nine countries. Nuclear weapons destroy on a vast scale and jeopardize the environment for future generations. [7]. Since we have a history of conventional wars with our neighboring countries, Pakistan believes in no first use of nuclear weapons and declares that they would be used only if the conventional means failed [8]. With the growth of global terrorism and rapid advancements in the field of science, the threat of chemical, biological, radiological and nuclear attack remains imminent. Healthcare professionals must be prepared to deal with such casualties to minimize mortality. In the wake of the present global situation, the knowledge and preparedness of first responders matter a lot and need to be enhanced to deal with CBRN emergencies [9]. There is a lack of research regarding the knowledge and preparedness of healthcare professionals in Pakistan in case of a CBRN attack. So, the rationale of our study is to find out the knowledge gap among medical professionals, as they are the first-line responders for any CBRN emergency. These agents have become increasingly common all around the world. With terrorism on the rise, healthcare professionals must have the knowledge and training and be able to perform efficient emergency management.

This study aims to assess the Knowledge and preparedness regarding CBRN Warfare among Doctors and Medical students at Combined Military Hospital (CMH) Lahore Medical College.

METHODS

This cross-sectional study was conducted at CMH Lahore Medical College using a non-probability convenience sampling technique. Data collection took place between November 2022 and May 2023. The inclusion criteria were participants who fully completed the questionnaire. Undergraduates, graduate trainees and doctors of CMH Lahore Medical College were eligible to participate. Participants who submitted incomplete questionnaires were excluded. Verbal consent was taken. Answering the questionnaire means that the respondents agreed to participate. Confidentiality and anonymity were ensured. Ethical approval was taken from the Institutional Review Board (648/ERC/CMH/LMC). The questionnaire was designed based on a thorough literature review. Cronbach's alpha value was 0.78. It included socio demographic information (age, gender, academic level, and further qualifications), CBRN knowledge, and preparedness levels. The participants' level of knowledge and preparedness was assessed using a 10-point ordinal scale. Additionally, a 9-item quiz containing theoretical questions was included to evaluate the participants' understanding of CBRN Warfare. Sample size was calculated through WHO statistics calculator, based on 5% margin of error and 95% confidence level. Statistical analysis was carried out using SPSS version 26.0. Chi-square test of significance was used to see association between level of education and CBRN knowledge and ability to deal with emergencies. $p<0.05$ was considered statistically significant (Figure 1).

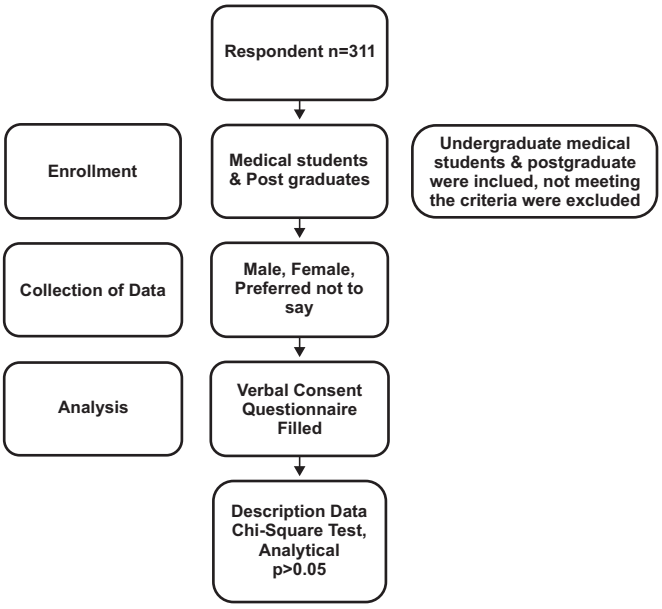

Figure 1: Graphical Presentation

RESULTS

In this study, we surveyed 311 medical students and doctors affiliated with CMH Lahore Medical College and Hospital to evaluate their knowledge of CBRN (Chemical, Biological, Radiological, and Nuclear) warfare. The mean age of the respondents was 19.96 years ± 1.9 SD. The range of age was 17-28 years. Out of 311 respondents, 96 (30.9%) were in their first year, 42 (13.5%) were in their second year, 35 (11.3%) were in their third year, 89 (28.6%) were in their fourth year, 38 (12.2%) were in final year and 11 (3.5%) were postgraduate students. 300 were MBBS students, 3 were fellows of the College of Physicians and Surgeons (FCPS), 3 were MPhil, and 5 had postgraduate degrees in other specialities. Among the participants, 167 (53.7%) were male, 141 (45.3%) were female, & 3 (1%) preferred not to say, all of whom completed the questionnaire (Figure 2).

DOI: https://doi.org/10.54393/pjhs.v5i11.2290

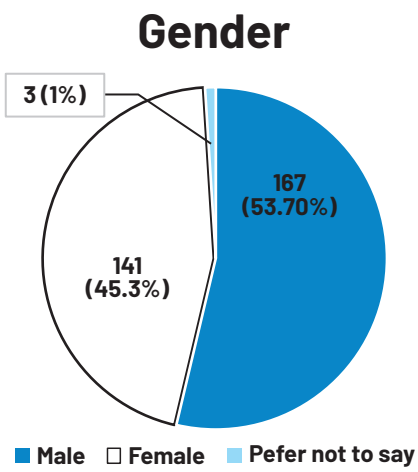

Figure 2: Gender Distribution

Surprisingly only 22(7.1%) heard the term CBRN, and 289(93%) out of the 311 respondents had not previously heard before entering into the medical profession, indicating a significant knowledge gap in this area (Figure 3).

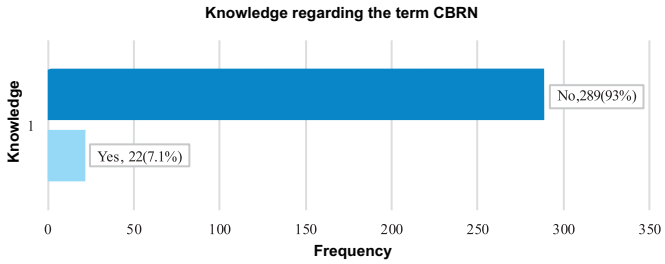

Figure 3: Level of Knowledge Regarding CBRN Warfare

There was a slightly greater knowledge deficit among females than male, the difference did not reach statistical significance (p-value: 0.07) (Figure 4).

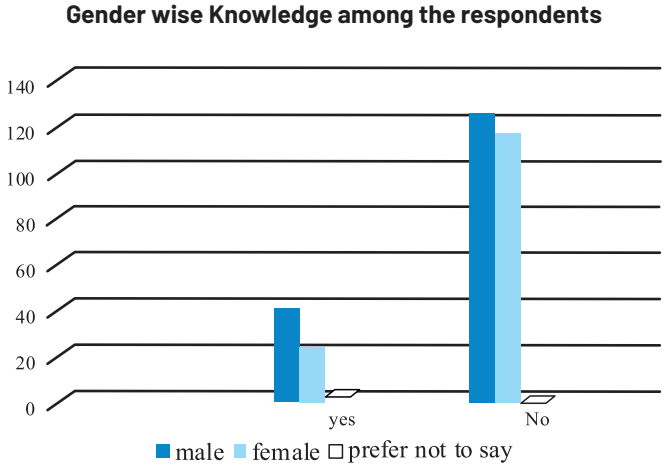

Figure 4: Knowledge About CBRN among Male and Female Students

Students in their 3rd, 4th, and final years exhibited a more substantial understanding of CBRN when compared to those in their initial years of study, and postgraduates had better knowledge regarding CBRN, p=0.008 (Figure 5).

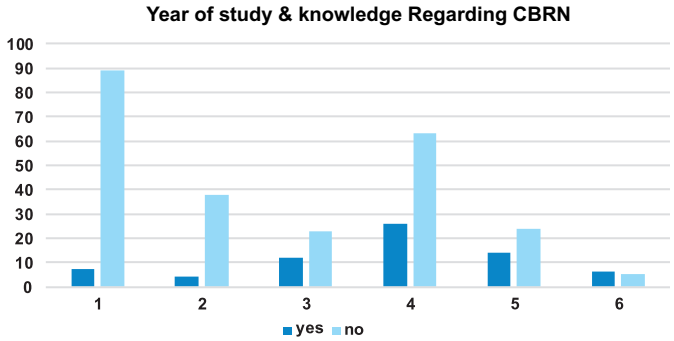

Figure 5: Figure 5: Comparison of Knowledge among Different Professional Levels

Sixty-eight (21.9%) respondents exhibited awareness regarding CBRN warfare; after joining the medical profession, while 243 (78.1%) were still unaware of it. Out of 68 respondents who were aware of the term, 21(6.8%) knew, & proper training in emergency management. Out of 300 medical students, 112 (37.3%) wanted to become physicians, 51 (17%) wanted to excel in emergency medicine, and 148 (49.3%) showed interest in other specialities. Sixteen (5.1%) lived within a 20 km radius of a nuclear or chemical installation, and 291 (93.6%) did not. Twenty-five (8.0%) were involved in disaster management beyond their military and medical careers, 286 (91.9%) were not. Regarding inclusion of CBRN training in the curriculum, which should prepare the graduates to deal with such incidents; 162 (52.1%) strongly agreed, 36 (43.7%) felt it should, and 13 (4.2%) considered it unnecessary. Only 30 (9.6%) respondents knew how to respond to patients affected by chemical chain collisions. 289 (90.3%) did not. Regarding iodine tablets preventing internal radiation; 96 (30.9%) answered correctly. Out of which 52 (31.1%) were male and 44 (31.2%) were female. The first step in chemical decontamination is to wash with water and soap, which was correctly answered by 155 (50%) respondents. Limiting the exposure and increasing the distance, limits the damage by radiation was correctly answered by 152 (49%) respondents. The first step in nuclear irradiation decontamination is to remove clothes and shoes as soon as possible, which was answered by 95 (30%) respondents only. Regarding all the questions on the visual scale, the higher the year of study the better was knowledge & capability to deal with the patient. There was a positive correlation between years of study and their knowledge and capability to deal with emergencies related to chemical, and biological nuclear incidents (Table 1).

DOI: https://doi.org/10.54393/pjhs.v5i11.2290

Table 1: Correlation between Knowledge, Capacity to Deal with Emergencies and Year of Study

Control Year of Study	Nuclear	Chemical	Biological	Contagious Disease Incidence	Capability to Deal with the Nuclear Incident Patients	Capability to Deal with the Chemical Incident Patients	Capability to Deal with the Biological Incidents Patients
Nuclear	0.001	-	-	-	-	-	-
Chemical	-	0.001	-	-	-	-	-
Biological	-	-	0.001	-	-	-	-
Contagious Disease Incidence	-	-	-	0.001	-	-	-
Capability to Deal with the Nuclear	-	-	-	-	0.001	-	-
Capability to Deal with the Chemical Incident	-	-	-	-	-	0.001	-
Capability to Deal with the Chemical Incident	-	-	-	-		-	0.001

DISCUSSION

Our study aimed to evaluate CBRN warfare knowledge and preparedness among 311 medical students and doctors at CMH Lahore. In our study, the mean age of the respondents was 19.96 years ± 1.9 SD. Male respondents were 53.69 %, and females 45.33%. Forty-three percent of the respondents in another study belonging to the same age bracket exhibited a low level of knowledge [9]. Out of 311 respondents, 93% of participants had not previously encountered the term "CBRN", and only 7 % of the respondents heard the term. Similar results were seen in another study, in which 24.1 % of the respondents had ever heard the term CBRN [10]. A gender-wise slightly higher knowledge gap was seen among females, although this difference did not reach statistical significance (p-0.07). The professional level that the respondents wanted to achieve was 36% physicians, 16.4% emergency physicians, and 47.6% interested in other specialities. We found that only 21 (6.8%) respondents had formal training regarding disaster management, and felt capable of dealing with CBRN emergencies. A study revealed that there were insufficient healthcare providers and their awareness levels were very low regarding CBRN emergency management and were not skilled enough to deal with the situation, even in the presence of emergency plans [11-13]. When asked whether CBRN training should be included in the curriculum, 52.1% of respondents agreed, 43.7% said it should be, and 4.2% said that it's useless. A study depicted poor knowledge and preparedness regarding CBRN incidents. They stressed the inclusion of necessary training for medical and nursing staff to deal with such events, 50 % of the respondents considered themselves not prepared for CBRN warfare management. Similarly, seven out of ten hospitals had emergency plans, but only two were conducting drills and were lacking planning and adequate training for the medical staff to deal with emergencies [14, 15]. In the current study, the initial years of undergraduate medical students exhibited less knowledge as compared to clinical years, which indicates that the level of education in the higher level of medical study provided knowledge regarding CBRN. This is consistent with the results of a study, which states that case-based CBRN training in medical undergraduates enhances healthcare provider's knowledge and capacity to deal with such emergencies [16]. Out of 300 medical students, 112 (37.3%) wanted to become physicians, 51 (17%) wanted to excel in emergency medicine (EM), and 148 (49.3%) showed interest in other specialities. In another study in Saudi Arabia, only 7% of the students preferred emergency medicine as their first choice and 33,2% considered it in their top three possible career options [17]. Regarding inclusion of CBRN training in the curriculum, which should prepare the graduates to deal with such incidents; 162 (52.1%) strongly agreed, 36 (43.7%) felt it should, and 13 (4.2%) considered it unnecessary. Similarly, Timely response and preparedness combined with specialized training enable the healthcare responders to deal with CBRN emergencies. 94% of the respondents agreed to the inclusion of emergency aid, and disaster management in their curriculum [18, 19]. Regarding all the questions on the visual scale, the higher the year of study the better was knowledge and capability to deal with the patient. There was a positive correlation between the year of study and their knowledge and capability to deal with emergencies related to chemical, and biological nuclear incidents. These findings are similar to another study on medical students, in which the level of knowledge was found to be a significant predictor for emergency readiness [20]. The present study underscores the urgent need for improved education and training on CBRN warfare among medical students and doctors. The substantial knowledge gap identified in this research emphasizes the importance of further investigation to identify contributing factors and develop effective strategies for addressing this issue.

DOI: https://doi.org/10.54393/pjhs.v5i11.2290

CONCLUSIONS

It was concluded that the current study highlights a notable knowledge gap concerning CBRN warfare among medical students, especially those in their early years. To address this, comprehensive education and training on CBRN hazards and management are essential to prepare future first responders effectively.

Authors Contribution

Conceptualization: FA, TR
Methodology: FA, FS, TR, GS, BA
Formal analysis: FA, FS, GS
Writing review and editing: FA, FS, GS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2362

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Frequency of Respiratory Symptoms among Marble Workers in Cutting and Grinding sections of Marble Factories, Lahore

Imran Maqsood Butt[1*], Seema Hasnain[1], Aneela Chaudhary[2], Misbah Jehangir Kishmiri[1], Javeid Iqbal[3] and Faisal Mushtaq[4]

[1]Department of Community Health Sciences, Fatima Memorial Hospital College of Medicine and Dentistry, Lahore, Pakistan
[2]Department of Pulmonology, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Pakistan
[3]Department of Medicine, Fatima Memorial Hospital College of Medicine and Dentistry, Lahore, Pakistan
[4]Department of Biostatistics, Institute of Public Health, Lahore, Pakistan

ARTICLE INFO

Keywords:
Occupational Exposure, Respiratory Symptoms, Marble Workers, Silica Dust, Obstructive Lung Disease

How to Cite:
Butt, I. M., Hasnain, S., Chaudhary, A., Kishmiri, M. J., Iqbal, J., & Mushtaq, F. (2024). Frequency of Respiratory Symptoms among Marble Workers in Cutting and Grinding sections of Marble Factories, Lahore: Respiratory Symptoms in Marble Workers. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2362

***Corresponding Author:**
Imran Maqsood Butt
Department of Community Health Sciences, Fatima Memorial Hospital College of Medicine and Dentistry, Lahore, Pakistan
imran20600@yahoo.com

Received Date: 15th October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Occupational exposure to dust particles was a public health problem in developing countries. One of the main dust which is responsible for higher prevalence of obstructive lung diseases is silica dust present in marble factories. **Objective:** To compare the frequency of respiratory symptoms among individuals working in cutting and grinding sections of marble factories, Lahore. **Methods:** A cross sectional study was conducted in marble factories situated in Ichra market, Ferozepur Road Lahore, during April to September 2022. Forty-one marble employees each from wet cutting and dry grinding sections were selected after obtaining written consent from the respondents. Data were collected in a pretested standardized questionnaire regarding socio demographic and respiratory symptoms. The data were analyzed by SPSS version 24.0. **Results:** The mean age of workers was 29.93 ± 6.18 years while mean years of work experience was11.19 ± 5.66 years. 20 (48.78%) workers of dry cutting had cough as compared to 14 (34.14%) workers of wet cutting section. Similarly, 11 (26.8%) workers of grinding section had experienced phlegm whereas 6 (14.63%) from wet cutting workers complained of this symptom. Similarly, breathlessness and chest tightness were more prevalent among grinding workers as compared to marble cutting workers showing statistically significant association (p-value < 0.005). Greater than 15 years of work exposure, respiratory symptoms were significantly (p-value < 0.001) more common in grinding workers than in cutting workers. **Conclusion:** Respiratory symptoms were more marked among grinding workers than among wet cuttings workers.

INTRODUCTION

Occupational lung diseases have been a serious threat to global health since the beginning of civilization [1]. Because of growing urbanization, over 90% of the world's population is susceptible to the negative impacts of air pollution [2]. According to estimates from the World Health Organization (WHO), the 13th leading cause of mortality worldwide is due to the presence of the deadliest Particulate Matter (PM), specifically airborne particles with a diameter of 2.5 micrometers. These particles are thought to cause approximately 800,000 premature deaths annually [3]. By 2060, it is predicted that 6.9 million people will die from air pollution-related causes annually, if severe control measures are not put in place [4]. One of the most common air pollutants is dust. The marble sector is one of them which produces such type of dust containing silica, a hazardous material. The term "silica" is a generic term for minerals with the chemical formula SiO2, or Silicon Oxide [3, 4]. The most common mineral on earth is thought to be silica. Free silica has been labelled a group 1 carcinogen by the International Agency for Research on Cancer (IARC), which causes lung cancer in people with underlying silicosis [5, 6]. Nowadays, it is estimated that 23 million employees in China, 11.5 million in India, 3.2 million in the European Union, and 2.3 million in the US are exposed to

DOI: https://doi.org/10.54393/pjhs.v5i11.2362

quartz or Respirable Crystalline Silica (RCS) on the workplace [6, 7]. In many different industries, workers are exposed to the dust that is produced by crystalline silica [2, 7]. Grinding, cutting, polishing, and cleaning are the main types of activities performed by the marble workers in the marble factories. One of the most chronic work-related illnesses in human history is silicosis. Long-term inhalation of silica compounds results in this chronic, nodular, fibrotic, and granuloma formation [7, 8]. There has been a noticeable increase in silica exposure due to the growing usage of artificial marble, which is made up of 85–93% RCS and responsible for a sharp rise in the number of silicosis cases, which are primarily recorded in Spain, Australia, and Israel [4, 7]. Due to the increasing demand for work involving silica exposure and the absence of adequate protection, the incidence of silicosis is rising globally [8]. In addition to silicosis, silica exposure can result in a number of other illnesses. Prior studies have shown a link between increasing silica exposure and the development of pulmonary tuberculosis, lung cancer, Chronic Obstructive Pulmonary Disease (COPD), renal problem rheumatoid arthritis, radioactive disease, autoimmune disorder and benign respiratory diseases [9-13]. A lot of research has been done on this topic globally, however limited literature is available in Pakistan [14]. There is a scarcity of scientific research in Pakistan regarding respiratory issues brought on by occupational dust exposure. Moreover, there is a lack of understanding among the workforce regarding workplace safety.

The study objective was to investigate the occupational health of marble workers exposed to silica dust, and to compare the occupational health impacts between two exposure categories within the marble industry i.e. grinding (dry cutting) and wet cutting sections.

METHODS

This cross-sectional study took place in Ichra Market on Ferozepur Road, Lahore, a heavily urbanized industrial area where marble factories were located. The focus was on marble workers from the grinding (dry cutting) and wet cutting sections. The data were collected over a six-month period from April to September 2022, after getting approval from UHS (No; UHS/Education/126-19/1001). The study group included male marble workers aged 18 to 40 who worked 30 hours or more per week and had been exposed to marble dust for over a year. Workers with chronic respiratory conditions were excluded from the study. In this study, the cough was defined as the rapid, harsh sound produced when air was expelled from the lungs, persisted for longer than eight weeks, while a wheeze was characterized by a persistent, high-pitched, whistling, or rattling sound that comes from the chest during expiration for more than 12 weeks [15, 16]. To determine the sample size, the WHO sample size calculator was utilized, with assumptions made on 5% significance level, 90% study power, population variance ($\sigma 2$) = 0.5329, and anticipated percentages of respiratory problems of study groups I and II ($\mu 1$) = 35.5% and ($\mu 2$) 16.2%, respectively. A total of 82 subjects were the study sample size, forty-one subjects were from each marble section working in the grinding and cutting section respectively [17]. The study population was selected through a simple random sampling method, with 41 individuals chosen for both the marble wet cutting and the marble dry cutting (grinding) group. Each participant was informed about the study, and written informed consent was obtained from those who agreed to participate. All participants were personally interviewed using a functional proforma developed by the American Thoracic Society [18]. All the collected data were entered and analyzed by SPSS version 25.0 Frequency tables were created for categorical variables, whereas mean and standard deviations were computed for continuous variables. Chi square test was used for the comparison among marble workers with years of work exposure. For all analyses, a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The sociodemographic characteristics between the marble wet cutting and grinding (dry cutting) group were compared and no association ($p > 0.05$) was noted (Table 1).

Table 1: Demographic Characteristics of Marble Workshop Workers Wet Cutting and Grinding (Dry Cutting) Group

Study Variables	Marble Workers (Wet Cutting) Group N (%)/(Mean ± SD)	Marble Workers Grinding (Dry Cutting) Group N (%)/(Mean ± SD)	p-Value
Age (Years)			
21-25	08 (19.51%)	14 (34.15%)	0.068
26-30	12 (29.27%)	13 (31.71%)	
31-35	06 (14.63%)	08 (19.51%)	
36-40	15 (36.59%)	06 (14.63%)	
Mean ± SD	31.17 ± 6.70	28.68 ± 5.42	
Marital Status			
Single	21 (51.22%)	22 (53.66%)	0.822
Married	20 (48.79%)	19 (46.34%)	
Educational Status			
Middle	31 (75.60%)	32 (78.04%)	1.000
Matric	05 (12.20%)	05 (12.20%)	
Intermediate	05 (12.20%)	02 (04.88%)	
Graduation	00 (00.00%)	02 (04.88%)	
Height (cm)	172.59 ± 10.82	173.10 ± 9.66	0.822
Weight (Kg)	75.66 ± 15.60	73.12 ± 11.71	0.408
Experience (Years)	11.03 ± 06.19	11.35 ± 05.16	0.802

Marble workers of the grinding section experienced more coughs (48.78%) cough as compared to 14 (34.14%) wet cutting workers, which was statistically insignificant ($p=0.262$). Similarly, the percentage of grinding workers who reported phlegm 11 (26.86%) was also higher than that of wet cutting workers 6 (14.63%), with insignificant ($p=0.276$) findings. Grinding workers also had a higher rate of breathlessness, 10 (24.39%) and chest tightness 8

DOI: https://doi.org/10.54393/pjhs.v5i11.2362

(19.51%), than wet cutting workers 4 (9.76%) and 1 (2.44%) respectively. A statistically significant result (p=0.015) was noted in chest tightness, while on the other hand no difference (p=0.140) was observed in breathlessness (Table 2).

Table 2: Respiratory Symptoms among Marble Workers by Study Group (n=82)

Respiratory Symptoms	Grinding		2-Sided Significance
	Wet Cutting Group N (%)	Dry Cutting Group N (%)	
Cough	14 (34.14%)	20 (48.78%)	0.262
Phlegm	6 (14.63%)	11 (26.86%)	0.276
Breathlessness	4 (09.76%)	10 (24.39%)	0.140
Chest Tightness	1 (02.44%)	8 (19.51%)	0.015
Wheezing	0 (00.00%)	2 (04.88%)	0.494

Among marble grinding workers, the primary respiratory symptoms included cough, phlegm, and breathlessness, typically emerging after 6-10 years of occupational exposure. In contrast, cutting workers experienced these symptoms after 11-15 years of exposure, with phlegm specifically appearing after 16-20 years. (Figure 1-3)

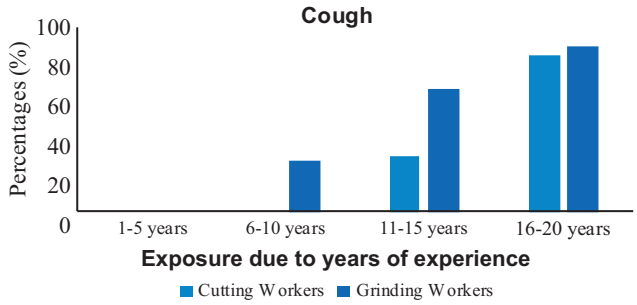

Figure 1: Comparison of Cough with Years of Exposure among Marble Workers

The Chi square test was applied, which showed that with increased duration of 16-20 years of work exposure, the maximum rate of cough 9 (90%), 11 (84.61%) were noted in grinding (dry cutting) and wet cutting workers respectively, which were statistically insignificant (p<0.05). Figure 1

More incidence 8 (98%) of breathlessness was reported in grinding workers as compared to 3 (23.1%) marble cutting workers. A highly statistically significant (p<0.001) result was noted when the Chi square test applied. (Figure 2)

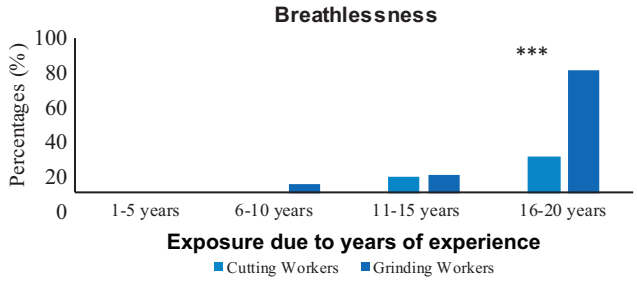

Figure 2: Comparison of Breathlessness with Years of Exposure among Marble Workers

Similarly, with same work exposure the maximum rate of phlegm 9 (90%), 6 (46.2%) were noted in grinding (dry cutting) and wet cutting workers respectively, which were statistically (p<0.05) significant. (Figure 3)

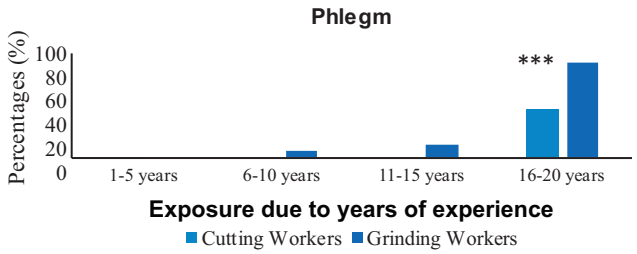

Figure 3: Comparison of Phlegm with Years of Exposure among Marble Workers

Chest tightness emerged as the only respiratory symptom common to both groups after 16-20 years of work exposure. It was also more prevalent, affecting 7 (70%) of grinding workers and 1 (7.7%) of wet cutting workers and a statistically significant (p<0.001) result was observed. (Figure 4)

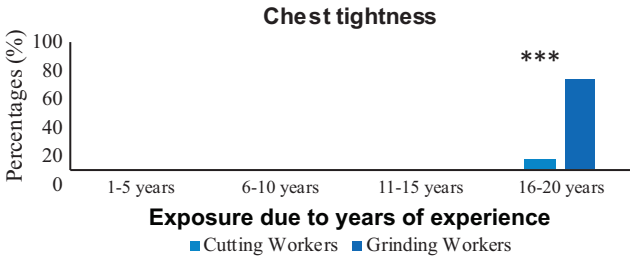

Figure 4: Comparison of Chest Tightness with Years of Exposure among Marble Workers

Wheezing was exclusively reported among grinding (dry cutting) workers during the same period (20%), and it was statistically highly significant (p < 0.005). Figure 5

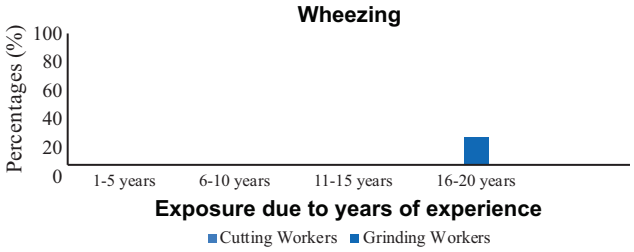

Figure 5: Comparison of Wheezing with Years of Exposure among Marble Workers

df = 1, Statistically Significant at $\alpha \leq 0.05$ (***p-value≤0.05)

DISCUSSION

Cough, phlegm, breathlessness, and chest tightness were the most predominant reported respiratory symptoms in this study. The investigation's results were comparable to those of previous studies carried out in Bangladesh and Turkey [21, 22]. It was determined that individuals working in marble areas were more susceptible to respiratory problems due to prolonged exposure to silica dust. Additionally, they provided evidence of a high correlation between respiratory impairment and prolonged exposure to silica dust [21, 22]. The study findings indicated that cough was the most reported respiratory complaint. This

DOI: https://doi.org/10.54393/pjhs.v5i11.2362

finding was in consistent with earlier studies conducted by Ullah (50%), Isara (35.5%) and Priya (50.24%), while several authors, including Aydin (14.46%), Thongtip (17%) and Nemer (11.4%), reported a considerably lower prevalence of cough than this study's result [14, 20, 23-25]. Phlegm was the second most prevalent respiratory condition identified in the current study. Like this study, nearly similar type of prevalence rate (21.1%) was reported by Isara but several researchers Thongtip (3%), Aydin (9.95%) and Priya (13.6%), found relatively low prevalence [20, 22-24]. Their working knowledge, routine medical examinations, understanding of personal protective equipment, high standards, and regulatory restriction were probably the main causes of the low prevalences of these symptoms. Most of the previous researchers Aydin, Ullah, had documented in their studies that all these respiratory symptoms linked to marble dust generated during marble crushing activities and with increased work exposure were significantly ($P < 0.005$) associated with worsening of respiratory ventilation which were consistent with the findings of this study [22, 14]. In contrast to current study findings, stone crushing workers in Bangladesh reported extremely high rates of cough (66.5%), chest tightness (76.00%), shortness of breath (74.5%), wheezing (45.5%), and phlegm (29.5%) [21]. The research author claimed that these symptoms were significantly ($P>0.005$) associated with respiratory issues. He also came to the conclusion that the use of old-fashioned, outdated tools, poor exhaust ventilation, crowded work areas, a lack of government regulations, a lack of knowledge about personal protective equipment, and long work hours are the most likely causes of the high respiratory prevalence. Study limitation includes recall errors, information bias and harmful substances in the workplace, chemical compounds present in the stone, undetectable amounts of dust particles other than silica, which were not addressed in this study. Marble workers should undergo pre-employment screening and to enhance the working environment there was a need for health education, and rationalization of working procedures (like ergonomics, protective equipment, safety method, government regulations, longitudinal or interventional studies) in marble factories. In future more longitudinal or intervention studies with larger sample sizes were recommended to determine the temporal association between pulmonary system and numerous variables for better worker knowledge and understanding of health risks based on observation.

CONCLUSIONS

Respiratory symptoms were found to be more common in grinding (dry cutting) workers soon after 1-5 years of dust exposure as compared to the wet cutting workers, who developed after 6-10 years of exposure. The present study showed that working in the marble factories constantly for more than 15 years led to the higher prevalence of respiratory symptoms, this would ultimately disrupt their state of health.

Authors Contribution

Conceptualization: IMB
Methodology: IMB, SH, AC, MJK, JI, FM
Formal analysis: IMB, FM
Writing, review and editing: IMB, SH, AC, MJK, JI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research,

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DOI: https://doi.org/10.54393/pjhs.v5i11.1911

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

The Impact of Lifestyle Factors on the Development of Kidney Stones

Nisar Ahmad[1], Ijaz Ur Rehman[2], Khalid khan[1], Mian Latif Javed[1], Mohammad Faisal[3] and Rida Naz[4*]

[1]Department of Urology, Sahiwal Medical College, Sahiwal Teaching Hospital, Sahiwal, Pakistan
[2]Department of Urology, Gomal Medical College, District Head Quarter Teaching Hospital, Dera Ismail Khan, Pakistan
[3]Department of Community Medicine, Gomal Medical College, Dera Ismail Khan, Pakistan
[4]Regional Blood Centre, Dera Ismail Khan, Pakistan

ARTICLE INFO

Keywords:
Hydration, Kidney Stones, Lifestyle Factors, Physical activity

How to Cite:
Ahmad, N., Rehman, I. U., Khan, K., Javed, M. L., Faisal, M., & Naz, R. (2024). The Impact of Lifestyle Factors on the Development of Kidney Stones: Lifestyle Factors on the Kidney Stones Development. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1911

***Corresponding Author:**
Rida Naz
Regional Blood Centre, Dera Ismail Khan, Pakistan
dr.ridaanaz@gmail.com

Received Date: 27th September, 2024
Acceptance Date: 19th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Kidney stones are a common urological condition affecting millions worldwide, and lifestyle factors significantly influence their risk. **Objectives:** To assess the correlation between the risk of kidney stones and dietary habits, physical activity levels, hydration status, and body mass index in a cohort of 220 participants at Gomal Medical College, Dera Ismail Khan. **Methods:** A cross-sectional study was executed, with 220 adults stratified into two groups based on presence (n=111) or absence (n=109) of kidney stones. Validated structured questionnaires assessing hydration level, physical activity, body mass index, socioeconomic level, and dietary intake; animal protein, oxalates, and sodium were used to compile data. Chi-square testing and logistic regression allowed one to compute the odds ratios for kidney stone risk. **Results:** Significant risk factors for kidney stones were shown by high intake of animal protein (OR=3.88, p<0.001), high sodium intake (OR=1.98, p<0.05), and high oxalate intake (OR=1.65, p<0.05). High physical activity and adequate hydration were protective against kidney stones. A greater body mass index (OR=2.33, p<0.01) was linked to a higher risk. Socioeconomic level and stone frequency showed an association; the lower status was linked to a higher prevalence of stones (OR=1.75, p<0.05). **Conclusions:** It was concluded that the study underlined the strong relationships between particular lifestyle choices and kidney stone development probability. Good preventive measures are keeping an active lifestyle, making sure one is hydrated enough, and controlling their food. These findings highlight the importance of including lifestyle modifications in the clinical management of kidney stones.

INTRODUCTION

Kidney stones affect millions of people globally [1], and lifestyle choices, which follow complex pathways, greatly affect the recurrence and production of kidney stones. Diet affects the production of kidney stones [2, 3]. Animal protein consumption increases uric acid and calcium levels in urine while reducing citrate, a molecule that inhibits stone formation. Low urine volume due to inadequate hydration concentrates calcium, oxalate, and uric acid in the urine, leading to stone formation [4, 5]. One's degree of hydration mostly determines the development of kidney stones. Inappropriate fluid consumption causes low urine volume, which concentrates compounds such as calcium, oxalate, and uric acid, which can precipitate and form stones [6, 7]. Studies repeatedly show that increasing fluid intake dilutes urine and lowers the risk of stone development, thereby stressing the need for constant and enough water intake as a preventative action against kidney stones [8-10]. Furthermore, the likelihood of kidney stones includes physical inactivity and obesity. Excess body weight is associated with metabolic alterations that help kidney stones to develop, including insulin resistance and raised urine excretion of calcium and oxalate [11, 12]. Regular physical activity helps to maintain a good weight; it also improves metabolism and lowers the risk of stone development [13].Preventing kidney stones depends on lifestyle changes including maintaining a healthy weight through consistent exercise, enough hydration, and dietary adjustments [14]. Healthcare providers must understand the implications of these elements for persons at risk of kidney stones as well as for those implementing preventative policies. As research clarifies kidney stone development, the major preventive strategy of lifestyle

DOI: https://doi.org/10.54393/pjhs.v5i11.1911

modification remains a pillar of management. This non-invasive approach works well in treating this painful disorder.

This study aimed to assess the correlation between the risk of kidney stones and dietary habits, physical activity levels, hydration status, and body mass index in a cohort of 220 participants at Gomal Medical College, Dera Ismail Khan.

METHODS

Gomal Medical College in Dera Ismail Khan, Pakistan was the site of this observational study spanning June 2023 to September 2024. The study recruited 220 total participants, and the sample size was determined using G*Power software, based on the expected prevalence of kidney stones in the target population and the hypothesized odds ratios for key risk factors such as dietary habits and physical activity levels. The calculation aimed to achieve a power of 80% and a significance level of 5%. The expected prevalence was 10%, as mentioned by the National Kidney Foundation and USA. The primary outcome variable was the presence or absence of kidney stones, with key predictors being dietary intake (animal protein, oxalates, and sodium), physical activity levels, and body mass index (BMI). This study used a non-probability consecutive sampling technique to recruit participants from the Urology outpatient department of Gomal Medical College. The criteria were adults between the ages of eighteen and sixty-five who offered informed consent. Those receiving dialysis, those with metabolic problems impacting the kidney, such as hyperparathyroidism, or those with chronic renal illnesses were eliminated. Participants were asked to complete the validated structured questionnaire to provide thorough information on their dietary patterns (including their consumption of animal protein, oxalate-rich foods, and salt), fluid intake, physical activity levels, BMI, and medical history about kidney stone formation. The questionnaire also includes demographic data on age, gender, socioeconomic level, and socioeconomic background. To assess hydration status, both urine output and urine specific gravity were measured. Urine output, recorded in milliliters per day, helps indicate hydration levels, with outputs below 1.5 liters per day classified as inadequate, suggesting a higher risk for stone formation due to concentrated solutes. Urine-specific gravity, measured using a refractometer or dipstick (normal range: 1.000–1.030), provides further insight, with values above 1.020 indicating concentrated urine and potential dehydration, while values below 1.010 suggest adequate hydration. These parameters, collected during routine visit, were cross-referenced with participants' reported fluid intake to ensure accurate classification of hydration status. Dietary intake of sodium and oxalates was quantified using a validated food frequency questionnaire (FFQ). Sodium intake was determined based on participants' reported frequency and portion sizes of high-sodium foods, converted into daily intake values using standardized nutrient content databases. Daily intakes exceeding 2,300 mg were classified as high, as this threshold is linked to increased kidney stone risk. Oxalate intake was assessed through reported intake of oxalate-rich foods like spinach, nuts, and beans. Estimated daily intakes over 100 mg were classified as high, correlating with increased risk for oxalate-type kidney stones. Dietary assessments using a validated meal frequency questionnaire included items raising kidney stone risk. Participants' daily fluid intake was matched with urine output and specific gravity readings acquired during regular visits to evaluate hydration levels. The International Physical Activity Questionnaire (IPAQ) assessed participants' weekly physical activity using METs based on self-reported activities. Physical activity was categorized into high (≥3,000 MET-minutes/week), moderate (600–3,000 MET-minutes/week), and low (<600 MET-minutes/week) levels. Participants reported the frequency, duration, and intensity of activities (e.g., walking, moderate and vigorous exercise), with MET values assigned per IPAQ standards. Weekly MET scores were then calculated to categorize activity levels and evaluate their association with kidney stone risk. Quantitative variables included age, BMI, daily fluid intake, urine output, MET scores, and dietary intake of animal protein, oxalates, and sodium. These variables were analyzed using descriptive statistics such as means and standard deviations. For comparative analysis, independent t-tests and chi-square tests were employed to assess differences between participants with and without kidney stones. Binary logistic regression analysis was employed to evaluate the associations between the presence of kidney stones (primary outcome) and key predictors, including dietary intake (animal protein, oxalates, and sodium), physical activity levels, hydration status, and BMI. The Gomal Medical College IRB's research proposal was approved vide letter No. 29/GIMS/JC and then the study was conducted from June 2023 to September 2024. Every participant completed a written informed permission form before the study began. Throughout the research, participants' privacy and confidentiality of their data were maintained.

RESULTS

This study found among the Gomal Medical College, Dera Ismail Khan participants the correlation between lifestyle choices and kidney stone development. Comprehensive statistical analyses including chi-square tests and regression models were done on a sample of 220 people almost equally split between those with and without kidney stones. The results underlined the significant impact on kidney stones materialization of dietary patterns, hydration level, physical activity level, and body mass index. These results highlighted the possibility of lifestyle changes in the therapy and prevention of kidney stones, therefore guiding clinical practices and patient counseling with great relevance. Our demographic and lifestyle data

DOI: https://doi.org/10.54393/pjhs.v5i11.1911

clearly show the significant differences between people with kidney stones and those without. Participants with kidney stones were significantly older ($p<0.05$). Participants with kidney stones also had a much greater intake of animal protein, oxalate-rich foods, and salt ($p<0.05$), whereas BMI (29 kg/m^2) differed considerably from 27 kg/m2. Stone presence was also significantly correlated with hydration status and physical activity levels, with high physical activity levels and adequate hydration being protective against stone formation ($p<0.05$)(Table 1).

Table 1: Characteristics Features of Participants

Characteristic	Total (n=220)	No Kidney Stones (n=109)	With Kidney Stones (n=111)	χ^2	p-value
Age (Years)	45 ± 10	43 ± 11	43 ± 11	3.85	0.050*
Gender					
Male	119	59	60	1.22	0.271
Female	101	50	51		
BMI (kg/m^2)	28 ± 5	27 ± 4	29 ± 6	5.77	0.024*
Dietary Habits					
High Animal Protein	102	33	69	19.5	0.001*
High Oxalate Foods	92	39	53	6.5	0.019*
High Salt Intake	107	44	63	8.1	0.004*
Hydration Status					
Adequate	147	79	68	5.4	0.022*
Inadequate	73	30	43		
Physical Activity Levels					
High	58	37	21	9.8	0.002*
Moderate	82	44	38	5.1	0.025*
Low	80	28	52	16.2	0.001*
Socioeconomic Status					
High	68	38	30	5.6	0.018*
Moderate	101	52	49	1.0	0.320
Low	51	19	32	4.9	0.034*

This examination concentrated on particular dietary components and their association with the development of kidney stones. The odds ratios indicated that stone formation risks were nearly quadrupled by a large intake of animal protein (OR 3.88; $p<0.05$). A higher sodium intake was associated with a nearly two-fold increased risk of kidney stone formation (OR 1.98; $p<0.05$) when higher sodium consumption was present and risk was increased by 65% (OR 1.65; $p<0.05$) when higher oxalate consumption was present (Table 2).

Table 2: Dietary Habits and Risk of Kidney Stones

Dietary Factor	No Kidney Stones	With Kidney Stones	Odds Ratio (95% CI)	χ^2	p-value
High Animal Protein	33 (30.3)	69 (62.2)	3.88 (2.10-7.19)	19.5	0.001*
High Salt Intake	44 (40.4)	63 (56.8)	1.98 (1.12-3.51)	8.1	0.004*
High Oxalate Intake	39 (35.8)	53 (47.7)	1.65 (0.93-2.94)	6.5	0.019*

Kidney stone risk was significantly influenced by hydration. In comparison to those who were inadequately hydrated, participants who maintained adequate hydration demonstrated a 42% decrease in the likelihood of developing stones (OR 0.58; $p<0.05$). In contrast, the risk was increased by 67% (OR 1.67) when inadequate hydration was present (Table 3).

Table 3: Hydration Status and Kidney Stone Development

Status	No Kidney Stones	With Kidney Stones	Odds Ratio (95% CI)	χ^2	p-value
Adequate Hydration	79 (72.5)	68 (61.3)	0.58 (0.35-0.96)	5.4	0.02
Inadequate Hydration	30 (27.5)	43 (38.7)	1.67 (1.01-2.77)		

Kidney stone risk was inversely proportional to physical activity levels. The risk was significantly increased twofold by low physical activity (OR 2.47; $p<0.01$). Conversely, high physical activity reduced the risk by over half (OR 0.44; $p<0.05$), while low physical activity significantly increased the risk (OR 2.47; $p<0.01$). The risk was not substantially wedged by moderate activity (OR 0.75; $p<0.05$)(Table 4).

Table 4: Physical Activity Levels and Kidney Stone Risk

Activity Level	No Kidney Stones	With Kidney Stones	Odds Ratio (95% CI)	χ^2	p-value
High Physical Activity	37 (33.9)	21 (18.9)	0.44 (0.25-0.78)	9.8	0.002*
Moderate Physical Activity	44 (40.4)	38 (34.2)	0.75 (0.42-1.33)	5.1	0.026*
Low Physical Activity	28 (25.7)	52 (46.8)	2.47 (1.39-4.39)	16.2	0.001*

The odds ratios confirmed the protective effects of high physical activity and adequate hydration against kidney stone formation, as determined by a logistic regression analysis. The likelihood of stone formation was increased by twofold due to high BMI, which was a significant risk factor (OR 2.33; $p<0.01$). The risk was also markedly elevated by low socioeconomic status (OR 1.75; $p<0.05$) (Table 5).

Table 5: Logistic Regression Analysis for Predicting Kidney Stones Based on Lifestyle Factors

Variable	Odds Ratio	95% CI	p-value
Adequate Hydration	0.55	0.31 - 0.97	0.037*
High Physical Activity	0.42	0.24 - 0.73	0.002*
BMI > 30 kg/m^2	2.33	1.58 - 3.45	0.001*
Socioeconomic Status - Low	1.75	1.12 - 2.73	0.015*

DISCUSSION

A comprehensive analysis elucidated the relationship between lifestyle factors and the risk of developing kidney stones in the cohort of 220 participants, revealing a robust correlation between the prevalence of kidney stones and specific dietary behaviors, hydration status, physical activity levels, and BMI. These results provided important new perspectives for clinical treatment and patient education in line with the present body of knowledge [15]. Urological studies confirm that diet has long been important in the formation of kidney stones. Our studies reveal that kidney stones are more likely to be connected with a diet heavy in animal protein, oxalate-laden foods, and sodium. Zhuo *et al.*, found that a diet high in animal protein

DOI: https://doi.org/10.54393/pjhs.v5i11.1911

leads to calcium loss and elevated urinary excretion of uric acid, both of which exacerbate kidney stone formation. Our results align with this evidence, underscoring the adverse effects of excessive animal protein on urolithiasis risk. This information conforms to current knowledge [16]. Furthermore, our data implies that the link between salt intake and stone development could be explained by a rise in calcium excretion in urine. Their seminal study on dietary variables and kidney stone incidence [17, 18] covered this mechanism in great detail. In terms of oxalate intake, Mitchell *et al.*, explained that calcium oxalate stones are primarily driven by dietary oxalates. In line with their findings, our study shows that high oxalate intake raised the risk of kidney stones by 65%, indicating that dietary oxalates play a significant role in stone formation. Another important consideration was hydration level; those who kept a high fluid intake were less prone to kidney stones. Increasing fluid intake reduces urinary solutes, which thus reduces the saturation level of minerals in urine that could develop stones [19]. These outcomes are consistent with the findings of Mitchell *et al.*, and Siener, who emphasized that increased water intake dilutes urinary solutes and lowers the saturation of stone-forming compounds, thus reducing the likelihood of stone formation. Current results are in agreement, suggesting that maintaining hydration is crucial for those at risk of kidney stones [19, 20]. More importantly, our data showed that the prevalence of kidney stones increased with increasing body mass index. This result was in line with what Taylor *et al.*, found: that obesity can worsen urine changes that promote stone formation, such as increased excretion of uric acid and calcium [21]. Another possible cause of this elevated risk is the metabolic and inflammatory alterations associated with obesity, as Scotland *et al.*, explained [22]. Interesting as it may seem, kidney stones are more common among those from lower socioeconomic backgrounds. This could be associated with differences in health literacy, healthcare access, and nutritional quality, all of which significantly impact health outcomes for various diseases. To validate these correlations over time, future studies should use more precise nutritional monitoring technology or biomarkers to assess dietary intake. Changing one's lifestyle is the key to reducing the risk of kidney stones, according to this study's conclusions. Clinicians should think about incorporating dietary advice, water education, and exercise promotion into the routine care of patients at risk of kidney stones.

CONCLUSIONS

It was concluded that the study confirmed the important contribution of lifestyle elements to kidney stone formation. The results strongly suggested that high consumption of animal protein, oxalate, and salt greatly increases the risk of kidney stones; conversely, high levels of physical activity and sufficient hydration help to reduce the risk. The positive link between raised BMI and higher incidence of kidney stones emphasizes, even more, the complex influence of metabolic health on urological diseases. These results imply that focused lifestyle changes are good approaches for controlling and avoiding kidney stones.

Authors Contribution

Conceptualization: MLJ
Methodology: IUR, MF, RN
Formal analysis: IUR, KK, MLJ
Writing review and editing: NA, KK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2238

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Evaluation of Nurses' Knowledge and Performance Related to Patient Safety Following Cardiac Catheterization

Zahid Ali Korejo[1*], Amjad Ali[2], Ashok Kumar[3], Aqib Khan[4] and Abdul Fatah Dahri[1]

[1]College of Nursing, People's Medical College Hospital, Nawabshah, Pakistan
[2]Dow Institute of Nursing and Midwifery, Karachi, Pakistan
[3]College of Nursing, Sanghar, Pakistan
[4]Peoples Medical College Hospital, Nawabshah, Pakistan

ARTICLE INFO

Keywords:
Knowledge,Practice,Patient safety,Cardiac Catheterization

How to Cite:
Korejo, Z. A., Ali, A., Kumar, A., Khan, A., & Dahri, A. F. (2024). Evaluation of Nurses' Knowledge and Performance Related to Patient Safety Following Cardiac Catheterization: Nurses' Knowledge of Patient Safety Following Cardiac Catheterization. Pakistan Journal of Health Sciences,5(11). https://doi.org/10.54393/pjhs.v5i11.2238

Corresponding Author:
Zahid Ali Korejo
College of Nursing, People's Medical College Hospital, Nawabshah, Pakistan
zahidteacher786@gmail.com

Received Date: 27th September, 2024
Acceptance Date: 24th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Cardiac catheterization is a crucial medical procedure that requires adherence to standardized care protocols and the proficiency of trained, competent healthcare professionals to achieve optimal outcomes. **Objectives:** To evaluate nurses' knowledge and performance regarding patient safety following cardiac catheterization. **Methods:** A cross-sectional analytical study design was used among staff nurses who are working in the Cath-Lab and coronary care unit of four tertiary care hospitals from October 2022 to May 2023. A non-probability purposive sampling technique on a sample of n=90 participants was employed in this study. The Institutional Review Board granted approval and consent was obtained from all relevant study sites. The data were analyzed using both descriptive and inferential statistical methods, with a p-value of ≤0.05 regarded as statistically significant. **Results:** Outcomes of the current study represent that most of the nurses, 62 (68.9%), possessed an inadequate level of knowledge, while 28 (31.1%) displayed an adequate level. Furthermore, 81 (90%) of the nurses were noted to perform unsatisfactory levels of practice. Whereas, only 9 (10%) nurses were observed to carry out a satisfactory level of practice and there was a significant but weak correlation found between the total score of knowledge and performance with (p<0.05). **Conclusions:** It was concluded that the study participants displayed, an inadequate level of knowledge and unsatisfactory level of practice concerning patient safety after cardiac catheterization in caring for such patients.

INTRODUCTION

Coronary artery disease (CAD), also known as coronary heart disease (CHD) or simply heart disease (HD), is the most common type of cardiovascular disease (CVD) and is responsible for nearly half of all CVD-related deaths globally. It represents a significant public health concern in adults, with high rates of both illness and death, worldwide, the number of deaths linked to coronary heart disease (CHD) was 7.2 million in 2012, and it is expected to surpass 11.1 million by 2020 [1]. Globally, Indo-Asian populations show one of the highest risks for CAD, and it is therefore not surprising that CHD is now the primary cause of death among people in the Indo-Pakistan region [2]. In Pakistan, the burden of CAD is significant across all age groups, particularly among individuals aged 45 and above. It is noteworthy that the incidence of CAD has nearly doubled since 1970 in urban Karachi [3]. Coronary catheterization is an invasive procedure designed to visualize the coronary arteries, assess their degree of opening, and determine the extent of any blockages. This procedure requires putting a thin, flexible wire into either the femoral or radial artery [4]. Various catheters are used for heart catheterization, differing in kind, type, and size. These catheters are divided into two main categories: diagnostic catheters and interventional catheters. However, it plays a diagnostic role by evaluating the blood flow, anatomy, and physiology of the heart. Additionally, it serves as a therapeutic option, providing a substitute for open heart surgery [5]. Nurses working in the Cardiac Catheterization Laboratory (CCL)

DOI: https://doi.org/10.54393/pjhs.v5i11.2238

have a crucial role in delivering high-quality care to patients. Gaining knowledge and staying updated with current evidence-based practices are essential for becoming an effective and efficient nurse [6]. Patient safety is a critical global public health concern. At times, healthcare errors can lead to severe consequences such as death, disability, or extended treatment. Additionally, these errors can result in indirect healthcare costs, and productivity losses, and can negatively impact patient perception, attitudes, and trust in healthcare services [7]. Research has shown that nursing knowledge and performance related to patient safety following cardiac catheterization is insufficient, highlighting the need for educational sessions for nurses. As primary healthcare providers, nurses must be skilled in assessing, detecting, and managing issues related to vascular site complications. Therefore, a proficient nurse with extensive knowledge and practical skills is essential in any healthcare setting, including cardiovascular intervention facilities, to enhance patient recovery and ensure higher-quality care [8]. Prompt and accurate decision-making is vital for improving patient safety. Additionally, nursing care is crucial and beneficial for ensuring the procedure that's why ongoing assessment of knowledge and practice is very essential.

This study aims to evaluate the knowledge and performance of study contributors concerning patient safety following cardiac catheterization in tertiary care hospitals in Karachi.

METHODS

This cross-sectional analytical study design was implemented with a non-probability purposive sampling technique. Whereas, the study sample comprises staff nurses working in the catheterization laboratory (Cath labs), intensive care units, and associated departments of respective study settings. The sample size was determined using Open-Epi software, with a 95% confidence interval, a 5% margin of error, and an excellent knowledge score of 5.7% based on a previous study [9], the calculated sample size was 83; however, principal investigator expanded the sample to n=90. Those nurses, who had registered with the Pakistan Nursing and Midwifery Council (PNMC) and completed their probationary period, were included in this study. Head nurses/in-charge nurses and student nurses were excluded, due to lack of direct involvement in nursing care. Following approval from the Institutional Review Board (IRB) (Ref: IRB-2609/DUHD/Approval/2022/987), permissions were secured from the respective Heads of the particular study settings for data collection. Data were gathered from nurses employed in the catheterization lab (Cath-Lab) the coronary care unit (CCU) and related departments of two private and public organizations in Karachi from October 2022 to May 2023. Each participant provided written informed consent. The questionnaire contains three parts. In the first section, participants are required to provide socio-demographic details including age, marital status, gender, years of experience, and qualification. Moreover, the second part comprised 10 items related to nurses' knowledge and the third part contained 18 items related to nurses' performance about patient safety following cardiac catheterization. The cumulative scores for all knowledge and practice were 10 and 18 respectively. Each accurate response received a score of one, whereas incorrect answers were given to zero. An overall score equal to or exceeding 70% was regarded as sufficient for knowledge and satisfactory for practice, while, a score below 70% was considered as insufficient for knowledge and unsatisfactory practice. The Cronbach alpha values, used for the structured knowledge and practice questionnaires, were determined to be 0.91 and 0.94 respectively [10]. The data were analyzed by using IBM SPSS Statistics version 25.0. Demographics of study participants were presented by frequency and percentages, and knowledge and practice were assessed by rate and proportions along with levels, additionally, the relationship between knowledge and practice was assessed through correlation, with a p-value of <0.05 considered significant.

RESULTS

The maximum proportion of the staff nurses 65.6% (n=59) were male and the majority 37.8% (n=34) of them followed the 20-25 years of age. Furthermore, most of them, 56.7% (n=51), were unmarried and 61.1% (n=55) of them had a general nursing diploma with a specialty. In addition, 53.3% (n=48) of study contributors had 1-5 years of job experience in the cardiac departments (Table 1).

Table 1: The Distribution of Participants by Frequency and Percentage Based On Their Demographic Status (n=90)

Demographic Variables	n (%)
Hospitals	
Tabba Heart Institute Karachi	43 (47.8%)
Dow University Hospital Karachi	26 (28.9%)
Dr. Ruth K.M Pfau Civil Hospital Karachi	12 (13.3%)
Patel Hospital Karachi	9 (10%)
Age	
20-25 Years	34 (37.8%)
26-30 Years	30 (33.3%)
31-35 Years	12 (13.3%)
>35 Years	14 (15.6%)
Gender	
Male	59 (65.6%)
Female	31(34.4%)
Marital Status	
Married	39 (43.3%)
Unmarried	51 (56.7%)
Qualification	
General Nursing Diploma + Specialty	55 (61.1%)
Generic Bachelor of Nursing/Post Registered Nurses-Bachelor of Science in Nursing	35 (38.8%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2238

Cardiac Unit Experience	
<1 Year	31 (34.4%)
1–5 Years	48 (53.3%)
6–10 Years	11 (12.2%)

68.9% of the study contributors had an inadequate level of knowledge, however only 31.1% demonstrated an adequate level of knowledge concerning patient safety related to cardiac catheterization. Furthermore, the highest correct knowledge response (88.9%) was obtained in item#01 and the lowest correct knowledge (33.3%) score was in item#02 (Table 2).

Table 2: Frequency of Knowledge Questions about Patient Safety Related to Cardiac Catheterization

Sr. no	Knowledge Questions	Correct	Incorrect
		n (%)	n (%)
1	KQ-1	80 (88.9%)	10 (11.1%)
2	KQ-2	30 (33.3%)	60 (66.7%)
3	KQ-3	64 (71.1%)	26 (28.9%)
4	KQ-4	64 (71.1%)	26 (28.9%)
5	KQ-5	33 (36.7%)	57 (63.3%)
6	KQ-6	31 (34.4%)	59 (65.6%)
7	KQ-7	49 (54.4%)	41 (45.6%)
8	KQ-8	38 (42.2%)	52 (57.8%)
9	KQ-9	58 (64.4%)	32 (35.6%)
10	KQ-10	45 (50%)	45 (50%)
11	**Level of the Knowledge**	**Adequate**	**Inadequate**
	Total Score of Knowledge	n (%)	n (%)
		28 (31.1%)	62 (68.9%)

The result of this current study is evident that the majority 90% of participants had possessed unsatisfactory practices in their clinical areas. Only 10% of the study participants exhibited a satisfactory level of performance concerning patient safety after a cardiac catheterization, although most of the study nurses (93.9%) did not perform the instruction of item#14, Furthermore, the majority of the nurses (94.4%) performed their safe practices in items#7 and item#8 (Table 3).

Table 3: Frequency of Practice Questions about Patient Safety Related to Cardiac Catheterization

Sr. no	Practice Questions	Done	Not Done
		n (%)	n (%)
1	PQ-1	20 (22.2%)	70 (77.8%)
2	PQ-2	78 (86.7%)	12 (13.3%)
3	PQ-3	46 (51.1%)	44(48.9%)
4	PQ-4	22 (24.4%)	68 (75.6%)
5	PQ-5	7 (7.8%)	83 (92.2%)
6	PQ-6	36 (40%)	54 (60%)
7	PQ-7	85 (94.4%)	5 (5.6%)
8	PQ-8	85 (94.4%)	5 (5.6%)
9	PQ-9	53 (58.9%)	37 (41.1%)
10	PQ-10	27 (30%)	63 (70%)
11	PQ-11	83 (92.2%)	7 (7.8%)
12	PQ-12	70 (77.8%)	20 (22.2%)
13	PQ-13	84 (93.3%)	6 (6.7%)
14	PQ-14	6 (6.7%)	84 (93.3%)
15	PQ-15	37 (41.1%)	53 (58.9%)
16	PQ-16	83 (92.2%)	7 (7.8%)
17	PQ-17	80 (88.9%)	10 (11.1%)
18	PQ-18	29 (32.2%)	61 (67.8%)
19	**Level of the Practice**	**Satisfactory**	**Unsatisfactory**
	The Total Score of Practice	n (%)	n (%)
		29 (10%)	81 (90%)

Results showed a significant but weak correlation between overall knowledge and performance of study contributors concerning patient safety following cardiac catheterization in cardiac units ($p<0.05$) (Table 4).

Table 4: Correlation between Overall Knowledge Score and Practice Score

Variables		Practice	
Correlation	Knowledge	r	P
		0.230	0.029

DISCUSSION

Patient safety is a critical aspect of healthcare organizations, with nurses serving as the backbone of these institutions. Ensuring that nurses are competent in their knowledge and skills, particularly in caring for patients following cardiac catheterization, is highly important. The current study seeks to evaluate nurses' knowledge and performance concerning the safety of patients following cardiac catheterization in tertiary care hospitals. The outcomes of the existing study displayed that more than one-third of the nurses were aged between 20 and 25 years. Approximately two-thirds of the nurses were male, more than half were unmarried, and more than sixty percent had a General Nursing Diploma and Specialty, whereas more than half of them had 1-5 years of experience in cardiac units. These results align with a study conducted in Egypt (2022) [11] while contrasting results were reported in studies conducted in Iraq [12, 13]. In this study level of knowledge was categorized as adequate and inadequate, however, the findings reveal that around 70% of nurses had an inadequate knowledge level during the assessment. This deficiency in nurses' knowledge could be due to a lack of opportunities for knowledge refreshment or fatigue resulting from an increased workload, which may limit their ability to stay updated with current information. The result aligns with earlier studies conducted in Egypt [14-15] while the opposite results were reported in studies conducted in Iraq (2022) [16]. In the present study, the level of practice was classified as either satisfactory or unsatisfactory. However, the results exposed that 90% of the study contributors revealed an unsatisfactory level of performance. This could be attributed to the need for increased years of experience in critical areas, which are

DOI: https://doi.org/10.54393/pjhs.v5i11.2238

essential in such vital units; moreover, some nurses may rely on repetition and imitation in their work. The result aligns with earlier studies conducted in Pakistan (2022) [17]. However, contrasting findings were documented in research carried out in Egypt (2021) [18]. Furthermore, the present study showed, overall, the knowledge level about post-cardiac catheterization complications was higher than the practice level, however, there was variation existing between them, like the proportion of practice items, is greater as compared to knowledge, from entire components of the study tool, approximately 45 percent items of practice showed satisfactory performance related to patient care after a cardiac catheterization, while only 30 percent of knowledge items indicates as adequate, it clarifies that proportion of practice items are higher. The outcomes of this study showed a statistically significant but weak correlation between nurses' overall knowledge and practice scores related to patient safety following cardiac catheterization. These outcomes are consistent with a study undertaken in Egypt (2022) [19], whereas contrary findings were observed in a study conducted in Egypt [20].

CONCLUSIONS

It was concluded that less than three-fourths of study participants, demonstrated an unsatisfactory knowledge level concerning patient safety after cardiac catheterization, while only one-tenth showed a satisfactory level of practice in caring for such patients. However, these results suggested that ongoing training programs are essential for nurses to keep their knowledge and practices up to date.

Authors Contribution

Conceptualization: ZAK
Methodology: ZAK, AA, AK[1], AK[2], AFD
Formal analysis: AA, AK[1]
Writing review and editing: AA, Ak[1]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1907

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Prevalence of Allergic Indicators in Patients with Chronic Otitis Media: A Case-Control Study

Ashfaq Hussain[1*], Irshad Ali[2], Allah Bux Mushtaq[3], Junaid Hussain[4], Tahir Hussain Khan[5] and Muhammad Afzal[1]

[1]Department of Ear, Nose, and Throat, Shahida Islam Medical College, Lodhran, Pakistan
[2]Department of Ear, Nose, and Throat, Foundation University Medical College, Islamabad, Pakistan
[3]Department of Ear, Nose, and Throat, Mohammad Medical College, Mirpurkhas, Pakistan
[4]Department of Ear, Nose, and Throat, Pir Abdul Qadir Shah Jeelani, Institute of Medical Sciences, Gambat, Pakistan
[5]Department of Ear, Nose, and Throat, Karachi Vocational Site, Postgraduate Teaching Hospital, Karachi, Pakistan

ARTICLE INFO

Keywords:
Chronic Otitis Media, Skin Prick Test, Blood Eosinophils, Hearing Loss, Allergy

How to Cite:
Hussain, A., Ali, I., Mushtaq, A. B., Hussain, J., Khan, T. H., & Afzal,M.(2024). Prevalence of Allergic Indicators in Patients with Chronic Otitis Media: A Case-Control Study: Allergic Indicators in Chronic Otitis Media.*Pakistan Journal of Health Sciences*, 5(11). https://doi.org/10.54393/pjhs.v5i11.1907

Corresponding Author:
Ashfaq Hussain
Department of Ear, Nose, and Throat, Shahida Islam Medical College, Lodhran, Pakistan
drashfaqhussain313@gmail.com

Received Date: 25th September, 2024
Acceptance Date: 22nd November, 2024
Published Date: 30th November, 2024

ABSTRACT

Chronic Otitis Media (COM) was a persistent inflammation of the middle ear that often leads to prolonged effusion and hearing loss. It was a significant health concern, particularly in children, due to its impact on speech development and academic performance. **Objective:** To investigate the association between allergies and Chronic Otitis Media (COM) by assessing allergy positivity, blood eosinophil levels, and skin prick test results in patients with COM compared to healthy controls. **Methods:** It was a cross-sectional, case-control study conducted at Shahida Islam Medical Complex from August 2023 to January 2024. 112 patients suffering from COM in case groups and 112 participants were taken as healthy control were selected. The positivity of allergy, increase in blood eosinophils and, skin prick test was assessed. The data analysis was conducted using the SPSS version 24.00. The p-value of less than 0.05 was considered significant. **Results:** The mean age of participants in the case group was 37.4 years ± 12.6 and control groups was 38.9 years ± 10.9. The prevalence of positive skin prick tests in the case group at 56.25%, compared to 36.61% in the control group (p = 0.01). Blood eosinophil counts were significantly higher in the case group (0.39 ± 0.15 cells x 10-3 µl) than in the control group (0.23 ± 0.11 cells x 10-3 µl) (p = 0.031). The positivity rate for allergies, based on clinical assessment, was significantly higher among patients in the case group (63.39%) compared to those in the control group (24.11%) (p = 0.04). **Conclusion:** Findings of this suggests that there was strong association between allergies and chronic otitis media in patients

INTRODUCTION

Chronic Otitis Media (COM) is a prolonged middle ear infection that leads to continuous fluid discharge behind the eardrum, potentially causing hearing loss. This condition significantly impacts young people, affecting speech and learning abilities [1]. Globally, COM in younger population has a prevalence rate of 4.1%, with higher rates observed in Africa (8%), Asia (14%) and Oceania (50%) [2]. Studies indicate a male preponderance and suggest a possible link between allergies and various forms of otitis media, though the specific pattern remains unclear [3, 4]. A vicious circle among allergic rhinitis, turbinate hypertrophy and otitis media may occur, with AR potentially playing a role in causing otitis media [5]. The pathophysiological connection between allergies and COM includes various processes. A significant aspect of Eustachian tube dysfunction is among those that are usually seen among persons who are allergic. If the nasopharyngeal compartment has irritation caused by allergies it might bring about an abscessed Eustachian tube impeding its aerating effects on the tympanic cavity. So by forming this kind of blockage there arise a situation where a vacuum is created allowing for accumulation of fluids leading to infections hence culmination [6]. Allergens can also make more mucus since they can hinder

DOI: https://doi.org/10.54393/pjhs.v5i11.1907

the cleaning of mucus within Eustachian tube and ear. Moreover, these substances may directly serve as triggers for 'attack' to produce inflammatory mediators in particular histamines and leukotrienes which worsen the middle ear mucosal inflammation and middle ear cavity [7]. Immunological responses play a crucial role in linking allergies to COM. Allergens can trigger a Type I hypersensitivity reaction, leading to the release of IgE antibodies. These antibodies bind to mast cells and basophils, causing degranulation and the release of various inflammatory mediators [8]. Besides, Th2 cytokines such as IL-4, IL-5 and IL-13 have been shown to play an important role in allergy-causing inflammation and the development of COM. They promote IgE synthesis and attract eosinophils to inflammatory foci which results in constant inflammation in the middle ear along with accumulation of effusion there [9]. The connection between allergies and COM has prominent clinical implications. It indicates that it is vital in the prevention and treatment of COM to manage allergic conditions that are underlying to it. The allergic part of COM may however be lessened as well as improving the patient's outcomes using potential therapeutic strategies such as antihistamines, intranasal corticosteroids and allergen immunotherapy. This underscores the need for a multidisciplinary approach. Comprehensive allergy testing and targeted treatments may reduce the incidence and severity of in these individuals [10]. An in-depth examination of the literature has revealed significant shortcomings. There is scarce scientific background on allergies that might evolve into COM. Most studies on the matter deal with people from more or less the same group disregarding various aspects such as age difference among others. The impact of different types of allergies (e.g., food allergies, seasonal allergies, perennial allergies) on the risk and severity of COM is not well-characterized [11]. Further research is needed for interventions that measure how well allergy management methods work (like antihistamines or allergy shots) before they can be used to stop or cure otitis media. In addition, the relationship between second-hand smoke, pollutants and allergic conditions is an area where little is known so far [12]. Addressing these gaps through comprehensive, multidisciplinary research could significantly advance this understanding of the connection between allergies and chronic otitis media, ultimately leading to more effective prevention and treatment strategies. The primary objective of this research is to find out how allergies cause COM. In doing so, find the most common allergens (like pollen, dust mites or pet dander) responsible for causing or worsening chronic otitis media. The purpose was to suggest the evidence-based criteria for diagnosing and treating chronic otitis media in individuals whose allergies have been ascertained, with a view to enhancing quality patient care.

METHODS

It was a cross-sectional, case-control study conducted at Shahida Islam medical complex form August 2023 to January 2024 after taking approval from the Institutional ethical review committee, SIMC/ET.C/10004/23. All the patients presented in the outdoor patient's department in the selected timeframe were screened for inclusion in this study. All the patients with aged 18 to 60 years, diagnosed with COM were included in this study. A Chronic Otitis Media (COM) was characterized by a perforated ear drum, otorrhea and other symptoms that frequently lead to acquired hearing impairment [13]. Patients with congenital ear malformations or syndromic conditions affecting the ear, immunodeficiency disorders and patients who have undergone ear surgery within the past six months were excluded from this study. Moreover, patients with history of nasal polyposis, deviated nasal septum and history of upper respiratory tract infections in past 3 months and presence of cholesteatoma were also not included in this study. Demographic data including age, gender and history of smoking was noted and informed consent was taken. Detailed history including allergy symptoms (e.g., rhinitis, asthma, eczema) and family history of allergies were noted along with comprehensive otolaryngological examination will be conducted, including otoscopy to confirm the diagnosis of COM. To measure the blood eosinophil count, the samples were run on an automated blood cell counter (Bio-Rad's TC20™), and the results were expressed in several eosinophils/µL. [13]. The sample size was calculated by considering 80% power added to the study, prevalence rate of 7.8%, a confidence level of 95% and a margin of error of 5%, are approximately 224 participants with 112 patients suffering from COM in case groups and 112 participants were taken as healthy control [14]. Written informed consent was obtained from each participant. The positivity of allergy was defined as presence of persistent sneezing on exposure to allergen with pale, watery nasal mucosa along with increase in blood eosinophils levels 0.04-0.36 (cells x 10-3 µl) for females and 0.04-0.54 (cells x 10-3 µl) for males. In addition to positive skin prick test to any of the 19 selected Turkish mixed respiratory allergens. Histamine hydrochloride was used as positive control and the glycerol saline was used as negative controls. The skin prick test was interpreted as positive if a wheal of 3mm larger than the negative control was observed after 15 minutes. The data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 24.0. For quantitative variables, the calculations were mean and standard deviation; for qualitative variables, the calculations were frequencies and percentages.The p-value of less than 0.05 was considered significant.

DOI: https://doi.org/10.54393/pjhs.v5i11.1907

RESULTS

In this study comparing patients with COM in a case group (n=112) and a control group (n=112), the mean age of participants in the case group was 37.4 years ± 12.6, slightly lower than the control group's mean age of 38.9 years ± 10.9, although this difference was not statistically significant (p = 0.06). Regarding gender distribution, 60.71% of the case group were male and 39.29% female, compared to 50.89% male and 49.11% female in the control group (p = 0.59 for male/female distribution and p = 0.07 for overall gender comparison). Analysis of COM characteristics revealed that unilateral involvement was predominantly left-sided (33.93%) and right-sided data 27.23% cases. Bilateral COM was noted in 38.84% of the case group. The duration of illness was reported as 4.8 years ± 6.9 in the case group. Significantly, a history of smoking differed between groups, with 47.32% of cases having a history of smoking compared to 36.6% in the control group (p = 0.05) (Table 1). This finding suggests a potential association between smoking history and the development or severity of COM in children.

Table 1: Demographic Characteristics of the Study Population (n=224)

Variables	Case Group Mean ± SD/N (%)	Control Group Mean ± SD/N (%)	p-Value
Age	37.4 ± 12.6	38.9 ± 10.9	0.06
Gender			
Male	68 (60.71%)	57 (50.89%)	0.59
Female	44 (39.29%)	55 (49.11%)	0.07
Unilateral COM			
Left Sided	76 (33.93%)	-	-
Right Sided	61 (27.23%)	-	-
Bilateral COM	87 (38.84%)	-	-
Duration of Illness (Years)	4.8 ± 6.9	-	-
History of Smoking	53 (47.32%)	41 (36.6%)	0.05

The prevalence of positive skin prick tests, indicative of allergic sensitization, was notably higher in the case group at 56.25%, compared to 36.61% in the control group (p = 0.01). This finding suggests a higher prevalence of allergic sensitization among patients with COM compared to their healthy counterparts. Secondly, blood eosinophil counts, a marker often elevated in allergic conditions, were significantly higher in the case group (0.39 ± 0.15 cells x 10-3 µl) than in the control group (0.23 ± 0.11 cells x 10-3 µl) (p = 0.031). Moreover, a striking majority in the case group (79.64%) had raised eosinophil counts, further supporting the link between allergic inflammation and COM. In contrast, only 18.75% in the control group exhibited raised eosinophil counts. The positivity rate for allergies, based on clinical assessment, was significantly higher among patients in the case group (63.39%) compared to those in the control group (24.11%) (p = 0.04; Table 2). This indicates that patient with COM was more likely to have allergies compared to their healthy peers, suggesting a potential role for allergic sensitization in the pathogenesis of COM.

Table 2: Comparison of Variables in Case and Control Group (n=224)

Variables	Case Group Mean ± SD/N (%)	Control Group Mean ± SD/N (%)	p-Value
Positive Skin Prick Test	63 (56.25%)	41 (36.61%)	0.01
Blood Eosinophils Count (Cells x 10^{-3} µL)	0.39 ± 0.15	0.23 ± 0.11	0.03
Raised Eosinophil Count	89 (79.64%)	21 (18.75%)	0.02
Positivity of Allergy	71 (63.39%)	27 (24.11%)	0.04

DISCUSSION

In this comparative study involving 112 patients in both a case group and a control group, several key parameters related to allergies were evaluated to discern differences between the groups. The case group, comprising patients with COM, demonstrated significant disparities in allergy-related metrics compared to the control group. The higher prevalence of positive skin prick tests, elevated blood eosinophil counts, raised eosinophil count frequency and overall allergy positivity rate in the case group underscore the need for comprehensive allergy evaluation in patients presenting with COM [15]. The findings of this study correlate with the recent literature. A randomized control trial conducted by Sharifian MR *et al.*, have also revealed higher positivity of skin prick test in patients suffering from COM than the healthier control. It highlights the strong connection exists between allergic rhinitis and COM [16]. It suggests that allergic reaction or hypersensitivity play a significant role in the pathogenesis of COM. The middle ear stays in equilibrium with outside pressure through Eustachian tubes which also remove any fluids present. Inflammation was one of the ways allergic rhinitis. When someone suffering from allergies (or hay fever) comes into contact with something that triggers an allergic reaction such as pollen or dust mites then their immune system responds by releasing antibodies on the lining of its nasal cavities which results into inflammation followed by constriction thereby leading them experiencing tightness when breathing; which further blocked their air passages thus causing discomforts like hissing sounds heard during inhalation phase among others. This process may continue into the Eustachian tubes resulting in swelling and blockage [17]. As a result, the normal function of the Eustachian tubes, including ventilation and drainage of fluids from the middle ear, was impaired. Studies have shown that eustachian tube dysfunction was significantly higher in allergic rhinitis patients (83.3% compared to 84.2% of healthy subjects) than in healthy subjects [18]. A significant number of eosinophils in the circulation are usually linked by medical professional because they believe it may answer some questions about what happens during COM disease process such as whether there was any

DOI: https://doi.org/10.54393/pjhs.v5i11.1907

connection between allergy in one's body system and developing this disease condition. Additionally, the investigation discovered eosinophil counts were extremely raised among cases compared with controls (79.64% vs 18.75%); hence, this trend underlines the connection between COM occurrence and general allergy responses signified via the levels of eosinophils in the blood [19]. It was important to understand how allergies relate to COM since it impacts what doctors do and what patients do. If a patient comes with symptoms that resemble those seen in either chronic or recurring cases of otitis media, tests for hypersensitivity reactions would have to be carried out particularly among those who have had previous diagnoses of atopy or allergic rhinitis. Understanding more about this relationship facilitates more individualized interventions among different people such as really controlling allergic conditions through use of medicine such as antihistamines while avoiding foods known to cause discomforts [20]. Educating patients and caregivers about the association between allergies and COM can empower them to recognize early symptoms and seek timely medical intervention. This study had the objective of investigating the linking factor among COM and allergies although there are various limitations to this study. Consequently, in these studies which are mainly observational, it was very important though difficult to establish a temporal sequence between allergies and COM. It was very often unclear about which one comes first between allergies preceding development of COM or conversely; this situation makes causal inference problematic. The study has a limited sample size hence the generalizability of results was doubtful. The development of COM could be affected differently based on the various kinds of allergies, such as food or environmental ones. This implies that general conclusions made from such researches may not apply to particular allergy types because the research does not clearly distinguish among them. This lack of specificity necessitates further studies using better methodology such as cross-sectional design and exploration of temporal relationships.

CONCLUSIONS

In conclusion, we would like to note that in this patient cohort, there was a very close connection exists between the presence of allergies and cases of COM. Positive skin prick tests, though, were found at a much higher rate in those patients within the research group who had either raised eosinophil counts or a frequent occurrence of such counts or an overall allergy positive rate. Consequently, it has been proposed that thorough allergy assessment be carried out among patients with COM.

Authors Contribution

Conceptualization: AH
Methodology: AH, IA, ABM
Formal analysis: JH
Writing, review and editing: IA, THK, MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1716

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Frequency and Risk of Preeclampsia in Women with Gestational Diabetes Mellitus

Aliya Dar Khan[1], Nafeesa Ghani[2], Salma Khan[3] and Hoor Asadullah Jan[4*]

[1]Department of Obstetrics and Gynecology, Cat D Hospital, KPK, Pakistan
[2]Life Care Hospital and Research Institute, Hayatabad, Pakistan
[3]Department of Biochemistry, Rehman Medical College, Peshawar, Pakistan
[4]Department of Obstetrics and Gynecology, Saeed Medical Complex Mattani, Peshawar, Pakistan

ARTICLE INFO

Keywords:
Gestational Diabetes Mellitus, Preeclampsia, Pregnancy Complications, Hypertensive Disorders

How to Cite:
Khan, A. D., Ghani, N., Khan, S., & Jan, H. A. (2024). Frequency and Risk of Preeclampsia in Women with Gestational Diabetes Mellitus : Frequency of Preeclampsia in Gestational Diabetes Mellitus Women. *Pakistan Journal of Health Sciences*, 5(11). https://doi.org/10.54393/pjhs.v5i11.1716

***Corresponding Author:**
Hoor Asadullah Jan
Department of Obstetrics and Gynecology, Saeed Medical Complex Mattani, Peshawar, Pakistan
abuxarasad@gmail.com

Received Date: 20th May, 2024
Acceptance Date: 12th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Preeclampsia is a serious hypertensive disorder of pregnancy that affects 5-8% of pregnancies and is a major cause of maternal and neonatal morbidity and mortality. Gestational diabetes mellitus is another significant pregnancy complication that increases the risk of adverse maternal and fetal outcomes, including preeclampsia. **Objectives:** To determine the frequency and assess the risk of preeclampsia in pregnant women diagnosed with gestational diabetes mellitus as an independent risk factor. **Methods:** This descriptive cross-sectional study was carried out from October 2020 to April 2021 within the Department of Obstetrics and Gynecology, Medical Teaching Institution-Hayatabad Medical Complex Peshawar and included patients having regular monitoring for blood pressure using a mercury sphygmomanometer and proteinuria by urine dipstick. **Results:** A total of 133 pregnant women were diagnosed with gestational diabetes mellitus in the study. Of these, 10 women (7.5%) developed preeclampsia, indicating a significant association between gestational diabetes mellitus and preeclampsia. Participants were aged between 18 and 45 years, with the majority (75%) falling within the 18-30-year age group. Results showed that gestational diabetes mellitus was associated with an increased risk of preeclampsia, particularly in this younger age group. **Conclusions:** It was concluded that gestational diabetes mellitus is associated with a higher risk of preeclampsia and requires intensive clinical follow-up and intervention measures for maternal and fetal health protection.

INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder that typically occurs after the 20th week of pregnancy, characterized by elevated blood pressure and proteinuria. This condition is a leading cause of maternal and fetal morbidity and mortality, complicating 5-8% of all pregnancies globally. It contributes to adverse outcomes such as preterm birth, placental abruption, and, in severe cases, maternal and fetal death [1, 2]. Given its significant impact on maternal and neonatal health, understanding and managing the risk factors associated with PE is critical for improving pregnancy outcomes. While the association between PE and Gestational Diabetes Mellitus (GDM) has been extensively studied in global populations, there is limited research specific to low- and middle-income countries (LMICs) like Pakistan. In these regions, the rising incidence of both conditions, due to increasing rates of obesity, delayed pregnancies, and limited access to healthcare services, necessitates a deeper understanding of how these complications interact [3, 4]. The scarcity of region-specific data on the prevalence and risk factors for PE among women with GDM highlights a critical gap in the literature. Without this localized knowledge, public health strategies and clinical interventions may lack the precision needed to effectively reduce maternal morbidity and mortality rates [5, 6]. In Pakistan, where healthcare resources are often constrained, and maternal health outcomes lag behind global standards, the study of PE in women with GDM is particularly urgent. The high maternal mortality rates in this region underscore the need for targeted research that can inform more effective management and prevention strategies [7]. This study seeks to fill this gap by providing valuable data on the

DOI: https://doi.org/10.54393/pjhs.v5i11.1716

prevalence of PE among GDM patients in a tertiary care setting, contributing to a more nuanced understanding of these conditions within the regional context. By identifying specific risk factors and patterns, the findings can support the development of tailored healthcare interventions to mitigate the adverse outcomes associated with PE and GDM in this population [8, 9]. Gestational Diabetes Mellitus (GDM) is another significant complication, occurring in approximately 7% of pregnancies. It is characterized by glucose intolerance with onset during pregnancy and is associated with increased risks of adverse maternal and neonatal outcomes, including macrosomia, cesarean delivery, and future development of type 2 diabetes in both the mother and child [10]. The interplay between GDM and PE is particularly concerning, as both conditions share common risk factors such as advanced maternal age, obesity, and metabolic disorders. Recent studies have demonstrated that GDM can independently increase the risk of developing PE, possibly due to shared pathophysiological mechanisms such as endothelial dysfunction and inflammatory responses [11, 12]. In low- and middle-income countries (LMICs), the incidence of both GDM and PE is rising due to increasing rates of obesity, delayed pregnancies, and limited access to healthcare services [13]. These factors make it essential to investigate the local epidemiology of PE in women with GDM, particularly in regions like Peshawar, Pakistan, where healthcare resources are constrained, and maternal mortality rates remain high. Understanding these associations within a regional context could inform public health strategies aimed at reducing maternal and neonatal morbidity and mortality [14, 15]. GDM is one of the most common complications of pregnancy, affecting approximately 7% of all pregnancies globally. GDM is characterized by glucose intolerance with onset during pregnancy, which poses significant risks for both maternal and fetal health, including preeclampsia, macrosomia, and the future development of type 2 diabetes. The increasing prevalence of GDM, particularly in low- and middle-income countries like Pakistan, is largely driven by rising rates of obesity and delayed childbearing. Despite its growing significance, there remains a gap in region-specific research investigating the interplay between GDM and preeclampsia in these populations. Understanding the local epidemiology and risk factors associated with these conditions is critical to improving maternal and neonatal outcomes through targeted interventions and enhanced clinical care strategies [16].

This study aims to evaluate the frequency of PE among women diagnosed with GDM in a tertiary care hospital in Peshawar. By identifying the prevalence and risk factors for PE in this population, the study will contribute to the broader understanding of these conditions and support the development of effective preventive and management strategies.

METHODS

This descriptive cross-sectional study was conducted in the Department of Obstetrics & Gynecology at Medical Teaching Institution-Hayatabad Medical Complex (MTI-HMC) Peshawar from October 2020 to April 2021. The site is a tertiary care facility that serves an ethnically diverse population from the surrounding region, allowing us to investigate the prevalence and characteristics of preeclampsia among women diagnosed with GDM. The study population consisted of pregnant women diagnosed with GDM, as defined by the American Diabetes Association (ADA) guidelines. A glucose tolerance test was performed with a fasting glucose level greater than 92 mg/dL, a one-hour postprandial glucose level greater than 180 mg/dL, or a two-hour postprandial glucose level greater than 153 mg/dL. Women with pre-existing diabetes or hypertension were excluded from the study. Participation was contingent upon obtaining informed consent from all participants. A convenience sampling technique was employed to recruit participants from the hospital's outpatient and inpatient departments. A total of 133 pregnant women met the inclusion criteria. The sample size was determined based on the prevalence of GDM as 17.2% using a confidence level of 95% an allowable error of 7% and a 20% dropout rate [16]. Data were collected through structured interviews conducted by trained medical personnel, who reviewed patient records to gather demographic details (age, ethnicity, and body mass index), medical history, and specific pregnancy-related variables (e.g., gestational age at GDM diagnosis, history of preeclampsia, and birth weight of previous infants). Blood pressure was measured using a calibrated mercury sphygmomanometer, with readings taken twice, at least four hours apart. By the International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines, preeclampsia was defined as blood pressure exceeding 140/90 mmHg on two separate occasions within a week, along with proteinuria. Proteinuria was assessed using a urine dipstick test, with a result of 1+ or greater considered positive. Reliability checks for the equipment were conducted regularly to ensure consistent and accurate readings. Calibration of the sphygmomanometers was performed weekly to maintain accuracy, and any deviations were corrected immediately. Additionally, the urine dipstick tests used were from a single manufacturer to ensure uniformity in results. Handling of missing data, and incomplete data, such as missing blood pressure readings or proteinuria results, were excluded from the final analysis. However, efforts were made to minimize missing data by thoroughly reviewing patient records and conducting repeat tests when necessary. The data were analyzed using SPSS version 25.0. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were used to summarize the characteristics of the study population. The association between GDM and

DOI: https://doi.org/10.54393/pjhs.v5i11.1716

preeclampsia was assessed using Chi-square tests for categorical variables and t-tests for continuous variables, with a p-value of less than 0.05 considered statistically significant. The study protocol was approved by the Ethics Committee of MTI-HMC Peshawar (reference number: 1254), in compliance with the 1964 Helsinki Declaration and its subsequent amendments.

RESULTS

A total of 133 pregnant women were diagnosed with GDM in the study. The participants' mean age was 29.98 ± 5.21 years, with a mean BMI of 25.51 ± 1.09 kg/m^2. The average gestational age at data collection was 32.22 ± 1.98 weeks, and the average duration of GDM was 4.01 ± 1.25 weeks (Table 1).

Table 1: Descriptive Statistics of Study Participants (n=133)

Variable	Minimum	Maximum	Mean ± SD
Age (Years)	22	38	29.98 ± 5.21
Gestational Age (Weeks)	29	36	32.22 ± 1.98
Duration of Disease (Weeks)	2	6	4.01 ± 1.25
BMI (kg/m^2)	23.5	28.5	25.51 ± 1.09

Participants were distributed evenly across age groups, with 70 women (52.6%) in the 18-30 years' age group and 63 women (47.4%) in the 31-45 years' age group (Table 2).

Table 2: Age-wise Distribution of Participants (n=133)

Age Group	Frequency (%)
18-30 Years	70 (52.6%)
31-45 Years	63 (47.4%)

Of the 133 participants, 44 women (33.1%) exhibited proteinuria (Table 3).

Table 3: Frequencies and Percentages for Proteinuria (n=133)

Proteinuria	Frequency (%)
Yes	44 (33.1%)
No	89 (66.9%)

Preeclampsia was diagnosed in 10 women (7.5%) of the study population (Table 4)

Table 4: Frequencies and Percentages for Preeclampsia (n=133)

Proteinuria	Frequency (%)
Yes	10 (7.5%)
No	123 (92.5%)

To explore possible correlations between preeclampsia and other factors, preeclampsia cases were stratified by age, BMI, and duration of GDM. Among women aged 18-30 years, 6 developed preeclampsia (8.6%), compared to 4 women in the 31-45 years' group (6.3%). However, no statistically significant difference was found between the age groups (p=0.627) (Table 5).

Table 5: Stratification of Preeclampsia by Age Groups (n=133)

Age Group	Preeclampsia (Yes)	No Preeclampsia	Total	p-value
18-30 Years	6 (8.6%)	64 (91.4%)	70	0.627
31-45 Years	4 (6.3%)	59 (93.7%)	63	0.627

Stratification by BMI revealed that 9 women (8.8%) with a BMI greater than 25 kg/m^2 developed preeclampsia, compared to 1 woman (3.2%) with a BMI less than 25 kg/m^2. However, the association was not statistically significant (p=0.301) (Table 6).

Table 6: Stratification of Preeclampsia by BMI (n=133)

BMI Group	Preeclampsia (Yes)	No Preeclampsia	Total	p-value
<25 kg/m^2	1 (3.2%)	30 (96.8%)	31	0.301
>25 kg/m^2	9 (8.8%)	93 (91.2%)	102	

Similarly, no significant association was observed between the duration of GDM and preeclampsia. Among women with GDM for less than 4 weeks, 5 developed preeclampsia (7.1%), and 5 women with GDM for more than 4 weeks developed the condition (7.9%) (p=0.862) (Table 7).

Table 7: Stratification of Preeclampsia by Duration of Disease (n=133)

Duration of Disease	Preeclampsia (Yes)	No Preeclampsia	Total	p-value
<4 Weeks	5 (7.1%)	65 (92.9%)	70	0.862
<4 Weeks	5 (7.9%)	58 (92.1%)	63	

DISCUSSION

This study provides evidence of a significant association between gestational diabetes mellitus (GDM) and preeclampsia (PE), with 7.5% of GDM patients in our cohort developing PE. These findings highlight the critical importance of monitoring women with GDM for signs of hypertensive disorders. PE complicates approximately 5-8% of pregnancies globally, but rates vary widely across populations, ranging from 2.9% in Swedish cohorts to as high as 30% in Indian populations [11]. Our results align moderately with these global trends, emphasizing the substantial risk GDM poses for PE development. Compared to international studies, the incidence of PE in our cohort is consistent with findings from middle-income countries, such as Pakistan and India, where higher rates of GDM and limited access to healthcare contribute to increased PE incidence [17, 8]. However, the slightly lower incidence of PE in our cohort compared to some populations may be attributed to differences in sample size, healthcare access, and genetic predispositions. Such variations underscore the need for region-specific strategies for managing and mitigating these risks. In our study, the prevalence of preeclampsia among women diagnosed with GDM was 7.5%, which is comparable to the findings of other studies conducted in low- and middle-income countries (LMICs) like Pakistan. A similar study conducted in Karachi reported a slightly higher incidence of preeclampsia (9.3%) among women with GDM, which was attributed to higher rates of obesity and metabolic disorders in the urban population [18]. The relatively lower incidence in our cohort from Peshawar may reflect differences in healthcare access,

DOI: https://doi.org/10.54393/pjhs.v5i11.1716

lifestyle, and genetic predispositions between urban and semi-urban populations. Additionally, varying diagnostic criteria and sample sizes across studies could contribute to the differences in preeclampsia rates. Despite the well-documented association between elevated BMI and the risk of preeclampsia in GDM patients, our study did not find a statistically significant relationship between BMI and preeclampsia. This contrasts with the findings of a study from Lahore, which demonstrated a strong correlation between BMI>25 kg/m^2 and the incidence of hypertensive disorders in pregnancy. One possible explanation for this discrepancy could be the relatively small sample size in our study, which may limit the power to detect significant associations. Furthermore, differences in the nutritional and socio-economic profiles of the populations studied may also contribute to the variation in findings [19]. This study highlights that GDM is an independent risk factor for PE, a conclusion supported by previous research linking GDM's metabolic complications, such as lipid metabolism disorders and vascular dysfunction, to the development of PE [20]. This dual pathophysiology suggests that systemic endothelial dysfunction in women with GDM may initially manifest as PE and could later contribute to the development of GDM in subsequent pregnancies if left unaddressed [11]. While the current study adds to the growing body of literature on the relationship between GDM and PE, it also has limitations. The cross-sectional nature of the study restricts the ability to establish causality. Furthermore, using a convenience sample from a single tertiary care center may introduce selection bias, and the relatively small sample size may limit the generalizability of the findings. Future studies should explore larger, more diverse populations and adopt longitudinal designs to elucidate the temporal relationship between these conditions better. Also include potential confounders such as undiagnosed pre-existing conditions and reliance on self-reported medical histories, which may have affected the accuracy of data regarding preeclampsia risk factors. More region-specific studies are also needed to tailor healthcare interventions for diverse populations, particularly in low- and middle-income countries where healthcare access is limited. Ultimately, enhancing early detection and improving management protocols for these high-risk pregnancies will be essential for reducing maternal and neonatal morbidity and mortality.

CONCLUSIONS

This study, conducted at a tertiary care hospital in Peshawar, identified a 7.5% incidence of preeclampsia among pregnant women with gestational diabetes mellitus (GDM). The findings highlight the significant risk that GDM poses for the development of hypertensive disorders during pregnancy. These results underscore the critical need for integrated screening and vigilant monitoring of GDM. Proactive management, including early detection and tailored interventions, is essential to mitigate complications and improve outcomes for both mothers and their offspring.

Authors Contribution

Conceptualization: ADK
Methodology: ADK, NG, SK, HAJ
Formal analysis: ADK
Writing review and editing: NG

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2350

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Ankle-Brachial Index as a Predictor of Peripheral Arterial Disease in Newly Diagnosed Hypertensive Patients

Safdar Ali Pervez[1*], Munir Ahmed Channa[2], Mahesh Kumar[2], Abdul Hayee Phulpoto[1], Abdul Qayoom Memon[1] and Asif Aziz[3]

[1]Department of Medicine, Khairpur Medical College, Civil Hospital, Khairpur, Pakistan
[2]Department of Medicine, Muhammad Medical College and Hospital, Mirpurkhas, Pakistan
[3]Department of Medicine, Gambat Medical College, Gambat, Pakistan

ARTICLE INFO

Keywords:
Hypertension, Peripheral Arterial Disease, Ankle-Brachial Index, Blood Pressure, Cardiovascular Risk

How to Cite:
Pervez, S. A., Channa, M. A., Kumar, M., Phulpoto, A. H., Memon, A. Q., & Aziz, A. (2024). Ankle-Brachial Index as a Predictor of Peripheral Arterial Disease in Newly Diagnosed Hypertensive Patients: Peripheral Arterial Disease in Hypertensive Patients. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2350

***Corresponding Author:**
Safdar Ali Pervez
Department of Medicine, Khairpur Medical College, Civil Hospital, Khairpur, Pakistan
sufee1981@gmail.com

Received Date: 5th October, 2024
Acceptance Date: 21st November, 2024
Published Date: 30th November, 2024

ABSTRACT

Hypertension was a major risk factor for cardiovascular disorder including Peripheral Arterial Disease (PAD). **Objective:** To evaluate the risk of Peripheral Arterial Disease (PAD) in newly diagnosed hypertensive patients using Ankle-Brachial Index (ABI) measurements and to determine its potential role as a predictor of cardiovascular risks in this population. **Methods:** The study was an observational, cross-sectional study. This study was conducted in Khairpur Medical College Civil Hospital Khairpur Mirs. The duration of this study was six months, from November 2023 to April 2024This study include n= 246 newly diagnosed hypertension. Three levels of ABI had been identified through determining the ABI in both legs: low ABI (<0.9), normal ABI (0.9-1.4), and high ABI (>1.4). Student's t-test. Pearson correlation test have been utilized when assessing the significance of the association between ABI levels and blood pressure values. **Results:** ABI was normal in 60% of the 246 participants, low in 20% and high in 20% of them. In comparison to those who had normal and high ABI, participants who had low ABI showed considerably higher SBP in both lower limbs ($p < 0.001$). Furthermore, there was additionally a significant distinction ($p < 0.001$) in the SBP and DBP among people who had high ABI. Participants with average ABI had higher SBP in their right upper limb than those who suffered from elevated ABI ($p < 0.001$). **Conclusions:** This study showed that in individuals who have recently identified high blood pressure, there was a significant relationship among ABI levels and arterial pressure levels.

INTRODUCTION

The heart pumps blood throughout the body, it exerts force on the artery walls. This force is known as Blood Pressure (BP). Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) are the two standard values used to express it [1]. Blood pressure is measured in two ways: diastolic blood pressure is the pressure in the arteries during diastole, or the time between heartbeats, and systolic blood pressure is the pressure in the arteries during a heartbeat. When taken collectively, these metrics offer a significant indicator of cardiovascular health [2, 3]. Both alcohol abuse and smoking have direct and indirect effects on blood pressure, further compounding the risk [4]. Specifically, in elderly people, Peripheral Artery Disease (PAD) is a widespread condition which is strongly connected to cardiac risk factors such as atherosclerosis, and hypertension [5]. Whenever utilized as an evaluation instrument for recently identified high blood pressure people with disabilities, the Ankle-Brachial Index (ABI) provides essential details concerning premature PAD being recognized. Ankle to brachial systolic Arterial Blood flow ratio (ABI) is an easy to understand, minimally invasive diagnostic. ABI scores < 0.9 are predictive of PAD and point to restriction or congestion of the vasculature [6, 7]. It additionally seems essential to recognize PAD early due to enhances the chance of unfavourable cardiovascular complications, such as haemorrhage and myocardial infarction, which can be fatal. The pharmaceutical therapies, changes in behaviour, and, if needed surgery alternates may collectively minimize such hazards for those who have lower ABI scores as they get early

DOI: https://doi.org/10.54393/pjhs.v5i11.2350

treatment [8, 9]. Clinicians may more effectively recognize subclinical cardiovascular disease and start adequate prevention efforts via incorporating ABI examination into typical clinical care for recently identified people with high blood pressure [10]. With respect to either the greatest or minimum degrees of ankle stress, there are different methods for figuring out ABI. The most elevated ankle pulse has been adopted as an average in the latest recommendations released by the American Heart Association (AHA) and the Inter-Society Consensus for the Handling of Peripheral Arterial Disease (TASC II). These suggestions, at the same time, have not been frequently embraced and therefore could overestimate the real frequency of PAD [11]. What is the prevalence of Peripheral Arterial Disease (PAD) in newly diagnosed hypertensive patients, as determined by Ankle-Brachial Index (ABI), and how effectively can ABI serve as a predictor of cardiovascular risk in this population?

This study aimed to evaluate the risk of Peripheral Arterial Disease (PAD) in newly diagnosed hypertensive patients using Ankle-Brachial Index (ABI) measurements and to determine its potential role as a predictor of cardiovascular risks in this population.

METHODS

The study was an observational, cross-sectional study, conducted in Department of Hypertension and Cardiovascular at Khairpur Medical College Civil Hospital Khairpur Mirs. The duration of this study was six months, from November 2023 to April 2024. A total of 246 participants were enrolled using convenience sampling method. Inclusion criteria were participants aged between 30-55 years, newly diagnosed Hypertensive Patient without any antihypertensive medications, of both sex were involved in study. Exclusion criteria were diabetic participants, long standing hypertension, and peripheral nervous system disorder. The formula for estimating proportions was as follows: n= Z2. P. (1-P)/d2, n=sample size, Z= (1.96 or 95% confidence level), P=estimated proportion (0.20 or 20%), d= margin of error (0.05 or 5%). The required sample size was n=246. Each participant had their body measurements conducted in a lab following along to a set procedure. Weight/height2 was used to compute BMI. A computerized oscillometric devices (Watch BP Office, Microlife, Widnau, Switzerland) was employed to evaluate the ABI. Before having their blood pressure quantified, every individual was permitted to lie down in a lying down position for no less than of 5 minutes. Before the test, the individuals had been warned not to drink any tea, coffee, or other cardiomodulator agents. ABI was determined through determining the highest brachial systolic arterial blood pressure of each arm (Rt or Lt) and multiplying it by the mean systolic blood pressure from either ankle. Every three minutes, for a length of one minute, the systolic and diastolic Blood Pressures (BP) were taken into consideration. The blood pressure was taken, the cuffs were taken off, and the patients were free to depart. The ABI was computed and the blood pressure data was recorded daily. Data were analyzed by using SPSS version 21.0. Continuous variables such as age and blood pressure were expressed as mean ± SD. Categorical variables, including smoking status and gender, were presented as percentages. Student's t-test was used to evaluate the relationship between ABI and blood pressure. Student's t-test was used to compare the means of ABI between different groups (blood pressure levels), which was appropriate for comparing the means of two independent groups. Pearson Correlation Test was applied to analyze the linear relationship between ABI and blood pressure parameters. $P<0.005$ was considered as significant. The study was approved by the Institutional Review Board (KMC/RERC/74), ensuring adherence to ethical standards. Informed consent was obtained from all participants prior to their involvement in the study.

RESULTS

This study of 246 newly diagnosed hypertensive individuals, with a mean age of 50 years and 60% male, assessed their risk for Peripheral Artery Disease (PAD) using the Ankle Brachial Index (ABI). The participants had an average BMI of 25–29.9, indicating overweight status, and 25% were smokers. The mean LDL cholesterol was 110 ± 35 mg/dL, triglycerides 150 ± 40 mg/dL, and total cholesterol 195 ± 30 mg/dL. Additionally, 40% of participants were sedentary, increasing their risk for PAD progression. These findings were detailed in table 1.

Table 1: Demographic Variables of study participants (n=246)

Demographics	Variables	Total Number of Participants Mean ± SD/ N (%)
Age	-	50 ± 10
Gender	Male	146 (60%)
	Female	198 (40%)
BMI (Kg/m^2)	-	27.5 ± 4.2
Smoking Status	Smokers	62 (25%)
	Non-Smokers	184 (75%)
Hypertension Stage	Stage 1	172 (70%)
	Stage 2	74 (30%)
ABI Categories	Normal (1.0-1.4)	148 (60%)
	Borderline (0.91-0.99)	49 (20%)
	PAD (<0.9)	49 (20%)
Lipid Profile	Total Cholesterol	195 ± 30
	LDL Cholesterol	110 ± 35
	HDL Cholesterol	45 ± 10
	Triglycerides	150 ± 40
Physical Activity	Sedentary	98 (40%)
	Active	148 (60%)

The right Ankle-Brachial Index (ABI) showed significant negative correlations with systolic blood pressure (SBP) in both the right upper limb ($r = -0.310$, $p = 0.021$) and the left upper limb ($r = -0.340$, $p = 0.010$). Conversely, a positive correlation was observed between right ABI and SBP in the

DOI: https://doi.org/10.54393/pjhs.v5i11.2350

right lower limb (r = 0.510, p < 0.001). The left ABI demonstrated a significant negative correlation with SBP in the left upper limb (r = −0.390, p = 0.005). However, diastolic blood pressure (DBP) correlations were not significant (p > 0.05). Pearson correlation analysis was employed to assess these relationships. These findings highlight the potential value of ABI in evaluating systolic blood pressure, as shown in table 2.

Table 2: Correlation of ABI with Blood Pressure (BP) Variables (n=246)

Variables	Left ABI (p)	Right ABI (r)	Right ABI (p)	Left ABI (r)
SBP Right Upper Limb (mmHg)	-0.310	0.021	-0.340	0.010
SBP Left Upper Limb (mmHg)	-0.200	0.150	-0.390	0.005
SBP Right Lower Limb (mmHg)	0.510	<0.001	0.130	0.300
SBP Left Lower Limb (mmHg)	0.280	0.040	0.150	0.250
DBP Right Upper Limb (mmHg)	-0.190	0.170	-0.110	0.450
DBP Left Upper Limb (mmHg)	-0.170	0.190	-0.180	0.180
DBP Right Lower Limb (mmHg)	0.070	0.550	0.010	0.920

Patients with low ABI, indicating PAD, have significantly higher systolic (SBP) and diastolic blood pressure (DBP) compared to those with normal or high ABI, suggesting elevated peripheral resistance. Statistically significant differences in SBP (p<0.001) and DBP (p=0.001-0.004) were observed across ABI groups, with a t-value of 5.51 (p<0.001), indicating a clear association between blood pressure and ABI levels (Table 3).

Table 3: Left ABI as a Predictor of Blood Pressure Variations in Diagnosed Hypertensive Participants

Predictor Markers	Right Upper Limb (SBP) Mean ± SD	Left Upper Limb (SBP) Mean ± SD	Right Lower Limb (SBP) Mean ± SD	Left Lower Limb (SBP) Mean ± SD	Right Upper Limb (DBP) Mean ± SD	Left Upper Limb (DBP) Mean ± SD	Right Lower Limb (DBP) Mean ± SD	Left Lower Limb (DBP) Mean ± SD	t-value	p-Value
Low ABI (<0.9)	160 ± 20	158 ± 22	165 ± 19	163 ± 20	95 ± 14	94 ± 12	97 ± 13	96 ± 11	-	>0.001*
Normal ABI (0.9-1.4)	135 ± 15	130 ± 14	145 ± 17	130 ± 16	85 ± 8	84 ± 7	87 ± 9	86 ± 7	-	-
High ABI (>1.4)	145 ± 18	143 ± 17	150 ± 19	148 ± 21	90 ± 10	89 ± 12	91 ± 11	92 ± 13	5.51	>0.001*
p-Value	<0.001	<0.001	<0.001	<0.001	0.001	0.001	0.001	0.003	0.004	-

Participants with low ABI (<0.9) showed significantly higher systolic and diastolic blood pressure (SBP and DBP) compared to those with normal or high ABI, indicating a link to PAD. For example, right upper limb SBP was 160 ± 21 mmHg for low ABI versus 136 ± 17 mmHg for normal ABI. Similarly, DBP in the low ABI group was 96 ± 13 mmHg in lower limbs compared to 85 ± 9 mmHg for normal ABI. The high ABI group had higher BP than the normal group, suggesting arterial stiffness, but less than the low ABI group. A t-value of 7.1 and p-value < 0.001 confirmed these differences were statistically significant (Table 4).

Table 4: Right ABI as a Predictor of Blood Pressure Variations in Diagnosed Hypertensive Participants

Predictor Markers	Right Upper Limb (SBP) Mean ± SD	Left Upper Limb (SBP) Mean ± SD	Right Lower Limb (SBP) Mean ± SD	Left Lower Limb (SBP) Mean ± SD	Right Upper Limb (DBP) Mean ± SD	Left Upper Limb (DBP) Mean ± SD	Right Lower Limb (DBP) Mean ± SD	Left Lower Limb (DBP) Mean ± SD	t-value	p-Value
Low ABI (<0.9)	160 ± 21	158 ± 19	165 ± 23	162 ± 22	96 ± 13	94 ± 15	97 ± 11	96 ± 15	-	>0.001*
Normal ABI (0.9-1.4)	136 ± 17	130 ± 11	145 ± 10	130 ± 11	85 ± 9	84 ± 6	88 ± 6	88 ± 7	-	-
High ABI (>1.4)	145 ± 18	146 ± 17	152 ± 20	91 ± 11	90 ± 11	95 ± 11	93 ± 12	92 ± 13	7.1	>0.001*
p-Value	<0.001	<0.001	<0.001	<0.001	0.001	0.001	0.003	0.004	-	-

DISCUSSION

ABI measurements that were important, a comprehensive clinical history, and an assessment of physical characteristics enable healthcare workers to assess the patient's whole cardiovascular health [12]. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) for each of the legs showed consistently elevated among people having low ABI values an indication of PAD than in participants with normal or high ABI values [13]. In the current study to find that, the peripheral artery constriction, which lowers blood flow to the limbs, was the hallmark of Peripheral Artery Disease (PAD). The body raises blood pressure in an attempt to make up for the compromised perfusion. An increased risk of cardiovascular problems, such as heart attack, stroke, and further advancement of PAD, was indicated by elevated SBP and DBP in patients with low ABI [14, 15]. In the present study to find that, the relationship between the blood pressure in each ankle and the limbs; a significant correlation was found between the ABIs in both ankles and the blood pressure in the right upper and left lower limbs, and a significant correlation was found between the left ankle and the blood pressure in both upper and lower limbs. The participants' ABIs were all within the normal range for ABI, which was typically 0.9 to 1.3, indicating that none of the participants had severe peripheral artery disease [16]. In the current study to found that, this implies that arterial stiffness and abnormalities in arterial pressure especially among the limbs can be observed in the ABI. The purpose of this research was to examine the differences in blood pressure parameters across groups with low, normal, and high Ankle-Brachial Index (ABI) levels. By identifying these contrasts, the study aims to highlight the associations between ABI levels, hypertension, and Peripheral Arterial Disease (PAD). Specifically, it explores how low ABI

DOI: https://doi.org/10.54393/pjhs.v5i11.2350

(indicative of PAD) and high ABI (linked to arterial stiffness) relate to elevated systolic and diastolic blood pressures compared to normal ABI levels. The parameters of blood pressure were measured across different groups. The Upper Limb's SBP variations were far greater among those with Low ABI, but participants who had more ABI reported considerably greater SBP in the two lower limbs [17]. The participants in the normal ABI group may have adequate arterial regulation that suggests their arteries were capable of expanding to an appropriate level in reaction to increased blood circulation, according to their larger SBP. However, the heightened SBP could indicate that the above limbs' greater systolic arterial pressure has been triggered by other systematic variables, that include stress, heightened cardiac output, or initial stages hypertension. We were agreed from the previous study [18]. On the other hand, people with high ABI might be suffering from arterial stiffness that can cause peripheral artery systolic blood pressure to fall regardless of expanding essential hypertension. Patients having various levels of arterial stiffness might display different patterns of elevated blood pressure in the upper extremity on right side comparing to the lower extremities or the left upper limb, particularly where the arterial stiffness remains more confined [19]. While there was a correlation between higher mortality and high ABI values (≥1.3) indicating arterial stiffness, the risk was generally smaller than that of ABI values <0.9, which suggest more severe PAD (Peripheral Arterial Disease). In patients with underlying diseases such as hypertension, high ABI values were more concerning even though they were not as frequently associated with symptomatic PAD. In a similar vein, borderline-low ABI values (0.9–1.1) should be cautiously watched as they may signal early PAD or other cardiovascular problems. In general, a complete cardiovascular evaluation and continued monitoring were necessary to control and minimize any consequences that may arise from high or borderline-low ABI levels [20]. Based on the findings, incorporating ABI measurement into routine hypertension management could help identify early signs of Peripheral Arterial Disease (PAD), especially in patients with high Systolic Blood Pressure (SBP). Since ABI was correlated with SBP, particularly in the upper and lower limbs, it can serve as a valuable tool in assessing vascular health and PAD risk in hypertensive patients. Healthcare providers should consider using ABI to personalize treatment plans and detect PAD early, improving overall management and reducing cardiovascular risks.

CONCLUSIONS

This study reveals significant correlations between ABI and blood pressure, particularly Systolic Blood Pressure (SBP) in both upper and lower limbs. The findings underscore ABI's potential as a valuable tool for assessing hypertension severity and the risk of Peripheral Arterial Disease (PAD) in hypertensive patients. The positive correlation between ABI and SBP in the lower limbs suggests that higher blood pressure may increase PAD risk, highlighting the importance of including ABI measurement in routine hypertension management.

Authors Contribution

Conceptualization: SAP
Methodology: MAC, MK, AHP, AQM
Formal analysis: AHP, AQM
Writing, review and editing: AQM, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Sweetened Beverages Consumption and Self-Reported Oral Health among Young Adults: A Cross-Sectional Study in Peshawar

Aiman Niaz[1], Ruqayya Sana[2*], Rida Bahar[3], Muhammad Rizwan[3] and Malaika Spugmai[4]

[1]Department of Community Dentistry, Khyber Medical University, Peshawar, Pakistan
[2]Department of Community and Preventive Dentistry, Sardar Begum Dental College, Peshawar, Pakistan
[3]Department of Dental Surgery, Sardar Begum Dental College, Peshawar, Pakistan
[4]Sahara Medical College, Narowal, Pakistan

ARTICLE INFO

Keywords:
Young Adult, Oral Health, Sweetened Beverages, Energy Drinks

How to Cite:
Niaz, A., Sana, R., Bahar, R., Rizwan, M., & Spugmai, M. (2024). Sweetened Beverages Consumption and Self-Reported Oral Health among Young Adults: A Cross-Sectional Study in Peshawar: Sweetened Beverages Consumption and Oral Health among Adults.Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2512

***Corresponding Author:**
Ruqayya Sana
Department of Community and Preventive Dentistry, Sardar Begum Dental College, Peshawar, Pakistan
sana.ruqayya@gmail.com

Received Date: 11th October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Sweetened beverage consumption has become a growing concern due to its potential negative effects on oral health, particularly among young adults. **Objectives:** To assess the consumption patterns and self-reported oral health of sweetened beverages among young adults in Peshawar. To evaluate the association of self-reported oral health and sweetened beverage consumption among young adults. **Methods:** A cross-sectional study was conducted among 163 young adults in Peshawar. An online questionnaire was sent to study participants via convenience sampling. A structured questionnaire was used to collect data. Data were entered and analyzed using SPSS 26. The chi-square test was employed to assess the association between different categorical variables and $p<0.05$ was considered significant. **Results:** The mean age of the participants was 19.37 + 1.57 years. Soda was the most frequently consumed beverage (33.1%), followed by energy drinks (11.7%), favored tea (9.8%), packed juices (11.7%), and other beverages (14.8%). Around 41.7% of the participants experienced tooth sensitivity, 41.1% had dental caries and 37.4% had gum problems. Significantly more female than male consumed sweetened beverages daily. **Conclusions:** A positive link between increased intake of sugary drinks and poor oral health. To tackle this issue, it is crucial to implement public health initiatives, school-based programs, and policy reforms aimed at reducing sugary drink consumption and enhancing oral health.

INTRODUCTION

In recent times, energy drinks, soda and other soft drinks have become increasingly popular. There has been a significant hike in demand for sweetened beverages especially among the young population [1]. Fruit-favoured beverages with added artificial sweeteners and preservatives are liked by all young adults. The increase in consumption raises concern among health professionals and dentists [2]. Several health hazards are reported from the use of sweetened drinks including obesity, diabetes, and tooth decay, due to the high sugar content of these beverages [1, 3]. The rise in the consumption of sweetened beverages raises concerns about oral diseases, especially dental caries [4]. The high sugar content develops an active acidic environment in the oral cavity [2]. The combination of acid production and fermentable carbohydrates creates an environment conducive to bacterial growth, leading to tooth enamel breakdown and, consequently, dental caries [2, 3]. According to the World Health Organization, sugar intake should be limited to less than 10% of total energy consumption, and ideally, to less than 5% for optimal health benefits [3]. Regardless of these clear recommendations, the consumption of sweetened beverages is increasing at an alarming rate among young adults [4]. Studies have demonstrated a connection between sweetened beverage consumption and both oral health problems and general health issues [4-6]. In the United States, sugar-sweetened beverages contribute approximately 7% of the daily caloric intake

DOI: https://doi.org/10.54393/pjhs.v5i11.2512

among young adults [5]. A strong correlation exists between sugary drink consumption and dental caries in children and adolescents. While the evidence is limited, it's well-established that health and dietary habits formed during young adulthood often persist throughout life. Young adults are often involved in risk-taking behaviours while ignoring any preventive measures, and unhealthy eating and drinking habits are among those behaviours [1, 7]. Similarly, dietary choices are influencing oral health status among this vulnerable group, leading to a vicious health cycle [1, 8]. The perception of young adults regarding their oral health is important in shaping their eating habits. It serves as an indicator of oral health-related quality of life, thus affecting the psychological and social impact of oral health [1, 4]. Self-reported oral health is a fundamental factor in understanding individuals' views of their dental health, which can be affected by consumption patterns of artificial beverages [7]. More evidence is growing on the linkage of sugary beverages to poor oral health [9]. However, the research gap still exists in our understanding of how young adults perceive dietary habits with oral health. The implications of this research will extend beyond individual health, influencing public health strategies aimed at reducing diet-related dental diseases. Insights into young adults' perceptions of oral health and its connection to sweetened beverage consumption can guide targeted educational campaigns and preventive measures [3, 10]. Public health initiatives, including community-based programs and university health services, can utilize findings from this study to foster an environment that encourages healthier beverage choices and increased oral health awareness. Furthermore, exploring the relationship between sweetened beverage consumption and self-reported oral health can lead to the development of holistic strategies that address not only dietary behaviours but also the psychological and social aspects of health [11]. Pakistan has one of the highest rates of sweetened beverage consumption globally, with approximately 99.3% of the population consuming these drinks. Yemen shows the second-highest daily and weekly consumption rates around 60% [5]. The consumption of sugar-sweetened drinks poses a significant public health issue, particularly affecting the dental health of young adults.

This study aims to identify the patterns of sweetened beverage consumption among young adults. The secondary objectives are to assess the self-reported oral health of young adults and explore its association with their patterns of sweetened beverage consumption. By examining these dietary habits and health perceptions, the study seeks to provide a comprehensive understanding of their interplay, ultimately guiding future research interventions.

METHODS

A cross-sectional study was conducted from April to September 2024 among young adults. A sample size of 179 young adults was calculated using the Open-Epi calculator. The sample size was calculated assuming a proportion of 12% [12], a precision of 5%, and a 95% confidence interval, with a 10% non-response rate. This yielded a minimum required sample size of 163 participants, which was adjusted to 179 to account for a 10% non-response rate. A well-structured self-administered questionnaire was used to collect data. The questionnaire was pilot-tested on 5% of the sample size. Data collection was started after obtaining ethical approval from the Ethical Review Board of Gandhara University (Certificate No. GU/Ethical Committ/2024/160). Participants were recruited through a digital distribution strategy through the snowball sampling technique. The online questionnaire was shared via WhatsApp and social media groups among students of Gandhara University, Peshawar. Informed consent was obtained from each participant at the start of an online questionnaire. Participants aged 18-25 years who were residents of Peshawar were included in the study. Individuals who were younger than 18 or older than 25 years were excluded. Additionally, participants who were unable to understand or complete the questionnaire were not included in the study. All the collected data were entered and analyzed using SPSS version 26.0. Mean and standard deviation were calculated for the age of participants. Frequency tables and percentages were generated for categorical variables. The chi-square test was conducted to determine the association between different categorical variables and p-values less than 0.05 were considered significant.

RESULTS

A total of 179 questionnaires were distributed online to young adults for this cross-sectional study. After data cleaning and deletion of incomplete responses, a total of 163 complete responses were included in the study. The mean age of the participants was 19.37 + 1.57 years. Female participants were 69.9% (114), while male participants were 30.1% (49). All of the participants were college students, 69.3% (113) were 1st year students and 23.3% (38) were 2nd year students. Around 5.6% (9) were 3rd year students and 1.8% (3) were 4th year students. When asked how often the participants consume sweetened beverages in one week, 19% (31) of participants reported daily consumption, while 25.8% (42) once a week, 30.7% (50) reported 2-3 times per week, 11% (18) more than 4 times a week, and 13.50% (22) reported that they do not consume any sweetened beverages during the week. The consumption pattern of sweetened beverages in one week among young adults is shown in figure 1.

DOI: https://doi.org/10.54393/pjhs.v5i11.2512

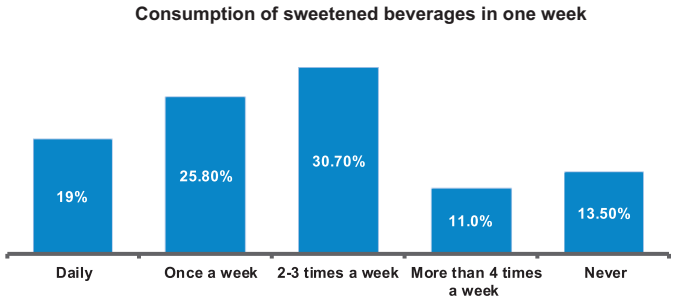

Figure 1: Consumption of Sweetened Beverages in One Week among Young Adults

The participants were asked about the type of beverages they consume. 54 (33.1%) soda and energy drinks were consumed by 19 (11.7%) and 16 (9.8%) consumed favoured tea. Approximately 19 (11.7%) packed juices and 55 (33.7%) consumed drinks other than those mentioned. A higher prevalence of sweetened beverage consumption was found in female than male. Several participants used a combination of different drinks, which were as follows; 3.7% soda and packed juices, 3.7% consumed energy drinks and packed juices, 2.5% soda and favoured tea, while 1.8% of participants consumed soda, energy drinks, packed juice, flavored tea, and other drinks in different combinations. The number of beverages consumed per day was analyzed. Results showed that 30.1% of participants do not consume any drink daily, one drink was consumed by 60.7% of participants, two drinks were consumed by 5.5% of participants, and 3.7% of participants consumed three drinks in a single day. The oral health practices and the self-reported dental problems of young adults are demonstrated in table 1.

Table 1: Oral Health Behaviors and Self-Perceived Oral Health Conditions of Young Adults

Oral Health Behaviour and Self-Perceived Oral Health Condition	n (%)
Tooth Brushing Frequency	
Once a Day	93 (57.1%)
Twice a Day	64 (39.2%)
Do Not Brush Their Teeth	6 (3.7%)
Use of Mouthwash	
No Use of Mouthwash	118 (72.4%)
Use Mouthwash	45 (27.6%)
Flossing	
Use floss	132 (81%)
Do Not Use Floss	31 (19%)
Previous Dental Visit	
In the last 6 Months	43 (26.4%)
In the 6-12 Months	20 (12.3%)
More Than A Year Ago	42 (25.8%)
Never Visited A Dentist	58 (35.5%)
Tooth Sensitivity	
Reported Tooth Sensitivity	68 (41.7%)
No Tooth Sensitivity	95 (58.3%)
Gum Problems	
Experienced Gum Problems	61 (37.4%)
No Gum Problems	102 (62.6%)
Tooth Cavities	
Had A Tooth Cavity	67 (41.1%)
Never Had A Tooth Cavity	96 (58.9%)
Bad Breath	
Experienced Bad Breath	56 (34.4%)
Never Had Bad Breath	107 (65.6%)
Tooth Pain After Consumption of Sweetened Beverage	
Never Experienced Tooth Pain	119 (73%)
Experienced Tooth Pain	44 (27%)
Tooth Sensitivity After Consumption	
Experienced Tooth Sensitivity	50 (30.7%)
Never Experienced Tooth Sensitivity	113 (69.3%)

The participants were asked whether they were aware of the health hazards of sweetened beverages, 141 (86.5%) reported that they were aware of the harmful effects of sweetened beverages while 22 (13.5%) were unaware. A greater number of female was aware of the negative impact of sweetened beverages on oral health compared to male ($p<0.05$). The participants were asked if they had received any information from a healthcare provider or any other source on oral health risks related to the use of sweetened beverages, 93 (57.1%) reported that they had received any such information while 70 (42.9%) denied receiving any such information. Chi-square test to examine the association between frequency of sweetened beverage consumption (daily, weekly, and non-consumers) and self-reported oral health conditions (tooth sensitivity, tooth cavities, gum problems, and bad breath). The findings of associations between sweetened beverage consumption and self-reported oral health conditions are highlighted in table 2.

Table 2: Association Between Oral Health Conditions and Frequency of Sweetened Beverage Consumption Among Young Adults

Oral Health Condition	Frequency of Sweetened Beverage Consumption	n (%)	p-Value
Tooth Sensitivity	Daily Consumers	18/31 (58.1%)	>0.05
	Once a Week	16/42 (38.1%)	
	2–3 Times/Week	21/50 (42.0%)	
	>4 Times/Week	8/18 (44.4%)	
	Non-Consumers	5/22 (22.7%)	
Tooth Cavities	Daily Consumers	19/31 (61.3%)	>0.01
	Once a Week	18/42 (42.9%)	
	2–3 Times/Week	19/50 (38.0%)	
	>4 Times/Week	9/18 (50.0%)	
	Non-Consumers	4/22 (18.2%)	
Gum Problems	Daily Consumers	17/31 (54.8%)	0.06
	Once a Week	15/42 (35.7%)	
	2–3 Times/Week	20/50 (40.0%)	
	>4 Times/Week	6/18 (33.3%)	
	Non-Consumers	5/22 (22.7%)	

DOI: https://doi.org/10.54393/pjhs.v5i11.2512

Bad Breath	Daily Consumers	14/31 (45.2%)	>0.05
	Once a Week	17/42 (40.5%)	
	2-3 Times/Week	17/50 (34.0%)	
	>4 Times/Week	7/18 (38.9%)	
	Non-Consumers	4/22 (18.2%)	

Daily consumers of sweetened beverages exhibited significantly higher rates of tooth sensitivity, cavities, and bad breath compared to less frequent or non-consumers ($p<0.05$). There was no association between gum diseases and consumption of sweetened beverages.

DISCUSSION

The current study was conducted to assess the patterns of sweetened beverage consumption and self-reported oral health status among young adults in Peshawar. There has been a marked increase in consumption of sugary sweetened beverages among young adults in recent years which has raised serious concerns among health professionals. The study revealed a concern high prevalence of sugar-sweetened beverage consumption among young adults in Peshawar. A substantial proportion of participants, 30.7%, were frequent consumers. Another study conducted in Pakistan stated that 12% of college students consume sweetened beverages [12]. A study conducted in Saudi Arabia found that 93.6% of participants consumed soft drinks weekly, with 40.8% consuming them daily. Another study reported that 98.5% of participants consumed soft drinks within three months [13]. A study done in Kuwait, also reported the majority of participants (93.8%) consumed weekly beverages and 32.6% consumed daily beverages [5]. The use of different types of beverages usually depends on the personal preferences and tastes of individuals. The results of the current study showed different variations according to the kind of beverage consumption. Soda was the most frequent and preferable drink among the individuals (33.1%) which comes in resemblance to other studies done in Lahore, Bahrain and Australia showing similar preference among young populations [14, 15]. Another drink that was most popular and frequently used among young adults was energy drinks (11.7%). The data from low-middle-income countries also showed evidence that carbonated drinks are consumed 1.39 times more among young adults. Moreover, 54.3% of adolescents consume at least one carbonated drink per day [16]. A notable finding was the diverse range of beverage combinations consumed by participants. For instance, 3.7% consumed a mix of soda and packed juices, while another 3.7% opted for energy drinks and packed juices. Additionally, 2.5% combined soda and flavoured tea, and 1.8% consumed a variety of beverages including soda, energy drinks, packed juices, flavored tea, and others. Our study found that the most common consumption pattern was one beverage per day, reported by 60.7% of participants. A smaller proportion, 5.5%, consumed two beverages daily, while 3.7% consumed three. A study done during COVID revealed that there was an increase of uptake of sugary beverage use increased by 32% and led to oral health emergencies in 18% of individuals. During this time one out of five individuals preferred using sweetened beverages, showing a shift in dietary habits [11]. Habitual consumption of sweetened beverages is linked to type 2 Diabetes as evident from research [17]. Most of the participants suffered from dental caries and tooth sensitivity in the past year. Bad breath was experienced more by female in comparison to male. A systematic review revealed an increase in the odds of caries and an increased Decayed, Missing and Filled teeth score as compared to no-sugar beverage users [14, 18]. Similarly, primary dentition showed an increase in caries prevalence up to two times in those taking sugary diets and drinks as compared to non-sugary consumers [4]. Similarly, caries prevalence is positively associated with sugar-sweetened beverages with 60.9% and 85 % more prevalence among consumers and non-consumers [19, 20]. Most of the participants in this study experienced tooth pain and sensitivity immediately after consumption of sweetened beverages. Similarly, a study on health professionals reported that 84% of daily consumers had sensitivity, along with 97% discoloration and 87% erosion [2, 20]. A strong understanding of the health risks associated with added sugar is crucial for making informed dietary choices. In our study, the majority of participants (86.5%) demonstrated adequate knowledge about the negative impact of sugar-sweetened beverages on both general and oral health. These findings align with previous research, which has also shown a positive relationship between awareness and knowledge and the consumption of sugar-sweetened beverages [12]. When asked about receiving information on the oral health risks associated with sugar-sweetened beverages, 57.1% of participants reported having been informed by a healthcare provider or other source. This aligns with findings from a study of medical and dental university students, which indicated that dental students, in particular, possessed a higher level of knowledge on the subject [12].

CONCLUSIONS

The findings reveal a significant association between daily consumption and increased rates of tooth sensitivity, cavities, and bad breath, compared to those who consume sugary drinks less frequently or not at all. A positive link between increased intake of sugary drinks and poor oral health. To tackle this issue, it is crucial to implement public health initiatives, school-based programs, and policy reforms aimed at reducing sugary drink consumption and enhancing oral health.

DOI: https://doi.org/10.54393/pjhs.v5i11.2512

Authors Contribution

Conceptualization: AN
Methodology: AN, RS, RB, MR, MS
Formal analysis: AN, RS
Writing review and editing: AN, RS, MR, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2538

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Evaluation of Maternal Near Miss (MNM) Events and Maternal Mortality at Tertiary Care Hospital

Hina Murtaza[1*], Shifa Panhyar[2], Erum Memon[3], Baby Uroosa[4], Farah Liaquat[5] and Mubashir Hussain[6]

[1]Department of Gynaecology and Obstetrics, Suleman Roshan Medical College and Hospital, Tandodam, Pakistan
[2]Government Dispensary, Lsb Colony–People's Primary Healthcare Initiative, Jamshoro, Pakistan
[3]Department of Gynaecology and Obstetrics, Jinnah Medical and Dental College, Karachi, Pakistan
[4]Rural Health Centre, Bhitshah, Pakistan
[5]Department of Gynaecology and Obstetrics, Baqai Medical University, Karachi, Pakistan
[6]Department of Community Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

ARTICLE INFO

Keywords:
Hemorrhage, Hypertensive Disorder, Maternal Near-Miss, Maternal Mortality

How to Cite:
Murtaza, H., Panhyar, S., Memon, E., Uroosa, B., Liaquat, F., & Hussain, M. (2024). Evaluation of Maternal Near Miss (MNM) Events and Maternal Mortality at Tertiary Care Hospital: Maternal Near Miss (MNM) Events and Maternal Mortality . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2538

Corresponding Author:
Hina Murtaza
Department of Gynaecology and Obstetrics, Suleman Roshan Medical College and Hospital, Tandoadam, Pakistan
doctormurtaza881@gmail.com

Received Date: 3rd October, 2024
Acceptance Date: 21st November, 2024
Published Date: 30th November, 2024

ABSTRACT

Maternal Near-Miss events are critical indicators of the quality of maternal healthcare, representing instances where women survive severe obstetric complications that could have resulted in death. **Objectives:** To find out the characteristics and causes of maternal near-miss events and maternal mortality at Liaquat University Hospital Hyderabad/Jamshoro. **Methods:** This cross-sectional study was conducted on 233 pregnant and postpartum women of were within 42 days of childbirth, who presented with severe morbidity or early maternal mortality. The duration of the study was from January 1 2021 to June 30 2021. Women undergoing uncomplicated cesarean sections or normal vaginal deliveries, as well as cases of mild anemia, mild-to-moderate hypertension, and Class I and II hemorrhages (less than 30% blood loss), were excluded. Data were collected on demographic characteristics and clinical details such as the mode of delivery, timing of near-miss events concerning admission, patient presentation, surgical interventions performed to save the mother's life, and obstetric complications. **Results:** The mean age of maternal near-miss cases was 25.5 ± 5.5 years. Most maternal near-miss cases occurred among multiparous, rural, un-booked women aged 26–30 years. The leading causes of maternal near-miss were hemorrhage (44.2%), hypertensive disorders (35.1%), and dystocia (12%), followed by sepsis and severe anemia (4.2% each). A significant proportion, 176 cases (75.5%), required intensive care unit admission, with a mean hospital stay of 14.5 days. **Conclusions:** It was concluded that hemorrhage and hypertensive disorder were found to be the most common causes of maternal near-miss cases.

INTRODUCTION

Maternal health is the key parameter of the overall quality and accessibility of healthcare the world over. World Health Organization (WHO) estimates more than 300,000 maternal deaths and about ten million women facing complications of pregnancy, childbirth or the post-natal period in a single year (2020). To address these, events of maternal near-miss (MNM) are identified as those that occur in women who were severely affected by complications during pregnancy or within 42 days following termination of pregnancy but survived [1, 2]. With multiple commonalities with maternal deaths; these show a vital means to identify gaps in the healthcare system [3]. Maternal health has benefits over the years on a global scale with such improvements being more pronounced in low and middle-income countries however there is still a long way to go. The maternal mortality rate (MMR) in Pakistan improved from 375 per 100,000 live births in 1995 to 178 per 100,000 live births in 2019 [4]. Such a decrease in MMR indicates improvements in maternal healthcare services focused on women. However, the maternal mortality rate is still a public health problem with most women dying from hemorrhage, hypertensive disorder and sepsis as documented causes

DOI: https://doi.org/10.54393/pjhs.v5i11.2538

[5]. MNM is gaining global attention as a useful measure of maternal health care. WHO defines it as "A woman who almost died but survived a complication of pregnancy, childbirth and pregnancy termination in the 42-days post-pregnancy" [3]. Survival does not occur by chance; it requires timely interventions to prevent death from severe obstetric complications that arise during pregnancy [6]. Different criteria for identifying MNM cases have been proposed, which can be categorized under disease-specific, management-specific and organ-system dysfunction-based approaches. Hemorrhage continues to be the leading cause of MNM and maternal mortality. A study reported hemorrhage as the cause in 44.2% of MNMs cases, hypertensive disorder in (35.1%), dystocia (12%) and sepsis (4.2%) [7]. These results highlight the importance of timely identification and management of lapses during obstetric complications. While global studies on MNM have provided valuable insights, there is limited research specific to the Pakistani population. Given the high burden of maternal complications in the region, understanding the prevalence and causes of MNM is essential to improve maternal outcomes. MNM investigations can help identify high-risk groups, plan interventions for managing obstetric emergencies, and strengthen healthcare systems to prevent maternal deaths.

This study aims to address this gap by evaluating the characteristics and causes of MNM in a tertiary care hospital in Pakistan.

METHODS

This cross-sectional study was conducted at the Department of Gynaecology and Obstetrics Unit-I, Liaquat University of Medical and Health Sciences, Hyderabad from January 1 2021 to June 30 2021. A sample size of 233 participants was included, consisting of pregnant and postpartum women within 42 days of childbirth who presented with severe morbidity or early maternal mortality. Exclusion criteria included women undergoing uncomplicated cesarean sections or normal vaginal deliveries, as well as cases of mild anemia, mild-to-moderate hypertension, and Class I and II hemorrhages (less than 30% blood loss). The sample size was calculated via Open Epi Sample Size Calculator with the prevalence of maternal near misses as 18.6% with a 5% margin of error and 95% confidence interval [4]. The study was approved by the Ethical Review Committee of Liaquat University of Medical & Health Sciences, Jamshoro, vide letter (NO.LUMHS/REC/-1003). All eligible patients meeting the inclusion criteria, as defined by the WHO protocol for maternal near-miss events [8], were registered using a pre-designed Performa. Informed written consent in local languages (Urdu and Sindhi) was taken from each participant after a complete debriefing about the study and before enrollment. The WHO clinical criteria include acute cyanosis, shock, or loss of consciousness lasting over 12 hours, while laboratory parameters include oxygen saturation below 90% for more than 60 minutes, creatinine ≥3.5 mg/dL, or lactate >5 mEq/mL [8]. Data were collected on demographic characteristics, including age, parity, gestational age at admission, booking status, referral status, and mode of admission. Clinical details such as the mode of delivery, timing of near-miss events concerning admission, patient presentation, surgical interventions performed to save the mother's life, and obstetric complications leading to MNM events or maternal deaths were documented. Additionally, data on organ-system dysfunction or failure, Intensive Care Unit (ICU) admissions, and maternal mortality were collected. Patients were categorized by final diagnosis into direct causes (e.g., hypertension, hemorrhage, sepsis) and indirect causes (e.g., anemia, cardiac disease) contributing to maternal near-miss events and deaths. The collected data were analyzed using SPSS version 23.0, focusing on descriptive statistics to identify characteristics and causes of MNM events and maternal mortality.

RESULTS

The mean age of maternal near-miss (MNM) cases was 25.5 ± 5.5 years, with most women (44.2%) aged between 26–30 years. A majority resided in rural areas (57.1%) and were un-booked for antenatal care (73.8%). Multiparous women accounted for 82.4% of cases. Emergency admissions were predominant (88.0%), and 57.9% of cases had gestational ages ≥34 weeks (Table 1).

Table 1: Demographic Characteristics of Maternal Near-Miss Cases (n=233)

Demographic Characteristics	n (%)
Mean Age (Years ± SD)	25.5 ± 5.5
Age Groups	
20–25 Years	96 (41.2%)
26–30 Years	103 (44.2%)
31–35 Years	20 (8.6%)
36–40 Years	14 (6.0%)
Residence	
Urban	100 (42.9%)
Rural	133 (57.1%)
Booking Status	
Booked	61 (26.2%)
Un-booked	172 (73.8%)
Parity Status	
Primipara	41 (17.6%)
Multipara	192 (82.4%)
Mode of Admission	
Emergency	205 (88.0%)
Outpatients Department (OPD)	28 (12.0%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2538

Amongst mode of delivery, most of the participants i.e. 55% (n=128) had emergency cesarean sections, followed by assisted/spontaneous vaginal deliveries i.e. 40% (n=93). Elective cesarean sections were reported in least proportion i.e. 5% (n=12) (Figure 1).

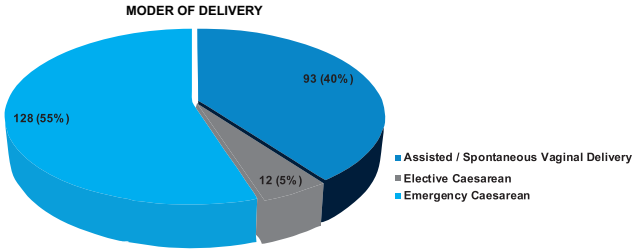

Figure 1: Mode of Delivery among participants with MNM (N=233)

Hypertensive disorders were the leading causes of MNM, with eclampsia (24.9%) and severe pre-eclampsia (10.3%) being significant contributors. Severe hemorrhage, including ectopic pregnancy (15.5%), abortion (5.6%), antepartum hemorrhage (9.9%), and postpartum hemorrhage (13.3%), accounted for 44.3% of cases. Other notable causes included uterine rupture (11.6%), puerperal sepsis (3.4%), severe anemia (4.3%), and chorioamnionitis (0.9%) (Table 2).

Table 2: Causes of Maternal Near-Miss (n=233)

Causes of MNM	n (%)
Hypertensive Disorders	
Severe Pre-Eclampsia	24 (10.3%)
Eclampsia	58 (24.9%)
Severe Hemorrhage in Early Pregnancy	
Ectopic	36 (15.5%)
Abortion	13 (5.6%)
Severe Hemorrhage in Late Pregnancy	
Antepartum Hemorrhage	23 (9.9%)
Severe Hemorrhage After Pregnancy	
Postpartum Hemorrhage	31 (13.3%)
Sepsis	
Puerperal Sepsis	8 (3.4%)
Chorioamnionitis	2 (0.9%)
Dystocia	
Uterine Rupture	27 (11.6%)
Impending Rupture	1 (0.4%)
Anemia	
Severe Anemia	10 (4.3%)

Regarding complications, 75.5% of women required ICU admission, 79.4% were discharged within seven days, and 20.6% had prolonged hospital stays. Organ dysfunction was observed in various systems, with neurological (10.7%), hematological (9.9%), and coagulation (8.2%) dysfunctions being the most frequent (Table 3).

Table 3: Complications Related to Maternal Near-Miss among study participants (n=233)

Complications	n (%)
Total ICU Admissions	176 (75.5%)
Duration of Hospital Stay	
≤7 Days	185 (79.4%)
>7 Days (Prolonged Hospital Stay)	48 (20.6%)
Organ Dysfunctions	
Neurological	25 (10.7%)
Respiratory	10 (4.3%)
Cardiac	8 (3.4%)
Hematological	23 (9.9%)
Coagulation	19 (8.2%)
Hepatic	10 (4.3%)
Renal	16 (6.9%)
Uterine	13 (5.6%)
Multiple System Involvement	7 (3.0%)

DISCUSSION

The mean age of maternal near-miss cases in this study was 25.5 years, consistent with findings by Zafar *et al.*, [9] (24.58 years) and Wasim *et al.*, (28.9 years) [10]. Most cases occurred in women aged 20–30 years, which is comparable to studies by Yasmin *et al.*, and Naik *et al.*, showing that the majority of maternal near-miss cases fell within this age range [11, 12]. Rural residency was predominant among the cases, with 57.08% coming from rural areas, similar to findings by Ojha *et al.*, where 74.8% of near-miss cases were from rural regions [13]. Un-booked status was a significant factor, with 74% of cases being un-booked. This finding aligns with Zahoor *et al.*, where 84.16% of cases were un-booked, highlighting the critical role of antenatal care in preventing maternal morbidity [14]. Multi-parity was more common among maternal near-miss cases (82.4%) compared to primiparity (17.5%), which aligns with studies by Yasmin *et al.*, and Naik *et al.*, both reporting higher proportions of multiparous women among near-miss cases [11, 12]. Regarding gestational age, 57.08% of patients were ≥34 weeks at admission, consistent with findings from Naik et al., where the majority of cases occurred after 34 weeks of gestation [12]. Socioeconomic disparities were evident, with 70.8% of cases belonging to socioeconomically poor groups, corroborating findings by Ojha *et al.*, and Naik *et al.*, who reported similar trends [14, 12]. Emergency admissions accounted for 88% of maternal near-miss cases, as seen in studies by Ugwa *et al.*, and Yasmin *et al.*, emphasizing the importance of timely referrals and interventions to prevent adverse outcomes [15, 11]. Emergency cesarean sections were the most common mode of delivery (55%), followed by spontaneous vaginal deliveries (40%), similar to the distribution reported by Yasmin *et al.*, [11]. A notable proportion of cases (55.3%) were referred from other healthcare facilities, which aligns with findings by Verma *et al.*, where 88.7% of near-miss cases were referrals [16]. Hemorrhage (44.2%) was the leading cause of maternal near-miss followed by hypertensive disorders (35.1%) and dystocia (12%). Wasim *et al.*, and Yasmin *et al*, reported similar findings as

DOI: https://doi.org/10.54393/pjhs.v5i11.2538

hemorrhage and hypertensive disorders were the most common cause of maternal near-miss [10, 11]. Sepsis and severe anemia, which stresses the multi-causative nature of maternal morbidity, also contributed. Similar to the results by Wasim *et al.*, [10], cases of maternal mortality were more often due to hemorrhage and hypertensive disorders [17]. An organ dysfunction was commonly seen among maternal near-miss cases. Neurological (10.7%), hematological (9.8%), coagulation, renal, uterine, hepatic, and respiratory dysfunction were the four most frequent types of dysfunction observed Such results were also similar to those reported by Manyahi *et al.*, and the work of Chama *et al.*, who described similar organ dysfunction patterns among near-miss cases [18, 19]. Surgical and therapeutic procedures were frequent; laparotomy (27%), hysterectomy (5.5%) and hypertension disorders of pregnancy based on an indication received magnesium sulfate therapy in 24.4% of individuals. A total of 27.8% of patients required blood transfusions, and 6.4% needed ventilator assistance. The interventions were similar to those reported by Manyahi *et al.*, and Ingole *et al.*, [18, 20]. The findings of this study highlight the critical need for improving access to antenatal care, particularly for women in rural areas and low socioeconomic groups. Strengthening emergency obstetric care and ensuring timely referrals from lower-level facilities can significantly reduce maternal morbidity and mortality.

CONCLUSIONS

It was concluded that maternal near-miss cases primarily involved un-booked, rural, and multiparous women, emphasizing the need for improved antenatal care and timely access to emergency services. Hypertensive disorders and severe hemorrhage were the leading causes, with ICU admissions and organ dysfunctions being significant complications.. Expanding critical care access and implementing targeted interventions can significantly improve maternal health outcomes and reduce near-miss events.

Authors Contribution

Conceptualization: HM

Methodology: HM, SP, EM, BU, MH

Formal analysis: FL

Writing review and editing: SP, EM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2418

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Forensic Analysis of Injury Patterns among Occupants in Fatal Motor Vehicle Accidents in Karachi, Pakistan

Abdul Waheed[1*], Syed Perwez Alam[2], Hari Ram[3], Sadia Abdul Qayyum[4], Farzana Azam Khan[4] and Iqbal Ahmed Khan[5]

[1]Department of Forensic Medicine and Toxicology, Karachi Institute of Medical Sciences, Karachi, Pakistan
[2]Department of Forensic Medicine and Toxicology, Liaquat College of Medicine and Dentistry, Karachi, Pakistan
[3]Department of Forensic Medicine and Toxicology, Shaheed Mohtarma Benazir Bhutto Medical College, Karachi, Pakistan
[4]Department of Forensic Medicine, Liaquat National Hospital and Medical College, Karachi, Pakistan
[5]Department of Forensic Medicine, Fazaia Ruth Pfau Medical College, Karachi, Pakistan

ARTICLE INFO

Keywords:
Motor Vehicle Accidents, Forensic Analysis, Passengers, Fatalities, Injury Patterns

How to Cite:
Waheed, A., Alam, S. P., Ram, H., Qayyum, S. A., Khan, F. A., & Khan, I. A. (2024). Forensic Analysis of Injury Patterns among Occupants in Fatal Motor Vehicle Accidents in Karachi, Pakistan: Forensic Analysis in Fatal Motor Vehicle Accidents. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2418

Corresponding Author:
Abdul Waheed
Department of Forensic Medicine and Toxicology, Karachi Institute of Medical Sciences, Karachi, Pakistan
chundrigarwaheed@yahoo.com

Received Date: 1st October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Drivers and passengers in Motor Vehicle Accidents (MVAs) may sustain a wide range of injuries. **Objective:** To investigate the patterns of injuries and factors responsible for differences between drivers and passengers in fatal motor vehicle accidents in Karachi, Sindh. **Methods:** Retrospective study was conducted carried out from 2nd July 2022 to 30th June 2024 by Department of Forensic medicine and Toxicology, Karachi Institute of Medical Sciences, Karachi. All victims involving drivers and passenger's road traffic accidents fatalities, belongs to either gender, of any age from three major tertiary care hospitals in Karachi, Sindh were investigated and evaluated. Incomplete information, those of other fatalities and pedestrian related data were excluded. **Results:** Most (70.8%) were drivers, 20.0% were front-seat passengers, and 9.2% were rear-seat passengers. Over two-third, 80.5% died within one hour after the crash whereas, majority, 67.3% of the deaths occurred in front crashes, 13.7% in near edge hits, 13.5% in rollovers, and 5.5% in other accidents. Fatal injuries to the abdomen, thorax, head, and neck in 63.6%, 10.7%, 61.6%, and 27.4% of cases, respectively. Compared to drivers, those in the front seats experienced less heart and spleen traumas. In comparison to drivers, passengers in the front and back seats experienced a higher frequency of seat belt abrasions and a lower frequency of fractures to the extremities. **Conclusions:** The findings revealed significant differences in the types and frequency of injuries between drivers and passengers, highlighting the greater vulnerability of drivers to severe abdominal and head injuries.

INTRODUCTION

Road Traffic Accidents (RTAs) continue to be a major global public health and safety concern despite global efforts at mitigation and prevention. Road accidents cause a great deal of mortality and disability and cost societies a significant amount of money [1]. According to the "Global Status Report on Road Safety 2023" over 1.19 million people worldwide died in traffic-related deaths in 2021, or 15 deaths per 100,000 people. Road fatality rates worldwide are still far too high, and current trends suggest that this problem will not go away for some time. This is true even in nations where efforts to minimize traffic collisions have made significant progress [2, 3]. Drivers and passengers in Motor Vehicle Accidents (MVAs) may sustain a wide range of injuries. Whether the victim was a car occupant (driver or passenger) not has a significant impact on the pattern and epidemiology of fatal and non-fatal transport injuries [4]. Investigation of injuries connected with transportation and traffic may require the use of all forensic sciences and medicolegal knowledge. Forensic experts are called upon in the aftermath of a potentially fatal motor vehicle collision to determine the cause of death, the mechanisms causing injuries, and, if possible, the involvement of each occupant, including their seating position at the time of contact [5]. Studies have reported limited differences in injury patterns

DOI: https://doi.org/10.54393/pjhs.v5i11.2418

among the drivers and passengers, except from skin bruising from seat belts with opposing patterns. However, drivers reported to be prone than passengers to suffer brain damage and skull fractures, whereas front-seat passengers were more likely to experience splenic injuries [6]. On the other hand, based on bigger incident data sets, studies comparing front and rear seat occupants have demonstrated that rear seat passengers are far more probable than front seat occupants to die or suffer serious injuries [7]. A significant decline in in the RTA related mortalities have reported in developed nations due to advancements in safety features in the motor vehicles for protecting lives of drivers as well as the occupants [8]. On the other side, the developing countries (low- and middle-income countries) like Pakistan ranks among the top 50 countries in Asia for road traffic accident-related fatalities. The World Health Organization estimates that the country loses over 30,000 lives to traffic accidents each year, resulting in a mortality rate of 20 deaths per 100,000 people annually due to such incidents [9]. The country is still facing a serious challenge of RTA specially injuries sustained by the drivers and the occupants. Among these countries' improper road conditions, behavior of population towards the road traffic safety measures, lack of knowledge related to rules of road safety as well as substandard quality of vehicle manufacturing etc. are reported as important factors. Furthermore, accident-related events, such as drinking alcohol or using other psychoactive substances, are frequently documented for driver fatalities but have received far less attention when it comes to passenger fatalities among countries like Pakistan [10, 11]. All these factors reported to be responsible for the fatal injuries and higher mortalities among these countries. Comprehending these injuries is crucial in order to optimize road safety regulations, interventions, and safety measures. A better understanding of passenger fatalities may provide crucial insights about the mechanisms underlying injuries and help identify populations at greatest risk [11]. Limited studies and a lack of data regarding the patterns of injuries and factors affecting drivers and passengers in fatal motor vehicle accidents in Karachi have been noted. In light of these gaps, the present study aims to investigate various aspects related to vehicle information, injury locations, safety equipment, conditions, and toxicology that contributed to the fatalities of drivers and occupants in Karachi over a two-year period.

The objective of the study was to investigate the pattern of injuries and responsible factors for between drivers and passengers in fatal motor vehicle accidents in Karachi, Sindh.

METHODS

Retrospective study was conducted carried out from 2nd July 2022 to 30th June 2024 by Department of Forensic medicine, Karachi Institute of Medical Sciences (KIMS) in collaboration with Shaheed Mohtarma Benazir Bhutto Medical College (SMBBMC), Lyari and Liaquat National Hospital and Medical College (LNHMC), Karachi. Public hospitals were selected using a non-random purposive sampling technique, targeting main hospitals across various localities in Karachi that were authorized to perform autopsies. A total sample size of 401 was determined using the OpenEpi online calculator, based on a prevalence rate of 64% for Road Traffic Accidents (RTAs) among car occupants [13]. The calculation was conducted with a confidence level of 95% and a margin of error of 5%. This approach ensures that the selected hospitals were representative of the population of interest while adhering to the criteria necessary for conducting autopsies within the region. All victims involving drivers and passenger's road traffic accidents fatalities, belongs to either gender, of any age from three major tertiary care hospitals in Karachi, Sindh were investigated and evaluated for all sudden, unexpected, violent or suspicious deaths within their jurisdictions. Incomplete information, those of other fatalities and pedestrian related data were excluded. Data from all the hospitals were also collected (LGHK (Est.) 4151/52). All applicable ethical guidelines for performing forensic assessment of victims were followed. The permission mentioned refers to consent from the victim's immediate family members for conducting the autopsy assessment. This is distinct from institutional or hospital administration approval, which is typically obtained by the researcher to conduct the study. In this case, family consent ensures ethical compliance for performing the autopsy. The full autopsy findings of all victims were recorded with the help of medico-legal officers on duty. A written structured questionnaire was used for recording details including information of the vehicle occupants, vehicle seating arrangements, safety equipment's, age and sex of deceased, the distribution of injuries, post-injury survival time, as well as toxicology results. Moreover, data related to features associated with collisions include kind of collision, direction of contact, types of vehicles involved, years of vehicle model etc. were also collected [10]. The driver, front seating passenger, and back seating passenger were all considered occupant in the current study, regardless of where they were in the car. Three distinct groups were used to classify the placement of the occupants: driver, forward seating passenger, and the backward seating passenger. Drivers and forward seating passengers were grouped together as forward seating row occupants and contrasted with backward seating

DOI: https://doi.org/10.54393/pjhs.v5i11.2418

passengers in a subgroup evaluation. For statistical analysis, all of the passengers in the different back seating positions were combined into a single group due to the limited number of passengers in each position. The data was analyzed in SPSS version 28.0. The data was presented as frequency and proportions. The chi-square test for binomial categorical variables were used for bivariate analysis of data while multivariate logistic regression analysis was performed. P value < 0.05 was taken as significant.

RESULTS

The study included 401 fatalities from motor vehicle collisions that were forensically examined. Of the total victims, a significant majority of the cases involved drivers followed by front-seat passengers and rear-seat passengers. Overall, there were not many kid fatalities 11 (2.7%), and forward seat passengers had a significant percentage 91 (22.7%) of elderly people. Majority of the victims were drivers, followed by forward seat passengers, and back seat passengers. Between drivers and passengers, there were notable differences in the distributions of age and gender. The driving group was clearly predominately male (Table 1).

Table 1: Demographic Characteristics of Occupants in RTA Fatalities(n=401)

Variables	N (%)
Gender	
Male	296 (73.8%)
Female	105 (26.2%)
Age	
<25 Years	106 (26.4%)
25-34 Years	87 (21.6%)
35-44 Years	84 (21.0%)
45-54 Years	74 (18.4%)
55 and above	50 (12.6%)
Seat Occupancy	
Driver	284 (70.8%)
Front-seat	80 (20.0%)
Rear-seat	37 (9.2%)
Types of Accident	
Front Crashes	270 (67.3%)
Near Edge Hits	55 (13.7%)
Rollovers	54 (13.5%)
Other Accidents	22 (5.5%)
Fatal Injuries by Body Region	
Head	247 (61.6%)
Neck	152 (38.0%)
Thorax	97 (24.2%)
Abdomen	201 (50.2%)
Reported Time of Death	
Within 1 Hour	323 (80.5%)
More than 1 Hour	78 (19.5%)

Table 2 presented the incidence of various fatal injuries among different occupant types. Similar rates of fatal injuries to the abdominal region were seen in drivers and front-seat passengers, however, the rate was lower in rear-seat passengers. In comparison, fatal thoracic injuries were more common among rear-seat passengers. A high rates of head injuries were observed across all groups, with drivers having the highest percentage. A notable difference in seat belt abrasions, with front-seat passengers and rear seat passengers experiencing more abrasions while a higher frequency of extremity fractures observed in rear-seat passengers (Table 2).

Table 2: Proportional Distribution of Injury Patterns According to Seat Occupancy

Injury Pattern	Seat Occupancy N (%)		
	Driver's	Front	Rear
Seatbelt Abrasions	10.0%	35.0%	30.0%
Extremity Fractures	20.0%	12.5%	14.0%
Fatal Injuries to Head	61.6%	58.8%	51.4%
Fatal Injuries to Neck	27.4%	30.0%	21.6%
Fatal Injuries to Thorax	10.7%	7.5%	13.5%
Fatal Injuries to Abdomen	63.6%	65.0%	51.4%

The results of bivariate analysis comparing injury patterns between drivers and passengers were presented in table 3. A statistically significant ($p<0.01$) strong association between occupant type and abdominal injuries and seat belt abrasions were observed (Table 3).

Table 3: Bivariate Analysis of Injury Patterns by Seat Position

Injury Pattern	Occupant Type	p-Value
Seat Belt Abrasions	Drivers versus Passengers	<0.001*
Extremity Fractures	Drivers versus Passengers	0.09
Fatal Injuries to Head	Drivers versus Passengers	0.06
Fatal Injuries to Abdomen	Drivers versus Passengers	<0.01*

*Statistically significant (Chi-square)

Table 4 was assessing the impact of various factors on the likelihood of sustaining fatal injuries employing multivariate analysis. The odds ratio of 0.30 with a p-value of <0.001 indicates a strong protective effect of seat belt use, significantly reducing the likelihood of fatal injuries, while the odds ratio of 2.05 suggested that individuals involved in front-impact collisions were more than twice as likely to sustain fatal injuries (Table 4).

Table 4: Multivariate Analysis of Injury Patterns

Variables	Odds Ratio (OR)	95% C.I	p-Value
Occupant type (Driver)	1.00 (Reference)	-	-
Seat Belt Use (Yes)	0.30	0.15 - 0.60	<0.001*
Crash Type (Front Impact)	2.05	1.30 - 3.25	<0.01*
Front Seat Passenger	0.75	0.52 - 1.08	0.12
Rear Seat Passenger	0.50	0.25 - 1.01	0.05

* Statistically significant f (Multivariate Analysis)

DOI: https://doi.org/10.54393/pjhs.v5i11.2418

DISCUSSION

The present study presents the investigation into mobile vehicle collision occupant fatalities reveals critical insights into the demographics and injury patterns of drivers and passengers. The data demonstrated that a significant majority of fatalities involve drivers (70.8%), with front-seat passengers accounting for 20% and rear-seat passengers for only 9.2%. This distribution highlights the heightened risk faced by drivers and front-seat occupants, consistent with findings from recent studies which also emphasize the vulnerability of these individuals in fatal accidents. The predominance of male drivers aligns with trends observed in other studies. For instance, a study by Mohamed J *et al.*, reported that male drivers were involved in a disproportionately high number of fatal accidents, likely due to riskier driving behaviors [12]. This investigation further reveals notable differences in gender distributions between drivers and passengers. Similar findings reported by different researchers from Somalia, Australia and Pakistani studies who highlighted the increased risk of injury among male passengers compared to their counterparts. Older passengers in frontal collisions [12, 13, 14]. Young age people were more likely to have more aggressive behaviors as compared to older drivers. This study observed that majority of population of victims were of younger age up to 35 years of age (48.1%) were involved in more severe injuries compared to the older age group victims. Whereas, amongst the victims, 26.4% were under 25 years and 21.6% were 25-34 years old. This finding offers supportive evidence of the demographic factors influencing the high burden of traumatic injury in Pakistan. Study by Gorge J *et al.*, reported around 71% of the accident victims in their study belong to age up to 35 years [15]. Whereas, in their study majority (46.7%) were under 25 years old. Another study by Farid R *et al.*, along with Rahman MA *et al.*, also reported consistent findings of involvement of age groups under 35 years [16, 17]. The analysis of fatal injuries reveals significant insights into the types of injuries sustained by different occupant types. Notably, abdominal injuries were prevalent among both drivers (63.6%) and front-seat passengers (65.0%), echoing findings from recent literature that underscore the critical nature of abdominal protection in vehicle design [10, 17]. Conversely, rear-seat passengers exhibited a lower incidence of abdominal injuries (51.4%), which may reflect differences in restraint systems, seating positions, and the angles of impact during collisions. Specifically, frontal impacts, typically occurring at angles close to 0 degrees, often result in severe abdominal injuries, while side impacts at angles ranging from 30 to 60 degrees can exacerbate such injuries in rear-seat occupants due to their proximity to the vehicle's side structure. Interestingly, the higher incidence of thoracic injuries in rear-seat passengers (13.5%) compared to drivers (10.7%) suggests that this group may be more susceptible to such injuries due to less effective restraint systems or vehicle design. The biomechanics involved, such as the angle of impact particularly in oblique collisions at angles of approximately 45 degrees can lead to increased forces on the thorax of rear-seat passengers [18, 19]. This finding supports the need for enhanced safety measures, particularly for rear-seat occupants, whose protection has historically been overlooked in vehicle safety standards. The significant difference in seat belt abrasions between drivers (10.0%) and passengers (front: 35.0%, rear: 30.0%) raises important considerations regarding seat belt compliance and effectiveness. These results were consistent with findings from a study by O'Donovan S *et al.*, and Wasif M *et al.*, which emphasized the role of passive restraint systems in reducing injury severity [4, 10]. The disparity in seat belt use suggests that promoting proper seat belt usage, particularly among drivers, could be a key intervention to improve safety outcomes. The multivariate analysis indicates that seat belt use significantly reduces the odds of injury (OR = 0.30, $p < 0.001$), reinforcing the critical importance of seat belts in occupant safety. This finding was supported by a meta-analysis conducted by Masumitsu A *et al.*, and Diego Febres J *et al.*, which concluded that consistent seat belt use was associated with a substantial reduction in fatal outcomes [5, 20]. Additionally, the odds of severe injury were higher for front impact crashes (OR = 2.05, $p < 0.01$), highlighting the need for ongoing improvements in vehicle crashworthiness, particularly for frontal collisions. While this study provides valuable insights, it was essential to acknowledge its limitations. The analysis was based on autopsy data, which may not capture all aspects of occupants' behavior or vehicle dynamics like driving speed, alcohol consumption, or other risk-taking behaviors during collisions. Future studies should consider incorporating real-world crash data to provide a more comprehensive understanding of the factors influencing occupant injuries.

CONCLUSIONS

The study findings reveal significant differences in injury types and frequencies between drivers and occupants, highlighting the greater vulnerability of drivers to severe abdominal and head injuries. Conversely, front and rear-seat passengers exhibited higher rates of seat belt abrasions and fewer extremity fractures, suggesting varying injury profiles based on seating position and restraint use. Stricter enforcement of seat belt laws, improved vehicle safety standards, and educational programs to raise awareness about the risks associated with motor vehicle accidents were strongly recommended.

DOI: https://doi.org/10.54393/pjhs.v5i11.2418

Authors Contribution

Conceptualization: AW
Methodology: AW, HR, SAQ, FAK, IAK
Formal analysis: AW
Writing, review and editing: AW, SPA, HR, SAQ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2579

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Comparison of Efficacy of Tofacitinib versus Betamethasone Pulse Therapy in the Treatment of Vitiligo

Hira Shafquat Memon[1*], Hafiz Bashir Ahmed[1], Abeer Memon[2], Madiha Shah[2], Nazish Memon[1] and Bedar Bakhat Khan[2]

[1]Department of Dermatology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[2]Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

ARTICLE INFO

Keywords:

Tofacitinib, Betamethasone Pulse Therapy, Vitiligo, Re-Pigmentation

How to Cite:

Shafquat, H., Ahmed, H. B., Memon, A., Shah, M., Memon, N., & Khan, B. B. (2024). Comparison of Efficacy of Tofacitinib versus Betamethasone Pulse Therapy in the Treatment of Vitiligo: Tofacitinib Versus Betamethasone Pulse Therapy in the Treatment of Vitiligo. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2579

***Corresponding Author:**

Hira Shafquat Memon
Department of Dermatology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
hira.shafquat@hotmail.com

Received Date: 5th October, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Vitiligo is a chronic autoimmune skin disorder characterized by depigmentation due to melanocyte destruction, significantly impacting patients' quality of life. Emerging treatments, including Janus kinase inhibitors like tofacitinib, offer promising alternatives to conventional therapies such as corticosteroids. **Objective:** To compare the efficacy of tofacitinib with betamethasone pulse therapy in achieving re-pigmentation in vitiligo patients. **Methods:** This quasi experimental study was conducted on 42 patients of vitiligo of either gender with ages between 12 and 65 years and had a history of vitiligo for over one year with a body surface area affected by vitiligo exceeding 5%, and a vitiligo area scoring index score of more than 10 were included in the study. Patients were divided into 2 equal groups using alternate assignments. Group A were treated with betamethasone pulse therapy of 4mg twice a week. Group B were treated with tofacitinib at a dose of 5 mg twice a day. **Results:** Optimal recovery (vitiligo area scoring index decrease ≥20% from baseline) was observed in 14 (66.7%) of the tofacitinib group compared to 6 (28.6%) in the betamethasone group, highlighting tofacitinib's superior efficacy in achieving significant vitiligo area scoring index reduction. Over three months, the BSA affected by vitiligo decreased in both groups, with a significantly greater reduction in Group B (tofacitinib) compared to Group A (betamethasone). **Conclusions:** It was concluded that tofacitinib may be more effective than betamethasone pulse therapy in reducing both the extent and severity of vitiligo.

INTRODUCTION

Vitiligo is an idiopathic skin condition that causes permanent, non-contagious loss of melanocytes resulting in depigmented patches on the skin. Affecting nearly 1% of people around the world, it has significant effects on quality of life from a cosmetic point of view and social stigma. The precise aetiopathogenesis of vitiligo is unknown, but it appears to be multifactorial with contributions from genetic, environmental and autoimmune aspects that ultimately result in dysregulation followed by apoptosis of the melanocyte [1, 2]. Several approaches to treating it are designed to halt disease progression or facilitate re-pigmentation, but no universally effective therapy is available. The pathogenesis of vitiligo involves IFN-γ production by CD8+ T cells, leading to CXCL9/10 expression by keratinocytes, which recruits additional CD8+ T cells, ultimately destroying melanocytes. Janus kinase (JAK) inhibitors, such as tofacitinib, target this pathway and show promise in managing vitiligo [3-5]. Recently developed JAK inhibitors (immune-modulating agents) introduce new options for treating vitiligo and have brought significant changes to its management. Humanitarian compassionate treatment with pulse therapy has been widely practiced for vitiligo using betamethasone, a highly potent corticosteroid, due to its strong anti-inflammatory and immunosuppressive effects which inhibit melanocyte destruction [6, 7]. Pulse therapy is characterized by the use of high doses in a short period, and mitigates adverse effects related to long-term administration of corticosteroids. A dose-pulse of betamethasone can achieve re-pigmentation in patients with vitiligo, but prolonged use may have side effects including skin atrophy, hyperglycemia and further

DOI: https://doi.org/10.54393/pjhs.v5i11.2579

susceptibility to infections [8]. Tofacitinib (JAK inhibitor) is a new alternative for the treatment of vitiligo. Tofacitinib is an inhibitor of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway that may provide targeted immunosuppression by inhibiting a key driver of immune response and inflammation, with fewer side effects compared to those associated with corticosteroids [9]. It is proven to stabilize vitiligo and induce re-pigmentation, particularly with concomitant phototherapy [10]. In contrast to corticosteroids, JAK inhibitors target cytokine signalling involved in autoimmune pathways and therefore would be expected to have an improved safety profile for long-term management [11]. Comparative studies on the efficacy of tofacitinib and betamethasone pulse therapy are limited, but some evidence suggests that JAK inhibitors could be a valuable alternative, particularly for patients experiencing adverse effects with corticosteroid-based therapies.

This study aimed to compare the efficacy of tofacitinib with betamethasone pulse therapy in achieving re-pigmentation in vitiligo patients.

METHODS

This quasi experimental study was conducted from March 2023 to August 2023 at the Skin Out Patient Department (OPD) of Liaquat University Hospital, Hyderabad, on 42 patients with vitiligo. Patients of either gender with ages between 12 and 65 years and had a history of vitiligo for over one year with a body surface area (BSA) affected by vitiligo exceeding 5%, and a Vitiligo Area Scoring Index (VASI) score of more than 10 were included in the study. Pregnant and lactating women and patients receiving chemotherapy or other immunosuppressive treatments were excluded from the study. The sample size was calculated via Open Epi Sample Size Calculator by taking the means of VASI in betamethasone treatment as 10.57 ± 4.03 at 3 months with that of tofacitinib as 7.08 ± 3.90 with 80% power of the study and 95% confidence interval [12]. The study was approved by the Ethical Review Committee of Liaquat University of Medical and Health Sciences, Jamshoro vide letter no. NO. LUMHS/REC/-189. The sampling technique was convenient and all the included patients were divided into 2 equal groups using alternate assignments. Informed written consent was taken from every participant. Group A was treated with betamethasone pulse therapy (betamethasone sodium phosphate) of 4mg twice a week orally. Group B were treated with tofacitinib given as tofacitinib citrate, at a dose of 5 mg twice a day orally. The total duration of treatment for both groups was 3 months. Both groups were advised to have daily sun exposure for 30 minutes in the morning. Participants underwent monthly follow-ups over three months from the date of enrollment. At each visit, the VASI and BSA scores were measured at baseline and the end of the first, second, and third months. A decrease in VASI of ≥10% at each visit from baseline was considered indicative of effective treatment, and a final VASI decrease of ≥20% from baseline was regarded as optimal recovery. SPSS version 22.0 was used for the analysis of data. Quantitative data were measured as mean + SD. Categorical data was measured using frequency and percentages. Independent T-test was used to measure the difference in mean in VASI and BSA between both groups.

RESULTS

Group A (betamethasone) and Group B (tofacitinib) had similar mean ages (35.6 ± 14.2 vs. 34.8 ± 13.6), as well as similar gender distributions, with 57% of participants in Group A and 52% in Group B being male. Baseline measures of disease extent, such as BSA (8.5 ± 2.1 vs. 8.7 ± 2.3) and VASI scores (12.4 ± 3.2 vs. 12.3 ± 3.1),were also closely matched (Table 1).

Table 1: Descriptive Statistics Regarding Study Participants

Variable	Group A (Betamethasone)	Group B (Tofacitinib)	p-value
Age (Mean ± SD)	35.6 ± 14.2	34.8 ± 13.6	0.85
Gender			
Male	12 (57%)	11 (52%)	-
Female	9 (43%)	10 (48%)	
Duration of Vitiligo (Years)	2.8 ± 1.4	3.1 ± 1.2	0.64
Baseline BSA (%)	8.5 ± 2.1	8.7 ± 2.3	0.85
Baseline VASI	12.4 ± 3.2	12.3 ± 3.1	0.92

Over three months, the Body Surface Area (BSA) affected by vitiligo decreased significantly more in the tofacitinib group (Group B) than in the betamethasone group (Group A). At baseline, the mean BSA was similar (p=0.84). By month one, reductions in BSA were 8.2% in Group A and 25.3% in Group B (p=0.47). By month two, Group B showed a significantly greater reduction (40.2% vs. 18.8%, p=0.2). This trend persisted at month three, with reductions of 46.0% in Group B and 25.9% in Group A (p=0.01), demonstrating the superior efficacy of tofacitinib (Table 2).

Table 2: Comparison of Body Surface Area (BSA) At Baseline and Over 3 Months

Follow Up	Group A (n=21) (Betamethasone BSA%) (Change in % from Baseline)	Group B (n=21) (Tofacitinib BSA%) (Change in % from Baseline)	p-value
Baseline	8.5 ± 2.1	8.7 ± 2.3	0.84
End of Month 1	7.8 ± 2.0 (8.2%)	6.5 ± 1.8 (25.3%)	0.47
End of Month 2	6.9 ± 1.9 (18.8%)	5.2 ± 1.7 (40.2%)	0.2
End of Month 3	6.3 ± 1.8 (25.9%)	4.7 ± 1.5 (46.0%)	0.01*

Over the three-month follow-up, the reduction in VASI percentage was consistently greater in Group B (tofacitinib) compared to Group A (betamethasone). At the end of month one, the VASI reduction in Group B was 27.6%, compared to 9.7% in Group A (p=0.32). By month two, the reductions were 43.1% and 21.8% for Groups B and A, respectively (p=0.71). At the end of month three, Group B achieved a significantly greater VASI reduction of 54.5%, compared to 33.9% in Group A (p<0.001), demonstrating the superior efficacy of tofacitinib over betamethasone in improving vitiligo. (p<0.001*)(Table 3).

DOI: https://doi.org/10.54393/pjhs.v5i11.2579

Table 3: Comparison of Vitiligo Area Scoring Index (VASI) At Baseline and Over 3 Months

Follow Up	Group A (n=21) Betamethasone VASI Change in % from Baseline	Group B (n=21) Tofacitinib VASI Change in % from Baseline	p-value
End of Month 1	9.7%	27.6%	0.32
End of Month 2	21.8%	43.1%	0.71
End of Month 3	33.9%	54.5%	< 0.001*

Optimal recovery among both groups was analyzed (Table 4).

Table 4: Optimal Recovery among Both Groups

Optimal Recovery	Group A (n=21) Betamethasone	Group B (n=21) Tofacitinib	p-value
Achieved	6 (28.6%)	14 (66.7%)	1.34
Not Achieved	15 (71.4%)	7 (33.3%)	

Optimal recovery (VASI decrease ≥20% from baseline) was observed in 14 (66.7%) of the tofacitinib group compared to 6 (28.6%) in the betamethasone group, highlighting tofacitinib's superior efficacy in achieving significant VASI reduction (Figure 1).

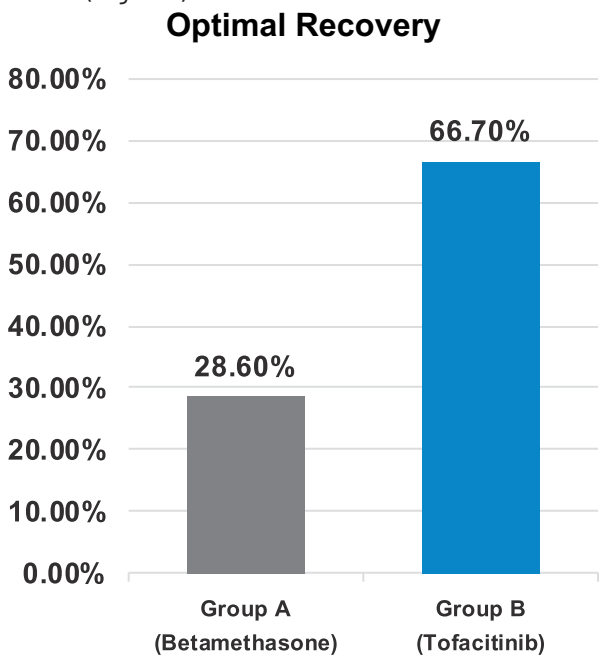

Figure 1 : Outcome in Terms of Optimal Recovery in Both Groups

DISCUSSION

In this study, we observed significantly faster and more consistent re-pigmentation in vitiligo patches treated with tofacitinib compared to betamethasone. The tofacitinib group demonstrated a greater reduction in VASI and BSA scores over three months, achieving the study's primary objective of optimal recovery. Jabbari et al., reported enhanced re-pigmentation with tofacitinib combined with sun exposure, particularly in sun-exposed areas [13]. However, our study did not measure the difference in recovery in sun-exposed areas vs un-exposed areas (which is one of the limitations of our study). Custurone et al., described a case of significant facial vitiligo that showed improvement after one-month treatment with tofacitinib 5 mg twice daily [14]. Various studies support the effectiveness of betamethasone therapy as a treatment of vitiligo [15, 16]. Likewise, in our study, betamethasone pulse therapy showed a modest reduction in both VASI and BSA scores, indicating its effectiveness in managing vitiligo. However, its efficacy was significantly lower compared to tofacitinib, particularly in achieving faster and greater re-pigmentation. While a case of a 17-year-old boy with stable non-segmental vitiligo showed promising results with topical tofacitinib [17]. Rapid and nearly complete facial re-pigmentation was also observed with oral tofacitinib and low-dose Narrowband-Ultra-Violet B (NB-UVB) [18]. Our study aligns with these findings, demonstrating fast and consistent re-pigmentation with oral tofacitinib combined with natural sun exposure [19]. Additionally, a case report by Kim et al., highlighted a 40-year-old female with comorbid rheumatoid arthritis and vitiligo who achieved significant re-pigmentation using tofacitinib without sun exposure [20]. However, in our study, tofacitinib showed significant efficacy in both sun-exposed and sun-protected areas, further supporting its utility as a robust therapeutic option. Overall, the results of this study add to the growing body of evidence supporting the use of tofacitinib in vitiligo treatment. However, future studies with longer follow-up periods and larger sample sizes are required to confirm the durability of re-pigmentation and assess outcomes following treatment discontinuation.

CONCLUSIONS

It was concluded that tofacitinib may be more effective than betamethasone in reducing both the extent and severity of vitiligo.

Authors Contribution

Conceptualization: HSM
Methodology: HSM, HBA, AM, MS, NM, BBK
Formal analysis: NM
Writing review and editing: HBA, AM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2173

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Analysis of Current Knowledge and Social Implications of Minimal Intervention Prosthodontics

Uzma Khalil[1*], Priyanka Chandar Lohana[2], Hira Shafique[3], Paras Talpur[4], Farhan Javed[5] and Anum Fatima[6]

[1]Department of Prosthodontics, Rehman College of Dentistry, Peshawar, Pakistan
[2]Department of Dentistry, Isra Dental College, Hyderabad, Pakistan
[3]Department of Community and Preventive Dentistry, Islam Dental College, Sialkot, Pakistan
[4]Department of Prosthodontics, Muhammad Dental College, Mirpurkhas, Pakistan
[5]Department of Periodontology, Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan Institute of Medical Sciences, Islamabad, Pakistan
[6]Department of Dentistry, Islamabad Medical and Dental College, Islamabad, Pakistan

ARTICLE INFO

Keywords:
Minimal Intervention Prosthodontics, Patient Awareness, Atraumatic Restorative Treatment, Adhesive Restorations, Dental Healthcare

How to Cite:
Khalil, U., Lohana, P. C., Shafique, H., Talpur, P., Javed, F., & Fatima, A. (2024). Analysis of Current Knowledge and Social Implications of Minimal Intervention Prosthodontics: Minimal Intervention Prosthodontics Analysis. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2173

Corresponding Author:
Uzma Khalil
Department of Prosthodontics, Rehman College of Dentistry, Peshawar, Pakistan
uzmakhalil853@gmail.com

Received Date: 15th September, 2024
Acceptance Date: 19th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Minimal Intervention Prosthodontics (MIP) focuses on preserving healthy tooth structure while providing functional and aesthetic restorations. **Objective:** To evaluate the knowledge and social implications of Minimal Intervention Prosthodontics (MIP) among patients at Rehman College of Dentistry, Peshawar, Pakistan. **Methods:** A cross-sectional survey was conducted on 173 patients aged 35 years and above. Data were collected through a structured questionnaire that assessed patients' understanding of MIP principles, clinical applications, and perceived social impacts. Statistical analysis was performed to determine associations between knowledge of MIP and demographic factors, such as age, gender, and educational level. **Results:** Among the respondents, 74% had some awareness of MIP, with higher knowledge levels observed in individuals with advanced education. However, only 41% were familiar with the specific procedures involved in MIP, such as adhesive restorations, sealants and Atraumatic Restorative Treatment (ART). The majority of participants (68%) perceived MIP as beneficial for patient comfort and reducing healthcare costs, though 56% recognized the increased time and expertise required for its application. Additionally, 62% of respondents acknowledged the social benefits of MIP, including preserving natural dentition and improving overall quality of life. **Conclusions:** The study revealed a moderate level of awareness and understanding of MIP among patients, with educational level significantly influencing knowledge. Despite recognizing its advantages, there was a need for improved patient education to enhance the acceptance and implementation of MIP in dental care.

INTRODUCTION

An individual's overall health is greatly influenced by their oral health. The physiology of the body is negatively impacted by tooth loss, but the individual's mentality is also disrupted. This is closely tied to the patient's acceptance of the prosthesis [1]. Anatomical, physiological, psychological, and prosthodontic considerations can be used to identify elements that affect a patient's acceptance and adaptability to a new dental prosthesis. Above all, a patient's attitude regarding receiving prosthetic treatment is crucial [2]. Prosthetic therapy varies greatly, ranging from full rehabilitation of severely damaged teeth to functional form to replacement of a lost tooth in a healthy partial dentition [3]. The patient can reconstruct lost teeth with a variety of prosthetic choices, such as overdentures, implant-supported procedures, complete dentures, and detachable or fixed partial dentures [4, 5]. Comfort, functionality, and aesthetics are the three primary determinants of whether a prosthetic therapy is accepted and successful. Comfort and function are determined by biological and mechanical variables.

DOI: https://doi.org/10.54393/pjhs.v5i11.2173

Individual attitudes and beliefs, as well as social and cultural influences, shape a patient's acceptance of aesthetic aspects [6, 7]. Understanding a patient's knowledge and attitude regarding replacement of any prosthetics before receiving therapy is essential, since importance is to be focused on patient-mediated issues in prosthetic treatment arrangement [8-10]. This may out to be a useful tool for forecasting satisfaction with a newly provided prosthesis [11]. The decision to receive dental prosthetic therapy has also been associated with demographic factors, including interest, gender, age, education, and economic status. Patients' awareness and attitudes toward prosthetic rehabilitation of missing teeth at the University Dental Hospital in Riyadh, Kingdom of Saudi Arabia, were assessed by Ramalingam S *et al.*, they came to the conclusion that 53.1% of those questioned had not had their teeth replaced. They have placed a strong emphasis on the necessity of patient education and motivation in order for them to make wise decisions [12]. Arora Jr K *et al.*, conducted a survey on patients' attitudes toward tooth replacement at the Institutes of Dental Sciences in Belgaum, India, and found that most research participants were only aware of the mastication function that teeth serve [13]. The majority of research on Pakistani patients' attitudes and knowledge on tooth replacement is location-specific and cannot be broadly applied.

The research aimed to assess the current knowledge and social implications of Minimal Intervention Prosthodontics (MIP) among patients for replacement of missing teeth, visiting the dental Outpatient Department (OPD) of the Rehman College of Dentistry (RCD), Hayatabad, Peshawar, Pakistan.

METHODS

The study was conducted at Rehman College of Dentistry (RCD), Hayatabad, Peshawar, Pakistan, which was associated with a tertiary care hospital. The study employed a cross-sectional design, targeting patients aged 35 years and above. Patients of both genders who were willing to participate and provided informed consent were included in the study. The participants were required to have adequate cognitive abilities to understand the questionnaire and provide accurate responses about their knowledge and perceptions MIP. The participants with cognitive or communicative impairments and those who refused or were unable to provide informed consent were excluded from the study. The findings of the pilot study revealed that the proportion of the prevalence of knowledge about prosthodontic rehabilitation at approximately 50%. Using this proportion value from the pilot study, the sample size was determined using the formula for calculating sample size in a cross-sectional study:

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

Where: n = required sample size, Z = Z-value (1.96 for 95% confidence level), p = estimated prevalence of knowledge and positive attitude towards MIP (assumed to be 0.5 for maximum sample size), d = margin of error (0.05), However, considering a finite population correction for the study population at RCD, the final sample size was adjusted to 173 participants. A stratified random sampling technique was employed to select the participants from the target population. This approach ensured that each member of the population had an equal chance of being included in the study, thus minimizing selection bias. A structured, self-administered questionnaire, adopted from previous literature was used to collect data [14]. The questionnaire was developed based on existing literature and modified to suit the local context and the objectives of this study. It consisted of three main sections: 1: Demographic Information: age, gender, educational level, and professional role. 2: Knowledge of MIP: Questions assessing the participants' understanding of minimal intervention prosthodontics, including its principles, benefits, and clinical applications. 3: Social Implications of MIP: Questions related to the perceived impact of MIP on patient outcomes, healthcare costs, and overall acceptance within the community. The self-administered questionnaire was pre-tested on a small group of participants (not included in the final sample) to ensure clarity, relevance, and reliability. Data collection was conducted over a period of 12 months, from August 2023 to July, 2024. The study protocol was reviewed and approved by the Ethics Committee of the RCD Research Cell, with the approval number RCD/09/23/154. Informed consent was obtained from all participants, and the study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. Participants' knowledge of Minimal Intervention Prosthodontics (MIP) was assessed using a scoring system based on responses to knowledge-related questions. A total score was calculated, and participants were classified as having "high knowledge" if they scored 60% or higher and "low knowledge" if they scored below 60%. For analysis, the gathered data were put into a statistical software program (SPSS version 27.0). Frequencies and percentages were employed in descriptive statistics to condense the replies and demographic features pertaining to MIP knowledge and societal ramifications. To evaluate relationships between demographic factors and knowledge/attitude ratings, the chi-square test was used. Statistical significance was attained when the p-value was less than 0.05.

DOI: https://doi.org/10.54393/pjhs.v5i11.2173

RESULTS

A total of 173 participants, were included in the study. The demographic characteristics of the participants were summarized in table 1.

Table 1: Demographic Characteristics of Participants

Demographic Variable	Category	N (%)
Gender	Male	98 (56.6%)
	Female	75 (43.4%)
Age Group	26-35 Years	98 (56.6%)
	36-45 Years	53 (30.6%)
	46+ Years	22 (12.7%)
Education Level	Primary School	62 (35.8%)
	High School	36 (20.8%)
	Undergraduate	50 (28.9%)
	Graduate	25 (15.4%)

The participants' knowledge of MIP was assessed through a series of questions, and the results were presented in Table 2. The majority of the participants (74%) were aware of the concept of MIP, with 59.5% familiar with its clinical applications. A significant proportion (66.5%) understood the benefits of preserving tooth structure, while slightly over half (56.6%) had knowledge of the materials used in MIP.

Table 2: Knowledge of Minimal Intervention Prosthodontics

Questions	Responses N (%)
Aware of the Concept of MIP	128 (74.0%)
Familiar with the Clinical Applications of MIP	103 (59.5%)
Understands the Benefits of Preserving Tooth Structure	115 (66.5%)
Knowledge of Materials used in MIP	98 (56.6%)

Participants were asked about the perceived social implications of adopting MIP in dental practice. The responses were summarized in table 3. A large majority of participants (78%) agreed that MIP improves patient comfort and satisfaction, and 66.5% believed it reduces healthcare costs. Additionally, 73.4% felt that MIP was more acceptable to patients, though 56.6% acknowledged that it requires more time and skill from the dentist.

Table 3: Social Implications of Minimal Intervention Prosthodontics

Questions	Agree N (%)	Neutral N (%)	Disagree N (%)
MIP Improves Patient Comfort and Satisfaction	135 (78.0%)	25 (14.5%)	13 (7.5%)
MIP Reduces Healthcare Costs	115 (66.5%)	35 (20.2%)	23 (13.3%)
MIP is More Acceptable to Patients	127 (73.4%)	28 (16.2%)	18 (10.4%)
MIP Requires More Time and Skill from the Dentist	98 (56.6%)	40 (23.1%)	35 (20.2%)

Chi-square tests were conducted to assess the relationship between demographic variables and knowledge of MIP. No significant difference in knowledge of MIP was found between males and females ($p = 0.245$). Although younger participants (18-25 years) showed slightly lower knowledge (52.9%) compared to older age groups, the association between age and knowledge was not statistically significant ($p = 0.172$). A significant association between education level and knowledge of MIP was observed ($p = 0.022$), with participants who had higher educational attainment (high school and above) demonstrating greater knowledge of MIP compared to those with primary or no education (Table 4).

Table 4: Correlation between Demographic Variables and Knowledge of MIP

Demographic Variable	High Knowledge N (%)	Low Knowledge N (%)	p-Value
Gender			
Male	59 (60.2%)	39 (39.8%)	0.245
Female	41 (54.7%)	34 (45.3%)	
Age Group			
18-25 Years	45 (52.9%)	40 (47.1%)	0.172
26-35 Years	35 (66.0%)	18 (34.0%)	
36-45 Years	14 (63.6%)	8 (36.4%)	
46+ Years	6 (46.2%)	7 (53.8%)	
Education Level			
Primary School	39 (41.5%)	55 (58.5%)	0.022*
High School	74 (61.7%)	46 (38.3%)	
Undergraduate	47 (64.4%)	26 (35.6%)	
Graduate	40 (83.3%)	8 (16.7%)	

DISCUSSION

The significance of teeth for one's overall health and wellbeing has already been a known debate. Therefore, it is required to understand the necessity of replacing lost teeth, which depends on an individual's attitude and level of information regarding the many kinds and methods of artificial tooth replacement [15]. In this research, conducted at Rehman College of Dentistry (RCD), Hayatabad, Peshawar, Pakistan, a significant gap in knowledge regarding minimal intervention prosthodontics was identified, reinforcing the importance of patient education in this field. In a study, Leles CR et al., came to the conclusion that a person's reluctance to have lost teeth restored at an advanced age may be influenced by perceptions that alter with age, such as the belief that one was too old to adjust to dentures and artificial teeth and a lack of interest in aesthetics [16, 17]. The research population's knowledge profile about the positioning of missing teeth was found to be inadequate in the current survey, with 44% of participants showing insufficient knowledge. The most likely explanation was that 40.21% of the population only had a primary education. This was comparable to a study by Chen L *et al.*, that discovered that the consequences of unawareness seem to be a barrier to receiving dental health care services, and that a lack of education was linked to a lack of awareness of the

DOI: https://doi.org/10.54393/pjhs.v5i11.2173

significance of oral health [18, 19]. According to the results of the current poll, 40.5% of participants had a favorable opinion of fixed prostheses as a method of replacing teeth, while just 20.1% thought removable prostheses would be a preferable choice. These findings were also supported by a study conducted by Al- Alshadidi AA *et al* [20]. A comparable study conducted in United Arab Emarates revealed that almost half of the participants favored detachable partial dentures, and the remaining 25% preferred fixed partial dentures. This outcome contradicted what we had discovered [21]. Just 15.6% of the total individuals thought implants were a better way to restore missing teeth. It corroborated a previous research paper with comparable findings [20, 21]. According to a poll done in Peradeniya, Sri Lanka, 32% of the 425 respondents were aware that implants may be used as a substitute. According to the study, this was a larger percentage than that of several other studies on the Asian population. The authors have suggested that the reason for this discrepancy may be the nation's better health and educational standards when compared to those of its neighboring nations [22]. In this study, 33.1% of participants in the current study felt positively about having missing bodily parts replaced. In response to questions about maintaining the hygiene of artificial teeth, 74.8% of respondents expressed a positive outlook and agreed that maintaining prosthesis hygiene was crucial. Chaudhary MA *et al.*, observed similar outcomes from Pakistan. When asked how to maintain a prosthesis, 97.5% of respondents gave a good response, according to the authors [23]. Patients were unable to receive therapy because they were unaware of the several prosthodontic treatment choices available to them. According to a study, dental camps and prosthodontic outreach programs were one strategy to address attitude change, raise awareness, and impart knowledge about the methods and means of replacing artificial teeth [15]. The study has certain limitations, including a small sample size and the fact that it was conducted in an institutional setting where the cost of prosthetic treatment was different from that of private dental care facilities. In this study, we also observed that socio-economic constraints played a significant role in the decisions regarding prosthodontic care. A comparable survey can be carried out across a sizable population in the clinical and hospital sectors. Given that the current study's attitude factor toward dental implant therapy was unfavorable, a similar survey on knowledge and attitudes regarding implants as a method of tooth replacement might be undertaken.

CONCLUSIONS

Within the constraints of the study, we were able to draw the conclusion that patients had a good attitude toward maintaining prosthesis cleanliness and favored fixed over removable tooth replacement. The majority of people knew that maxillofacial components could be replaced with prosthetics, but their knowledge about replacing teeth with prosthetics was below average. The patient felt negatively about dental implants as a method of tooth replacement

Authors Contribution

Conceptualization: UK
Methodology: UK
Formal analysis: HS, PT
Writing, review and editing: AF, PCL, FJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2173

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DOI: https://doi.org/10.54393/pjhs.v5i11.2359

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Association of Bacterial Vaginosis with Preterm Labour in Pregnant Women

Ayesha Qamar[1*], Moizza Aziz[2], Najia Riffat[3], Saema Tehseen[4], Shagufta Yaqoob[5] and Fareeha Zaheer[5]

[1]Department of Gynaecology, Pakistan Air Force Hospital, Mushaf, Sargodha, Pakistan
[2]Department of Gynaecology, Pakistan Air Force Hospital, Islamabad, Pakistan
[3]Department of Gynaecology, Pakistan Air Force Hospital, Kamra, Attock, Pakistan
[4]Department of Gynaecology, Pakistan Air Force Hospital, Faisal, Karachi, Pakistan
[5]Department of Gynaecology, Pakistan Aeronautical Complex Hospital, Kamra, Attock, Pakistan

ARTICLE INFO

Keywords:
Bacterial Vaginosis, Preterm Labor, Parity, Obstetric History, Preterm Delivery

How to Cite:
Qamar, A., Aziz, M., Riffat, N., Tehseen, S., Yaqoob, S., & Zaheer, F. (2024). Association of Bacterial Vaginosis with Preterm Labour in Pregnant Women: Bacterial Vaginosis and Preterm Labor in Pregnant Women. *Pakistan Journal of Health Sciences*, 5(11). https://doi.org/10.54393/pjhs.v5i11.2359

***Corresponding Author:**
Ayesha Qamar
Department of Gynaecology, Pakistan Air Force Hospital Mushaf, Sargodha, Pakistan
ashley.virk90@gmail.com

Received Date: 5th October, 2024
Acceptance Date: 22nd November, 2024
Published Date: 30th November, 2024

ABSTRACT

Bacterial Vaginosis (BV) was a common vaginal infection associated with adverse pregnancy outcomes, including premature birth. **Objective:** To evaluate the association between the BV and the risk of preterm Labor in pregnant women and to assess whether BV prevalence differs based on obstetric history, including parity and prior delivery outcomes. **Methods:** This case-control study was conducted in the Obstetrics and Gynecology Department at PAF Hospital Mushaf, Sargodha, from July 2022 to January 2023. A total of 130 participants were included in the study. BV was diagnosed using laboratory and diagnostic methods. Participants were enrolled using non-probability consecutive sampling. Data were analyzed using SPSS version 21.0. Chi-square tests and odds ratios were employed to assess the association between bacterial vaginosis and variables such as age, gravida, and history of preterm delivery, with a p-value ≤ 0.05 considered statistically significant. **Results:** The mean age of the participants was 25.32±6.8 years. Parity also had a notable impact, with multiparous women showing a significantly higher prevalence of BV (46.2%) compared to controls (18.2%), with an OR of 3.86; P=0.006. However, the difference among primiparous women was insignificant (P=0.477, OR=1.56). Women with no prior delivery history had a higher BV prevalence in the case group, 41.5%, compared to the control group, 20.0%, with an OR of 2.83; P=0.130. **Conclusions:** Bacterial vaginosis was significantly associated with older maternal age and multiparity, but no strong correlation was found with previous preterm delivery. Timely diagnosis and management of BV may help reduce the risk of preterm labor.

INTRODUCTION

An imbalance in the natural vaginal flora, including a reduction in lactobacilli as well as a proliferation of anaerobic bacteria like *Gardnerella vaginalis* and *Atopobium vaginae*, results in Bacterial Vaginosis (BV), a frequent vaginal illness. Preterm labor, along with preterm delivery, are among the unfavorable pregnancy outcomes that have been strongly linked to BV [1]. The intricate microbial community found in the female lower vaginal tract plays a significant role in a woman's ability to reproduce. Bacterial Vaginosis (BV), one of the most prevalent gynecologic disorders affecting women of reproductive age worldwide, can result from imbalances in this microbiota [2]. As of right now, it is known that Lactobacillus species predominate in the healthy vaginal microbiome. In contrast, *Gardnerella vaginalis*, *Prevotella*, *Bacteroides*, *Mobiluncus*, and *Mycoplasma hominis* are among the species that cause BV. Lactobacillus species are also relatively rare in BV [3]. The most typical vaginal infection among fertile women is bacterial vaginosis. The prevalence is estimated to be between 12% and 30% for premature Indian women, over 50% for women in East/Southern Africa, and less than 1% for Australian women [4]. BV has been linked to severe and expensive reproductive and obstetric complications, raising the risk of pelvic inflammatory illness, miscarriage, low birth weight, and preterm delivery for women. Inflammation occurs in the genital tract as a result of BV. Preterm labor can develop from this inflammation by inducing the release of

DOI: https://doi.org/10.54393/pjhs.v5i11.2359

prostaglandins and cytokines, which can lead to early cervical softening, membrane rupture, and contractions in the uterus [5]. Intra-amniotic inflammation and infection can result from the bacteria responsible for Bacterial Vaginosis (BV) growing through the female reproductive tract to the cervix as well as amniotic sac. It is believed that this starts the premature labor process [6]. The absence of protective lactobacilli, specifically *Lactobacillus crispatus*, diminishes lactic acid production, resulting in an alkaline vaginal environment which encourages the growth of pathogenic bacteria. This atmosphere is permissive to infections that raise the likelihood of preterm uterine contractions [7]. Preterm birth is characterized by a child being born before its 37th week of gestation. This has a significant impact on public health, as fifteen million preterm births occur each year. One of the primary causes of perinatal mortality and morbidity is preterm delivery. Preterm births can result from a number of causes, but lower genitourinary tract illnesses are one of the main ones [8, 9]. Although several variables can cause a fetal membrane to rupture prematurely, intrauterine infections have the potential to cause preterm labor activity prior to the membrane's burst. Numerous studies have demonstrated the possible connection between premature labor and bacterial vaginosis [10, 11]. A frequent vaginal infection that has been connected to unfavorable pregnancy outcomes, including preterm Labor, is Bacterial Vaginosis (BV). Despite mounting evidence of this link, there is little study examining how BV prevalence varies with mother age, parity, and delivery history, particularly in local communities. By examining the connection between BV and preterm labor in a group of expectant mothers.

This study seeked to close this knowledge gap and offer crucial information for better prenatal care. To evaluate the association between the Bacterial Vaginosis (BV) and the risk of preterm labor in pregnant women and to assess whether BV prevalence differs based on obstetric history, including parity and prior delivery outcomes.

METHODS

The study was case control study. The study was carried out in the Obstetrics and Gynecology Department at the PAF Hospital Mushaf, Sargodha for a period of six months from July 2022 to January 2023. To calculate the sample size for investigating the association between Bacterial Vaginosis (BV) and preterm labor, use a formula based on proportions for case-control studies, n = (p1−p2) 2 (Zα/2+Zβ) 2 · [p1(1−p1) + p2(1−p2)] , n = sample size, Zα/2= (1.96 or 95% confidence level), Zβ = (0.84 for 80% power), p1 = 0.50, p2 = 0.20. n= (0.50−0.20) 2 (1.96+0.84) 2 · [0.50 (1−0.50)+0.20(1−0.20)] = 130. The required sample size was N=130. The inclusion criteria included women aged 15 to 45 years with singleton pregnancies. Participants were selected from the gynecological unit of Sargodha's labor room. Following that, the patients were split up into two groups: cases and controls. All laboring women with preterm labor were categorized as cases, while all laboring women with term labor were considered controls. The inclusion criteria for the control group specified term pregnancies (≥ 37 weeks of gestation) without clinical or laboratory evidence of bacterial vaginosis (BV) and no history of preterm labor or other pregnancy complications in the current or previous pregnancies. Exclusion criteria encompassed cervical defects, fetal malformations, uterine deformities, pregnancy complications, and twin pregnancies. A comprehensive medical history was obtained, covering details about menstruation and pregnancy. Gestational age was determined using the last menstrual period, clinical examinations, and ultrasonography findings. For the control group, exclusion criteria included women with preterm pregnancies (< 37 weeks of gestation), those diagnosed with vaginal infections other than BV (e.g., candidiasis or trichomoniasis), or a history of antibiotic use within the preceding two weeks, as it could alter the vaginal flora. With both written and verbal agreement, an examination of the abdomen was done using a speculum and vagina. When the nature of the waste was identified, vaginal swabs were taken for bacteriologic testing. To get the samples, the patient was put in a dorsal supine position, and sterile cotton swabs were used to take vaginal swabs from the posterior fornix. A piece of nitrazine paper was used to measure the pH of the fluid from the vagina. More than 90% of individuals with BV possess a pH of greater than 5, and the test was sensitive. Informed consent was obtained from all participants, and approval from the Institutional Review Board (IRB) was secured for the study. This study was approved by institutional review board IRB reference number MSF(H)/308/3/1Trg, PAF Hospital Mushaf, Sargodha. The data were analyzed using SPSS version 21.0. Age and blood pressure were examples of continuous variables that were represented by the mean ± SD. Preterm along with bacterial Vaginosis were the categorical features represented by percentages and frequency. The bacterial viremia between the two groups was compared using the chi-square technique. A significant value of P<0.005 was indicated.

RESULTS

In all, 130 individuals were observed, 65 in each group. With a mean age of 25.32 years as well as a standard deviation of 6.8 years, the participants' ages vary from 15 to 45. This suggests that the population was young with a wide age range, while most participants were in the 25–30 age group. 47 women, or 36.2% of the total, were primiparous, or first-time mothers; that is, they have never given birth. 63.8% of the population, or 83 women, were multiparous, indicating they have given birth to children before. This

DOI: https://doi.org/10.54393/pjhs.v5i11.2359

indicates that most women in this research have given birth before. 44 women, or 33.8% of the total, had previously given birth. 86 women, or 66.1%, have never given birth before. This implies that first-time mothers make up a sizable part of this population. 42 women, or 32.3% of the group, tested positive for bacterial vaginosis, meaning that almost one-third of them have the illness. 88 women, or 67.7%,had negative results for bacterial vaginosis, indicating that the majority did not have the condition see Table 1.

Table 1: Sociodemographic Variables

Variables	Category	Mean ± SD / N (%)
Age	15-45 Years	25.32 ± 6.8
Parity	Primi	47 (36.2%)
	Multi	83 (63.8%)
History of Delivery	Yes	44 (33.8%)
	No	86 (66.1%)
Bacterial Vaginosis	Yes	42 (32.3%)
	No	88 (67.7%)

Table 2 showed the prevalence of Bacterial Vaginosis (BV) across different age groups in women with preterm and term pregnancies. Women aged 36 years and older had a significantly higher BV prevalence (60.0%) compared to controls (10.0%), with a strong odds ratio of 13.5 (P=0.039). In the 26-35 age group, BV was present in 47.4% of cases, but this was not statistically significant (P=0.265). For those under 25 years, 39.0% of cases had BV, also lacking significance (P=0.072).

Table 2: Influence of Age on Bacterial Vaginosis Prevalence in Preterm and Term Pregnancies (n=130)

Age	Bacterial Vaginosis	Case N (%)	Control N (%)	Odds Ratio	p-Value
<25 Years	Yes	25 (39.0%)	13 (20.0%)	2.56	0.072
	No	40 (61.0%)	52 (80.0%)	-	-
26-35	Yes	31 (47.4%)	19 (30.0%)	2.1	0.265
	No	34 (52.6%)	46 (70.0%)	-	-
≥36	Yes	39 (60.0%)	6 (10.0%)	13.5	0.039
	No	26 (40.0%)	59 (90.0%)	-	-

The prevalence of Bacterial Vaginosis (BV) in women carrying preterm and term babies was shown in the table according to parity. 38.5% of primiparous women and 28.6% of controls had BV, however P=0.477 indicates that the difference was not statistically significant. On the other hand, multiparous women had a higher risk of BV, as evidenced by their considerable BV prevalence of 46.2% compared to 18.2% in controls (Table 3).

Table 3: Influence of parity on Bacterial Vaginosis Prevalence in Preterm and Term Pregnancies

Parity	Bacterial Vaginosis	Yes N (%)	No N (%)	Odds Ratio	p-Value
Primi	Case	25 (38.5%)	40 (61.5%)	1.56	0.477
	Control	19 (28.6%)	46 (71.4%)	-	-
Multi	Case	30 (46.2%)	35 (53.8%)	3.86	0.006
	Control	12 (18.2%)	53 (81.8%)	-	-

Based on the delivery history, the table displays the prevalence of Bacterial Vaginosis (BV) in pregnant women, both term and preterm. 45.8% of those with a history of delivery had BV, compared to 25.0% of controls; nevertheless, P=0.153 indicates that this difference was not statistically significant. 41.5% of women without a history of childbirth had BV, compared to 20.0% of controls; this difference was not statistically significant (P=0.130) Table 4.

Table 4: Influence of History of Delivery on Bacterial Vaginosis Prevalence in Preterm and Term Pregnancies

History of Delivery	Bacterial Vaginosis	Yes N (%)	No N (%)	Odds Ratio	p-Value
Yes	Case	30 (45.8%)	35 (54.2%)	2.54	0.153
	Control	16 (25.0%)	49 (75.0%)	-	-
No	Case	27 (41.5%)	38 (58.5%)	2.83	0.130
	Control	13 (20.0%)	52 (80.0%)	-	-

DISCUSSION

The most common vaginal illness among both pregnant as well as non-pregnant women was Bacterial Vaginosis (BV), which was also the leading cause of vaginitis. The prevalence of BV varies between 5 and 51% in different geographical areas. Many risk factors may be associated with BV including race and ethnicity, low socio-economic status, antibiotic therapy, multiple sex partners, smoking, and young or teenage age. Nonetheless, most BV cases were asymptomatic, unreported, and untreated [12]. Preterm rupture of the membranes, PTD, and PTL have all been linked to a diagnosis of BV in the middle and late stages of pregnancy. Additionally, in one study, BV in the early stages of pregnancy was linked to an elevated risk for these unfavorable pregnancy outcomes, but not in another [13]. Preterm delivery has been the primary focus of most epidemiologic research aimed at examining the relationship between BV and unfavorable pregnancy outcomes; however, a few of these studies erroneously coupled preterm labor with a premature breakdown of the membrane. In any event, these studies have repeatedly demonstrated that women with BV, especially those identified in the first trimester of pregnancy, have a doubled chance of premature delivery [14]. A recent meta-analysis that reviewed research on the relationship between BV and preterm delivery found that pregnant women with BV had a 60 percent higher risk of premature delivery (summary odds ratio: 1.6). Fewer research has examined the relationship between BV and the outcomes of low birth weight, preterm rupture of the membranes, and premature labor [15]. 2.6-fold higher likelihood of preterm birth (95% confidence interval: 1.3, 4.9), a 6.9-fold raised threat of preterm birth (95 percent confidence interval: 2.5,

DOI: https://doi.org/10.54393/pjhs.v5i11.2359

18.8), as well as a 7.3-fold elevated risk of preterm, premature rupture of the layers (95 percent confidence interval: 1.8, 29.4), were found in the previous study that looked at several pregnancy outcomes related to BV identified during the first trimester of pregnancy [16]. Among the first studies to examine the connection between bacterial vaginosis and premature labor were Eschenbach and associates. In their investigation, bacterial vaginosis was present in 24% of the full-term group and 49% of the preterm group. Subsequent research demonstrated the link between premature labor, chorioaminiotis, and bacterial vaginosis [17]. In a previous study conducted, 27.7% of preterm patients had BV prevalence. The outcomes of the present investigation were similar to those of prior studies. A greater incidence of BV was discovered in those who had previously had an abortion in their second trimester as opposed to those who had an early abortion, according to a 1996 English study that assessed 500 instances of repeated abortion. 20% of pregnant women with no symptoms had bacterial vaginosis [18, 19]. Resolving the link between BV and premature labor was crucial for the general public's health. To improve pregnancy outcomes, strategies to lower the prevalence of BV in expectant mothers were being investigated. These strategies include education, good hygiene habits, and possible therapies [20]. Future research should explore the underlying mechanisms connecting these variables and the potential role of microbiome changes in pregnancy. Longitudinal studies examining the long-term effects of BV treatment on pregnancy outcomes will provide valuable insights.

CONCLUSIONS

Bacterial vaginosis was significantly associated with older maternal age and multiparity, but no strong correlation was found with previous preterm delivery. Timely diagnosis and management of BV may help reduce the risk of preterm labor.

Authors Contribution

Conceptualization: AQ, MA
Methodology: AQ, MA, NR, ST, SY, FZ
Formal analysis: ST, SY
Writing, review and editing: NR, ST, SY, FZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2047

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Comparative Efficacy of Intravenous Ciprofloxacin against Ceftriaxone in Spontaneous Bacterial Peritonitis Patients

Muhammad Imran Sheikh[1], Muhammad Usman Yaqub[1], Farhan Saeed[1], Asim Maqsood[1] and Muhammad Asad Raza[1]

[1]Department of General Medicine, Avicenna Medical College and Hospital, Lahore, Pakistan

ARTICLE INFO

Keywords:
Spontaneous Bacterial Peritonitis, Cirrhosis, Ciprofloxacin, Ceftriaxone

How to Cite:
Sheikh, M. I., Yaqub, M. U., Saeed, F., Maqsood, A., & Raza, M. A. (2024). Comparative Efficacy of Intravenous Ciprofloxacin against Ceftriaxone in Spontaneous Bacterial Peritonitis Patients : Intravenous Ciprofloxacin Against Ceftriaxone in Spontaneous . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2047

***Corresponding Author:**
Muhammad Imran Sheikh
Department of General Medicine, Avicenna Medical College and Hospital, Lahore, Pakistan
imransheikh4@yahoo.com

Received Date: 16th August, 2024
Acceptance Date: 13th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Cirrhotic individuals with spontaneous bacterial peritonitis were treated empirically with ciprofloxacin or ceftriaxone. **Objective:** To compare the effectiveness of intravenous ciprofloxacin against ceftriaxone in cirrhotic patients who developed spontaneous bacterial peritonitis. **Methods:** This prospective interventional analysis was conducted at the Department of Medicine GHURKI Trust and Teaching Hospital, Lahore from Aug 2018 to 2023, and comprised 356 patients of spontaneous bacterial peritonitis. After getting informed written consent patients with ages 35-70 years were included. Equally divided cases into two groups, 178 patients in group I received intravenously ciprofloxacin 200mg and 178 patients in group II received intravenously ceftriaxone 1g for 6 days after every 12 hours. Post-treatment efficacy of both drugs was compared. **Results:** Patients under study had a mean age of 53.15 ± 11.67 years and had a body mass index of 24.8 ± 6.20 kg/m2. In group I efficacy was found in 142 (79.8%) and in group II effectiveness was found in 160 (89.9%) with p-value=0.002. We found a reduction in ascetic fluid polymorph nuclear count in both groups after 6 days with p<0.003. The frequency of complications in group II was higher found in 16 (8.9%) cases and in group I found in only 5 (2.8%) cases. 4 cases in group I and 2 cases in group II left against medical advice. The mortality rate was also non-significant among both groups. **Conclusion:** It was concluded that intravenous ciprofloxacin is equally efficacious as ceftriaxone in treating spontaneous bacterial peritonitis in cirrhotic individuals.

INTRODUCTION

A significant number of hospitalized cirrhotic patients with ascites develop spontaneous bacterial peritonitis (SBP), which is a potentially fatal complication [1, 2]. When treating SBP, third-generation cephalosporin administered intravenously is considered the therapy of choice [3]. Several trials have demonstrated that antibiotics administered intravenously first, with subsequent oral step-down dosing (switch treatment) work just as well [1]. This study did not compare ciprofloxacin switch therapy with an intravenous third-generation cephalosporin. Previous studies demonstrated that it is efficacious in treating both severe and simple SBP [4]. Researchers found that ofloxacin taken orally was just as effective as intravenous (IV) cefotaxime. However, they only ascertained those with simple SBP [5]. A further reduction in effective arterial blood volume as a result of the infection is believed to be the aetiology of type 1 HRS [6]. Administering intravenous albumin in conjunction with antibiotic therapy is an efficient means of preventing HRS. Vasoconstrictors such as Ornipressin, Terlipressin, Noradrenaline, or Midodrine [7]. Patients with cirrhosis who develop spontaneous bacterial peritonitis may not always need ceftazidime or ceftriaxone; ciprofloxacin may be an appropriate substitute. There was an 82% resolution rate for spontaneous bacterial peritonitis in the ceftriaxone group and a 91% resolution rate in the intravenous ciprofloxacin group [8]. Decompensated cirrhosis of the liver patients accounts for 13% of all cases of spontaneous bacterial peritonitis, which is defined as an infection of ascetic fluid [9]. In the case of spontaneous bacterial peritonitis, germs in the intestinal lumen invade the lymph nodes, leading to bacteremia and contamination of the ascetic fluid. Streptococcal pneumonia and Escherichia coli are the most prevalent bacteria and

DOI: https://doi.org/10.54393/pjhs.v5i11.2047

viruses. The diagnosis is confirmed when the PMN count in the ascetic fluid is equal to or more than 250/mL. To detect early infections, diagnostic paracentesis is commonly performed on hospitalized cirrhotic patients with ascites. Many patients have fever, nausea, vomiting, mental abnormalities, and ileus as symptoms of infection; however, some individuals may not experience any symptoms at all [9]. Therapeutic options for Spontaneous Bacterial Peritonitis include several medications. It has been usual practice to utilize quinolones and third-generation cephalosporins. Two trials found that 78.3 to 78.4% of patients treated with Ciprofloxacin ended up with spontaneous bacterial peritonitis resolution, compared to 67% with Ceftriaxone [10]. This study aims to contrast the efficacy of Ceftriaxone with intravenous Ciprofloxacin in treating spontaneous bacterial peritonitis in a single setting and to determine comparative efficacy.

METHODS

This prospective interventional study was conducted at the Department of Medicine GHURKI Trust and Teaching Hospital, Lahore after getting approval with reference # 3335/HR/GTH. Non-probability sampling technique was used. A sample size of 356 patients (178 in each group) is calculated with a 5% level of significance, 95% power of the test and by taking an expected percentage of efficacy IV Ciprofloxacin as 93% and for Ceftriaxone as 81.4% for Spontaneous bacterial peritonitis patients with 95% CL [11, 12]. The following formula was used for the sample size n; $n=(Z\alpha/2+Z\beta)2 * (p1(1-p1) + p2(1-p2)) / (p1-p2)2$, where $Z\alpha/2$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), $Z\beta$ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p1 and p2 are the expected sample proportions of the two groups. Cirrhosis patients with SBP were included if they were 35–70 years old. Exclusion criteria were patients with a history of hemorrhagic ascites or systolic blood pressure (SBP) caused by trauma (RBC >50000/mm3) on ascites fluid testing. All patients with liver cirrhosis who met the inclusion criteria were chosen after the study received permission from the Institutional Review Board. Ultrasound of the abdomen revealed cirrhosis of the liver. Demographic data such as age, sex, residence, and socioeconomic status, were obtained after informed written consent. A sterile diagnostic ascitic fluid aspiration was conducted using a 20 cc syringe to confirm the diagnosis of SBP, which was based on the patient's medical history and physical examination. The 178 patients in group I were given 200 mg of ciprofloxacin intravenously every 12 hours, whereas the 178 patients in group II were given 1 g of ceftriaxone intravenously every 12 hours for six days. After six days of treatment, the effectiveness of the treatment was assessed by analyzing clinical symptoms. These symptoms included a normalization of the patient's temperature (from 98.6°F to 98.2°F) and the absence of abdominal pain (from palpatory testing to clinical examinations of the abdomen). Additionally, the hospital laboratory tested 20 cc of ascitic fluid (obtained by sterile paracentesis) for the neutrophil count. A performance was used to record all of the data that was obtained. After data collection was complete, SPSS version 23.0 was used for analysis. The mean and standard deviation were used to show quantitative variables such as age, body mass index (BMI), and ascitic fluid polymorphonuclear neutrophil count. Frequency and percentage are the best ways to display qualitative characteristics such as effectiveness and sex. A Chi-Square test was used to compare the two groups' effectiveness. Any p-value less than 0.05 was deemed to be statistically significant.

RESULTS

There were a majority of 220 (61.8%) male and 136 (38.2%) female in all cases (Figure 1).

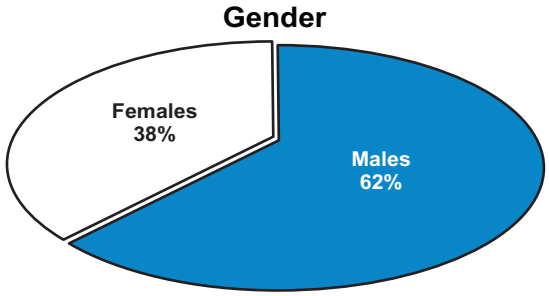

Figure 1: Distribution of Gender in All Cases

Patients in group I had a mean age of 53.21 ± 8.22 years with had body mass index of 24.6 ± 7.38 kg/m2 and in group II mean age was 53.15 ± 11.67 years and had a body mass index of 24.8 ± 6.20. There was the majority of cases from urban areas 208 (58.4%). 130 (36.5%) cases had poor socio-economic status, 178 (50%) cases were from the middle class and 48 (13.5%) cases had upper class.The most common symptom was abdomen pain, fever, hepatic encephalopathy and ileus (Table 1).

Table 1: Baseline Information of the SBP Patients

Characteristic	Group I (178)	Group II (178)	Total (356)
Mean Age (years)	53.21	53.15	106.36
Mean BMI (kg/m^2)	24.6	24.8	49.4
Area of Residence			
Urban	102 (28.7%)	106 (29.8%)	208 (58.4%)
Rural	76 (21.3%)	72 (20.2%)	148 (41.6%)
Socio-economic status			
Poor	60 (16.9%)	70 (19.7%)	130 (36.5%)
Middle	85 (23.9%)	93 (26.1%)	178 (50%)
Upper	33 (9.3%)	15 (4.2%)	48 (13.5%)
Clinical Symptoms			
Abdomen Pain	80 (22.5%)	50 (14.04%)	130 (36.5%)
Fever	60 (16.9%)	70 (19.7%)	130 (36.5%)
Hepatic Encephalopathy	20 (5.6%)	30 (8.4%)	50 (14.04%)
Ileus	18 (5.1%)	28 (7.9%)	46 (12.9%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2047

In group I efficacy was found in 142 (79.8%) and in group II effectiveness was found in 160 (89.9%) with p-value=0.007 (Table 2).

Table 2: Comparison of Effectiveness of Both Medicines

Variables	Group I (178)	Group II (178)	p-value
Efficacy			
Yes	142 (79.8%)	160 (89.9%)	0.007
No	36 (20.2%)	18 (10.1%)	

A reduction in ascetic fluid polymorph nuclear count in both groups was found after 6 days with p<0.003 (Table 3).

Table 3: Comparison of AFPN in Patients After 4 Days

Variables	Group I	Group II	p-value
At Start	7015 ± 158	7156 ± 237	0.000
After Treatment	967 ±147	1026 ± 465	>0.003

AFPN=Alpha-fetoprotein Negative

The frequency of complications in group II was higher found in 16 (8.9%) cases and in group I found in only 5 (2.8%) cases. 4 cases in group I and 2 cases in group II left against medical advice (AMA). The mortality rate was also non-significant among both groups (Table 4).

Table 4: Association of Adverse Events

Variables	Complications	Cases Left AMA	Mortality Rate
Group I	5 (2.8%)	4 (2.2%)	4 (2.2%)
Group II	16 (9.0%)	2 (1.1%)	5 (2.8%)
p-value	<0.0133	0.009	0.010

AMA=Against Medical Advice

Among 21 cases of complications, renal failure was found in 12 cases, followed by gastrointestinal hemorrhage in 6 cases and hepatic encephalopathy in 3 cases. (Table 5).

Table 5: Post-treatment Complications in Both Groups

Variables	Group I (178)	Group II (178)
Complications		
Renal Failure	3 (1.7%)	9 (5.1%)
Gastrointestinal Hemorrhage	1 (0.6%)	5 (2.8%)
Hepatic Encephalopathy	1 (0.6%)	2 (1.1%)
Total	5 (2.8%)	16 (9.0%)

DISCUSSION

Cirrhosis with ascites is a potentially deadly consequence. Even with conventional therapy, the infection-related death rate linked with SBP can reach 27%. Patients with chronic liver illness may first experience a symptomatic SBP as a kind of ascites. Patient lives can be saved by detecting infections early and administering antibiotics promptly. These antibiotic alternatives include ceftriaxone, cefotaxime, ampicillin, ciprofloxacin, ofloxacin, and metronidazole. Norfloxacin and ciprofloxacin are examples of fluoroquinolones; these antibiotics are efficient against most enterobacteria and aerobic gram-negative bacilli, thus they look like a good choice for prophylaxis. A previous case-control study found that 120 patients with cirrhosis with upper gastrointestinal bleeding who were given 500 mg of ciprofloxacin twice a day for seven days following endoscopy had a lower rate of confirmed bacterial infection (10% vs. 45%), but no mortality [13]. The empirical therapy of choice for cirrhotic individuals suffering spontaneous bacterial peritonitis was cefotaxime or ceftriaxone. Patients with cirrhosis who develop spontaneous bacterial peritonitis may benefit from using ciprofloxacin instead of cefotaxime or ceftriaxone. The percentage of spontaneous bacterial peritonitis cases resolved in the groups treated with intravenous ciprofloxacin (80%) and ceftriaxone (83%). Based on these findings, intravenous ciprofloxacin is a cost-efficient and almost equally effective alternative to cefotaxime and ceftriaxone for treating spontaneous bacterial peritonitis in cirrhotic patients [14, 15]. The frequency of SBP in cirrhotic patients and its reaction to various treatment regimens has been the subject of several local and international investigations. Famous antibiotics Ciprofloxacin (Fluoroquinolone) and ceftriaxone (3rd Generation Cephalosporin) were the subjects of this comparative investigation. Due to the rise of multiple drug resistance, there has been a noticeable drop in the effectiveness of both treatments recently; hence, it was important to determine if they are equivalent or not. With a p-value of 0.002, this research indicated that both Ciprofloxacin and ceftriaxone were very successful in treating SBP, with 79.8% and 89.1% of patients, respectively, benefiting from treatment. According to additional research, oral ciprofloxacin had a somewhat higher efficacy than ceftriaxone (80% vs. 76%). According to the previous study, the infection clearance rate with ciprofloxacin was 78.4% and with ceftriaxone, it was 80% [16]. Current findings are quite consistent with those of these investigations. Ceftriaxone was shown to be effective in curing 91% of SBP patients in a comparable past trial [17]. The results showed that there is no substantial difference in the effectiveness of the two drugs, cefotaxime and ciprofloxacin when it comes to treating SBP. In the current study majority, 220 (61.8%) were male and 136 (38.2%) were female in all cases. Included patients who had a mean age of 53.15 ± 11.67 years and had a body mass index of 24.8 ± 6.20 kg/m2. There were the majority of cases from urban areas 208 (58.4%). 130 (36.5%) cases had poor socio-economic status, 178 (50%) cases were from the middle class and 48 (13.5%) cases had high status. These results were comparable to the previous study conducted by MacIntosh [18]. Current analysis revealed a reduction in ascetic fluid polymorph nuclear count in both groups after 4 days with p<0.003, similar to the findings of previous studies [17]. The Frequency of

DOI: https://doi.org/10.54393/pjhs.v5i11.2047

complications in group II was higher found in 16 (8.9%) cases and in group I found in only 5 (2.8%) cases. 4 cases in group I and 2 cases in group II left against medical advice. The mortality rate was also non-significant among both groups. These were in line with the previous findings [19, 20]. Ciprofloxacin and ceftriaxone both have the potential to save lives and improve the prognosis of SBP, but they require more clinical trials in this context due to limited access to healthcare. Its main drawback is that it is a single-center research with a small sample size. To validate and generalize these findings, a large-scale randomized multicenter clinical investigation is necessary.

CONCLUSIONS

It was concluded that the effectiveness of ciprofloxacin and ceftriaxone in resolving infections caused by spontaneous bacterial peritonitis is comparable and does not differ significantly.

Authors Contribution

Conceptualization: MUY
Methodology: MIS, FS, MAR
Formal analysis: MUY, FS, AM, MAR
Writing review and editing: MIS, AM, MAR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2427

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Association between Clinical Manifestations and Candida Carriage in Patients with Oral Sub-Mucous Fibrosis

Muhammad Zain-Ul Abedeen[1], Muhammad Talal Rafiq[1], Abid Hussain Kanju[2], Sahrish Liaqat[2], Muhammad Abi Waqas[1*] and Muhammad Mashood Riaz[1]

[1]Department of Dentistry, Multan Medical and Dental College, Multan, Pakistan
[2]Department of Dentistry, Nishtar Institute of Dentistry, Multan, Pakistan

ARTICLE INFO

Keywords:
Oral Sub-Mucous Fibrosis, Infection, Candida Carriage, Saliva

How to Cite:
Zain-Ul Abedeen, M., Rafiq, M. T., Kanju, A. H., Liaqat, S., Abi Waqas, M., & Riaz, M. M. (2024). Association between Clinical Manifestations and Candida Carriage in Patients with Oral Sub-Mucous Fibrosis: Clinical Manifestations and Candida Carriage in Patients with Oral Sub-Mucous Fibrosis.Pakistan Journal of Health Sciences,5(11). https://doi.org/10.54393/pjhs.v5i11.2427

***Corresponding Author:**
Muhammad Abi Waqas
Department of Dentistry, Multan Medical and Dental College, Multan, Pakistan
abivaqas@gmail.com

Received Date: 6th October, 2024
Acceptance Date: 22nd November, 2024
Published Date: 30th November, 2024

ABSTRACT

A chronic, progressive disorder known as oral sub-mucous fibrosis causes the oral mucosa to become inflamed and fibrotic, which limits mouth opening, causes a burning sensation, and reduces salivary flow. **Objectives:** To assess the relationship between candida carriage in oral sub-mucous fibrosis patients and demographic traits, tobacco use, and clinical parameters such as burning sensation, salivary flow rate, and mouth opening. **Methods:** A comparative cross-sectional study was conducted from May 2024 to Oct 2024. This study was conducted in Multan Medical and Dental College. The total number of patients was 384 divided into 192 with oral sub-mucous fibrosis and 192 control participants split into groups with and without risk exposure. Clinical characteristics such as mouth opening, salivary flow rate, and burning sensation (measured using a visual analogue scale) were evaluated. Data were analyzed with descriptive, mean, Post Hoc analysis, and Chi-square tests. **Results:** Comparing the oral sub-mucous fibrosis positive group (93%) to the negative group (7%), the oral sub-mucous fibrosis group had a considerably greater prevalence of candida carriage. Reduced salivary flow rate (≤0.2 ml/min), restricted mouth opening (≤20 mm), and severe burning sensation (3-5 (Visual Analogue Scale)) were shown to be strongly correlated with candida positivity ($p<0.001$). A greater prevalence of candida colonization was also seen in patients who used tobacco more frequently ($p<0.001$). **Conclusions:** It was concluded that comprehensive treatment methods should include patient education on oral hygiene and quitting smoking, given the major impact that these behaviours play in candida's carriage.

INTRODUCTION

Oral Sub-Mucous Fibrosis (OSMF) is a progressive and painful condition predominantly affecting individuals who frequently consume areca nuts and tobacco products [1]. Symptoms include a burning sensation, reduced salivary flow, and restricted mouth opening, resulting from inflammation and fibrosis of the oral mucosa. As the disease advances, these symptoms worsen, significantly impairing patients' quality of life and increasing their susceptibility to infections, including fungal colonization [2]. Candida species, particularly candida albicans, are naturally present in the oral cavity but can become pathogenic under altered oral conditions, such as those seen in OSMF, where epithelial abnormalities, reduced salivary flow, and poor oral hygiene facilitate Candida overgrowth [3]. Despite studies indicating an elevated prevalence of Candida among OSMF patients, the relationship between Candida colonization and specific symptoms like burning sensation, salivary flow rate, and mouth opening remain underexplored [4]. OSMF is recognized as a chronic disorder of the oral mucosa that may affect any oral area and occasionally extends to the pharynx, larynx, and oesophagus [5]. OSMF is a chronic, progressive condition characterized by the fibrotic transformation of the oral soft tissues, severely hindering mouth opening. Its complex pathogenesis arises from an interplay of genetic susceptibilities and environmental exposures, predominantly triggered by areca nut and tobacco use. The hallmark is excessive, irregular collagen

DOI: https://doi.org/10.54393/pjhs.v5i11.2427

deposition and disrupted extracellular remodeling in the oral mucosa and submucosa, inducing stiffness and inflexibility. Chief among the triggers are areca nut's alkaloids and polyphenols, which spur fibroblast proliferation and rampant collagen synthesis [6]. Moreover, reactive oxygen species from areca nuts and tobacco provoke oxidative stress, exacerbating fibrosis. An imbalance of collagen-modulating enzymes like lysyl oxidase promotes insoluble collagen development through aberrant crosslinking, making it resistant to degradation over time. This accumulated, non-degradable collagen in the lamina propria and submucosa ultimately leads to rigidity and scarring [7]. Inflammation plays a pivotal role in OSMF progression. Chronic irritation of the oral lining by areca nut or tobacco sustains inflammatory cell infiltration, such as macrophages, lymphocytes and mast cells. These immune cells secrete pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6, amplifying fibroblast activation and collagen deposition. Tissue remodeling is further altered by disproportionate matrix metalloproteinase and its inhibitors. Typically, matrix metalloproteinase breaks down surplus collagen, but in OSMF their inhibitors overwhelm this function, letting collagen accumulate unchecked [8]. There is substantial evidence establishing a link between candida overgrowth and the epithelial alterations occurring in oral sub-mucous fibrosis. The dysfunctional oral environment present in OSMF, characterized by impaired integrity of the epithelium and diminished immunity, sets the stage for unchecked candida proliferation. By excreting toxins and enzymes, disrupting epithelial barriers, and promoting oxidative stress, candida can exacerbate mucosal inflammation and precancerous changes, fueling persistent inflammation that serves to further the fibrosis and malignant transformation seen in OSMF [9]. Certain debilitating symptoms of OSMF, such as limited jaw opening, fiery sensations, and blanched mucosa, help enable candida colonization by compromising oral cleanliness and defence mechanisms. The fiery pain and ulcerations could stem from damage inflicted by candida, while the fibrosis handicaps the mucosa's capacity to stave off colonization. This interplay highlights the potential role of candida in exacerbating OSMF symptoms and hastening the progression to a more advanced disease [10].

The usage of areca nuts is the main cause of oral sub-mucous fibrosis (OSMF), a progressive, potentially malignant illness with substantial morbidity. Investigating this connection may provide fresh perspectives on the pathophysiology and possible treatment modalities for OSMF.

This study aims to determine the prevalence of candida carriage in patients with OSMF and investigate any correlations between it and particular clinical characteristics of the illness. We anticipate that by comprehending these connections, we will be able to pinpoint important indicators of candida colonization, which could lead to more focused and efficient treatment plans for OSMF patients.

METHODS

A comparative cross-sectional study was conducted from May 2024 to Oct 2024 at the Department of Dentistry at Multan Medical and Dental College. The total number of participants was n=384 including both genders, which divided into 192 with OSMF and participants split into two control groups non-habitual and habitual control group (each group contain n=92 participants). The non-habitual group consists of individuals who do not have any habits that may negatively affect oral health, such as tobacco, or smoking. They serve as a control group representing the normal, unaffected population without exposure to these risk factors. The habitual group includes individuals who have habits such as tobacco, and smoking but do not exhibit clinical signs or symptoms of oral sub-mucous fibrosis (OSMF). They serve as a comparison group to assess the early or subclinical effects of such habits on oral health including breathing sensation, salivary flow rate and mouth opening. Patients diagnosed with oral sub-mucous fibrosis (OSMF) were further categorized into three stages—early, moderate, and advanced—based on clinical criteria. For consistency in comparative analysis, an equal sample size of 64 patients was allocated to each stage. Inclusion criteria: The age range of the patients was 18-50 years diagnosis was confirmed through clinical examination, history of smoking, burning, difficulty opening the mouth, and changed salivary flow rate and each patient had to provide written informed consent. Exclusion criteria were diabetes, immunosuppressive conditions, patients who had taken antifungal medicine last six months. The sampling technique adopted for this study was convenience sampling. To calculate the sample size for the relationship between clinical features and candida carriage in oral sub-mucous fibrosis (OSMF) patients the following formula applies: n= Z2. P. (1-P)/d2, where, n=sample size, Z= (1.96 or 95% confidence level), p=estimated prevalence ratio (0.5 or 50%), d=margin of error (0.05 or 5%). According to this study, the prevalence of candida carriage in OSMF patients was reported as 30% [11]. The required sample size was n=384. Mouth opening (MO) was measured three times using an electronic Vernier caliper (0.005 mm resolution). Unstimulated saliva flow rate (SFR) was assessed between 9:00 a.m. and 12:00 p.m., with participants instructed to avoid eating, drinking, and oral products for 60 minutes prior. Before testing, they swallowed all saliva and kept their tongue on the hard palate. SFR was measured using the modified Schirmer

DOI: https://doi.org/10.54393/pjhs.v5i11.2427

test (MST). For candida assessment, patients were rinsed with 10 ml PBS and expectorated into a container. Samples were centrifuged, suspended, and cultured on Sabouraud's Dextrose Agar at 37°C for 24–48 hours. Colony-forming units per mL (CFU/mL) were calculated. Candida species were identified using germ tube testing, Gram staining, and CHRO-Magar. For comparisons of quantitative clinical features across groups, ANOVA was used for normally distributed data, and the Kruskal-Wallis test was applied for non-normally distributed data. In cases where one-way ANOVA was used, Tukey's Honest Significant Difference (HSD) post-hoc test was performed to identify specific group differences. The Chi-square test was employed for categorical data analysis. A p-value of <0.05 was considered statistically significant. The study was approved by the Institutional Review Board number (No: C-76-1030), ensuring adherence to ethical standards. Informed consent was obtained from all participants before their involvement in the research.

RESULTS

The study included participants with an average age of 34 years (standard deviation: 9.24), consisting of 201 female (52.3%) and 183 male (47.6%), indicating a slight female predominance. Tobacco use was reported by 200 participants (52%), while 184 (47%) indicated they did not use tobacco, suggesting that over half of the sample has a tobacco habit, which may impact the study's focus on candida carriage and related health outcomes. Most participants (60.94%) reported using tobacco more than 12 times daily, with 26.04% using it 7 to 12 times and only 13.02% using it 1 to 6 times per day. Regarding symptom duration, 39.06% reported experiencing symptoms for 3 years, 34.90% for 6 years, and 26.04% for 1 year. These findings underscore the significant role that tobacco use may play in influencing health outcomes related to candida carriage (Table 1).

Table 1: Demographic Characteristics (n=389)

Characteristics	Category	Frequency (%)
Age Range	-28 Years	110 (28.6%)
	29-39 Years	138 (35.9%)
	40-50 Years	137 (35.6%)
Gender	Male	183 (47.6%)
	Female	201 (52.3%)
Tobacco Habit	Yes	200 (52%)
	No	184 (47%)
Frequency/Day	1-6	50 (13.02%)
	7-12	100 (26.04%)
	>12	234 (60.94%)
Duration	1 Year	100 (26.04%)
	3 Year	150 (39.06%)
	6 Year	134 (34.90%)

The analysis showed significant differences between the groups for all clinical features. OSMF patients had higher burning sensation (Visual Analogue Scale (VAS): 7.5 ± 1.2), lower salivary flow rate (0.2 ± 0.05), and reduced mouth opening (28 ± 5 mm) compared to both non-habitual and habitual control groups, with p-values of 0.001 for all variables. These results highlight the discomfort and functional impairments in OSMF patients (Table 2).

Table 2: Comparison of Clinical Features Between OSMF Patients with Non-Habitual Control Group and Habitual Control Group

Sign and Symptoms	OSMF Group (n=192)	Non-Habitual Control Group (n=96)	Habitual Control Group (n=96)	p-Value
Burning Sensation (VAS)	7.5 ± 1.2	1.2 ± 0.8	2.0 ± 1.0	0.001
Salivary Flow Rate (ml/min)	0.2 ± 0.05	0.5 ± 0.1	0.4 ± 0.1	0.001
Mouth Opening (mm)	28 ± 5	45 ± 3	42 ± 4	0.001

As the disorder evolves, the burning sensation gets progressively worse, acquiring its highest VAS evaluations in the more severe phase (p=0.001). As OSMF expands, the salivary flow rate declines; the stage of advanced disease has among the lowest values (p=0.001). When the OSMF condition advances, mouth opening significantly decreases (p=0.001). Significant differences between all stages are shown by post-hoc analysis, the following a significant result in the initial analysis (p=0.001), a post-hoc test (Tukey's HSD) was applied to further analyze pairwise comparisons between the stages. The post-hoc results indicated significant differences across all pairwise comparisons (p<0.05), which reflects the symptoms' growing intensity (Table 3).

Table 3: Clinical Feature Comparison Across Early, Moderate, and Advanced Stages of OSMF

Variables	Early Stage (n=64)	Moderate Stage (n=64)	Advanced Stage (n=64)	p-value	Post Hoc Analysis
Burning Sensation	3.5 ± 0.8	5.8 ± 1.0	7.2 ± 1.2	0.001	Early vs Moderate, early vs Advanced, Moderate vs. Advanced (all significant)
Salivary Flow Rate	0.5 ± 0.1	0.3 ± 0.05	0.1 ± 0.02	0.001	
Mouth Opening	38 ± 3	30 ± 4	22 ± 5	0.001	

In our study sample, candida-positive cases were found in a high proportion of participants. Specifically, 93% of the sample tested positive for candida, while only 7% tested negative (Figure 1).

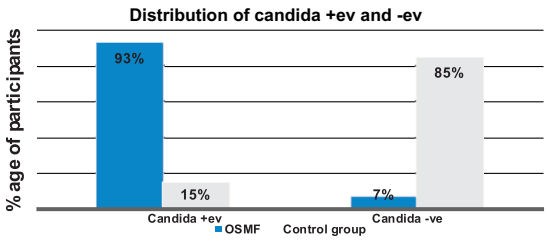

Figure 1: % Age of Patients Represent Distribution of Candida Positive and Negative Sample

DOI: https://doi.org/10.54393/pjhs.v5i11.2427

In the OSMF group, the highest number of candida colonies (83%) was 1-200 CFU/mL. Six patients (79%) had candida carriage with a colony count ranging from 201 to 400 CFU/mL. (85%) of the research group's participants showed colony counts between >400 CFU/mL (Figure 2).

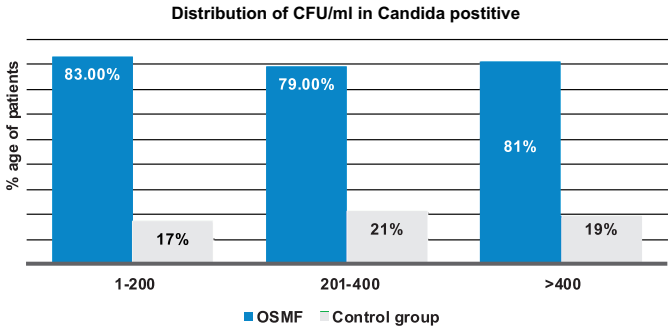

Figure 2: % Age of Patients Represent Candida Colonies

In this study, candida positivity was higher among OSMF patients aged 29-39, predominantly male, with a significant association with tobacco use (p=0.01). Higher tobacco frequency (1-6 times/day) and longer duration (over 1 year) were strongly linked to candida positivity (p<0.001), highlighting the role of demographic factors and tobacco use in candida carriage (Table 4).

Table 4: Impact of Demographic Factors and Tobacco Use on Candida Carriage in OSMF

Characteristics	Candida Positive (n=179)	Candida Negative (n=13)	p-value
Age			
18-28	60 (33.5%)	4 (30.8%)	0.11
29-39	80 (44.7%)	6 (46.2%)	
40-50	39 (21.8%)	3 (23.1%)	
Gender			
Male	90 (50.3%)	6 (46.2%)	0.55
Female	89 (49.7%)	7 (53.8%)	
Tobacco Habit			
Yes	120 (67.0%)	5 (38.5%)	0.01
No	59 (33.0%)	8 (61.5%)	
Frequency of Tobacco Use			
1-6	90 (50.3%)	2 (15.4%)	<0.001
7-12	50 (27.9%)	6 (46.2%)	
>12	39 (21.8%)	5 (38.5%)	
Duration of Tobacco Use			
1 Year	30 (16.8%)	4 (30.8%)	<0.001
3 Years	70 (39.1%)	5 (38.5%)	
6 Years	79 (44.1%)	4 (30.8%)	

Candida positivity was significantly associated with burning sensation (VAS 3-5) at 5.59%, low salivary flow rate (≤2 ml/min) at 27.93%, and mouth opening ≤20 mm at 39.11%. No significant association was found in other categories (Table 5).

Table 5: Association of Oral Symptoms and Candida Isolation in Patients with OSMF

Variables	Subgroups	OSMF (n=192)	Candida Positive (n=179)	Candida Negative (n=13)	X^2	p-value
Burning Sensation (VAS)	≤2 (VAS)	85	80(44.69%)	5(38.46%)	0.56	0.454
	3-5 (VAS)	11	10(5.59%)	1(7.69%)	5.52	0.019
	≥6 (VAS)	96	89(48.65%)	7(53.84%)	0.56	0.454
Salivary Flow Rate	≤2 ml/min	52	509(27.93%)	2 (15.38%)	9.34	0.011
	0.3-0.5 ml/min	105	100(55.87%)	5(38.46%)	15.2	0.001
	≥0.6 ml/min	35	29 (16.19%)	6 (46.15%)	0.79	0.374
Mouth Opening	≤20 mm	73	70 (39.11%)	3 (23.08%)	12.5	0.001
	21-30 mm	75	70 (39.11%)	5(38.46%)	0.78	0.376
	>30 mm	44	39(21.79%)	5 (38.46%)	0.43	0.514

DISCUSSION

The demographic profile of patients with Oral Sub-Mucous Fibrosis (OSMF) reveals critical insights into factors influencing candida carriage. Patients often show a high prevalence of tobacco use, a slight female predominance, and an age range from young to middle-aged. Given the substantial rates of tobacco consumption, health interventions should focus on educating individuals about the risks associated with tobacco use, particularly concerning OSMF, candida infections, and general oral health [12, 13]. Data highlight the significant impact of OSMF on oral health, showing marked differences in clinical features between OSMF patients and control groups. The intense burning sensation reported by patients is likely due to inflammation and fibrosis in the oral mucosa, which can impair sensory perception. Previous research indicates that Candida infections may exacerbate these symptoms, highlighting the need for comprehensive management strategies that address both sensory and physical components associated with OSMF [14, 15]. Decreased salivary flow is another common issue among OSMF patients, leading to dry mouth (xerostomia) and an increased risk of oral infections, including candidiasis. Saliva is vital for maintaining oral health, as it lubricates teeth, neutralizes acids, and possesses antibacterial properties [16]. Therefore, interventions aimed at enhancing salivary output are essential to mitigate complications associated with dry mouth in these patients. Additionally, the characteristic limited mouth opening in OSMF results from fibrous bands in the submucosal layer, which can hinder normal oral functions such as eating, speaking, and maintaining dental hygiene, ultimately reducing the quality of life [17]. Addressing the trismus linked to OSMF through physical therapy or surgical options is critical to improving patient outcomes [18]. As OSMF progresses, mucosal alterations and inflammation can worsen, intensifying discomfort and burning sensations. Patients in advanced stages may experience increased

DOI: https://doi.org/10.54393/pjhs.v5i11.2427

nerve damage and inflammatory responses, necessitating tailored management strategies for effective pain relief [19]. The loss of salivary flow can further worsen the quality of life and heighten the risk of opportunistic infections like candidiasis. Therefore, clinicians should prioritize treatments that boost salivary production or manage dry mouth symptoms, particularly for patients in intermediate to advanced stages of OSMF [20]. In this study, candida positivity was observed in 93% of OSMF patients, which is higher than the 60-70% prevalence suggesting a stronger association between candida and OSMF in our population. This difference may be due to variations in diagnostic methods or patient demographics. Regarding colony counts, 83% of Candida-positive cases had counts between 1-200 CFU/mL, low to moderate colonization. However, 81% of our participants had counts exceeding 400 CFU/mL, which is notably higher than where fewer than 50% showed high fungal loads. This suggests more persistent candida overgrowth in our study population, potentially contributing to OSMF progression [21]. Interestingly, the study found a statistically significant correlation between tobacco use and candida carriage; however, a significant relationship between the frequency of tobacco use and candida carriage was established ($p<0.001$). This intriguing result suggests complex interactions between tobacco use and oral microbiota dynamics that require further investigation. Moreover, compared to the control group, OSMF patients exhibited a significantly higher presence of candida ($p=0.048$), with 93% testing positive for candida versus only 15% in the control group [22]. These findings emphasize how decreased salivary flow can exacerbate oral infections and reinforce the importance of saliva in maintaining oral health, particularly in preventing candida colonization. Overall, these insights underscore the need for targeted interventions and comprehensive management approaches to address the multifaceted challenges faced by individuals with OSMF [23]. It is important to highlight in the discussion that cross-sectional study design restricted the capacity to demonstrate temporal or causal links between OSMF and candida carriage, whereas a case-control study may more robustly discern causative associations. This restriction implies that although correlations were noted, more case-control designs or longitudinal studies would be required to verify causality and examine the course of candida colonization in OSMF.

CONCLUSIONS

It was concluded that the study highlights how important it is to monitor patients' oral health closely when they have OSMF, especially when fungal infections are present. Candida colonization can be lessened by early detection and treatment of symptoms like a burning feeling, decreased salivary flow, and restricted mouth opening.

Authors Contribution

Conceptualization: MZUA
Methodology: MZUA, MTR, SL, MAW, MMR
Formal analysis: MTR, MAW
Writing review and editing: MAW

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2473

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

The Prevalence and Distribution of Beta Thalassemia Trait among Outpatient Individuals in A Tertiary Care Hospital of Lodhran, Pakistan

Farhan Ali Khanzada[1], Samreen Asghar[2], Uzma Chohan[3], Sumayya Najam[4], Khushbakhat Khanzada Rajput[5], Abdus Sami[6] and Rabia Ameer[7*]

[1]Department of Pathology, Sheikh Zayed Medical College/Hospital Rahim Yar Khan, Pakistan
[2]Department of Pathology, Lahore Medical and Dental College, Lahore, Pakistan
[3]Department of Pathology, Shahida Islam Medical College, Lodhran, Pakistan
[4]Test Zone Diagnostic Centre, Lahore, Pakistan
[5]Isfand Yar Bukkhari District Hospital, Attock, Pakistan
[6]Department of Pathology, Sheikh Zayed Medical Hospital, Lahore, Pakistan
[7]Pakistan Institute of Quality Control, Lahore, Pakistan

ARTICLE INFO

Keywords:
Genetic Disorder, Thalassemia, Mean Corpuscular Volume, Hematological Abnormalities

How to Cite:
Khanzada, F. A., Asghar, S., Chohan, U., Najam, S., Rajput, K. K., Sami, A., & Ameer, R. (2024). The Prevalence and Distribution of Beta Thalassemia Trait among Outpatient Individuals in A Tertiary Care Hospital of Lodhran, Pakistan: Prevalence of Beta Thalassemia Trait among Outpatient Individuals . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2473

***Corresponding Author:**
Rabia Ameer
Pakistan Institute of Quality Control, Lahore, Pakistan
rabiyaameer143@gmail.com

Received Date: 3rd October, 2024
Acceptance Date: 24th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Thalassemia is an autosomal recessive genetic disorder characterized by impaired synthesis of hemoglobin due to mutations affecting the production of alpha (α) or beta (β) globin chains. This imbalance causes ineffective erythropoiesis, microcytic anemia, and hematological abnormalities. **Objectives:** To assess the prevalence and distribution of β-thalassemia carriers for implementing targeted screening and preventive strategies. **Methods:** This retrospective observational study analyzed 108 samples from patients who were suspected of a complete blood count parameter; which included Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, and total red blood cell count. After that analysis of the suspected patients' blood for Hb A2 through Hb Electrophoresis for the screening of the thalassemia trait was carried out. The data were sourced from Shahida Islam Medical College Hospital, reflecting the carrier status of the participants. **Results:** The findings of the study are distributed between 62 male and 46 female and demonstrated the presence of β-thalassemia trait across various age groups (mean age 25) and found typically higher (52.8%) in the age of 21 to 30 years. Specifically, 68 out of the 108 patients tested positive for the β-thalassemia trait having raised Hb A2 level on the Hb electrophoresis. **Conclusions:** It was concluded that the β-thalassemia trait is widespread across diverse ethnic groups. It highlights the necessity for standardized blood testing protocols for β-thalassemia screening. Implementing comprehensive screening programs, coupled with enhanced public awareness and educational campaigns, is crucial to mitigate the incidence of thalassemia major. These measures are essential for populations to prevent the transmission of this genetic abnormality.

INTRODUCTION

Thalassemia represents a spectrum of inherited hematologic disorders due to defective hemoglobin (Hb) chain synthesis [1]. Beta-thalassemia arises from impaired or absent beta-globin chain production, similar to alpha-thalassemia, which affects alpha-globin chain synthesis. Imbalances in globin chains disrupt erythropoiesis and induce hemolysis [2]. Thalassemia is derived from Greek terms meaning "sea" and "blood," thalassemia encompasses three main types: Thalassemia Minor (beta-thalassemia carrier or trait) and Thalassemia Major (also called Cooley's Anemia or Mediterranean Anemia) and Thalassemia Intermedia [3]. Thalassemia is characterized by inadequate Hb production, leading to the generation of unstable, unpaired globin chains that damage red cell membranes, reducing erythropoiesis and contributing to the clinical symptoms of the disease [4]. Thalassemia is among the illnesses that result in Hb that is not produced properly [5]. The formation of beta chains is faulty in β-thalassemia, resulting in the production of unpaired chains. These structures are unstable, which leads to

DOI: https://doi.org/10.54393/pjhs.v5i11.2473

membrane damage, poor erythropoiesis, and other disease-related clinical characteristics [6]. The majority of people with thalassemia traits are discovered by chance irrespective of age, some people are diagnosed with older age above 50 years and some with an early age, when a slight microcytic anemia is detected on a complete blood count [7]. In severe cases, infants under two years old may present with profound microcytic anemia, mild jaundice, and hepatosplenomegaly, suggestive of thalassemia major. Thalassemia intermedia, while presenting with similar symptoms, manifests later and is often milder [8]. Carriers typically remain asymptomatic but may occasionally exhibit minor hematologic findings. Over 200 mutations affecting the beta-globin gene have been documented, mostly point mutations in functionally critical regions, with deletions being rare [9]. The beta-thalassemia trait, like other inherited characteristics such as hair or eye colour, is passed from parent to child [10]. Generally asymptomatic and often referred to as beta-thalassemia minor, this trait does not typically affect health [11]. If one parent carries the trait, each child has a 50% chance of inheriting it. 50% (1 in 2) of parents who have beta thalassemia trait have a kid who has it. 50% (1 in 2) of parents do not have a characteristic in their child. In thalassemia minor, Hb A levels are significantly reduced, while Hb F and Hb A2 levels are markedly elevated [12]. Beta-thalassemia minor, also referred to as the carrier trait, typically presents as mild anemia, and carriers are generally asymptomatic. When both parents carry the beta-thalassemia trait, there is a 25% risk in each pregnancy of having a child affected by beta-thalassemia major. The moderate anemia-like symptoms of beta thalassemia are minor like fatigue, weakness or dizziness, frequent migraines and yellowish skin [11]. Evaluation of Thalassemia trait key important parameters of complete blood count (CBC) are important like mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) red cell count along with a patient's medical history can help exclude certain etiologies. In cases of thalassemia minor, the MCV typically falls below 80 fL, whereas in iron deficiency, it rarely drops below 80 fL unless the hematocrit level is under 30%, same as MCH is also low or borderline normal and the red blood cells (RBC) count is slightly higher (5.5 x106/dL) and this is accompanied by elevated Hb A2 levels [13]. On peripheral blood smear examination, red blood cells (RBCs) in carriers exhibit minimal morphological abnormalities compared to those seen in affected individuals, and erythroblasts are generally absent [14]. The prevention of beta-thalassemia heavily depends on prenatal diagnostic techniques, carrier screening, and genetic counselling. Genetic counselling aims to educate individuals and couples at risk (e.g., carrier-carrier pairs) about inheritance patterns, genetic risks, disease progression, and available or emerging treatment options.

This study aims to assess the occurrence rate of the β-thalassemia trait as indicated by suspected abnormalities in complete blood count (CBC) parameters among patients in a tertiary care hospital.

METHODS

This retrospective study was conducted at Shahida Islam Medical College Hospital, a Tertiary Care Centre in Lodhran, Pakistan. The duration of the study was July to September 2024, 3 months of records of hematological reports. The sample size of 108 was determined using a formula based on a 95% confidence level (Z=1.96) and a predefined margin of error [15]. A non-probability convenience sampling method was employed after obtaining approval from the Institutional Review Board (Letter No: SIMC/ET.C./00010/24). Patient selection was based on complete blood count (CBC) parameters indicative of suspected β-thalassemia trait, including low mean corpuscular volume (MCV) less than 80 (normal values 80 – 105 fL), low or borderline-normal mean corpuscular Hb (MCH) less than 29 (normal values 27–30 pg), and slightly elevated red blood cell (RBC) counts specifically ≥5.5x106 / dL (normal values 4.5–6.0 x106/dL). These criteria were used to identify potential carriers of β-thalassemia. Hb A2 levels were measured to confirm the diagnosis, utilizing the high-performance liquid chromatography (HPLC) technique commonly used in Hb electrophoresis test [16]. Hb electrophoresis is a laboratory technique used to separate and identify different types of Hb based on their electrical charge and structure. This technique is especially useful in diagnosing hemoglobinopathies, such as thalassemia, and other Hb variants. In the case of beta-thalassemia, electrophoresis helps identify abnormal Hb patterns, including elevated levels of HbA2 and sometimes Hb F, which are characteristic of the disease. HPLC provided precise separation and quantification of Hb variants, enabling the identification of β-thalassemia carriers [17]. Data were collected using a structured self-designed performance. Categorical variables were summarized as frequencies in the form of percentages. Categorical variables were summarized as frequencies and percentages. Mean and standard deviation (SD) were calculated for continuous variables. Statistical analysis was performed using SPSS version 28.0, and significance was also assessed at a 5% level. The prevalence of the β-thalassemia trait which was measured through the HPLC technique also present in the tabular as well as graphical chart form.

DOI: https://doi.org/10.54393/pjhs.v5i11.2473

RESULTS

This study included 108 outdoor patients. Among them 62 (57.4%) were male and 46 (42.6%) were female (Table 1).

Table 1: Gender Distribution Table (n=108)

Gender of Patients	Frequency (%)
Male	62 (57.4%)
Female	46 (42.6%)
Total	108 (100%)

According to the data, the age of patients is divided into 6 groups and the mean age of 25 years. 1-10 years, 11-20 years, 21-30 years, 31-40 years, 41-50 years and 51-60 years. There were 8 (7.4%) patients with age 1-10 years, 17 (15.7%) patients with age 11-20 years, 57 (52.8%) patients with age 21-30 years, 18 (16.8%) patients with age 31-40 years, 5 (4.6%) patients with age 41-50 years and 3 (2.7%) patients with age 51-60 years (Table 2).

Table 2: Distribution of Patients by Age (n=108)

Age of Patients	Frequency (%)
1-10	8 (7.4%)
11-20	17 (15.7%)
21-30	57 (52.8%)
31-40	18 (16.8%)
41-50	5 (4.6%)
51-60	3 (2.7%)
Total	108 (100%)

Table 3 categorizes patients based on their Mean Corpuscular Volume (MCV) values, reflecting the average size of red blood cells. Among the 108 patients, the largest group (45, 41.7%) had MCV values between 65–75 fL. This was followed by 33 patients (30.6%) with MCV values in the 75–80 fL range, representing borderline low levels. The smallest group (30, 27.8%) had MCV values below 65 fL, consistent with suggestive of severe microcytosis with combined iron deficiency. These findings highlight the predominance of low MCV values in the study population, aligning with the inclusion criteria focused on identifying the β-thalassemia trait. Results present the distribution of patients based on their Mean Corpuscular Hemoglobin (MCH) levels, which indicate the average Hb content per red blood cell. The majority (50, 46.3%) exhibited MCH values in the borderline low values range of 25–27 pg, while 40 patients (37.0%) had MCH levels below 25 pg which suggested the combined iron deficiency or any microcytic cause. A smaller proportion (18, 16.7%) had MCH values between 27–29 pg which is borderline normal. The predominance of low and borderline-normal MCH levels (less than 29 pg) supports the focus on diagnosing conditions like β-thalassemia trait. Results classify patients based on their red blood cell (RBC) count, an important parameter in diagnosing hematological disorders. Over half of the patients (60, 55.6%) had RBC counts between 5.5–6.5×10^6/µL, reflecting the characteristic erythrocytosis seen in β-thalassemia carriers. A significant minority (28, 25.9%) exhibited RBC counts above 6.5×10^6/µL, while 20 patients (18.5%) had RBC counts of exactly 5.5×10^6/µL. These results emphasize the diagnostic value of elevated RBC counts in identifying β-thalassemia carriers. Results summarize the distribution of patients based on their Hb A2 levels, a key diagnostic parameter for identifying β-thalassemia trait. Among the 108 patients, the majority (68, 62.9%) had Hb A2 levels greater than 3.5%, which is diagnostic of the β-thalassemia trait. Elevated Hb A2 levels are a hallmark of this condition, as they result from reduced beta-globin chain production and increased delta-globin chain compensation. A significant proportion (29, 26.9%) exhibited Hb A2 levels in the range of 2–3%. These levels are considered within the normal range. A smaller subset of patients (11, 10.2%) had HbA2 levels below 2% (Table 3).

Table 3: Biochemical characteristics of the study participants

Mean Corpuscular Volume (MCV) fL	
Unit (fL)	**Frequency (%)**
<65	30 (27.8%)
65–75	45 (41.7%)
75–80	33 (30.6%)
Total	108 (100%)
Mean Corpuscular Hemoglobin (MCH) pg	
Unit (pg)	**Frequency (%)**
<25	40 (37.0%)
25–27	50 (46.3%)
27–29	18 (16.7%)
Total	108 (100%)
Red Blood Cell Count (RBC count) 10^6/µL	
Unit (10^6/µL)	**Frequency (%)**
≤ 5.5	20 (18.5%)
5.5–6.5	60 (55.6%)
> 6.5	28 (25.9%)
Total	108 (100%)
According to the Results of Hb A2	
Hb A2 (%)	**Frequency (100%)**
>3.5%	68 (62.9%)
2-3%	29 (26.9%)
<2%	11 (10.2%)
Total	108 (100%)

Further study presents the results of the screening for β-thalassemia trait in the study population of 108 patients which are based on the HbA2 results which are measured by Hb Electrophoresis. Among the participants, 68 patients (62.9%) were screened out for the β-thalassemia trait. This group represents those who also exhibited the characteristic hematological and genetic markers for the trait, including elevated Hb A2 levels, low levels of MCV and MCH, and increased red blood cell count. These findings

DOI: https://doi.org/10.54393/pjhs.v5i11.2473

confirm the presence of the β-thalassemia trait. And 40 patients (37.1%) did not show evidence of the β-thalassemia trait due to normal levels of Hb A2 either their CBC meets the suggestive line (Table 4).

Table 4: Suggestive of Beta Thalassemia Trait (n=108)

According to the Results of Hb A2	Frequency (%)
Detected	68 (62.9%)
Not Detected	40 (37.1%)
Total	108 (100 %)

DISCUSSION

The objective of this study was to assess the occurrence rate of the β-thalassemia trait based on abnormalities in complete blood count (CBC) parameters among patients in a tertiary care hospital. The findings of this study highlight the CBC parameters also give us an idea of the suggestive carrier of Thalassemia, so according to our we see a significant association between CBC parameters, such as mean corpuscular volume (MCV), mean corpuscular Hb, red blood cell (RBC) count, and HbA2 levels, in the detection of β-thalassemia trait. In total, 108 outdoor patients were included in this study. The gender distribution revealed that 57.4% of the participants were male, while 42.6% were female. The study's age distribution showed that the majority of patients fell within the 21-30-year age range, which constituted 52.8% of the sample. This finding is consistent with previous studies, which have shown that thalassemia traits are often detected in young adults, typically between the ages of 20 and 30 years, due to routine screening or clinical symptoms appearing in this age group [18, 19]. The mean corpuscular volume (MCV) and mean corpuscular Hb are critical hematological parameters used in the initial identification of microcytic anemia, a hallmark feature of the β-thalassemia trait. The majority of patients in this study had MCV values between 65–75 fL (41.7%) and MCH values between 25–27 pg (46.3%). These findings are consistent with typical characteristics of β-thalassemia carriers, where a decrease in MCV and MCH is commonly observed due to reduced Hb production and the presence of unpaired globin chains in the red blood cells [20]. Elevated RBC counts were also observed in the majority of patients, further suggesting erythrocytosis, which is often seen in individuals with thalassemia traits as the body compensates for reduced Hb production [21]. Hb electrophoresis, particularly through high-performance liquid chromatography (HPLC), plays a vital role in the definitive diagnosis of β-thalassemia trait. In this study, 62.9% of the participants exhibited HbA2 levels greater than 3.5%, which is diagnostic of the β-thalassemia trait. Elevated HbA2 levels are a key marker for β-thalassemia, as they result from the reduced production of beta-globin chains, leading to an increase in delta-globin chains [22]. This finding aligns with existing literature, which states that a HbA2 level above 3.5% is diagnostic of the β-thalassemia trait in the presence of suggestive hematological features, such as low MCV and MCH [23]. While 37.1% of the patients did not exhibit elevated HbA2 levels, their CBC parameters still met the criteria suggestive of the β-thalassemia trait. This discrepancy could be attributed to variations in genetic factors or the possibility of other factors influencing HbA2 levels, such as coexisting iron deficiency or other hemoglobinopathies. It highlights the importance of using multiple diagnostic tools, including Hb electrophoresis, to confirm the presence of the β-thalassemia trait [24]. This study found that 62.9% of the patients screened showed evidence of the β-thalassemia trait, which is consistent with global prevalence rates of β-thalassemia in populations with high carrier rates, such as those in the Mediterranean, Middle East, and South Asia regions, including Pakistan. A similar study conducted in a neighboring region found a prevalence of approximately 60% in the general population [25]. These results emphasize the need for widespread screening programs, especially in regions with a high frequency of thalassemia, to prevent the transmission of the disorder and reduce the burden of severe thalassemia.

CONCLUSIONS

It was concluded that this study demonstrates a high prevalence of the β-thalassemia trait among patients in a tertiary care hospital in Pakistan, with 62.9% of the participants showing elevated HbA2 levels, which were indicative of the trait. The findings underline the importance of CBC parameters, such as MCV, MCH, and RBC count, in the early detection of potential β-thalassemia carriers. The study also highlights the crucial role of Hb electrophoresis in confirming the diagnosis. These results can inform future research and the development of screening programs aimed at early identification and genetic counselling for thalassemia carriers in Pakistan.

Authors Contribution

Conceptualization: FAK
Methodology: UC, SN, RA
Formal analysis: KKR, AS
Writing review and editing: FAK, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v5i11.2473

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DOI: https://doi.org/10.54393/pjhs.v5i11.2532

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Prevalence of Hyperprolactinemia in Patients Undergoing Long-Term Proton Pump Inhibitor Therapy

Muhammad Zubair[1*], Javaria Amil[1], Sadia Noureen[1], Muhammad Ikram Ul Haq[1], Saddiqa Azmat[2] and Sadia Majeed[3]

[1]Department of Medicine, Niazi Medical and Dental College, Sargodha, Pakistan
[2]Department of Obstetrics and Gynaecology, Niazi Medical and Dental College, Sargodha, Pakistan
[3]Department of Pharmacology, Continental Medical College, Lahore, Pakistan

ARTICLE INFO

Keywords:
Long-Term Therapy, Proton Pump Inhibitors, Hyperprolactinemia, Prolactin

How to Cite:
Zubair, M., Amil, J., Noureen, S., Ikram Ul Haq, M., Azmat, S., & Majeed, S. (2024). Prevalence of Hyperprolactinemia in Patients Undergoing Long-Term Proton Pump Inhibitor Therapy: Hyperprolactinemia in Patients Having Long-Term Proton Pump Inhibitor Therapy. *Pakistan Journal of Health Sciences*, 5(11). https://doi.org/10.54393/pjhs.v5i11.2532

***Corresponding Author:**
Muhammad Zubair
Department of Medicine, Niazi Medical and Dental College, Sargodha, Pakistan
dr_zubair201@yahoo.com

Received Date: 8th October, 2024
Acceptance Date: 23rd November, 2024
Published Date: 30th November, 2024

ABSTRACT

Proton pump inhibitors used to treat gastrointestinal disorders cause various threatening effects and lead to an increase in serum prolactin levels. **Objectives:** To evaluate serum prolactin and macroprolactin levels in long-term proton pump inhibitor therapy patients. **Method:** An observational cross-sectional study was done between February 2023 and June 2024, at Niazi Welfare Foundation Teaching Hospital, Sargodha after approval from the institutional review board. Patients of either gender using proton pump inhibitors for ≥3 months, alone or in combination with histamine 2 receptor antagonists or pro-kinetics were included to measure serum prolactin levels. A duration of >3 months was taken as long-term therapy to see the impact on prolactin levels. The data were analyzed using SPSS version 25.0. **Results:** Out of the 166 patients, 102 (61.4%) were female, and 64 (38.6%) were male. The patient's mean age was 42.6 ± 14.3 years, and serum prolactin level was 23.2ng/mL. Among the participants, 97 (58.4%) had normoprolactinemia, while 69 (41.6%) had hyperprolactinemia. A significant increase in hyperprolactinemia with longer proton pump inhibitor treatment duration was revealed. **Conclusions:** It was concluded that prolonged use of proton pump inhibitors has the potential to raise serum prolactin levels, highlighting the importance of thorough evaluation for optimal clinical management.

INTRODUCTION

Proton pump inhibitors (PPIs) are frequently prescribed drugs, widely used to treat a variety of gastrointestinal (GI) problems like dyspepsia, peptic ulcer disease, gastroesophageal reflux disease (GERD), H. pylori eradication, and other disorders including Zollinger-Ellison syndrome. Over the past two decades, PPI usage has significantly risen due to their superior acid-suppressive effects [1, 2]. Combining PPIs with histamine 2 receptor antagonists (H2RAs) has shown greater benefits compared to using PPIs alone [3]. Additionally, PPIs are often paired with pro-kinetics in clinical practice, and this combination has proven effective in numerous studies [4]. Research studies have highlighted several threatening effects potentially linked to prolonged PPI use including risk of bone fractures, deficiencies in vitamin B12, and calcium, kidney disorders, a higher incidence of pneumonia, dementia, and cardiac events [5, 6]. Hyperprolactinemia can be classified as physiological, pathological, and pharmacological. Physiological hyperprolactinemia occurs due to natural processes such as pregnancy and stress, while pathological hyperprolactinemia is caused by hypothalamic-pituitary disorders, including tumors. The pharmacological form is triggered by medications like antipsychotics [7, 8]. In women, elevated prolactin levels can lead to symptoms such as infertility, painful intercourse, reduced libido, irregular menstrual cycles, oligo-menorrhea, amenorrhea, galactorrhea, and lower bone density. In men, hyperprolactinemia may result in

DOI: https://doi.org/10.54393/pjhs.v5i11.2532

erectile dysfunction, reduced sex drive, infertility, osteoporosis and weight gain. Additionally, results in galactorrhea and gynecomastia [9, 10]. PPI therapy's impact on endocrine hormones especially prolactin has been explored in various studies [11]. Many of these studies have found minimal or no effects on prolactin with short-term PPI use [12]. Some case studies noted a link of PPIs in causing hyperprolactinemia. These cases indicate that PPIs, whether used alone or in combination with pro-kinetics, can lead to varying increases in serum prolactin levels [13]. Studies have indicated an association of sexual and reproductive issues including gynecomastia with lansoprazole and omeprazole usage [14]. Moreover, there is a lack of studies on hormonal profiling with long-term PPI use, highlighting the need for such screening. Most research on the short-term effects of PPIs on endocrine hormones has focused primarily on male subjects. There is also a notable gap in information regarding long-term PPI use and hormonal issues in females. This underscores the necessity for studies that include both males and females to assess any gender-specific changes in biochemical hormonal profiles. Many medications, including PPIs, have been known to affect serum prolactin levels. Several studies conducted in tertiary care hospitals have identified PPIs as a common cause of drug-induced hyperprolactinemia [15, 16]. Proton pump inhibitors (PPIs) are frequently prescribed drugs, used to treat a variety of gastrointestinal (GI) problems. Although, PPIs are safe drugs research shows potential endocrine effects, particularly on prolactin levels. PPI usage is linked to raising serum prolactin levels by altering the gastric PH and affecting the dopamine bioavailability which has a role in inhibiting prolactin secretion. Drug-induced hyperprolactinemia leads to multiple comorbidities such as infertility, reduced libido, irregular menstrual cycles, oligo-menorrhea, amenorrhea, galactorrhea, and erectile dysfunction and impacts patients' quality of life. So, it's crucial to investigate the ill effects of PPI usage. However, the impact of long-term PPI use on serum prolactin levels has not been thoroughly investigated.

This study aimed to address this gap in the literature by evaluating serum prolactin and macroprolactin levels in patients of both genders undergoing long-term PPI therapy. It is imperative to understand the mechanism contributing to multiple ailments in the clinical area. This study will help clinicians in the early identification and management of complications associated with long-term PPI therapy.

METHODS

An observational cross-sectional study was done between February 2023 and June 2024, involving patients from the gastroenterology outpatient clinics at Niazi Welfare Foundation Teaching Hospital, Sargodha. The study was conducted after approval from the institutional review board documented with Ref No. IRB/NM&DC/173 and IRB No. NM&DC-IRB-64. The sample size was calculated using the Cochrane formula n=Z2 P(1-P)/d2 on open Epi software [17] based on 42% prevalence from a recent research study [14] employing a statistical power of 80% with 7% margin of error. The samples were gathered using a non-probability sampling technique. Participants included were # of either gender who had been using PPIs for ≥3 months, either alone or in combination with H2RAs or pro-kinetics to treat a variety of gastrointestinal (GI) problems like dyspepsia, peptic ulcer disease, gastroesophageal reflux disease (GERD), H. pylori eradication, and other disorders including Zollinger-Ellison syndrome. Those who consented to participate were enrolled after providing informed consent. Exclusion criteria included patients using PPIs for depression, renal diseases, hypertension, diabetes, or thyroid disorders, patients with pituitary tumors, pregnant women, and those taking PPIs along with medications other than H2RAs or pro-kinetics. A physical examination was conducted on all subjects, and relevant data were extracted from their medical records. Additional data were collected individually regarding socio-demographic characteristics, medical history, and PPI usage. Serum prolactin levels were measured for all enrolled patients at a single time point after 3 months of PPI therapy. All participants were regular PPI users. A 5ml blood sample was collected from each participant [18]. The standard reference range for serum prolactin in Pakistani male is reported to be 3-15 ng/ml, and in female, 4-25 ng/ml [19]. The institutional laboratory established a normal serum prolactin range of 2.3-18 ng/ml for male and 3.6-25 ng/ml for female. For the current study, serum prolactin levels of 100 ng/ml were considered a marked increase. Additionally, the cut-off for female was set at >25 ng/ml, while for male it was >18 ng/ml. The quantitative measurement of prolactin in human serum was performed using an enzyme-linked immunosorbent assay (ELISA) kit (Calbiotech, Inc., 1935 Cordell Ct, Cajon, CA 92020, US) following the manufacturer's protocol. Initially, direct serum samples were used to screen prolactin levels. Macro-prolactinemia screening was carried out using the polyethene glycol (PEG) precipitation method [20]. All serum samples were treated with an equal volume of 25% PEG solution (PEG 6000, ROTIPURAN® Ph.Eur., Carl Roth GmbH, Germany, w/v). The mixture was vortexed and then centrifuged at 3000 rpm for 15 minutes. The supernatants were subsequently analyzed for prolactin levels. The outcomes of the direct serum prolactin test referred to as total prolactin, and the post-PEG treatment assay, referred to as free prolactin, were compared as a percentage. Patients were classified as having macro-pro-lactinemia if their prolactin recovery after PEG treatment was 40% or less of the original value [21]. The data were analyzed using SPSS

DOI: https://doi.org/10.54393/pjhs.v5i11.2532

version 25.0. Continuous variables were expressed as mean and SD, while frequencies and percentages were calculated for categorical variables. Statistical analysis involved an independent t-test and Fisher's exact test. Univariate and multivariate logistic regression analysis for odds ratios (OR) at 95% confidence intervals (CI) were performed. A p-value of <0.05 was considered significant.

RESULTS

Out of the 166 patients, 102 (61.4%) were female, and 64 (38.6%) were male. The patient's mean age was 42.6 ± 14.3 years, and serum prolactin level was 23.2ng/mL. Among the participants, 97 (58.4%) had normo-prolactinemia, while 69 (41.6%) had hyperprolactinemia. Among the patients, 20 (12%) were receiving combination therapy, while the remaining were on PPI monotherapy. There were no significant differences between hyperprolactinemic and normoprolactinemic patients regarding age, gender, or body mass index (p>0.05). The majority of participants, 150 (90.36%), were married. However, a significant difference (p=0.02) was observed between the groups in terms of mean treatment duration. Independent t-test and Fisher's exact test analysis revealed significant associations in the demographic variables of participants (Table 1).

Table 1: Demographics of Normo-Prolactinemic and Hyper-Prolactinemic Participants

Characteristics	Normo-prolactinomas 97	Hyper-prolactinemic 69	p-value
Mean Age (years)	42.13 ± 13.9	42.9 ± 14.6	0.725
Mean Treatment Duration (Months)	25.2 ± 25.3	37.73 ± 37.1	0.002
Mean BMI (kg/m2	24.7 ± 3.7	24.5 ± 3.9	0.654
Gender			
Male	35	30	0.425
Female	61	40	
Other Characteristics			
Smoking	2 (1.20)	4 (2.41)	0.241
Smokeless Tobacco	19 (11.4)	10 (6.02)	0.412
Exercise	13 (7.8)	14 (8.4)	0.292
Working Women	5 (4.9)	4 (3.9)	0.656
Housewife	13 (7.8)	14 (8.4)	0.292
Menstruating Women	5 (4.9)	4 (3.9)	0.656

An increase in mean serum prolactin levels beyond the normal cut-off range was observed in female patients compared to male patients. The overall prevalence of hyperprolactinemia was 42%, with 24% (40 patients) in female and 18% (30 patients) in male (Figure 1).

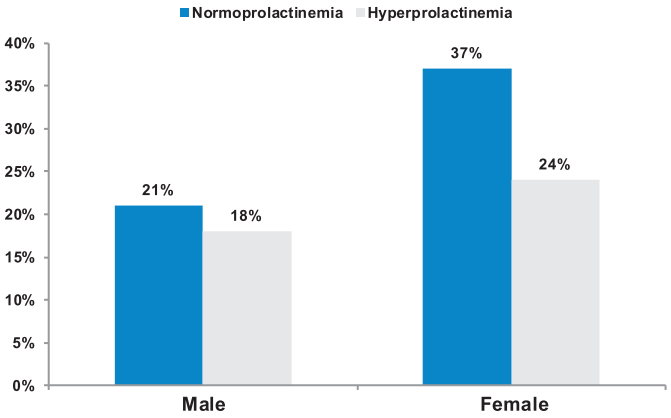

Figure 1: Prolactin Levels in Female and Male with Normoprolactinemia and Hyperprolactinemia

A high incidence of significantly elevated serum prolactin levels was observed in female patients. Macro-prolactinemia was detected in 21 (12.7%) patients, of whom 15 (9.1%) were female. Additionally, 49 (29.5%) patients had true hyperprolactinemia, with 25 (15%) being female (Figure 2).

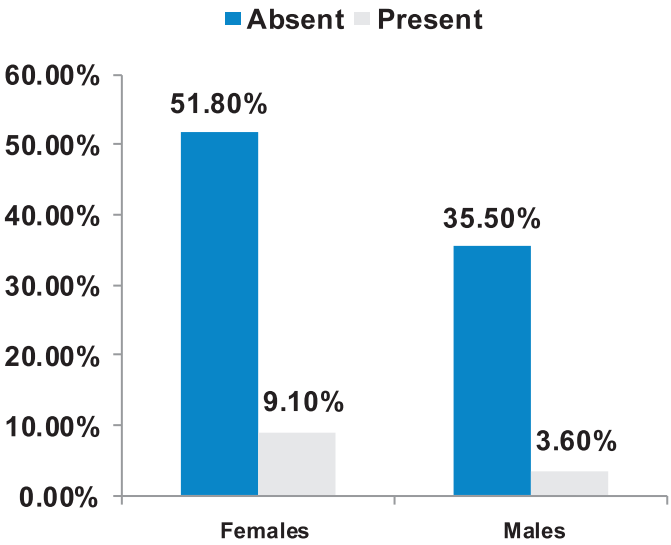

Figure 2: Frequency of Macroprolactinoma in Male and Female Using Long-Term PPIS

The mean serum prolactin level in the PPI monotherapy group was 30.7 ± 27.2 ng/mL, whereas, in the combination therapy group (PPI + pro-kinetics), it was 62.8 ± 41.02 ng/mL. Independent sample T-test shows that difference in prolactin levels between the PPI monotherapy group and the combination therapy group was statistically significant (p<0.05) (Table 2).

Table 2: Comparison of Mean Serum Prolactin Levels among Patients Using Proton Pump Inhibitors (PPI) Monotherapy and Combination Therapy

Variable	PPI Monotherapy (m + SD)	Combination Therapy (m + SD)	p-value
Prolactin Levels (ng/mL)	30.7 ± 27.2	62.8 ± 41.02	0.001

DOI: https://doi.org/10.54393/pjhs.v5i11.2532

In univariate analysis, compared to 3-10 months of PPI use, various subgroups with longer treatment durations were at significantly higher risk of developing hyperprolactinemia. The risk was elevated for patients using PPIs for 11-20 months (OR: 5.3; 95% CI: 1.8-15.5; p=0.002), 21-30 months (OR: 2.6; 95% CI: 1.0-6.7; p=0.05), 31-40 months (OR: 3.1; 95% CI: 1.0-9.5; p=0.048), and more than 40 months (OR: 5.6; 95% CI: 2.1-14.5; p=0.001), indicating a significant increase in hyperprolactinemia with longer PPI treatment duration (Table 3).

Table 3: Logistic Regression Analysis of Various Demographic and Clinical Characteristics Concerning Hyperprolactinemia

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender				
Female	Reference			
Male	1.3 (0.7-2.5)	0.4	1.7 (0.8-3.9)	0.18
BMI (Per Unit Increase)	1.04	0.150	1.03	0.210
Age (Years)				
≤30	Reference			
31-50	1.1 (0.5-2.5)	0.8	1.4 (0.5-3.5)	0.51
>50	1.8 (0.7-4.4)	0.2	2.1 (0.7-6.2)	0.18
Duration of PPI Use (Months)				
3-10	Reference			
11-20	5.3 (1.8-15.5)	0.002	4.9 (1.6-15.2)	0.006
21-30	2.6 (1.0-6.7)	0.05	2.2 (0.8-6.1)	0.15
31-40	3.1 (1.0-9.5)	0.048	2.6 (0.8-8.9)	0.13
>40	5.6 (2.1-14.5)	<0.001	6.3 (2.2-17.9)	0.001
Tobacco Use				
Smoking	2.8 (0.5-16.0)	0.2	3.2 (0.4-23.8)	0.25
Smokeless Tobacco	0.7 (0.3-1.6)	0.3	0.4 (0.1-1.0)	0.05
Clinical Characteristics				
Combination Therapy	6.2 (1.9-19.9)	0.002	4.6 (1.3-16.1)	0.01

DISCUSSION

This study was the first to find serum prolactin values in long-term PPI users. In both genders, mean serum prolactin levels were found to be elevated beyond their respective normal ranges. These findings suggest that long-term PPI use may be associated with increased serum prolactin levels. Similarly, medication-induced elevations in serum prolactin have been reported to varying degrees in other studies. In various case reports, elevated serum prolactin levels after PPI treatment have been reported to range from 32.9 ng/mL to 288 ng/mL [13]. In a recent study, the basal prolactin level was observed at 132 ± 68.7 ng/mL, and after discontinuing the medication, it decreased to 16.9±8.2 ng/mL. PPIs and pro-kinetics were identified as the primary contributors to hyperprolactinemia in 71.8% of the cases [15]. The exact mechanism by which PPIs raise serum prolactin remains unclear, and not all studies have depicted a significant relationship between PPI use and increased prolactin levels. The current study suggests that central stimulation may play a role in excessive prolactin secretion. Additionally, PPIs might interfere with prolactin clearance or excretion, contributing to higher serum prolactin levels. There were more cases of hyperprolactinemia among patients using PPIs for ≥3 months, whether alone or in combination with other medications. The prevalence observed in this study aligns with earlier findings [15]. However, comparing the results of this study with other research on drug-induced hyperprolactinemia is challenging for several reasons. Firstly, there is considerable variability in the cut-off points used to define hyperprolactinemia across different studies, which complicates direct comparisons. In this study, a cut-off point of >25 ng/mL for females and >18 ng/mL for males was used, which are commonly applied thresholds in hyperprolactinemia studies conducted in Pakistan [23, 24]. Secondly, different drugs vary in their potential to elevate serum prolactin levels, making direct comparisons challenging. This study is the first specifically designed to assess hyperprolactinemia in long-term PPI users, adding unique insights to the existing literature on drug-induced prolactin elevations. In the current study, 30% of patients were found to have macroprolactinemia, while 70% had true hyperprolactinemia among the total hyperprolactinemic patients, with no significant gender-specific variation. These findings are consistent with previous studies reporting a prevalence of 10-45% [22-24]. However, this study is the first to specifically screen for both macro-prolactin and monomeric prolactin in long-term PPI users, providing novel insights into the effects of prolonged PPI use on prolactin levels. The current study compared the mean serum prolactin levels between patients using PPI alone and those using it in combination with other medications. It was found that patients using PPI in combination may be more susceptible to elevated serum prolactin levels than those using PPI alone over a long-term duration. This observation was further supported by binary logistic regression analysis, which confirmed a higher likelihood of increased serum prolactin in individuals using combination therapy. These results reinforce previous findings, where the combination of PPIs and pro-kinetics accounted for 71.8% of all drug-induced hyperprolactinemia cases [15]. Understanding the impact of combination therapy on serum prolactin levels is crucial for a thorough evaluation of the potential hyperprolactinemic effects linked to long-term PPI use. This comprehensive approach helps clarify the increased risk associated with combination therapy compared to PPI monotherapy. In the current cross-sectional study, the majority of participants were using omeprazole and esomeprazole, with very few long-term users of other PPIs;

DOI: https://doi.org/10.54393/pjhs.v5i11.2532

notably, there were no users of rabeprazole. The low frequency of PPIs other than omeprazole and esomeprazole posed a limitation, preventing the study from adequately comparing mean serum prolactin levels among all PPI-treated groups. This necessitates the need for further research that includes a broader range of PPI medications to facilitate more comprehensive comparisons. The current study found no associations between various demographic variables—such as age, gender, body mass index (BMI), marital status, smoking, use of smokeless tobacco, exercise, employment status, and being a housewife when comparing normal prolactin and hyperprolactinemic groups. This suggests that none of these factors are likely to contribute to increases in serum prolactin levels.

CONCLUSIONS

It was concluded that a significant number of patients were found to have hyperprolactinemia, which was closely associated with the long-term use of PPIs. It is imperative to understand the mechanism contributing to multiple ailments in the clinical area. This study will help clinicians in the early identification and management of complications associated with long-term PPI therapy. Additionally, the duration of PPI use had a more pronounced effect on prolactin levels in male patients compared to female patients.

Authors Contribution

Conceptualization: MZ
Methodology: MZ, SN, SA, MIUH
Formal analysis: JA
Writing review and editing: SN, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2055

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Evaluating Patient Experiences and Perceptions in the Diagnosis and Management of Dentine Hypersensitivity: A Cross-Sectional Study

Tayyaba Nayab[1*], Ammara Chaudhry[1], Muhammad Saad Shaikh[2], Sana Ikram[3], Nimra Meraj[4] and Rabia Ijaz[4]

[1]Department of Oral Biology, The University of Lahore, Lahore, Pakistan
[2]Department of Oral Biology, Jinnah Sindh Medical University, Karachi, Pakistan
[3]Department of Oral Biology, Shahida Islam Medical Complex, Lodhran, Pakistan
[4]The University of Lahore, Lahore, Pakistan

ARTICLE INFO

Keywords:
Dentine Hypersensitivity, Quality of Life, Diagnostic Techniques, Therapy Approaches, Patient Perceptions

How to Cite:
Nayab, T., Chaudhry, A., Shaikh, M. S., Ikram, S., Meraj, N., & Ijaz, R. (2024). Evaluating Patient Experiences and Perceptions in the Diagnosis and Management of Dentine Hypersensitivity: A Cross-Sectional Study: Patient Experiences in Dentine Hypersensitivity Management. Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.2055

Corresponding Author:
Tayyaba Nayab
Department of Oral Biology, The University of Lahore, Lahore, Pakistan
tayyaba.nayab@ucd.uol.edu.pk

Received Date: 25th September, 2024
Acceptance Date: 21st November, 2024
Published Date: 30th November, 2024

ABSTRACT

Dentine Hypersensitivity (DH), or sensitive teeth, was a dental pain caused by exposure of dentinal tubules. Understanding patients' experiences and perceptions was crucial for developing effective diagnostic and treatment plans. **Objective:** To investigate the patients' experiences, perceptions, and diagnostic techniques for DH. The research also addresses the therapy approaches to limit dentine hypersensitivity for the better quality of life in patients. **Methods:** A non-probability convenience sampling technique was used to conduct the study for three months, from April 2024 to June 2024, in the University of Lahore's dental hospital and private dental clinics in Lahore. A close-ended questionnaire consisting of 20 items was used for data collection. The relationship between DH, gender, and other variables was examined using a chi-square test; P-value < 0.05 was considered statistically significant. **Results:** The study with 1105 participants found a slightly higher representation of females (51%) than males (49%), with both genders reporting similar rates of tooth pain during food consumption. DH was most prevalent in the 41-60 age group (33.8%), with 74% experiencing pain with certain foods, 88% not receiving professional treatment, and 99% acknowledging DH's significant impact on their quality of life. **Conclusions:** This study highlighted the significant prevalence of DH among adults, substantially impacting their quality of life. The findings emphasize the need for increased awareness, better diagnostic strategies, and patient-centred treatments to manage this condition effectively.

INTRODUCTION

Dentine Hypersensitivity (DH) is a prevalent oral health issue that significantly impacts a large number of people worldwide. DH affects 10%-30% of the global population, affecting 71% of adults. Studies conducted in Europe demonstrated that DH affected 42% of young adults. It is a painful condition, with 30% of adults in the United States experiencing it. Research shows DH is more prevalent among adults, with rates ranging from 25% to 40%. In Pakistan, DH epidemiology has been studied infrequently, with a 22% prevalence reported in Lahore and 36.4% in Karachi [1-3]. One of the major symptoms of DH is intense pain in response to stimuli such as hot, cold, sweet, and acidic foods, or brushing and flossing. This pain is sudden, fleeting, and can be quite uncomfortable. DH is more than just pain; it can interfere with daily activities such as eating, drinking, and maintaining dental hygiene, resulting in decreased quality of life [4]. The hydrodynamic theory suggests that external stimuli like temperature changes or mechanical forces stimulate the pulp-dentine interface's nerve terminals, causing a pain response. Dentinal tubule size, density, and patency affect fluid movement and pain. Extended exposure can make dentine nerve endings more sensitive, exacerbating pain perception. Different inflammatory mediators like prostaglandins, bradykinin,

DOI: https://doi.org/10.54393/pjhs.v5i11.2055

and histamine are generated, causing vasodilation, increased vascular permeability, and nerve fiber sensitization, intensifying pain perception and transmission [5, 6]. To manage DH, both non-invasive and invasive methods are used to obstruct dentinal tubules, desensitize nerve endings, and address underlying etiological causes. Research has indicated that there are several methods to strengthen enamel and reduce DH, such as desensitizing toothpaste, fluoride therapy, dental sealants, oxalate-based products, laser therapy, and Amorphous Calcium Phosphate (ACP) products [7, 8]. For tooth sensitivity, initial treatments often include over-the-counter desensitizing toothpastes that contain ingredients like potassium nitrate or stannous fluoride. For cases that don't respond to these methods, in-office treatments such as laser therapy, resin-based sealants, amorphous calcium phosphate products, and professional fluoride applications may be considered [9]. Additionally, lifestyle and behavioral changes, such as educating patients on proper oral hygiene, avoiding acidic foods and drinks, quitting smoking, and managing conditions like bruxism or gastroesophageal reflux disease, can aid in the long-term management of hypersensitivity. Customized treatment plans should be tailored to each patient's specific needs and preferences, with regular follow-up appointments to evaluate the effectiveness of the treatment and make any necessary adjustments [10]. Research has shown that DH can lead to a range of emotional responses, including anxiety, avoidance behaviors, irritation, and shame. These reactions can significantly affect a patient's psychological well-being, resulting in dietary changes, avoidance of certain foods and beverages, and withdrawal from social situations due to the fear of sharp pain episodes. Therefore, providing patient-centered care is crucial. For effective long-term management of dental hypersensitivity, it is important to educate patients about maintaining good oral hygiene and making lifestyle adjustments. Additionally, patient education should include guidance on the regular use of desensitizing products and the importance of regular dental check-ups for ongoing management and monitoring [11, 12]. Despite being a common issue, studies suggest that DH is often overlooked and improperly treated in clinical practice. Many individuals with DH may not seek medical attention because they believe their symptoms are just temporary sensitivity or an inevitable consequence of aging. The subjective nature of pain perception and the lack of established diagnostic standards further complicate the diagnosis and treatment of DH [13, 14]. Understanding patients' experiences and opinions on DH is crucial. By gaining insight into how this condition affects them, healthcare professionals can tailor their diagnostic and treatment approaches to better meet the needs and preferences of those with DH.

The study aimed to explore patient experiences, and perception of Dentin Hypersensitivity (DH), along with the diagnostic techniques and treatment approaches used. The goal is to better understand these aspects to guide future clinical procedures in addressing the complex issues associated with DH, ultimately reducing discomfort and improving patients' quality of life.

METHODS

A cross-sectional questionnaire-based study was conducted to evaluate the patient experiences and perceptions of DH. The adult patients presented with irritation, intraoral pain, or sensitivity in the individual dental clinics of Lahore, ranging in age from 25 to 65, were included in the study population without regard to gender. Patients with analgesics, mood alteration medications, teeth whitening agents in the last six months, orthodontic therapy, cognitive impairment, chronic pain conditions, fibromyalgia, and temporomandibular joint disorders were excluded. The Institutional Research and Ethics Committee provided ethical approval (ERC APPROVAL NO: UCD/ERCA/24/283). A non-probability convenience sampling technique was utilized to collect data from participants included in this research. A sample size of 1105 participants was calculated with a 90% confidence level, 2.6% margin of error, and by taking the expected percentage of DH and 26.4% respectively. A pre-validated self-administered questionnaire was used [15]. There were 20 items to the questionnaire for evaluating patients' perceptions of DH and 2 for demographic information. Data were collected over three months, from April 2024 to June 2024. The questionnaire was distributed simultaneously through Google Forms and survey handouts. On the other hand, during these months, The Out-Patient Department (OPD) at the University of Lahore examined 3605 patients. The participants were informed about DH before answering, and consent was obtained voluntarily. The study's aim, the identity of the researchers, and the fact that the questionnaire would be only used for the participants' responses and e-mail addresses would be stored only for the study. Participants' identities were kept anonymous and questionnaire answers were kept private. SPSS version 25.0 was used for data entry and analysis. Qualitative variables were presented with frequency and percentages. A chi-square test was applied to see the association of experience and perception towards DH with the age and gender of study participants. P-value < 0.05 was considered statistically significant.

RESULTS

The study comprised 1105 participants, with a slightly higher representation of females (51%) than males (49%).

DOI: https://doi.org/10.54393/pjhs.v5i11.2055

Both genders affirmed experiencing pain in their teeth while consuming certain food items, with comparable prevalence rates observed among females (37.3%) and males (36.8%). Among the participants, 481 fell within the 25-40 years' age bracket, 497 were aged 41-60 years, and 127 reported being over 60 years old. The age distribution revealed a higher prevalence of DH in the 41-60 age group (33.8%), followed by the 25-40 age group (31.8%), with a sharp decline in the over-60 age group (8.6%) (Figure 1).

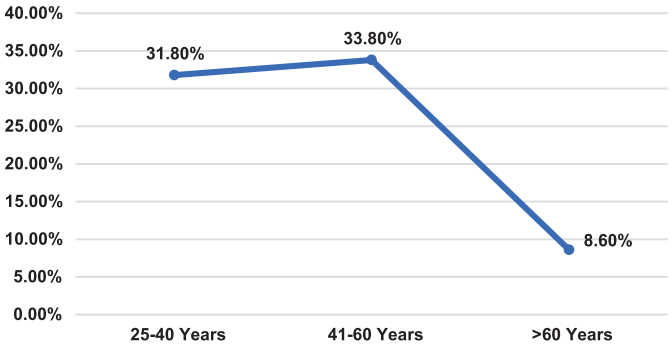

Figure 1: The Onset of Dentine Hypersensitivity in Different Age Groups

Out of the surveyed patients, 74% reported pain in teeth with certain food consumption. Additionally, 79% of the participants expressed concerns about sensitivity in teeth. 58% of the participants rejected the notion that the tooth's length continues to increase. A significant portion, 88% had not received any professional treatment for hypersensitivity, and 75% reported not using any agent for dentine sensitivity. However, 86% of patients also reported dissatisfaction with the agents they were currently using (Table 1).

Table 1: Patient Distribution Based on their Exposure to Hypersensitivity

Distribution of Patients	Responses	N (%)
Pain in Teeth During Consumption of Certain Food Items	Yes	819 (74.1%)
	No	286 (25.9%)
Concerned About Teeth Sensitivity	Yes	876 (79.3%)
	No	229 (20.7%)
The Length of the Tooth Goes on Increasing	Yes	400 (36.19%)
	No	641 (58%)
	Don't Know	64 (5.8%)
Professional Treatment for Hypersensitivity	Yes	132 (11.94%)
	No	973 (88.05%)
Use any Agent for Dentine Hypersensitivity	Yes	268 (24.3%)
	No	837 (75.7%)
Satisfied with the Agents Used	Yes	155 (14.02%)
	No	950 (85.97%)

In response to inquiries regarding the causes of hypersensitivity, 53% of participants reported decayed teeth as a cause, while 47% of participants were unaware of oral prophylaxis as a cause. Notably, 87% of respondents identified improper oral hygiene practices as a contributing factor, and 72% expressed skepticism regarding the impact of climate change. Stress was refuted as a causative factor by 42% of participants. A significant majority (93%) concurred with defective dental treatments as a primary cause. Moreover, a substantial proportion (91%) of participants recognized age as a significant factor predisposing individuals to hypersensitivity (Table 2).

Table 2: Patient Distribution According to their Perception of the Causes for Hypersensitivity

Distribution of Patients	Responses	N (%)
A Decayed Tooth is a Reason for Hypersensitivity	Yes	589 (53.3%)
	No	513 (46.4%)
	Don't Know	3 (0.27%)
Hypersensitivity is Caused due to Oral Prophylaxis	Yes	160 (14.5%)
	No	419 (37.9%)
	Don't Know	526 (47.6%)
Improper Hygiene Causes Dentine Hypersensitivity	Yes	961 (87%)
	No	144 (13%)
Impact on Exposure to Climate Change	Yes	235 (21.3%)
	No	797 (72.1%)
	Don't Know	73 (6.6%)
Stress Causes Tooth Abnormalities that lead to Hypersensitivity	Yes	379 (34.29%)
	No	459 (41.5%)
	Don't Know	267 (24.2%)
Kind of Defective Treatment Leads to Hypersensitivity	Yes	1030 (93.2%)
	No	6 (0.5%)
	Don't Know	69 (6.2%)
Age is a Factor in Hypersensitivity	Yes	1006 (91%)
	No	97 (8.8%)
	Don't Know	2 (0.2%)

72% of patients attributed their condition to harmful habits, while 63% reported concurrent gastritis. Nearly all participants (99%) had not undergone any tooth bleaching procedures, and a significant majority (92%) had no history of systemic diseases or medication use. Virtually all respondents (99%) acknowledged DH's profound impact on their quality of life. Additionally, 78% of participants noted a noticeable improvement in sensitivity following professional treatment interventions (Table 3).

Table 3: Patient Distribution Based on their Perceptions of the Variables Affecting Hypersensitivity

Distribution of Patients	Responses	N (%)
Any Deleterious Habits cause Hypersensitivity	Yes	803 (72.7%)
	No	162 (14.7%)
	Don't Know	140 (12.7%)
Have Acidity or Gastritis	Yes	691 (62.5%)
	No	414 (37.5%)
Recently Undergone a Tooth Bleaching Procedure	Yes	9 (0.8%)
	No	1096 (99.2%)

DOI: https://doi.org/10.54393/pjhs.v5i11.2055

Any Systemic Disease	Yes	92 (8.3%)
	No	1013 (91.7%)
Use of Long-Term Medications	Yes	90 (8.1%)
	No	1015 (91.9%)
Sensitivity Problems affect the Quality of Life	Yes	1099 (99.5%)
	No	7 (0.63%)
Improvement in Sensitivity following Professional Treatment	Yes	862 (78%)
	No	142 (12.9%)
	Don't Know	101 (9.1%)

The chi-square test results indicated a strong statistical significance in the variation of patient distribution related to their views on the factors impacting DH, with a ($P < 0.05$). The results indicated that females generally expressed greater concern about dentinal hypersensitivity, reported higher rates of professional treatment, and demonstrated greater satisfaction with treatment compared to males (Table 4). In contrast, the analysis of dentinal hypersensitivity across age groups revealed no significant differences in perceptions and experiences. Notably, younger and middle-aged individuals were more likely to identify decayed teeth as a contributing factor, and nearly all respondents, regardless of age, acknowledged that sensitivity issues affected their quality of life.

Table 4: Association of Patients' Experience and Perception towards Dentinal Hypersensitivity with Gender

Variables	Responses	Male N (%)	Female N (%)	p-Value
Pain in Teeth during Consumption of Certain Food Items	Yes	405 (73.9%)	410 (74.4%)	0.848
	No	143 (26.1%)	141 (25.6%)	
Concerned about Teeth Sensitivity	Yes	394 (71.9%)	477 (86.6%)	<0.001
	No	154 (28.1%)	74 (13.4%)	
Length of the Tooth goes On Increasing	Yes	162 (29.6%)	236 (42.8%)	<0.001
	No	322 (58.8%)	315 (57.2%)	
	Don't Know	64 (11.7%)	0 (0.0%)	
Professional Treatment for Hypersensitivity	Yes	38 (6.9%)	91 (16.5%)	<0.001
	No	510 (93.1%)	460 (83.5%)	
Use any Agent for Dentinal Hypersensitivity	Yes	172 (31.4%)	95 (17.2%)	<0.001
	No	376 (68.6%)	456 (82.8%)	
Satisfied with the Agents used	Yes	10 (1.8%)	144 (26.1%)	<0.001
	No	538 (98.2%)	407 (73.9%)	
Decayed Tooth is a Reason for Hypersensitivity	Yes	266 (48.5%)	319 (57.9%)	0.002
	No	279 (50.9%)	232 (42.1%)	
	Don't Know	3 (0.5%)	0 (0.0%)	
Hypersensitivity is Caused due to Oral Prophylaxis	Yes	9 (1.6%)	151 (27.4%)	<0.001
	No	230 (42.0%)	188 (34.1%)	
	Don't Know	309 (56.4%)	212 (38.5%)	
Improper Hygiene cause Dentinal Hypersensitivity	Yes	548 (100.0%)	407 (73.9%)	<0.001
	No	0 (0.0%)	144 (26.1%)	
Impact on Exposure to Climate Change	Yes	77 (14.1%)	156 (28.3%)	<0.001
	No	471 (85.9%)	322 (58.4%)	
	Don't Know	0 (0.0%)	73 (13.2%)	
Stress causes Tooth Abnormalities that Lead to Hypersensitivity	Yes	149 (27.2%)	228 (41.4%)	<0.001
	No	228 (41.6%)	230 (41.7%)	
	Don't Know	171 (31.2%)	93 (16.9%)	
Kind of Defective Treatment Leads to Hypersensitivity	Yes	478 (87.2%)	546 (99.1%)	<0.001
	No	3 (0.5%)	3 (0.5%)	
	Don't Know	67 (12.2%)	2 (0.4%)	
Age is a Factor in Hypersensitivity	Yes	539 (98.4%)	461 (83.7%)	<0.001
	No	9 (1.6%)	88 (16.0%)	
	Don't Know	0 (0.0%)	2 (0.4%)	
Any Deleterious Habits cause Hypersensitivity	Yes	335 (61.1%)	462 (83.8%)	<0.001
	No	79 (14.4%)	83 (15.1%)	
	Don't Know	134 (24.5%)	6 (1.1%)	

DISCUSSION

DH was a condition where dentinal tubules were exposed due to factors like gingival recession, enamel erosion, abrasion, attrition, and tooth whitening. These can cause pain and gradual enamel and dentine loss, while tooth whitening can temporarily increase hypersensitivity. Understanding these factors was crucial for developing targeted diagnostic strategies, and clinical examinations were the foundation for diagnosing DH. Dental practitioners can effectively reduce the discomfort associated with DH and improve patients' oral health-related quality of life by combining cutting-edge diagnostic techniques, evidence-based therapies, and patient-centered education [16]. To guarantee that those impacted by this common ailment receive the best care possible, further research was required to investigate innovative therapy modalities and improve currently implemented treatment regimens. The study's findings revealed a substantial prevalence of DH among the surveyed patients, with 74% reporting experiencing symptoms and 80% of the participants were concerned about their sensitivity. Notably, this aligns with previous epidemiological studies, reinforcing DH's status as a substantial oral health concern [16]. The study showed females exhibited a higher prevalence than males which was consistent with the study conducted by Idon PI *et al* [17]. Such gender disparities could potentially be attributed to a myriad of factors including hormonal influences, differential oral hygiene practices, or even varying pain thresholds, warranting further exploration in subsequent studies. Moreover, these findings shed light on age-related trends in DH prevalence, with the mid-age demographic of 41-60 years displaying heightened sensitivity, followed by a decline in prevalence beyond the age of 60 years. These findings were consistent

DOI: https://doi.org/10.54393/pjhs.v5i11.2055

with a similar study by Nausheen N et al which showed a greater trend in 40–55-year-olds [18]. Such age-related variations may be attributable to factors including lifetime dentine deposition, subsequent pulp atrophy, or even tooth loss in later age groups. In the study, 58% of participants did not notice an increase in tooth length. However, 36% reported an increase, which may indicate a gingival recession. Hatipoğlu Ö *et al.*, highlighted gingival recession as a significant cause of dentin hypersensitivity. They noted that the loss of periodontal attachment at the root surface can expose dentin, leading to sensitivity. If left untreated, gingival recession can result in the deposition of secondary dentin, pulp atrophy, and potentially tooth loss, especially in older individuals [19]. Moreover, this study found that 88% of patients had not received any professional treatment for DH and were not using any products to manage the condition. This was similar to the findings of Mosquim V *et al.*, who reported that 80% of participants were not using any products for DH [11]. This lack of professional intervention and appropriate use of management products signifies a large gap in the treatment and awareness of DH. In this investigation, participants identified several recurrent factors contributing to DH, including dental caries, inadequate oral hygiene practices, faulty dental treatments, and the natural aging process. Interestingly, the participants discounted stress as a significant contributor to DH and expressed uncertainty regarding its association with changing weather. These discernments align closely with findings reported by TA AS *et al* [15]. When asked about the variables affecting DH, 72% of patients identified deleterious habits as a cause. This finding was consistent with Mosquim V *et al.*, who identified parafunctional habits such as abrasion and attrition as causes, linking hard tissue loss to dentine exposure [11, 18]. Furthermore, 63% of patients reported experiencing gastritis. While Arua et al., identified acids as a cause of DH, Hatipoğlu Ö *et al.*, found no significant association between DH and conditions such as reflux, vomiting, and consumption of acidic foods [18, 19]. The alignment of these findings with similar studies underscores the multifaceted nature of DH, where both mechanical habits and biological factors play a role. In this study, more than 90% of patients did not have any systemic disease, nor were they taking any medication for it. However, 99% accepted that DH was affecting their quality of life. These results were consistent with similar findings in the literature, emphasizing the significant impact of lifestyle and dietary habits on DH, as well as the profound effect this condition has on patients' daily lives [20, 15]. The high percentage of patients reporting a diminished quality of life highlights the need for greater awareness and better management strategies for DH. Limitations of the study, including its cross-sectional design and reliance on self-reported data, must be considered when interpreting the findings. Future research employing longitudinal approaches could assess the long-term efficacy of different management strategies and investigate factors influencing patient adherence and treatment outcomes.

CONCLUSIONS

In summary, it was critical to comprehend patients' experiences and perspectives on DH to deliver individualized care and maximize treatment results. To reduce patients' suffering and enhance the quality of their oral health, a multimodal diagnostic approach and evidence-based care techniques were essential.

Authors Contribution

Conceptualization: TN
Methodology: AC, SI
Formal analysis: SI, NM
Writing, review and editing: MSS, NM, RI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2426

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Umbilical Cord Coiling Index as A Marker of Perinatal Outcome

Sadiq Jan[1], Ayesha Qamar[2*], Muhammad Asif Javed[3], Seharish Zulfiqar[4], Sara Jamil[5] and Moizza Aziz[6]

[1]Department of Gynecology, Islamic International Medical College, Islamabad, Pakistan
[2]Department of Gynecology, Pakistan Aeronautical Complex Hospital Kamra, Pakistan
[3]Department of Radiology, Imran Idrees Teaching Hospital, Sialkot, Pakistan
[4]Department of Anatomy, Rai Medical College, Sargodha, Pakistan
[5]Department of Gynecology, Frontier Medical College, Abbottabad, Pakistan
[6]Department of Gynecology, Pakistan Air Force Hospital, Islamabad, Pakistan

ARTICLE INFO

Keywords:
Pregnancy, Umbilical Cord, Gestational Period, Diabetes

How to Cite:
Jan, S., Qamar, A., Javed, M. A., Zulfiqar, S., Jamil, S., & Aziz, M. (2024). Umbilical Cord Coiling Index as A Marker of Perinatal Outcome: Umbilical Cord Coiling Index for Perinatal Outcome. *Pakistan Journal of Health Sciences*, 5(11). https://doi.org/10.54393/pjhs.v5i11.2426

***Corresponding Author:**
Ayesha Qamar
Department of Gynecology, Pakistan Aeronautical Complex Hospital Kamra, Pakistan
ashley.virk90@gmail.com

Received Date: 7th October, 2024
Acceptance Date: 24th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Umbilical cord coiling patterns have a considerable effect on both pregnancy outcomes and fetal health. **Objectives:** To assess the postnatal umbilical coiling index and investigate its association with normal coiling, hypo-coiling, and hyper-coiling patterns about maternal and perinatal outcomes. **Methods:** This cross-sectional study was conducted at the Obstetrics and Gynecology Department of Pakistan Aeronautical Complex Hospital Kamra from January 2024 to June 2024. The patterns of umbilical cord coiling were analyzed in 200 Livebirths. This study utilized convenience sampling to select a sample of live births for assessing the relationship between the umbilical cord coiling index and perinatal outcomes. Data were collected on maternal factors and neonatal outcomes, including Apgar scores. Statistical analysis was conducted using SPSS version 26.0, with descriptive statistics to summarize the data and inferential tests (e.g., chi-square test, t-test, regression analysis) to evaluate associations between umbilical cord coiling patterns and perinatal outcomes. **Results:** The study revealed that hypo-coiled cords were linked to older maternal age (≥35 years) and higher gestational diabetes rates. Hypo-coiled infants had a low birth weight incidence of 28.6%, significantly lower coiling index (0.07 ± 0.02), and lower Apgar scores at one minute (6.8 ± 1.2) and five minutes (8.2 ± 0.9). These results suggest umbilical cord coiling patterns are crucial indicators of maternal health and neonatal outcomes, highlighting the need for careful monitoring in at-risk pregnancies. **Conclusions:** It was concluded that there is a correlation between neonatal outcomes and factors such as maternal age, gestational diabetes, and abnormal umbilical cord coiling patterns.

INTRODUCTION

The umbilical cord, commonly known as the "funis," plays a crucial role in fetal development, health, and survival. It acts as the main pathway for delivering nutrients and oxygen from the placenta to the fetus while also facilitating the removal of waste products [1]. The structure and coiling patterns of the umbilical cord can greatly affect fetal health and the outcomes of pregnancy. An effectively functioning umbilical cord is vital for maintaining proper blood flow, which is essential for promoting healthy growth and development of the fetus [2]. Blood from the fetus can enter and exit the placenta through this tri-vascular channel. All 360-degree spiral loops of umbilical veins encircling the Wharton's jelly are referred to as coils. Unknown coiling origins exist in around 95% of umbilical cords. They calculated "The Index of Twist," a measurement of umbilical coiling, by dividing the total number of coils by the length of the umbilical cord [3]. Among the various features of the human umbilical cord, one of the most enigmatic and fascinating aspects is the blood vessels' twisted or spiral path. Though the names are used interchangeably to prevent confusion, the vessels of the cord are mathematically wrapped as cylindrical helices rather than spirals [4]. Restricted blood flow is one of the many issues linked to this illness. This might have negative

DOI: https://doi.org/10.54393/pjhs.v5i11.2426

effects like low birth weight, fetal growth limitation, and an increase in caesarean delivery rates [5]. Conversely, hyper-coiled cords, due to their excessively high number of coils, have an Umbilical Cord Index (UCI) that is more than the 90th percentile. Hyper-coiling can lead to complications including cord entanglement, compression, as well as torsion, which lead to potential fetal harm and adversely impact Apgar scores, however, it may look advantageous because of its extended length and apparent toughness [6]. Healthcare practitioners need to understand the importance of these coiling variations since improper coiling during pregnancy may suggest that stricter surveillance and intervention are necessary [7]. A recent study suggests that maternal characteristics such as age, and parity, along with underlying medical concerns may affect patterns of umbilical cord coiling. Thus, to enhance prenatal care and the overall health of women and fetuses, it is imperative to examine the relationships among cord coiling patterns, mother-related factors, and newborn outcomes [8]. The umbilical cord coiling index is a critical parameter that can influence neonatal outcomes. Variations in cord coiling have been associated with various maternal factors, such as age and gestational diabetes, which may impact fetal development and health. However, there remains a significant gap in the literature regarding the specific effects of these maternal factors on umbilical cord coiling patterns and their subsequent influence on neonatal outcomes. Previous studies have indicated that abnormal coiling patterns can lead to adverse perinatal outcomes; however, few have comprehensively examined how maternal characteristics contribute to these variations. By addressing this gap, we hope to provide valuable insights into the implications of cord coiling variations and inform clinical practices for monitoring pregnancies at risk.

This study aims to assess the postnatal umbilical coiling index (UCI) and investigate its association with normal coiling, hypo-coiling, and hyper-coiling patterns in maternal and perinatal outcomes

METHODS

This cross-sectional study was conducted in the Obstetrics and Gynecology Department at Pakistan Aeronautical Complex (PAC) Hospital Kamra from January 2024 to June 2024. Inclusion Criteria included singleton pregnancy, gestational age of 37 weeks or more and cephalic presentation. Exclusion Criteria included multiple pregnancies, intrauterine fetal death abnormal presentations and congenital malformations. The sample size was calculated using the formula for comparing proportions across three or more groups, we can use the following formula: $n=(Z\alpha/2+Z\beta)2\cdot(p1(1-p1)+p2(1-p2))+p3(p1-p3)2/(p1-p2)2$, where p1=0.30, p2=0.50, p3=0.70, $Z\alpha/2=1.96$ (90% confidence), and $Z\beta=0.84$ (80% power) and effect size (p2-p1=0.20). A total of 200 participants were enrolled in the study. For each participant, a detailed obstetric history and clinical examination were performed. After delivery, the umbilical cord was examined and clamped. The Umbilical Cord Coiling Index (UCI) was calculated as the number of coils per centimeter of cord length using the formula: UCI=Number of coils/Length of the umbilical cord in cm. The UCI was classified into three categories [9]. Normal Coiled Cord: UCI=0.1 to 0.3 coils/cm, hypo-coiled Cord: UCI < 0.1 coils/cm and hyper-coiled Cord: UCI >0.3 coils/cm. Various maternal factors, including Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores at one and five minutes, low birth weight (defined as less than 2,500 grams), meconium-stained amniotic fluid, delivery method (vaginal, assisted, or cesarean), "neonatal intensive care unit (NICU) admissions, and newborn morbidity and mortality were also recorded. Data were analyzed using SPSS version 26.0. Continuous variables were presented as means with standard deviations, while categorical variables were shown as frequencies and percentages. The chi-square test or Fisher's exact test was used to compare categorical outcomes among the UCI groups, and the t-test was used for continuous variables. Statistical significance was set at a p-value of less than 0.05. This study was conducted by the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Hospital Kamra (IRB approval number: PACH/1/Trg/4). Informed consent was obtained from all participants before their inclusion in the study.

RESULTS

In the hypo-coiled group, the mean maternal age is 30.1 years, compared to 28.6 years in the normal group and 29.4 years in the hyper-coiled group. However, a higher proportion of mothers aged 35 years or older is found in the hypo-coiled group (25.7%) compared to the normal (13.4%) and hyper-coiled (8.7%) groups. The hypo-coiled group also has the highest average parity (2.8). The prevalence of gestational diabetes is greater in the hypo-coiled group (22.9%) than in the normal (10.6%) and hyper-coiled (8.7%) groups. Hypertensive disorders are also more common in the hypo-coiled group (17.1%) compared to the normal (9.2%) and hyper-coiled (4.3%) groups. There is a significant difference in obesity prevalence, with 22.9% of the hypo-coiled group being obese compared to 12.7% in the normal and 8.7% in the hyper-coiled groups (p=0.04). Additionally, smoking rates are significantly higher in the hypo-coiled group (20.0%) than in the normal (9.2%) and hyper-coiled (4.3%) groups (p=0.02). Finally, the hypo-coiled group had an average of 5.3 antenatal care visits, slightly fewer than the normal (6.1) and hyper-coiled (5.9)

DOI: https://doi.org/10.54393/pjhs.v5i11.2426

groups, but this difference is not significant (p=0.09). The hypo-coiled group has a lower average birth weight (2590 ± 400 grams) than the normal (2900 ± 350 grams) and hyper-coiled (2780 ± 320 grams) groups, (Table 1).

Table 1: Maternal Factors and Their Association with Umbilical Cord Coiling Pattern

Maternal Factors	Hypo-coiled (n=35)	Normal Coiled (n=142)	Hyper-coiled (n=23)	p-value
Maternal Age (Years)	30.1 ± 4.5	28.6 ± 4.0	29.4 ± 3.8	0.15
Age ≥35 Years (%)	9 (25.7%)	19 (13.4%)	2 (8.7%)	0.04*
Parity (Mean ± SD)	2.8 ± 1.2	2.4 ± 1.1	2.5 ± 1.0	0.18
Primiparity (%)	14 (40.0%)	72 (50.7%)	9 (39.1%)	0.24
Gestational Diabetes (%)	8 (22.9%)	15 (10.6%)	2 (8.7%)	0.03*
Hypertensive Disorders (%)	6 (17.1%)	13 (9.2%)	1 (4.3%)	0.05*
Pre-pregnancy BMI (kg/m^2)	27.1 ± 4.2	25.8 ± 3.9	26.0 ± 4.0	0.12
Hypertensive Disorders (%)	6 (17.1%)	13 (9.2%)	1 (4.3%)	0.05*
Pre-pregnancy BMI (kg/m^2)	27.1 ± 4.2	25.8 ± 3.9	26.0 ± 4.0	0.12
Obesity (BMI ≥ 30) (%)	8 (22.9%)	18 (12.7%)	2 (8.7%)	0.04*
Smoking (%)	7 (20.0%)	13 (9.2%)	1 (4.3%)	0.02*
Antenatal Care Visits (Mean)	5.3 ± 2.1	6.1 ± 1.9	5.9 ± 2.0	0.09
Birth Weight (Grams)	2590 ± 400	2900 ± 350	2780 ± 320	0.02*
Meconium-Stained Amniotic Fluid (%)	2590 ± 400	2900 ± 350	2780 ± 320	0.02*
Low Birth Weight (<2500g) (%)	10 (28.6%)	20 (14.1%)	2 (8.7%)	0.01*
Cesarean Delivery (%)	15 (42.9%)	39 (27.5%)	5 (21.7%)	0.04*

A p-value of less than 0.001 indicates a significant difference in the mean coiling index between the hypo-coiled (0.07 ± 0.02) and hyper-coiled (0.35 ± 0.06) groups. The coiling patterns of the groupings differ statistically from one another. Furthermore, the umbilical cord length of the hypo-coiled group is 46.2 ± 5.1 cm, p-value<0.001, shorter than that of the hyper-coiled (60.1 ± 5.9 cm) and normal groups (53.8 ± 6.7 cm). It would appear from this that the length of the rope rises with the degree of coiling. At a p-value less than 0.001, the hypo-coiled group had an average of 6.2 ± 1.1 coils, which is substantially less than the normal (12.7 ± 2.3) and hyper-coiled (18.3 ± 2.9) groups. This suggests a lower number of coils when hypo-coiling occurs. The hypo-coiled group's mean chord diameter (1.2 ± 0.3 cm) is less than that of the normal (1.4 ± 0.4 cm) and hyper-coiled (1.6 ± 0.5 cm) groups, with a p-value of 0.02. This implies that there may be more coiling and thickness in the umbilical cords. Additionally, the hypo-coiled group had a larger percentage of single umbilical arteries (14.3%) with a p-value of 0.05 than the normal (5.6%) and hyper-coiled (4.3%) groups. All groups combined include a majority of people with two umbilical arteries; however, the hypo-coiled group has the lowest proportion (85.7%) in contrast to the hyper-coiled (95.7%) and normal (94.4%) groups. The difference in the number of arteries between the groups appear to be marginally significant, as indicated by the p-value of 0.05 (Table 2).

Table 2: Coiling Patterns and Structural Attributes of the Umbilical Cord

Characteristic	Hypo-coiled (n=35)	Normal Coiled (n=142)	Hyper-coiled (n=23)	Total (n=200)	p-value
Coiling Index (Mean ± SD)	0.07 ± 0.02	0.22 ± 0.05	0.35 ± 0.06	0.21 ± 0.10	<0.001*
Length of Cord (cm)	46.2 ± 5.1	53.8 ± 6.7	60.1 ± 5.9	52.1 ± 8.2	<0.001*
Number of Coils	6.2 ± 1.1	12.7 ± 2.3	18.3 ± 2.9	11.6 ± 5.2	<0.001*
Cord Diameter (cm)	1.2 ± 0.3	1.2 ± 0.3	1.6 ± 0.5	1.4 ± 0.4	<0.02*
Umbilical Arteries (%)					
Single Artery	5 (14.3%)	1.2 ± 0.3	1.6 ± 0.5	1.4 ± 0.4	0.05*
Two Arteries	30 (85.7%)	134 (94.4%)	22 (95.7%)	186 (93.0%)	0.05*

The analysis shows a weak but statistically significant negative correlation between the Umbilical Cord Coiling Index (UCI) and Apgar scores at 1 minute (r=-0.253, p=0.0003) and 5 minutes (r=-0.250, p=0.0003). This indicates that lower UCI values are associated with lower Apgar scores, reflecting poorer immediate neonatal outcomes. While UCI influences Apgar scores, other factors may also contribute to these outcomes (Table 3).

Table 3: Analysis of Correlation Between UCI and Apgar Scores

Variable Pair	Correlation Coefficient (r)	p-value	Interpretation
UCI vs.Apgar Score at1 Minute	-0.253	0.0003	Negative correlation; lower UCI linked to lower Apgar score at 1 minute.
UCI vs. Apgar Score at 5 Minutes	-0.250	0.0003	Negative correlation; lower UCI linked to lower Apgar score at 5 minutes.

The scatter plots illustrate the correlation between the Umbilical Cord Coiling Index (UCI) and Apgar scores at 1 minute. In the first plot, a negative trend is observed, indicating that lower UCI values are associated with lower Apgar scores at 1 minute. A reference line marks the critical threshold of Apgar <7 to highlight the clinical significance. These visual representations reinforce the finding that reduced UCI is linked to lower Apgar scores, aligning with the statistical analysis (Figure 1).

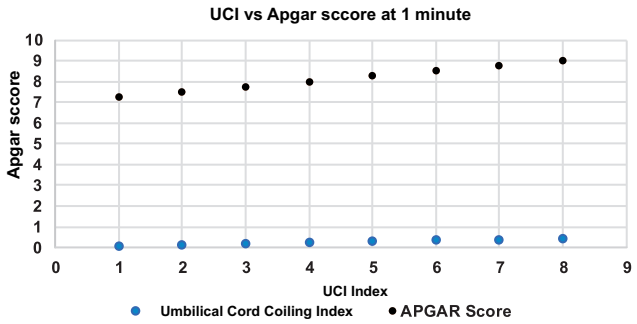

Figure 1: Scatter Plots Showing the Correlation Between the Umbilical Cord Coiling Index (UCI) and Apgar Scores at 1 Minute

DOI: https://doi.org/10.54393/pjhs.v5i11.2426

The scatter plots illustrate the correlation between the Umbilical Cord Coiling Index (UCI) and Apgar scores at and 5 minutes. the second plot demonstrates a negative relationship between UCI and Apgar scores at 5 minutes, with the critical threshold also emphasized. These visual representations reinforce the finding that reduced UCI is linked to lower Apgar scores, aligning with the statistical analysis (Figure 2).

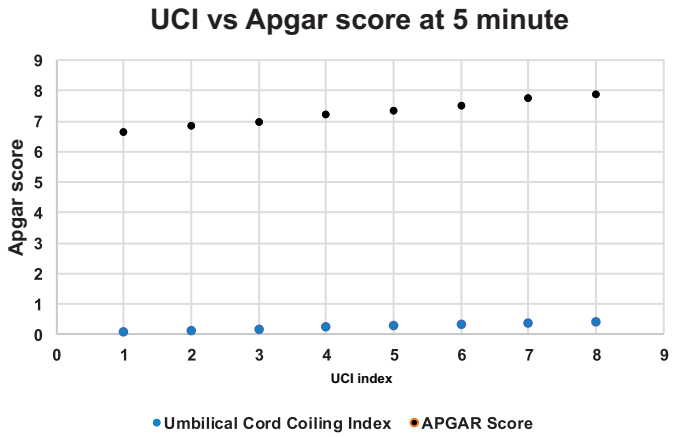

Figure 2: Scatter Plots Showing the Correlation Between the Umbilical Cord Coiling Index (UCI) and Apgar Scores at 5 Minutes

The analysis revealed that the hypo-coiled group had a significantly lower mean birth weight (2590 ± 400 grams) compared to the normal coiled (2900 ± 350 grams) and hyper-coiled groups (2780 ± 320 grams), with a p-value of 0.02. Additionally, a higher proportion of low-birth-weight infants (<2500 g) was observed in the hypo-coiled group (28.6%) compared to the normal coiled (14.1%) and hyper-coiled groups (8.7%), with a p-value of 0.01. These findings suggest that hypo-coiling is strongly associated with lower birth weight and a greater risk of low birth weight outcomes (Table 4).

Table 4: Analysis of Birth Weight Across the Three UCI Groups

Intrapartum Factor	Hypo-coiled (n=35)	Normal Coiled (n=142)	Hyper-coiled (n=23)	p-value
Birth Weight (Grams)	2590 ± 400	2900 ± 350	2780 ± 320	0.02
Low Birth Weight (%)	28.6% (n=10)	14.1% (n=20)	8.7% (n=2)	0.01

DISCUSSION

The umbilical coiling index (UCI) is the estimation of cord twists over a given length It is quantified by pregnancy ultrasound, and the possibility of using it as a marker of perinatal outcome has also been raised [10]. A typical UCI indicates the embryo in progress is satisfying necessities for oxygen and blood, which makes it beneficial for the strength of the embryo. Association with issues study has connected both hypo-coiling and hyper-coiling to poor prenatal outcomes. Fetal distress, an elevated risk of abnormal fetal heart rate, as well as stillbirth due to decreased blood flow or cord accidents are some of these possible effects [11]. Hypo-coiling is associated with preterm birth, intrauterine development limitation, and an increased risk of cesarean delivery due to fetal discomfort. Research that suggests the UCI might be used as a means of forecasting poor perinatal outcomes shows that an increased UCI can be associated with greater fetal cardiac variability, indicating enhanced fetal health, along with a low UCI is linked to higher levels of IUGR as well as low Apgar ratings at birth [12]. In the current study, emphasis on the Apgar scores, this study assesses the relationship between different maternal variables, patterns of umbilical cord coiling, and the outcomes of newborns. Different patterns of umbilical cord coiling are connected with maternal age, parity, pre-pregnancy BMI, and gestational diseases such as diabetes and hypertensive disorders [13]. The hypo-coiled group had notably higher rates of gestational diabetes and older mothers (≥35 years). These results imply the possibility of pregnancy and delivery problems due to the fetus being predisposed to aberrant cord coiling by specific maternal circumstances [14]. In all three groups, hypo-coiled babies weighed less at delivery than babies with normal or hyper-coiled cords, according to the study, which also showed significant variations in birth weight. One reason to be concerned about the hazards of inadequate cord coiling is the significant increase in the incidence of low birth weight (<2500g) in the hypo-coiled group [15]. Further evidence for the possible need for closer monitoring of pregnancies with atypical umbilical cord coiling patterns comes from the higher incidence of cesarean births and NICU admissions in the hypo-coiled group [16]. In the current study, the structural properties of the umbilical cord about its coiling patterns between the groups, there were notable differences in the coiling index, cord diameter, number of coils, and length of the rope. There may be a connection between the shape and function of cords because hypo-coiled cords had the lowest coiling index and several coils. The shorter hypo coiled cords and long umbilical cords may result in decreased oxygenation status of the fetus, affecting the transabdominal ultrasound fluid volume estimation which is a surrogate marker of fetal weight thereby explaining variation between birth weights [17]. Of note, cords that were hypo-coiled were more likely to exhibit a single umbilical artery, suggesting a potential relationship between abnormal coiling and congenital cord anomalies. A diminutive stream of blood flowing to even one artery can have implications for the growth and development of a fetus in general [18]. Association of umbilical cord coiling variations with Apgar scores at one and five minutes in the newborns' Hypo-coiled cords were also associated with lower scores on the Apgar scale compared to newborns with normal as well as hyper-coiled cords. Such a discrepancy suggests that poor nutritional support to the fetus in labour might be associated with inadequate umbilical cord coiling, possibly secondary by reduction in

DOI: https://doi.org/10.54393/pjhs.v5i11.2426

oxygen and nutrient supply. This is also particularly important for the larger group of babies scoring <7 (n=19 boys and 5 girls) both early and late concerning hypo-coiling as that could be a normal endpoint [19]. The findings of this study underscore the potential need for enhanced prenatal monitoring of umbilical cord coiling patterns, particularly in high-risk populations such as older mothers and those with gestational diabetes. Abnormal coiling has been associated with adverse neonatal outcomes, including low birth weight and lower Apgar scores, as demonstrated in our results. These outcomes align with previous studies, such as those by Kalluru et al., which also reported similar associations between hypo-coiling and poor perinatal outcomes [20]. The present findings underscore the significance of determining maternal attributes that might have links with overall attributes of the umbilical cord. More prenatal surveillance and perhaps earlier delivery may be indicated for pregnancies with abnormal umbilical cord coiling patterns to improve obstetric outcomes. Furthermore, the observational design of the study limits the ability to establish causation between maternal factors and umbilical cord coiling patterns. Future research with larger, more diverse populations and a longitudinal design could help clarify these relationships and improve the understanding of the implications of cord coiling variations in various maternal health contexts.

CONCLUSIONS

It was concluded that abnormal coiling patterns of the umbilical cord, gestational diabetes and maternal age showed a negative relation with newborn outcomes. Conclusion Because hypo-coiled umbilical cords are associated with lower birth weights and Apgar scores, enhanced surveillance with intervention methods is needed to improve the quality of maternal-fetal well-being.

Authors Contribution

Conceptualization: SJ
Methodology: SJ, AQ, MAJ, SZ, SJK
Formal analysis: AQ, MA
Writing review and editing: MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2091

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Association of Emotional Intelligence and Aggression with Physical Activity Among Undergraduate Medical Students

Muhammad Umair Chishti[1], Fajar Arif[1], Eamish Munir[1], Rimsha Shahbaz[1], Hafiz Haroon Tariq[1], Mian Ali Raza[2] and Wajida Perveen[1*]

[1]Department of Physical Therapy, School of Allied Health Sciences, Combined Military Hospital, Lahore Medical College and Institute of Dentistry, Lahore, Pakistan
[2]Department of Physical Therapy, Innovative Health Center, School of Allied Health Sciences, Combined Military Hospital, Lahore Medical College and Institute of Dentistry, Lahore, Pakistan

ARTICLE INFO

Keywords:
Aggression, Emotional Intelligence, Physical Activity, Undergraduate Medical Students

How to Cite:
Chishti, M. U., Arif, F., Munir, E., Shahbaz, R., Tariq, H. H., Raza, M. A., & Perveen, W. (2024). Association of Emotional Intelligence and Aggression with Physical Activity Among Undergraduate Medical Students: Emotional Intelligence and Aggression with Physical Activity. Pakistan Journal of Health Sciences, 5(11), 215-220. https://doi.org/10.54393/pjhs.v5i11.2091

***Corresponding Author:**
Wajida Perveen
Department of Physical Therapy, School of Allied Health Sciences, Combined Military Hospital, Lahore Medical College and Institute of Dentistry, Lahore, Pakistan
wajida_perveen@cmhlahore.edu.pk

Received Date: 11th September, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Emotional intelligence and physical activity, have a strong impact on students' well-being and health. Aggressive tendencies may interfere with a student's potential to acquire knowledge and become a good professional later on. **Objectives:** To determine the association of emotional intelligence and aggression with physical activity among undergraduate medical students. **Methods:** The analytical cross-sectional study was conducted on a sample of 267 students from five private medical colleges and universities offering allied health sciences courses after ethical approval in four months using Non-Probability Convenience sampling. Emotional intelligence, aggression and physical activity were measured using the Emotional Intelligence Questionnaire, Buss Perry aggression Questionnaire and short form of the International Physical Activity Questionnaire respectively. Correlation tests were applied to find the association ($p \leq 0.05$ as significant). **Results:** A positive association between Physical Activity Questionnaire and Aggression was found in male with ($p=0.020$) and a negative association in female with ($p=0.894$). Emotional intelligence had a negative association in both male and female undergraduate medical students except motivating oneself in males which had a positive association in males ($p=0.019$). **Conclusions:** It was concluded that the study highlights the strong relationship between emotional intelligence, physical activity and aggression among undergraduate medical students. Male exhibit aggressive behaviour more often than female do. Male showed a positive relation between emotional intelligence and physical activity.

INTRODUCTION

The term "emotional intelligence" refers to the ability to manage one's thoughts and feelings as well as the feelings of people other than oneself, detect them, and utilize this knowledge to influence decisions and actions, promote original ideas, concentrate attention on important topics, inspire others, and assist flexible planning [1]. According to the World Health Organization, any motion of the body caused by skeletal muscles that involve energy expenditure is considered physical activity (PA). Physical, mental, and social well-being are all correlated with physical activity (PA) [2]. Aggression is described as a tendency to harm others—whether they be people or animals—or respond violently or angrily towards them. Physical and relational aggression are two different subtypes of aggressive behaviour. Physical aggression refers to actions that cause bodily injury to a target (such as striking and shoving), whereas relational aggression describes actions that cause social harm to others (such as gossiping and social exclusion) [3]. Aggression, physical activity, and emotional intelligence are all associated. We

DOI: https://doi.org/10.54393/pjhs.v5i11.2091

will now talk about the connections between these three in undergraduate medical students. A medical student's life in medical school is quite demanding and busy. A student's medical career presented many difficulties, including pressure from professors, poor class performance, intense stress during viva, difficulty covering the entire syllabus in a day, intense study sessions but unsatisfactory results as well as the aggressive behaviour of college staff members, friends' company if they are not supportive, poor time management, insufficient physical activity, and excessive screen time. These difficulties contribute to the development of aggression and emotional instability [4]. PA may assist the students in overcoming these obstacles with ease, having better emotional control, and transforming angry behaviour into pleasant moods. Students who engage in physical activities feel relaxed, their moods change for the better, they are happier, and they feel more energetic. Students who are not physically active, are not involved in any activities, and who spend more time on their phones than on other activities are reported to have exceptionally high rates of emotional changes and anger [5]. Jiménez-Picón *et al.*, revealed a strong relationship between emotional intelligence and mindfulness, particularly the capacity to control emotions. Additionally, emotional exhaustion has a bad effect on mindfulness [1]. Ubago-Jiménez *et al.*, investigated the association evolved among emotional intelligence, physical activity and aggressive behaviors in 932 university students. They found that Men are more likely than women to engage in aggressive behaviours, and the relationship between physical activity and emotional intelligence is stronger across all of its dimensions [6]. Espaillat *et al.*, highlighted the presence, impact and responses to macroaggressions among medical learners. Female students reported encountering macroaggressions dominantly, while Second-year medical students were more likely than third-year students to get engaged in macroaggressions (31% versus 23%) [7]. Issah *et al.*, focus on various aspects of emotional intelligence, including recognition of oneself, control of one's emotions, inspiration from oneself, feelings for others, and social ability. They suggested that emotional intelligence can support change leadership by emphasizing team development and overcoming opposition [8]. Sundararajan *et al.*, examined medical students' emotional intelligence levels and their perceptions of how emotions play a part in clinical practice. When it came to emotional scenes, women performed better than males (p=0.056), and students who went to government high schools performed better than those who went to private educational institutions (p=0.044). Medical students at the university under investigation, both sexes, exhibited high emotional quotients [9]. Currently, aggression is observed commonly in undergraduate medical students and they are less aware of emotional intelligence. To make them wiser, emotional intelligence has been observed in the study. Physical activity plays an important role in the lives of students. Medical students deal with the harsh realities of life; hence they should have very high emotional intelligence to carry out their duties.

The study aims to find out the association of physical activity with emotional intelligence and aggression among undergraduate medical students.

METHODS

This analytical cross-sectional study was conducted for four months after ethical approval (Case #.709/ERC/CMH/LMC) from May to August 2023. The sample size was calculated from this formula [10], n= (Zα/2+Zβ)2/r2. Where Zα/2=critical value for the confidence level (for 95% confidence, Zα/2=1.96), Zβ=critical value for the power (for 80% power, Zβ=0.84) and r=expected correlation coefficient (r=0.1718). So, by putting these values, n=(1.996+0.84)^2/(-0.1718)^2. For an expected correlation coefficient (r=0.1718) [6], with 95% confidence and 80% power, approximately 267 participants are needed. Data were collected from Combined Military Hospital, Lahore, Medical College and Institute of Dentistry, Lahore, University of Lahore, Lahore, Rahbar Medical College, Lahore, University of South Asia, Lahore, University of Management and Technology, Lahore using non-probability convenience sampling technique with the consent of the participants. Both male and female, 18-26 years old and enrolled in any class from 1st to final year undergraduate medical students like MBBS, Bachelor of Dental Surgery (BDS), Doctor of Physical Therapy (DPT), Doctor of Pharmacy (PHARM-D), Medical Imaging Technology (MIT) and Nursing were included. Students other than these programs and those who were unwilling to take part, those diagnosed with mental and physical disabilities and those students diagnosed with psychological disorders were excluded from this study. The data were collected using the Emotional Intelligence Questionnaire [11], the International Physical Activity Questionnaire (IPAQ) [12] and the Buss-Perry Aggression Questionnaire (BPAQ) [13]. The emotional intelligence questionnaire (EIQ) measures five different emotional intelligence competencies including Self-awareness, controlling your emotions, self-motivation, empathy, and social skills. Each statement on the questionnaire is scored on a scale of 1 to 5 with 1 meaning that the statement doesn't apply to you at all, 3 meaning that it does around half the time, and 5 meaning that it always does. Total score ranges from 50 to 250 with 50 for each competent. A score core ranging from 35-50 is a strength, 18-34 needs attention and 10-17an is an area of development priority for each domain. The higher the total score is a strength and vice versa [11]. Short form of IPAQ (Short form of International Physical

DOI: https://doi.org/10.54393/pjhs.v5i11.2091

Activity Questionnaire) is a seven-item questionnaire, used to calculate the amount of time spent sitting and different kinds of physical activity that people engage in daily to their total weekly physical activity in Metabolic equivalents (MET) per minute. IPAQ has 7 items, scoring a high level of physical activity on the IPAQ means physical activity levels equate to approximately one hour of activity per day or more at least a moderate intensity activity level, scoring moderate level of physical activity on the IPAQ means the person is doing some the activity more than likely equivalent to half an hour of at least moderate intensity physical activity on most days. Scoring a low level of physical activity on the IPAQ means that the person is not meeting any of the criteria for either moderate or high levels of physical activity [12]. Buss Perry Aggression Questionnaire (BPAQ) is a 29-item scale with 4 subscales which involves items 1 through 9 make up the Physical Aggression Subscale, Items 10 through 14 make up the Verbal Aggression Subscale, Items 15 through 21 make up the Anger Subscale, and Items 22 through 29 make up the Hostility Subscale. Each scale's score is the total of the item ratings. Reverse scoring is used for the two items (7 and 18) that are phrased the other way from aggressive. The sum of these scale values is the aggressiveness level overall. The total score ranges from 29 to 145. The higher scores suggest more aggressive behaviours. The tool is valid for 9-88 years old individuals [13]. SPSS version 23.0 was used for statistical analysis; qualitative variables were presented in the form of frequency tables and percentages. A correlation test was used to find the correlation between variables, the standard significant p-value was less than 0.05.

RESULTS

The mean age of the participants was 20.91 ± 1.70 years ranging from 18 to 26 years. There were 23.20% male and 76.80% female. Most students who took the study form were 21-23 years old, with 48.31%, 44.19%, 18-20 years, and 7.49%, 24-26 years. The participants from each institution, year of study and the discipline in which students were enrolled are also listed below (Table 1).

Table 1: Demographic and Academic Status of the Participants (n=267)

Variables	n (%)
Gender	
Male	62 (23.20%)
Female	67 (71.3%)
Age (Years) Range 18-26 Years	
Mean ± SD	20.91 ± 1.70
18-20	118 (44.19%)
21-23	129 (48.31%)
24-26	20 (7.49%)
Institutions	
CMH Lahore Medical College	146 (54.68%)
University of Lahore	53 (19.85%)
Rahbar Medical College	23 (8.61%)
University of South Asia	26 (9.73%)
University of Management & Technology	19 (7.11%)
Year of Study	
1st year	63 (23.60%)
2nd year	50 (18.73%)
3rd year	63 (23.60%)
4th year	40 (14.98%)
5th year	51 (19.10%)
Discipline of Study	
MBBS	55 (20.60%)
BDS	42 (15.73%)
DPT	55 (20.60%)
Pharm D	32 (11.98%)
MIT	41 (15.35%)
Nursing	43 (16,10%)

The total mean score of Self-Awareness Score was 32.17 ± 73.21, Managing Emotions was 21.58 ± 25.44, Motivating Oneself was 37.19 ± 67.54, Empathy Score was 42.18 ± 48.28, Social Skill Score was 29.37 ± 69.18 while the total mean score of all subsets was 162.49 ± 23.65. The total of subsets of the Bus Perry Aggression Questionnaire included Physical Aggression Subscale 24.69 ± 72.51, Verbal Aggression Subscale 12.53 ± 32.11, Anger Subscale 20.34 ± 53.26, Hostility Subscale 26.92 ± 76.83 with a total mean score 162.49 ± 23.65. In terms of IPAQ Scores, the mean for low active was 68.26 ± 35.80, moderately active was 25.30 ± 51.63, and for highly active was16.87 ± 47.26 with an overall total mean of 109.43 ± 34.69 MET-Min (Table 2).

Table 2 : Mean Scores of Items of Questionnaires

Items of Questionnaires	Total score (Mean ± SD)
EIQ Subscales	
Self-Awareness Score (SAS)	32.17 ± 73.21
Managing Emotions (MES)	21.58 ± 25.44
Motivating Oneself (MOS)	37.19 ± 67.54
Empathy Score (ES)	42.18 ± 48.28
Social Skill Score (SSS)	29.37 ± 69.18
Emotional Intelligence Questionnaire Total Score	162.49 ± 23.65
BPAQ Subscales	
Physical Aggression Subscale (PAS): (Item 1-9)	24.69 ± 72.51
Verbal Aggression Subscale (VASS): (Item 10-14)	12.53 ± 32.11
Anger Subscale(ASS): (Item 15-21)	20.34 ± 53.26
Hostility Subscale (HSS): (Item 22-29)	26.92 ± 76.83
Bus Perry Aggression Questionnaire Total Score	84.48 ± 34.74
International Physical Activity Questionnaire (IPAQ) (MET-Min)	
Low Active	68.26 ± 35.80
Moderately Active	25.30 ± 51.63
Highly Active	16.87 ± 47.26
Total Score (MET-Min)	109.43 ± 34.69

EIQ: Emotional Intelligence Questionnaire, BPAQ: Bus Perry

DOI: https://doi.org/10.54393/pjhs.v5i11.2091

Aggression Questionnaire

Table 3 shows the association between IPAQS (International Physical Activity Questionnaire Score) and BPAQS (Bus Perry Aggression Questionnaire Score). p-Value based on the total score of all subscales of BPAQ and IPAQ in male was significant (p=0.020) and non-significant in female was 0.894. There was no significant association between scores of individual subscales of BPAQ and IPAQ among male and female. The association between physical activity and aggression based on gender is given (Table 3).

Table 3: Association between Physical Activity and Aggression (n=267)

Association	Male (n=62)		Female (n=205)	
	(r)	p-value	(r)	p-value
IPAQS Vs BPAQS	0.295	0.020*	-0.009	0.894
IPAQS Vs PAS	0.307	0.015*	-0.038	0.591
IPAQS Vs VASS	0.236	0.065	0.080	0.255
IPAQS Vs ASS	0.179	0.164	-0.038	0.589
IPAQS Vs HSS	0.052	0.689	-0.010	0.892

BPAQ: Bus Perry Aggression Questionnaire, PAS: Physical Aggression Subscale, VASS: Verbal Aggression Subscale, ASS: Anger Subscale, HSS: Hostility Subscale

While the association between physical activity and emotional intelligence based on gender is expressed. Further study shows a correlation between IPAQS and categories of Emotional Intelligence. The association between IPAQS (International Physical Activity Questionnaire Score) and SAS (Self Awareness Score) shows p-value in men was 0.224 and in women was 0.158 which is non-significant. The association between IPAQS and MES (Managing Emotions Sub-scale) shows p-value in male was 0.072 and in female was 0.19, which is non-significant. The association between IPAQS and MOS (Motivating Oneself Score) shows p-value in male was significant which is 0.034 and in female, it was 0.265 which is non-significant. The association between IPAQS and ES (Empathy Score) shows p-value in male was 0.787 and in female was 0.119 which is non-significant. The association between IPAQS and SSS (Social Skill Score) shows p-value in male was significant which is 0.005 and in female it was 0.19 which is non-significant (Table 4).

Table 4: Association between Physical Activity and Emotional Intelligence (n=267)

Association	Male (n=62)		Female (n=205)	
	(r)	p-value	(r)	p-value
IPAQS Vs SAS	0.157	0.224	0.099	0.158
IPAQS Vs MES	0.23	0.072	0.092	0.19
IPAQS Vs MOS	0.27	0.034*	0.078	0.265
IPAQS Vs ES	0.035	0.787	0.109	0.119
IPAQS Vs SSS	0.352	0.005*	0.092	0.19

SAS: Self Awareness Score, MES: Managing Emotions, MOS: Motivating Oneself, ES: Empathy Score, SSS: Social Skill Score

DISCUSSION

Examining the relationship between emotional intelligence, physical activity, and aggressive behaviour is the goal of the study. It highlights the effects that these factors have on undergraduate medical students, most of whom are in their first and third years. There was a significant association between violent behaviour and lack of exercise in male students. Female students displayed lower levels of aggressiveness than male students, both in their overt and covert displays. The majority of research studies relating to aggression and physical activity have similar findings. These results contrasted with the findings reported by Björkqvist, which revealed that in a sample of school students, women were more likely to engage in verbal violence (60%) than male were to engage in physical aggression (40%) [14]. Medical students in their first years were particularly fragile in terms of their mental health. Academic performance-related stress during the university years is what causes medical students to become aggressive and experience emotional changes. According to the categories of emotional intelligence and aggression, emotional intelligence showed a weak significant association. Self-awareness score, Managing Emotion Scale, Empathy Score, Self-Motivation Score, and Social Skill Score are the categories. Current findings indicate a negative correlation between aggression and social competence scores in undergraduate medical students, with a p-value of 0.787. Similar findings in 2023 show that children's aggressive behaviour is inversely correlated with their social adaptation abilities [15]. We found a significant association between a male's score on self-motivating behaviour and aggression, as well as a negative association between empathy and emotion management (p-value=0.019). These results contrasted with those of a study conducted by Myburgh et al., who discovered that interpersonal and intrapersonal factors including "positive inclination towards others, positive inclination towards self, and acting responsibly towards self" can predict violence. When a student acts with greater self-responsibility and has stronger positive inclinations towards others and lesser negative inclinations towards themselves, aggression is reduced [16]. The association between emotional intelligence categories and aggression has been discovered, and it demonstrates that it hurt undergraduate medical students' scores, except for the score for self-motivation. The p-value of the Motivating Oneself Score in males was significantly associated. However, the findings of the earlier study, carried out in 2021, indicate a positive relationship between emotional intelligence and mindfulness p-value for the correlation was 0.02 [1]. Current results provide support to the hypothesis that engaging in physical activity as a leisure

DOI: https://doi.org/10.54393/pjhs.v5i11.2091

activity is linked to emotional intelligence. Similar to a prior study done on undergraduate medical students, these experiences cause a variety of pleasant and negative emotions. Men do better than women in terms of LTPA levels (p=0.002) and Workplace physical activity (p=0.001) [17]. In contrast, a previous study conducted in 2017 on medical students in a college shows that women respond to emotional episodes and exhibit greater emotional intelligence than men. We discovered that emotional intelligence hurt undergraduate female medical students [10]. Current findings show that women had a negative association between physical activity and aggression compared to men. Different findings were seen in a 2019 study, which demonstrates that women experience greater macroaggression than men [10]. An insignificant correlation between aggressiveness and social skill score was found in present study of undergraduate medical students; similar findings were found in a 2019 study of 900 students that looked at the relationship between aggression and social cognitive theory. We found an insignificant association between physical activity and self-awareness scores in undergraduate medical students with a p-value of 0.224 in male and a p-value of 0.158 in females. Different analyses in Spanish of the relationship between quality of life and physical exercise among undergraduates at public and private universities demonstrate a favourable effect on male students with a p-value of 0.001 [18]. In current findings, we found a significant connection between the level of aggression and physical activity in males on the other hand female had an insignificant association. Similar findings were seen in the majority of research papers relating aggression to physical activity in 2021 showing a higher degree of aggression in men than women [6]. These results, however, differed from those that were reported in a study by Martnez-Monteagudo, who discovered that the categories of Gender X Course Year did not differ statistically significantly from one another. When it came to men, the p-value for aggression was constant at 0.06, whereas it remained consistent for women at 0.082. The probability of being a cyberbully aggressor dropped by 4% and 5% for every unit improvement in emotional knowledge, according to a 2019 study that found a similar outcome. On undergraduate students, we discovered a strong connection between physical activity and aggressive behaviour [3]. The brain's blood circulation is stimulated by exercise. Then, your brain cells are stimulated, which promotes cell development, particularly in the brain. A 2021 investigation had somewhat different findings. This demonstrates that physical exercise, motivation, and neuro-education were positively associated with both male and female students. It implies that students of both genders engage in physical activity. However, present findings indicate that men motivating themselves score and physical activity are positively correlated and men engage in more physical activity than women [19]. The low response rate from students and use of lengthy questionnaires proved to be a major limitation while, consideration of postgraduate medical students and inclusion of other disciplines as well i.e.; engineering, architects, aviation, literature etc. could be utilized to further implications. Zhu *et al.*, found that Interventions involving physical activity alone were more effective in reducing aggressive behaviour than those that combined physical activity with other activities, team-based physical activity might be used for preventing or reducing aggressive behaviour in children and adolescents [20]. Yu et al., found that physical activity is a potent method for decreasing aggressive behaviour and psychological issues in university students while additionally promoting self-efficacy and self-control. Increasing the intensity of PA may enhance the effectiveness of these chain benefits [21].

CONCLUSIONS

It was concluded that study highlighted the strong relationship between emotional intelligence, aggression and physical activity among undergraduate medical students. Male exhibit aggressive behaviour more often than female do. Male showed a positive relation between emotional intelligence and physical activity.

Authors Contribution

Conceptualization: FA, MAR, WP
Methodology: MUC, FA, EM, RS, HHT, MAR
Formal analysis: RS, WP
Writing review and editing: MUC, FA, HHT

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2529

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Predictive Factors of the Persistence and Remission of Irritable Bowel Syndrome at Tertiary Care Hospital

Khadim Hussain Samejo[1*], Ali Akbar Nangraj[2], Mona Humaira[3], Abeer Memon[3], Tahoor Ghani[4] and Sheeba Faryal[3]

[1]Department of Gastroenterology, Bilawal Medical College, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[2]Department of Medicine, Bilawal Medical College, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[3]Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[4]Department of Medicine, Pakistan Healthcare Trust Hospital, Karachi, Pakistan

ARTICLE INFO

Keywords:
Predictive Factors, Symptom Persistence, Remission, Irritable Bowel Syndrome

How to Cite:
Samejo, K. H., Nangraj, A. A., Humaira, M., Memon, A., Ghani, T., & Faryal, S.(2024). Predictive Factors of the Persistence and Remission of Irritable Bowel Syndrome at Tertiary Care Hospital: Predictive Factors of the Persistence and Remission of Irritable Bowel Syndrome.Pakistan Journal of Health Sciences, 5(11), 221-225. https://doi.org/10.54393/pjhs.v5i11.2529

***Corresponding Author:**
Khadim Hussain Samejo
Department of Gastroenterology, Bilawal Medical College, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
drkhsamejo@gmail.com

Received date: 29th September, 2024
Acceptance date: 20th November, 2024
Published date: 30th November, 2024

ABSTRACT

Irritable Bowel Syndrome is a functional gastrointestinal disorder that affects millions of people worldwide, characterized by chronic or recurrent abdominal pain associated with altered bowel habits in the absence of detectable structural or biochemical abnormalities. **Objectives:** To examine the clinical and demographic predictors of irritable bowel syndrome outcomes in a tertiary care hospital in Sindh, Pakistan **Methods:** A prospective study was conducted at the Department of Medicine and Gastroenterology of Liaquat University of Medical and Health Sciences, Jamshoro, from December 2022-July 2023. The study included 240 patients diagnosed with irritable bowel syndrome of all genders and ages of 18 to 60 years. Irritable bowel syndrome was diagnosed via Rome IV Criteria. Patients with clinical evidence of organic or metabolic diseases that may affect the bowel transit or cause abdominal pain along with the patients who were taking the medications for irritable bowel syndrome at the time of enrollment were excluded from the study. **Results:** Over six months, 167 (69.6%) participants showed symptom persistence, while 73 (30.4%) achieved remission. Irritable bowel syndrome D-subtype (p=0.03) and symptom duration under three years (54.8%; p=0.04) were significantly linked to outcomes. Psychological distress, especially stress, and non-digestive symptoms like backache and fatigue predicted persistence. **Conclusions:** The study concluded that a shorter symptom duration of less than 3 years along with irritable bowel syndrome D as a predictor of improved remission rates. Psychological distress, particularly high stress levels, along with non-digestive symptoms such as backache and fatigue, are significant predictors of symptom persistence.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder affecting millions worldwide. It is characterized by chronic or recurring abdominal pain linked to altered bowel habits, with no identifiable structural or biochemical abnormalities. IBS represents a significant public health concern, with global prevalence rates estimated between 5% and 20%, varying by geography and socioeconomic context. In Pakistan, prevalence is around 33.2% with higher rates reported among women and urban residents [1]. IBS is commonly divided into four subtypes based on dominant stool patterns: IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), mixed IBS (IBS-M), and unspecified IBS (IBS-U) [2]. Symptoms of IBS can be highly variable among individuals, adding to the challenges of managing this condition. The primary symptoms include abdominal pain, bloating, and altered bowel habits, such as diarrhea, constipation, or alternating between the two. Abdominal pain in IBS is often cramp-like and ranges from mild discomfort to severe, typically improving after defecation [3]. The chronic nature of IBS symptoms and limited treatment options can cause significant psychological distress, frequently manifesting as anxiety or depression. This connection between the gut and brain,

DOI: https://doi.org/10.54393/pjhs.v5i11.2529

known as the gut-brain axis, plays a crucial role in IBS pathophysiology [4]. The exact cause of Irritable Bowel Syndrome (IBS) remains unknown and is thought to result from a complex mix of genetic, environmental, and psychosocial factors. Evidence increasingly suggests that gastrointestinal infections, alterations in gut microbiota, and low-grade inflammation play key roles in IBS development [5]. Changes in gut microbiota—such as decreased diversity and shifts in bacterial composition—are associated with increased visceral sensitivity and abnormal gut motility, both of which are implicated in IBS [6]. Psychological factors like stress, anxiety, and depression are also known to worsen IBS symptoms by affecting the autonomic nervous system, which helps regulate gastrointestinal function [7]. The diagnosis of IBS is primarily clinical, based on excluding organic causes and applying established criteria. The Rome IV criteria are the most widely accepted guidelines for IBS diagnosis. They require recurrent abdominal pain at least one day per week over the past three months, along with two or more of the following: pain related to defecation, changes in stool frequency, and changes in stool form [8]. While IBS is not life-threatening, its chronic and relapsing nature often leads to significant morbidity and diminished quality of life. Some individuals experience periods of symptom remission, while others endure persistent or fluctuating symptoms over time [9]. Factors linked to persistent IBS symptoms include high baseline severity, psychological comorbidities, and ineffective coping mechanisms [10]. Conversely, those with milder symptoms, effective treatment response, and successful stress management have a better prognosis [11]. Various treatments ranging from dietary changes and medication to psychological therapies like cognitive-behavioural therapy have been shown to alleviate symptoms in some patients. However, no single treatment works for all, and management strategies often need to be individualized based on the patient's predominant symptoms and psychosocial profile [12]. Despite advances in the understanding of IBS pathophysiology and treatment, significant gaps remain, particularly regarding the long-term outcomes of IBS. Most research to date has focused on the prevalence, symptomatology, and short-term treatment responses in IBS patients, with limited attention to the factors that predict long-term persistence or remission of symptoms. Moreover, there is a lack of data from low- and middle-income countries, including Pakistan, where healthcare systems and environmental stressors may differ significantly from those in Western populations.

This study aims to address these gaps by examining the clinical and demographic predictors of IBS outcomes in a tertiary care hospital in Sindh-Pakistan. The study was conducted to provide locally relevant insights that can guide tailored interventions and improve the management of IBS in resource-limited settings, ultimately enhancing patient care and quality of life.

METHODS

A longitudinal prospective single-center study was conducted at the Department of Medicine and Gastroenterology of Liaquat University of Medical and Health Sciences, from December 2022 to July 2023. The study included 240 patients diagnosed with IBS of all genders and ages of 18 to 60 years. IBS was diagnosed via Rome IV Criteria [13]. Patients with clinical evidence of organic and or metabolic diseases that may affect the bowel transit or cause abdominal pain along with the patients who were taking the medications for IBS at the time of enrollment were excluded from the study. The sample size was calculated by taking the prevalence of IBS in Pakistan as 33.2% [1] with a 5 % margin of error, and a 90% confidence interval. The study was approved via REC-LUMHS (No. LUMHS/REC-258). All patients were included after taking informed written consent. Patients were divided into IBS sub-types according to Rome IV criteria into IBS-C, IBS-D, IBS-M and IBS-U [13]. The Rome IV Criteria are internationally recognized guidelines used for diagnosing functional gastrointestinal disorders, including Irritable Bowel Syndrome (IBS), with a focus on symptom-based diagnosis, requiring specific patterns of abdominal pain and bowel habit changes while ruling out organic causes. Patients were treated via standard treatment protocol (no specific treatment interventions were included in the study). Patients were followed up at 2, 4 and 6 months and persistence and remission of symptoms were noted down. During the index visit (enrollment phase), demographic, clinical digestive and non-digestive history were obtained. Details about symptoms were noted down at each follow-up along with the assessment of psychological well-being. DASS-21 scale was used to assess the psychological distress among patients [14]. The DASS-21 scale (Depression, Anxiety, and Stress Scale-21) is a brief, self-reported tool used to assess psychological distress across three dimensions: depression, anxiety, and stress, widely used in both clinical practice and research to evaluate the psychological factors that may influence physical and emotional well-being. Improvement in IBS was measured according to the patient's self-reported status of IBS and a decrease in the frequency of bowel problems and abdominal pain. SPSS version 21.0 was used for the analysis of data. Quantitative data like age and duration of symptoms were measured as mean + SD. Categorical data was measured using frequency and percentages. Chi-square was used to measure the association of different predictors (categorical variables) about the symptoms of perseverance and remission.

DOI: https://doi.org/10.54393/pjhs.v5i11.2529

RESULTS

The study presents the demographic and clinical characteristics of the study population consisting of 240 participants. The sample included 102 male (42.5%) and 138 female (57.5%), with a mean age of 35.8 ± 10.4 years. The distribution of IBS subtypes was as follows: IBS-C in 61 patients (25.4%), IBS-D in 89 patients (37.1%), IBS-M in 71 patients (29.6%), and IBS-U in 19 patients (7.9%). The mean duration of symptoms was 4.5 ± 2.3 years. Psychological distress, measured using the DASS-21 scale, revealed a mean depression score of 12.6 ± 6.3 (moderate category), an anxiety score of 15.5 ± 3.8 (severe category), and a stress score of 24.2 ± 7.2 (moderate category) (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Population (n=240)

Variables	n (%)
Gender	
Male	102 (42.5%)
Female	138 (57.5%)
Age (mean ± SD)	35.8 ± 10.4 years
IBS Subtype	
IBS-C	61 (25.4%)
IBS-D	89 (37.1%)
IBS-M	71 (29.6%)
IBS-U	19 (7.9%)
Duration of Symptoms (Mean ± SD)	4.5 ± 2.3 years
Psychological Distress (DASS-21)	
Depression (Mean ± SD)	12.6 ± 6.3
Anxiety (Mean ± SD)	15.5 ± 3.8
Stress (Mean ± SD)	24.2 ± 7.2

Results summarize the baseline non-digestive complaints among IBS patients at enrollment and the 6-month follow-up. Notably, anxiety symptoms increased from 120 patients (50.0%) at baseline to 135 patients (56.2%) at 6 months. Similarly, the prevalence of backache rose from 156 (65.0%) to 180 (75.0%). Other complaints, such as fatigue, headache, and halitosis, also showed significant increases at the 6-month mark. Conversely, the percentage of patients reporting depression decreased slightly from 126 (52.5%) at baseline to 117 (48.75%) at follow-up (Table 2).

Table 2 : Baseline Non-Digestive Complaints among IBS Patients at Enrollment and 6 Months (n=240)

Non-Digestive Symptoms	At Base Line	At 6-Months
Anxiety	120 (50.0%)	135 (56.2%)
Backache	156 (65.0%)	180 (75.0%)
Depression	126 (52.5%)	117 (48.75%)
Fatigue	144 (60.0%)	168 (70.0%)
Halitosis (Bad Breath)	69 (28.8%)	84 (35.0%)
Headache	135 (56.2%)	162 (67.5%)
Muscular pain	126 (52.5%)	150 (62.5%)
Palpitations	63 (26.2%)	78 (32.5%)
Polyuria	36 (15.0%)	45 (18.8%)
Stress	108 (45.0%)	120 (50.0%)

Among the 240 participants, 167 (69.6%) exhibited persistence of symptoms, while 73 (30.4%) achieved remission. The subtype-specific results indicated that IBS-C had a persistence rate of 46 (75.4%) and a remission rate of 15 (24.6%). In contrast, IBS-D showed a lower persistence rate of 54 (60.0%) but a higher remission rate of 36 (40.0%). IBS-M reported a persistence rate of 52 (73.2%) and a remission rate of 19 (26.8%). Lastly, IBS-U had the highest persistence rate of 15 (78.9%) and the lowest remission rate of 4 (21.1%) (Table 3).

Table 3: Persistence and Remission of IBS Symptoms at 6-Month Follow-Up (n=240) Based On the IBS Subtype

IBS Subtype	Persistence of Symptoms	Remission of Symptoms
Overall	167 (69.6%)	73 (30.4%)
IBS-C	46 (75.4%)	15 (24.6%)
IBS-D	54 (60.0%)	36 (40.0%)
IBS-M	52 (73.2%)	19 (26.8%)
IBS-U	15 (78.9%)	4 (21.1%)

Study depicts the trends in persistence and remission of IBS symptoms over a 6-month follow-up varied among the subtypes. IBS-C showed a decline in symptom persistence from 86.9% at Month 2 to 75.4% at Month 6, with remission rates increasing from 13.1% to 24.6%. Similarly, IBS-D's persistence decreased from 79.8% to 59.6%, while remission rose from 20.2% to 40.4%. For IBS-M, persistence fell from 85.9% to 73.2%, and remission improved from 14.1% to 26.8%. IBS-U had the highest initial persistence at 89.5%, decreasing to 78.9%, with remission increasing from 10.5% to 21.1% (Figure 1).

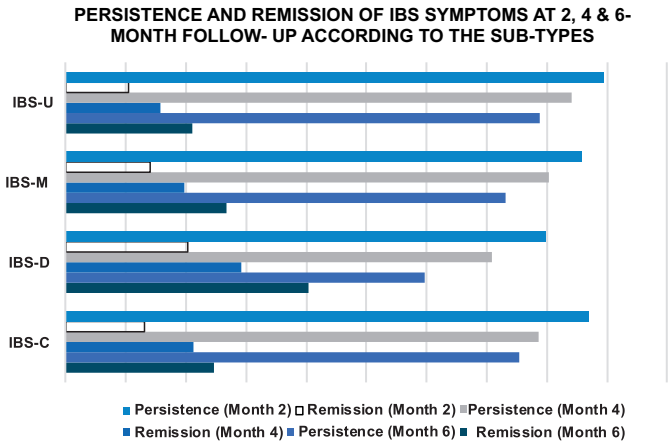

Figure 1: Persistence and Remission of IBS Symptoms At 2, 4 and 6-Month Follow-Up According to the Sub-Types

The predictive factors for the persistence and remission of IBS symptoms at the 6-month follow-up identified several significant associations. Particularly, the IBS-D subtype was linked to greater symptom persistence, with a statistically significant difference in remission rates

DOI: https://doi.org/10.54393/pjhs.v5i11.2529

(p=0.03). A shorter duration of symptoms (less than 3 years) was associated with higher remission rates (54.8%) (p=0.04). Psychological distress, particularly stress, emerged as a critical factor influencing symptom persistence, with those experiencing high-stress levels showing a significant correlation (p=0.01). Non-digestive symptoms, specifically backache and fatigue, were also significant predictors of symptom persistence (p=0.03 and p=0.02, respectively) (Table 4).

Table 4: Predictive Factors for Persistence and Remission of IBS Symptoms at 6-Month Follow-Up (n=240)

Predictive Factor	Persistence of Symptoms (n=167)	Remission of Symptoms (n=73)	p-value
Gender			
Male	74 (44.3%)	28 (38.4%)	>0.05
Female	93 (55.7%)	45 (61.6%)	
IBS Subtype			
IBS-C	46 (75.4%)	15 (24.6%)	>0.05
IBS-D	54 (60.0%)	36 (40.0%)	0.03*
IBS-M	52 (73.2%)	19 (26.8%)	>0.05
IBS-U	15 (78.9%)	4 (21.1%)	>0.05
Duration of Symptoms (Years)			
<3 Years	60 (35.9%)	40 (54.8%)	0.04*
≥3 Years	107 (64.1%)	33 (45.2%)	
Psychological Distress			
Depression (DASS-21)	89 (53.3%)	28 (38.4%)	>0.05
Anxiety (DASS-21)	97 (58.1%)	38 (52.1%)	>0.05
Stress (DASS-21)	101 (60.5%)	19 (26.0%)	0.01*
Non-Digestive Symptoms			
Backache	135 (80.8%)	45 (61.6%)	0.03*
Fatigue	129 (77.2%)	39 (53.4%)	0.02*
Headache	120 (71.9%)	42 (57.5%)	>0.05
Palpitations	63 (37.7%)	15 (20.5%)	>0.05
Muscular Pain	106 (63.5%)	44 (60.3%)	>0.05

DISCUSSION

This prospective longitudinal study assessed the natural history of IBS and predictors of symptom persistence or remission over six months. The current study observed IBS's clinical course and its potential predictors for persistence and remission of symptoms in outcomes and its relation with IBS subtypes (IBS-C, IBS-D, IBS-M, and IBS-U). In this study, nearly half the patients reported symptom persistence at the six-month follow-up, echoing previous findings where up to 50% of patients experienced unchanged or fluctuating symptoms over time [15]. Non-digestive symptoms, such as backache (p=0.03) and fatigue (p=0.02), were significant predictors of persistence, reflecting the multi-systemic nature of IBS, similar to findings from Norlin *et al.*, who reported that comorbid somatic symptoms are strong determinants of IBS severity and persistence [16]. The association of symptom duration under three years with higher remission rates (54.8%; p=0.04) emphasizes the importance of early diagnosis and intervention. This is consistent with Staudacher *et al.*, who identified shorter symptom duration as a favourable prognostic factor in IBS management [17]. Psychological distress, particularly stress, emerged as a significant predictor of symptom persistence (p=0.01), in line with the broader literature highlighting the role of the gut-brain axis in IBS pathophysiology. For example, Fadgyas *et al.*, demonstrated that stress exacerbates gastrointestinal symptoms by amplifying visceral hypersensitivity [18]. Depression and anxiety, though prevalent, did not show a significant association with outcomes in this study. Notably, the results showed that patients with severe symptoms at the time of enrollment had a higher likelihood of symptom persistence at six months, an association also supported by Ozer *et al.*, on IBS prognosis [19]. In terms of IBS subtypes, the findings align with previous studies indicating a significant remission rate observed in the IBS-D subtype (p=0.03) aligns with global data, including the study by Pereyra *et al.*, which highlights that diarrhea-predominant IBS may respond better to usual care and targeted therapies compared to other subtypes [20].

CONCLUSIONS

It was concluded that the study determined a shorter symptom duration of less than 3 years along with the IBS-D sub-type as a predictor of improved remission rates. Psychological distress, particularly high stress levels, along with non-digestive symptoms such as backache and fatigue, are significant predictors of symptom persistence. These findings highlight the importance of early intervention, particularly for individuals with a shorter symptom history, to improve remission outcomes. Incorporating mental health support and addressing non-digestive symptoms in the management of IBS may enhance treatment effectiveness and improve patients' overall quality of life.

Authors Contribution

Conceptualization: KHS
Methodology: KHS, AKN, MH, AM, TG, SF
Formal analysis: TG
Writing review and editing: AKN, MH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v5i11.2529

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DOI: https://doi.org/10.54393/pjhs.v5i11.2549

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Metabolic Syndrome in Obese and Non-Obese Individuals Presented at A Tertiary Care Hospital of Hyderabad, Pakistan

Javeria Tariq[1], Mona Humaira[1*], Atif Ahmed[2], Abeer Memon[1], Naila Memon[1] and Madiha Shah[1]

[1]Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[2]Department of Medicine, Bilawal Medical College, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

ARTICLE INFO

Keywords:
Metabolic Syndrome, Obesity, Dyslipidemia, Hypertension, Diabetes Mellitus

How to Cite:
Tariq, J., Humaira, M., Ahmed, A., Memon, A., Memon, N., & Shah, M. (2024). Metabolic Syndrome in Obese and Non-Obese Individuals Presented at A Tertiary Care Hospital of Hyderabad, Pakistan : Metabolic Syndrome in Obese and Non-Obese Individuals. Pakistan Journal of Health Sciences, 5(11), 226-230, https://doi.org/10.54393/pjhs.v5i11.2549

***Corresponding Author:**
Mona Humaira
Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
monaahmed2810@gmail.com

Received Date: 3rd October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Metabolic Syndrome (MetS) has proved to be of enormous negative impact on health of humans, even in case of non-obese people. **Objective:** To determine the frequency of metabolic syndrome in obese and non-obese individuals at Liaquat University Hospital Hyderabad/Jamshoro. **Methods:** This Cross sectional comparative study was conducted on 122 persons, 61 obese and 61 non-obese persons, chosen through Non probability consecutive sampling technique. Patients of either gender, aged between 30 to 60 years, visited the OPD or hospitalized were selected. The patients with acute or chronic Ischemic heart disease or stroke, liver, lung or kidney or thyroid diseases or suffering from malignancy along with Pregnant ladies and lactating mothers were excluded. MetS was diagnosed via IDF and AHA classification. **Results:** Metabolic Syndrome (MetS) was significantly more prevalent in obese individuals (70.5%) than in non-obese individuals (19.7%) ($p = 0.001$). Obese participants had a higher BMI (29.24 kg/m^2 versus 20.70 kg/m^2, $p = 0.001$), greater prevalence of dyslipidemia (63.9% versus 16.4%, $p = 0.001$), and uncontrolled diabetes (41.0% versus 13.1%, $p = 0.001$). Blood pressure was significantly elevated in the obese group, with mean systolic and diastolic pressures of 143.52 mmHg and 93.11 mmHg, respectively ($p = 0.001$). **Conclusion:** MetS was present in 45.1% of the participant and was found to be strongly consistent with obesity although it was also detected in noteworthy portion of non-obese persons.

INTRODUCTION

Metabolic syndrome is a metabolic syndrome is an emerging global health concern. Enormous number of people being diagnosed with met s and the world is significantly suffering from its consequences. On one hand it's the reflection of increase in burden of associated risk factors, on the other hand resultant morbidity and subsequent mortality is increased. It enhances the risk of myocardial infarction 34 folds and of stroke 24 folds [1]. It execute very high chances of development of Type 2 diabetes as likelihood is increased by 5 times, not only this but multiplies the risk of overall mortality by 1.5 fold [2]. Prevalence of metabolic syndrome is ranging from 10% to 84% worldwide, in USA it is about 35% 2 and the pooled prevalence in South Asia is stretched from 14% to 32.5% [3, 4]. Met s showed geographical disparity which also suggest role of genetic and environmental factors [3]. Detection of amplified number of new case reveal it like a noninfectious epidemic [4]. Metabolic syndrome is diagnosed by the presence of three of the five chief contributors i.e. increased waist circumference or belly fat, high plasma triglycerides two major lipids include fasting triglyceridemia >150 mg/dL and HDL cholesterol concentration <40 mg/dL, elevated blood pressure and high blood sugar [2]. In Pakistan burden of disease is still largely undocumented even pooled surveys are not on note but as the risk factors are very abundant in this country possibility is that huge number of Pakistanis also being suffered from the perilous effects of MetS [4]. Newer

DOI: https://doi.org/10.54393/pjhs.v5i11.2549

research pointed out that MetS is also found in non-obese persons. An international health organization discovered metabolic syndrome was present in 5% of non-obese and 60% of obese people [1]. This highlighted that metabolic pathologies are accountable for the occurrence of diabetes and heart disease. Many researchers suggest that insulin resistance is the main culprit behind the pathogenesis of MetS [1, 2]. Many of the features of MetS are the result of insulin resistance, e.g., diabetes, dyslipidemia, hyperuricemia, increased inflammatory markers, endothelial dysfunction, and thrombosis, etc [5]. The research objective was to assess the existence of metabolic syndrome among obese and non-obese persons at a tertiary care hospital in Sindh, where patients come from both rural and urban areas, with the majority belonging to a low socioeconomic class. This study focused on a socioeconomically disadvantaged population, shedding light on the unique challenges and health disparities faced by these groups. As very scanty data are available from Pakistan, this study represented a snapshot of the situation among poor people from the interior of Sindh.

The results would help in understanding the disease burden, and life-threatening consequences of MetS could be prevented by taking proper actions. This awareness would also be beneficial in the prevention of MetS in society.

METHODS

After approval from Ethical Review Committee, this comparative cross sectional study was conducted at Department of Medicine Liaquat University Hospital, Hyderabad for the period of six months from October 2022 to March 2023. The sample size of 122 patients was calculated via taking the average prevalence of metabolic syndrome as 19.1%, with d=7% and CI of 95%. Patients were divided into 2 groups; 61 obese and 61 non –obese persons were enrolled, through [8]. Non probability consecutive sampling technique was used due to the feasibility of accessing patients in a tertiary care hospital setting where significant issues of time constraints, and resource limitations were there. Subject to informed consent patients of either gender, aged between 30 to 60 years, visited the OPD or hospitalized fulfilling the exclusion criteria, were selected. The study was approved from Ethical Review Committee of Liaquat University of Medical and Health Sciences, Jamshoro vide letter no. NO. LUMHS/REC/-148; dated: 29/09/2022. The patients with acute or chronic Ischemic heart disease or stroke, liver, lung or kidney or thyroid diseases or suffering from malignancy were excluded. Patients using following substances were not included in the research; Alcohol, corticosteroids, betablockers, hormone replacement therapy, selective estrogen receptor modulators, anabolic or anti-obesity medication. Pregnant ladies and lactating mothers were also omitted from the study. Metabolic syndrome was diagnosed when a patient has at least ≥3 of the following five parameters: fasting glucose ≥100 mg/dL, blood pressure ≥130/85 mm Hg, triglycerides ≥150 mg/dL, HDLC < 40 mg/dL in men or < 50 mg/dL in women and waist circumference ≥90 cm (35 in) in men or ≥80 cm (32 in) in women. These parameters were assessed as part of usual standard hospital protocols. Both groups were compared for these parameters. Non-Obese were defined as those individuals with BMI of 18.522.9 kg/m2 and BMI ≥25 kg/m was defined as obese as per Asia Pacific guidelines [3, 4]. The data were analyzed by using SPSS version 26.0. The association of prevalence of metabolic syndrome and other categorical variables (Dyslipidemia, Uncontrolled Diabetes, Smoking, Hyperuricemia and Hypomagnesemia) were measured via Chi-square test while the difference of quantitative variables (Mean BMI, Mean Systolic BP and Mean Diastolic BP) between the groups was measured via independent T test. A p-value of ≤0.05 considered statistically significant while a p-value of ≤0.001 was considered as highly statistically significant.

RESULTS

The mean age of obese participants was 46.23 ± 9.30 years, while that of non-obese participants was slightly higher at 49.76 ± 5.50 years. In terms of gender distribution, males constituted a majority in both groups, accounting for 62.3% of obese participants and 52.5% of non-obese participants, while females comprised 37.7% and 47.5%, respectively. Smoking status showed that 32.8% of obese individuals were smokers compared to 45.9% among the non-obese group.

Table 1: Demographic Variables of Study Participants (n=122)

Demographic Variables		Obese Mean ± SD / N (%)	Non-Obese Mean ± SD / N (%)
Mean Age		46.23 ± 9.30 Years	49.76 ± 5.50 Years
Gender	Male	38 (62.3%)	32 (52.5%)
	Female	23 (37.7%)	29 (47.5%)
Smoking Status	Present	20 (32.8%)	28 (45.9%)
	Absent	41 (67.2%)	33 (54.1%)
Catchment	Urban	42 (68.9%)	30 (49.2%)
	Rural	19 (31.1%)	31 (50.8%)

Regarding the catchment area, the majority of obese participants (68.9%) were from urban areas, whereas non-obese participants were more evenly distributed, with 49.2% from urban and 50.8% from rural areas. (Table 1) Patient`s symptoms were shown in Figure 1.

DOI: https://doi.org/10.54393/pjhs.v5i11.2549

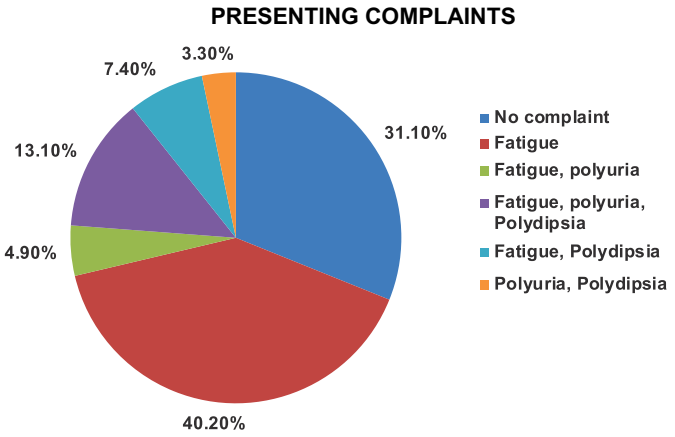

Figure 1: Presenting Complaints among study Patients

Metabolic Syndrome (MetS) was significantly more prevalent among obese patients (70.5%) compared to non-obese patients (19.7%) (p = 0.001). Obese individuals had a higher mean BMI (29.24 kg/m^2 versus 20.70 kg/m^2, p = 0.001) and showed greater prevalence of dyslipidemia (63.9% versus 16.4%, p = 0.001) and uncontrolled diabetes (41.0% versus 13.1%, p = 0.001). Additionally, mean systolic blood pressure (143.52 mmHg versus 120.81 mmHg) and mean diastolic blood pressure (93.11 mmHg versus 82.06 mmHg) were significantly higher in obese patients (p = 0.001). Hyperuricemia was also more common in obese individuals (24.6% versus 9.8%, p = 0.031), while hypomagnesemia did not differ significantly between the groups (11.5% versus 3.3%, p = 0.083) as shown in Table 2.

Table 2: Frequency of Metabolic Syndrome and Its Features among study participants

Mets Features	Present N (%)	Absent N (%)	Obese Patients N (%)/%	Non-Obese Patients N (%)/%	p-value
Metabolic Syndrome	55 (45.1%)	67 (54.9%)	43 (70.5%)	12 (19.7%)	0.001
			18 (29.5%)	49 (80.3%)	
Mean BMI Kg/m^2			29.24%	20.70%	0.001
Mean Systolic BP (mmHg)			143.52%	120.81%	0.001
Mean Diastolic BP (mmHg)			93.11%	82.06%	0.001
Dyslipidemia			63.9%	16.4%	0.001
Uncontrolled Diabetes			41.0%	13.1%	0.001
Smoking			32.8%	45.9%	0.138
Hyperuricemia			24.6%	9.8%	0.031
Hypomagnesemia			11.5%	3.3%	0.083

DISCUSSION

The concept of metabolic syndrome was dated back to 1970's, discovered particularly in relation with CVS diseases [6]. Many hypothesis being proposed but exact mechanism was still not clear for occurrence of MetS. It`s presence was a red alert sign for increase mortality and morbidity. Related to modern life style, physical inactivity and dietary habits metabolic syndrome was speedily growing set of interlinked diseases which has disastrous effect on life of people [7]. Overall, metabolic syndrome was present in 45.1% of these samples. This was a very alarming percentage, to make result generalized further trials were needed. In USA meta-analysis reported prevalence of METS as 37.6% [8]. In a South African study, authors detect the presence of MetS in 35% of obese as compare to 5% in normal weight subjects (P<0.01). Like this study they also noticed statistically suggestive relationship between obesity and presence of characteristic parameters of the condition [9]. In this study it was found that elderly people were more prone to develop MetS as compare to younger age group. This was noticed by other researchers as well [10]. It was found that often women were the victim of set of metabolic abnormalities in this community as compare to men; again this was also checked by other authors including researchers from neighbor country [3, 6]. 48.1% of female from these sample found to effect from this syndrome, majority of them were obese. In this study two groups were made of individuals; obese and non-obese, each consisting of 61 persons. Both groups were compared for the presence of MetS and its associated risk factors. This study demonstrated statistically noteworthy association of obesity with metabolic syndrome as analysis showed a p-value of 0.001. Their connection was a highlighted phenomenon and also found true in the people of lower socioeconomic class of interior of Sindh [11]. 70.5% of obese individuals were found to have MetS, while 29.5% did not exhibit this condition. In contrast, among non-obese participants, 19.7% were diagnosed with metabolic syndrome, leaving 80.3% without the condition. Pakistan belongs from third world countries but it stands on 9th position in obesity among 188 countries .Obesity was high in urban areas as compared to the rural area [12]. Presence of MetS in about 20% of non-obese individuals in this study was somewhat lesser than identified in a local meta-analysis, where the pooled prevalence was 28.8%. In South Asian countries, where dietary habits and habitat were much similar with this country pooled prevalence of the disease in non-obese persons was, 30% [13]. This dissimilarity may be because of different study design. In a research study, by using data from the Continuous NHANES, authors identified that non-obese MetS patients were more prone for cardiovascular mortality. Presence of this syndrome in non-obese person syndrome suggest that visceral fat deposition was more pathological, which was thought to take part in endocrine and inflammatory process [14]. It was documented that majority of these MetS patients were residents of urban areas. This demographic factor was noticed by others as well [15]. In this research Hypertension, dyslipidemia and diabetes were immensely accompanying with obesity 63.9% of obese persons found to be dyslipidemic as compared to

DOI: https://doi.org/10.54393/pjhs.v5i11.2549

16.4% of non-obese. In a meta-analysis conducted by Adil SO *et al.*, authors found 29.5% of hypertensive persons, 20.6% of diabetic persons and 35.8% of patients with hypertriglyceridemia were offended by the particular syndrome. Highest prevalence was seen in persons with low HDL level, which was 48.2% [4]. In another Pakistani research author estimate MetS prevalence in diabetics was 65.6% according to latest criteria by IDF [16]. Mitochondrial oxidative stress and involvement of various signaling pathways like NFkB, PKC, MAPK, polyol, JNK, ERK, and NOX were postulated to play fundamental role in production of metabolic syndrome and it`s consequence morbidity [17]. Individuals were enlisted mainly from the OPD with no or minor illnesses and exclude the patients with stroke or MI and other major disease, it was found that a large number of patients felt lethargic or fatigued, comprising 40.2%. The high occurrence of fatigue as the presenting complaint emphasizes the workup for the set of metabolic abnormalities in such persons. A smaller percentage of individuals experienced varied combination of symptoms of fatigue, polyuria, and polydipsia. In the study published in 2020 authors found significant link between the two conditions. They calculated that chronic fatigue was 2 fold more common in patients of metabolic syndrome than controls, as the number of risk factors increases chances of chronic fatigue increases by 30% [18]. In this study it was observed that obese persons were more troubled from Hyperuricemia as compare to non-obese person and it was statically proved in this study. A recent study from China give supporting evidence that Hyperuricemia was positively linked with MetS and most of its component diseases [19]. Further research is necessary to investigate the correlation between magnesium levels and Metabolic Syndrome (MetS). Magnesium's role in MetS is of particular interest due to its involvement in various bodily reactions and inflammatory processes. While previous studies have suggested a link between magnesium and parameters like obesity and diabetes [20], our research found no significant difference in magnesium levels between obese and non-obese individuals (p-value = 0.083). This suggests that magnesium levels may not be a distinguishing factor between obese and non-obese populations, warranting further exploration of its role in MetS. In this research it was spotted that there was no significant difference between magnesium levels of obese and non-obese persons with p value of 0.083. The use of non-probability sampling technique was a major limitation of the study as it poses the selection bias and the risk that broader population may not be adequately represented in the sample.

CONCLUSIONS

Frequency of MetS was found to be 45.1% in this study. Metabolic syndrome and its associated risk factors, including dyslipidemia, uncontrolled diabetes, hypertension, and hyperuricemia, were significantly more prevalent in obese individuals compared to non-obese individuals. These findings highlight the urgent need for targeted interventions to address obesity-related metabolic disturbances, particularly in populations with high prevalence rates, to reduce the burden of cardiovascular and metabolic diseases.

Authors Contribution

Conceptualization: JT
Methodology: JT, MH, AA, AM, NM, MS
Formal analysis: JT
Writing, review and editing: JT, MH, AA, AM, NM, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.1740

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Decoding Demise: A Comprehensive Analysis of Unnatural Deaths in Rahim Yar Khan

Qurrat Ul Ain Kamran[1*], Ummara Munir[1], Mobin Inaam Pal[2], Abdul Samad[3], Shahla Imran[4] and Mashooq Ali[5]

[1]Department of Forensic Medicine, Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan
[2]Department of Forensic Medicine, Faisalabad Medical University, Faisalabad, Pakistan
[3]Department of Forensic Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[4]Department of Forensic Medicine, Bilawal Medical College, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[5]Department of Forensic Medicine, Army Medical College, Rawalpindi, Pakistan

ARTICLE INFO

Keywords:
Medico-legal Autopsy, Unnatural Death, Homicide, Suicide

How to Cite:
Kamran, Q.- ul-A., Munir, U., Pal, M. I., Samad, A., Imran, S., & Ali, M. (2024). Decoding Demise: A Comprehensive Analysis of Unnatural Deaths in Rahim Yar Khan: Decoding Demise: A Comprehensive Analysis of Unnatural Deaths. Pakistan Journal of Health Sciences, 5(11), 231-235, https://doi.org/10.54393/pjhs.v5i11.1740

***Corresponding Author:**
Qurrat Ul Ain Kamran
Department of Forensic Medicine, Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan
dr.qurratulainkamran@yahoo.com

Received Date: 21st May, 2024
Acceptance Date: 21st November, 2024
Published Date: 30th November, 2024

ABSTRACT

A medico-legal autopsy is a systematic examination of a deceased body conducted under the law of the state to determine the cause, and manner of death and to verify or dismiss any potential involvement of foul play related to the deceased. **Objective:** To assess the spectrum of unnatural deaths in the district of Rahim Yar Khan. **Methods:** This retrospective descriptive study was done at the Department of Forensic Medicine and Toxicology, Sheikh Zayed Medical College, Rahim Yar Khan from 1st January 2021 to 31st December 2023. Variables were age, gender, cause and manner of death, weapon, and residence. All autopsies referred by police were included except hospital, police torture and custodial deaths, and putrefied or exhumed bodies. Data from police, hospital records, and autopsy reports were recorded on a pre-designed form. **Results:** There was male preponderance of 72.57% to female with 27.43%. In general, 78% of all deaths were homicidal, compared to 12% suicidal, 9% accidental and 1% remained undetermined. The 21-30-year age range is the most often afflicted group. Firearms as the leading cause of death followed by blunt objects, asphyxia and sharp weapons accounted for the majority of fatalities respectively. The instances involved 44.25 % urban inhabitants as compared to 55.75% peri-urban ones. **Conclusions:** It was concluded that men accounted for the majority of unnatural deaths. The most common cause of death was murder. Guns and blunt weapons were the leading causes of death. Compared to the surrounding area, the city had a higher number of unnatural fatalities.

INTRODUCTION

Ultimately, we will all face death, no matter how much we try to escape it. Despite being inevitable, it is not easily accepted. Things get trickier when they aren't natural—that is when they go against nature's order or are brought about too soon as a result of harm, aggression, or poison [1]. A lower figure for the frequency of unnatural fatalities in a certain location indicates a secure, peaceful, and hospitable community, which in turn reflects the law and order situation in that area. Many fatalities across the world are supposedly caused by supernatural forces [2]. According to medical science, a person is considered to have died when the heart, lungs, and brain no longer pump blood throughout the body. "Manner of death" denotes the circumstances or manner of death, such as accidental, homicidal, suicide, or others, whereas "cause of death" refers to the medical conclusion of what led to the individual's mortality. Injuries or poisoning are examples of unnatural causes of death, whereas diseases and ageing are common causes of natural death. Intentional injuries, such as those caused by murder or suicide, and accidental injuries, such as those sustained in car accidents, are two subsets of these exogenous variables [3]. The loss of a loved one has far-reaching consequences for those closest to them as well as for society as a whole, and suicide is one of the biggest killers on a global scale. An individual's risk of suicide increases due to a wide range of situations,

DOI: https://doi.org/10.54393/pjhs.v5i11.1740

including, but not limited to, a history of depression, substance misuse, relationship failure, and community violence [2]. One person commits suicide in Pakistan per hour, with a daily rate of 15–35 suicides [3]. A homicide occurs when one person intentionally causes the death of another. When a person's demise is due to anything that was not anticipated, it is referred to as an accidental death. When a person knowingly and voluntarily ends their own life, it is referred to as a suicide. Lack of clear results from toxicological tests and autopsies has left several unexplained deaths unsolved. Unexpected death rates are an indicator of the mental and social health of a society. The purpose of conducting a medico-legal inquiry into death is to determine responsibility and provide punishment in many nations. The results of a death inquiry are useful for more than just filling gaps in understanding; they are also essential for public health monitoring, epidemiological research, and enhancing community safety [4]. Conclusive toxicological testing or indecisive physical examination on autopsies leave many unexplained deaths unsolved. It is socially stigmatizing to die from certain causes, such as suicide or violent crimes, and the prevalence of unexpected deaths is an indication of the mental and social health of a society. The goals of justice and offering comfort to the grieving family and the society at large are achieved in most nations through medico-legal investigations into deaths that determine blame and appropriate punishment. As a society, we must prioritize this for the sake of peace, justice, and the prevention of crime. A medico-legal inquiry is required if it is known or suspected that an unnatural cause contributed to a death [5]. A police or magistrate inquiry, followed by a court review, is necessary in the event of an unexplained death in Pakistan. Licensed medical experts perform autopsies at public hospitals and other government-run facilities. If you want to know what killed someone, you need an autopsy. The method of death explains the process by which an illness or injury causes death and can be either natural, accidental, suicide, homicidal, or undetermined [3]. Deaths by suicide, animals or equipment, accidents, torture or ill-treatment, occupational illnesses, alleged medical malpractice, strange or unnatural deaths, fatalities after surgery or anesthesia, and bodies that cannot be recognized or have only their skeletons preserved are all examples of this [6]. Authorities such as police, magistrates, coroners, or medical examiners conduct inquests to collect evidence regarding a death. The police will safeguard the area and collect evidence on criminal charges. When a person dies in a murder, the medical examiner orders an autopsy to establish the cause of death. This can provide light on any circumstances surrounding the death, such as whether it was a suicide, an accident, an act of violence, or a crime. The use of both police and magistrate inquests is commonplace in Pakistan. In situations concerning alleged medical negligence, violent deaths, unexpected or mysterious deaths, and issues about surgical or medical procedures, an inquest is conducted by an authorized official or a police officer from a specific station in conjunction with an investigation. In cases of death while in custody, magistrates investigate the circumstances surrounding the death [7]. Sheikh Zayed Medical College's Forensic Medicine Department conducts medico-legal autopsy in Rahim Yar Khan. Sitting at the crossroads of the Punjab and Sindh provinces, this city is a hive of activity. Like any major city, Rahim Yar Khan has its fair share of criminal activity, but residents there tend to feel safer than in other parts of Pakistan. Police personnel from several stations within the district's urban and peri-urban legal jurisdiction refer cases that need autopsies.

This study aims to investigate the circumstances surrounding a death that occurs suddenly or for no apparent reason.

METHODS

This retrospective descriptive study was done at the Department of Forensic Medicine & Toxicology, Sheikh Zayed Medical College, Rahim Yar Khan from 1st January 2021 to 31st December 2023 after getting approval with reference no. 87/IRB/SZMC/SZH. A total of 226 cases, where police had requested autopsies, were conducted by authorized medical officers /demonstrators of the Forensic Medicine Department. Data were collected from respective official Police records, FIRs and post-mortem reports and recorded on pre-structured proformas. It was categorized based on the type of manner of death, cause of death, age groups involved, gender, weapon, residence and year-wise number of cases. Non-probability purposive sampling technique was used. The sample size was estimated using a prevalence of 18%, a margin of error of 10%, and a confidence interval of 95%. Male and female cases of all age groups, from the area of Police stations under the Department of Forensic Medicine, Sheikh Zayed Medical College, Rahim Yar Khan were included. Cases killed in police encounters were excluded from this study. The autopsies were meticulously performed in the mortuary, involving a thorough physical examination, examination of clothing, external and internal body inspection, and required investigations. Various details such as age, sex, address, circumstances leading to death, findings from the autopsy, laboratory test results, and the final opinion were compiled into a single document. The data were entered and analyzed by using Statistical Package for Social Science (SPSS) version 26.0. Results for gender are presented by using frequencies and percentages. Age is described by mean ± SD. All data for death are presented by years. Distribution of deaths by age,

DOI: https://doi.org/10.54393/pjhs.v5i11.1740

and gender, by gender and residential status, by years and manners of death, and by years and cause of death are presented in tables with frequencies.

RESULTS

There were 164 (72.5%) male deaths more than female deaths 62 (27.43%) and the mean age was 3.84 ± 1.55 years (Table 1).

Table 1: Demographic Profile of Participants (n=226)

Gender	Number (%)
Male	164 (72.57%)
Female	62 (27.435)
Mean Age (Years)	3.84 ± 1.552

The age range between 21-30 years showed more responses as compared to other age ranges. Total number of victims involved in the age range between 21-30 years is 28(26.5%)(Table 2).

Table 2: Comparison of Gender According to Age from 2021-2023 of Autopsies

Age (Years)	2021			2022			2023		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0-10	4	6	10	1	1	2	3	1	4
11-20	6	4	10	1	1	2	14	-	14
21-30	8	12	20	10	4	14	24	4	28
31-40	16	2	18	10	4	14	8	10	18
41-50	8	2	10	8	6	14	14	-	14
51-60	3	1	4	7	5	12	3	1	4
>71	-	-	-	-	-	-	-	-	-
Total	49	29	78	38	22	60	72	16	88

It showed the peri-urban residents had more responses 126 (55.75%) as compared to urban cases 100 (44.25%) involvement of victims(Table 3).

Table 3: Sex-Based Demographic Distribution of Autopsies

Area	2021		2022		2023		Total
	Male	Female	Male	Female	Male	Female	
Urban	20	12	20	10	32	6	100
Peri-urban	34	12	20	10	42	8	126
Total	54	24	40	20	74	14	226

In unnatural deaths, the homicidal manner is leading with 160 (70.79%) cases, followed by suicidal 26 (11%) and accidental 12(5.3%). The cases which remained undetermined were 28(12.3%)(Table 4).

Table 4: Manner of Death in Autopsies

Year	Manner of Death				Total
	Homicidal	Suicidal	Accidental	Undetermined	
2021	58	6	2	12	78
2022	44	8	4	4	60
2023	58	12	6	12	88

Firearms are the leading cause of 66(29.2%) cases followed by blunt weapons with 48(21.23%) deaths and asphyxia with 28(12.38%) causes of death(Table 5).

Table 5: Causes of Death in Autopsies

Year	Cause of Death								Total
	Sharp	Blunt	Fire arm	Asphy -xia	Drow -ning	Poison -ing	Accident	Undeter -mined	
2021	12	18	22	4	-	6	2	12	78
2022	-	14	20	8	4	-	4	4	60
2023	10	16	24	16	4	-	6	10	88
Total	22	48	66	28	8	6	12	26	226

DISCUSSION

As per the World Health Organization, the term "cause of death" encompasses "all illnesses, abnormal conditions, or injuries that directly led to death or played a role in the occurrence of death, along with the circumstances of any accidents or instances of violence that led to such fatal injuries." The realm of mortality encompasses both natural and unnatural causes. An individual becomes a casualty of unnatural demise when they expire under circumstances beyond their control. Medico-legal (ML) autopsies are conducted at the behest of the investigating authority in cases of ML deaths [8]. There were 12 (5.31%) accidental cases, 160 (70.79%) homicidal cases, 26 (11.50%) suicides, and 28 (12.39%) the cause of death could not be determined. Among the 62 (27.43%) unnatural deaths of females, 8 (12.9%) were suicides, 50 (80.64%) were homicides, and none were accidental. This study also shows out of 226 medico-legal deaths, the majority of cases involved being killed by another person (homicide) followed by committing suicide and accidents in last. These finding are consistent with other studies showing that the leading cause of unnatural deaths is homicide and also demonstrate the dominance of gunshot deaths in medico-legal mortality [9]. The second most common manner of death in our study in contrast with the statistics shows that suicides are more prevalent in the US in comparison with homicide with a ratio of 3:1[10]. According to the results of the current study, there were 164 male deaths (72.5%) more than female deaths 62 (27.43%), and the ratio of male to female deaths was 3:1. The male preponderance result is consistent with those of other authors [11, 12]. In general, distinct male domination in unnatural cases is likely the same as the result of a study done at Faisalabad [13]. Current findings are also in line with the findings of the study done in India [14] may be due to the same socio-economic conditions of both countries. It can also explain men's greater mobility, involvement in outdoor work activities, and travel in countries with similar socio-cultural values, which put them at greater risk than women. In this study, the victims' age group from 21 to 30 was the most severely affected 62 (27.43%). These results are similar to the studies of others that reported the highest rates of fatalities among this age group [12]. This can be because this age group is more energetic, emotional, and

DOI: https://doi.org/10.54393/pjhs.v5i11.1740

autonomous in their childhood, exposing them to all kinds of harshness and stressors. The present study showed that a major portion of victims was found to be peri-urban inhabitants, in contrast with the study in which urban cases are more than in peri-rural areas. The study shows that 66 (29.20%) deaths were caused by firearms. This could be explained in a way that people in this region may consider firearms as status symbols and keep guns at their place of residence. In the context of Punjabi music, Sharma posits that the portrayal of guns and violence may contribute to the reinforcement of traditional gender roles, as men are often depicted as powerful and dominant through the use of firearms [15]. Availability of firearm weapons and lack of education suggests A relationship exists between the high rate of guns and gun ownership and the number of homicides, suicides and injuries [16]. In the United States, from 2020 to 2021, the percentage of homicides and suicides attributed to firearm injuries increased from 79% to 81% and from 53% to 55%, respectively, resulting in the highest percentage for homicide in more than 50 years and the highest percentage for suicide since 2001 [10]. The second most predominant cause of death is blunt 48 (21.23%), as a variety of blunt weapons are readily accessible and commonly cited in crime cases, including items such as walking sticks, hammers, pipe wrenches, wrecking bars, and heavy-duty flashlights [17]. Asphyxia is the third main contributor as the cause of death with 28 (12.38 %) which is quite similar to the study done at Rawalpindi [18]. The results of our study are in accord with the results of a study done in India where the cases of hanging were all suicidal and smothering, strangulation and throttling were homicidal. Among the cases of drowning, 89.28% were accidental and 10.71% were suicidal [19]. According to the study, 12 (5.3%) participants were killed in automobile accidents which is very negligible in contrast with the study in the same region in which accidents were the most significant cause of death constituting 63.27% [20]. Non-violent methods including ingesting pesticides, being poisoned by fumes, suffocation, and drug overdose made up only a small proportion of the study. Poverty can lead to living in unsafe environments, inadequate access to healthcare services, and increased exposure to risk factors such as substance abuse and violence. Education levels can also impact mortality rates, as higher education is often associated with better health knowledge and behaviours.

CONCLUSIONS

It was concluded that the leading causes of death in the study were found to be accidents, suicide, and violent crimes. At the same socioeconomic level, male mortality was greater. Shooting deaths were created by the media's and society's portrayal of guns and their accessibility and significance. Victims of car accidents, suffocation, and sharp objects died in peculiar ways. South Punjab's road traffic accidents, poverty, and illiteracy all contribute to the region's high death toll, as predicted.

Authors Contribution

Conceptualization: QUAK
Methodology: QUAK, UM, MIP
Formal analysis: QUAK, UM, MIP, AS, SI, MA
Writing review and editing: UM, MIP, AS, MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2204

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Atrial Fibrillation in Patients with Acute ST Elevation Myocardial Infarction

Zakir Ullah[1], Shafiq Alam[2*], Javaid Ur Rehman[3], Younas Khan[4], Kashif Khan[5], Owais Qaisar[6], Muhammad Awais[7], and Zakir Ullah[8]

[1]Department of Cardiology, Mardan Medical Complex, Mardan, Pakistan
[2]Department of Cardiology, Bacha Khan Medical College, Mardan, Pakistan
[3]Department of Cardiology, Nowshera Medical College, Nowshera, Pakistan
[4]Department of Forensic Medicine and Toxicology, Swat Medical College, Swat, Pakistan
[5]Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan
[6]Department of Physiology, Jinnah Medical College, Peshawar, Pakistan
[7]District Head Quarter Hospital, Medical Teaching Institution, Bannu, Pakistan
[8]District Head Quarter Hospital, Kohat, Pakistan

ARTICLE INFO

Keywords:
Heart, Myocardial Infarction, Atrial Fibrillation, Acute ST Elevated Myocardial Infarction.

How to Cite:
Ullah, Z., Alam, S., Rehman, J. U., Khan, Y., Khan, K., Qaisar, O., Awais, M., & Ullah, Z. (2024). Atrial Fibrillation in Patients with Acute ST Elevation Myocardial Infarction: Atrial Fibrillation in Acute ST Elevation MI. Pakistan Journal of Health Sciences, 5(11), 236-240, https://doi.org/10.54393/pjhs.v5i11.2204

Corresponding Author:
Shafiq Alam
Department of Cardiology, Bacha Khan Medical College, Mardan, Pakistan
iamkhani@gmail.com

Received Date: 25th September, 2024
Acceptance Date: 23rd November, 2024
Published Date: 30th November. 2024

ABSTRACT

Atrial fibrillation (AF) can lead to complications such as stroke and heart failure. The prevalence of AF in patients with MI has garnered increasing attention due to its significant impact on clinical outcomes. Understanding its prevalence and associations with various risk factors is crucial for improving patient management and outcomes. **Objective:** To determine the frequency of atrial fibrillation in acute ST elevation myocardial infarction. **Methods:** Descriptive cross-sectional study, conducted at Department of Cardiology, Mardan Medical Complex, Mardan from September 2023 to August, 2024. About 118 patients, already diagnosed cases of acute ST segment elevation myocardial infarction, were enrolled in the study. Atrial fibrillation was considered positive on the absence of P waves and irregularly irregular QRS complexes on surface electrocardiography. Data were collected under the supervision of expert consultant and analyzed using SPSS version 20. **Results:** Atrial fibrillation was observed in 14% (n=17) of the patients with STEMI. The mean age of the cohort was 55 years (SD±9.29). The study population was predominantly male (66%) with a high prevalence of diabetes (71%) and hypertension (78%). Despite these factors, no significant correlation was found between atrial fibrillation and diabetes, smoking status, BMI, or hypertension ($p>0.05$). **Conclusions:** Our study concludes that the frequency of atrial fibrillation was found to be 14% in the participants presenting with acute STEMI. Identifying no significant associations between AF and the common risk factors analyzed, these findings underscore the necessity for more research to investigate additional factors and mechanisms that connect AF with STEMI.

INTRODUCTION

Myocardial infarction (MI), commonly known as a heart attack, occurs due to restricted blood supply causing damage or death of the heart muscle [1]. It is a key manifestation of acute coronary syndromes (ACS), which include unstable angina (UA), non-ST-elevation MI (NSTEMI), and ST-elevation MI (STEMI) [2]. While STEMI typically develops Q-waves, NSTEMI and UA are diagnosed based on cardiac enzyme levels. Globally, myocardial infarction is a significant contributor to cardiovascular morbidity and mortality, with approximately 1.5 million cases reported annually in the United States alone [3]. According to the World Health Organization (WHO), cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year [4]. The 2019 Global Burden of Disease study reported that the age-standardized incidence of CVD in Pakistan was 918.18 per 100,000 population (compared to the global rate of 684.33 per 100,000), while the age-standardized mortality rate was 357.88 per 100,000 (global rate: 239.85 per 100,000) [5]. Atrial fibrillation (AF), the most commonly

DOI: https://doi.org/10.54393/pjhs.v5i11.2204

encountered clinical arrhythmia, often coexists and complicates acute myocardial infarction (AMI) with an incidence between 6 and 21% [6, 7]. STEMI was reported in 44.9% while AF in 12.5% in Karachi while in Peshawar, STEMI in about 62.5% and new onset AF about 7.19% [8, 9]. AF is characterized by disorganized atrial activity and rapid, irregular ventricular response, leading to impaired atrial function. Its occurrence in AMI is often linked to localized necrosis, ischemic damage to the atria, or left ventricular failure. Recent studies have highlighted the prognostic significance of AF in AMI, with affected patients experiencing increased risks of thromboembolism, heart failure, and mortality [10]. Despite advancements in diagnostic tools such as ECG monitoring and echocardiography, AF remains underdiagnosed in AMI cases, especially in asymptomatic individuals [11]. In Pakistan, limited research has been conducted on the occurrence and implications of AF in STEMI patients. However, the growing burden of cardiovascular diseases, coupled with an aging and population growth [12], underscores the need for local studies. Data from Pakistan reveal similar trends but lack specificity regarding the role of arrhythmias like AF [13].

This study aimed to assess the frequency of AF in patients with acute STEMI and its association with clinical outcomes. By identifying the prevalence and risk factors of AF in this population, we hope to enhance early diagnosis and management strategies. Furthermore, the findings will contribute to the existing literature and guide targeted awareness and prevention programs tailored to the Pakistani context.

METHODS

This descriptive cross-sectional study was conducted in the Cardiology Department at Mardan Medical Complex over twelve (n=12) months, from September 2023 to August, 2024. The sample size of 118 was calculated using the WHO sample size calculator, based on a 26.6% prevalence rate of atrial fibrillation (AF) in acute STEMI cases, with a 95% confidence interval and an 8% margin of error [14]. A non-probability consecutive sampling technique was employed. Patients aged 30–70 years, of either gender, presenting with a confirmed diagnosis of acute STEMI were included in the study. Patients with a history of coronary artery bypass surgery, chronic renal failure, or previous percutaneous coronary intervention were excluded to minimize confounding factors and bias. Upon receiving approval from the hospital's Institutional Review Board (Ref. No: 570), data collection commenced. Eligible patients were enrolled through the cardiology department. The purpose of the study was explained to all participants, and informed written consent was obtained from those willing to participate. A detailed medical history was taken, including information on prior cardiac events, comorbid conditions (e.g., diabetes mellitus, hypertension), medication use, family history of cardiovascular diseases, and lifestyle factors such as smoking status. Routine investigations included complete blood count (CBC), fasting blood sugar (FBS), serum electrolytes, renal function tests, and cardiac enzyme levels. A thorough clinical examination included assessment of vital signs (heart rate, blood pressure), auscultation for murmurs or abnormal heart sounds, and evaluation for signs of heart failure, such as edema or jugular venous distension. Atrial fibrillation was diagnosed using a 12-lead ECG and rhythm strip analysis. Diagnostic criteria included the absence of P waves, irregularly irregular QRS complexes, and the presence of fibrillatory waves, particularly in lead II. All ECG findings were confirmed by a consultant cardiologist with over five years of experience. Patient demographic and clinical data, including age, gender, height, weight, body mass index (BMI), diabetes mellitus, hypertension, and smoking status, were meticulously recorded in a pre-designed proforma. Data were analyzed using SPSS version 20. Quantitative variables (e.g., age, height, weight, BMI) were expressed as mean ± SD, while categorical variables (e.g., gender, diabetes, hypertension, smoking status, and AF) were reported as frequencies and percentages. Stratification of AF by demographic and clinical factors was performed, and chi-square tests were used to assess associations, with statistical significance set at $p \leq 0.05$.

RESULTS

The study enrolled 118 participants, in which 66% (n=78) were male while female were about 34% (n=40). The majority, 84% (n=99) were falling within the 51-70 years age group, while 16% (n=19) were aged between 30-50 years. The mean age of the participants was 55 years±9.29. Regarding Body Mass Index (BMI), 22% had a BMI of 25 kg/m^2 or less (n=26), while 78% had a BMI greater than 25 kg/m^2 (n=92). The average BMI was 26 kg/m^2±5.56. Additionally, the mean weight was 90kg ±12.12, and the mean height was 1.5 meters (SD ±1.02). Diabetes mellitus was present in 71% of the patients (n=84), with 29% not having diabetes (n=34). Smoking was reported by 42% of the participants (n=50), while 58% were non-smokers (n=68). Hypertension was prevalent in 78% of the patients (n=92), and 22% did not have hypertension (n=26). Figure 1 illustrates the demographic characteristics of the participants.

DOI: https://doi.org/10.54393/pjhs.v5i11.2204

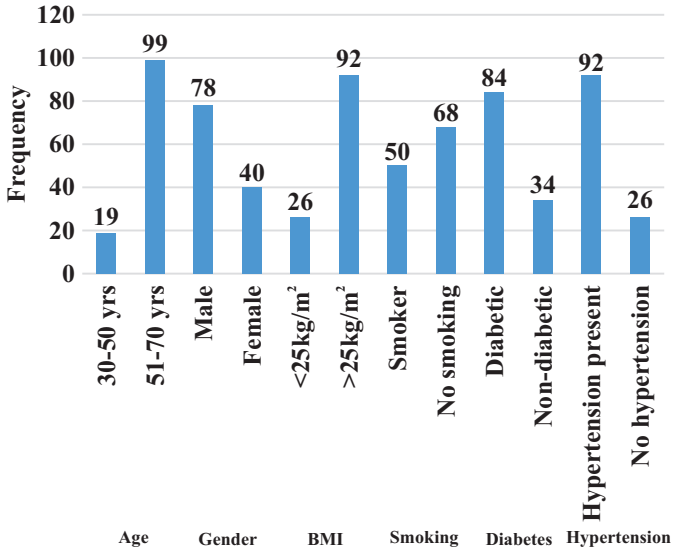

Figure 1: Demographic characteristics of the participants

AF was detected in 14% of the patients (n=17), while 86% did not exhibit signs of atrial fibrillation (n=101), as shown in figure 2.

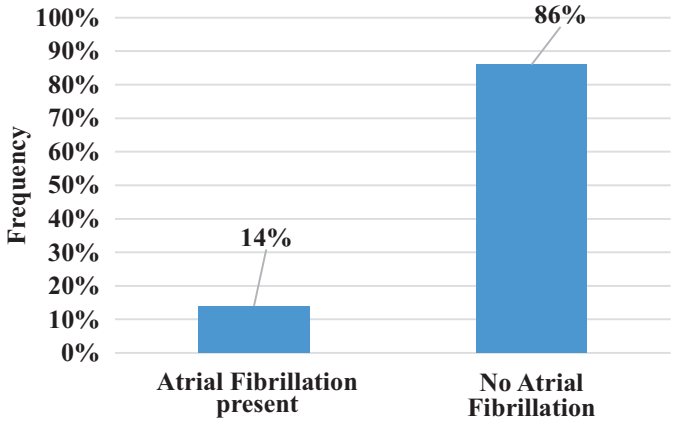

Figure 2 : Prevalence of Atrial Fibrillation

Table 1 shows the stratification of atrial fibrillation (AF) by demographic and clinical factors. Our study found no significant difference in AF prevalence across age groups (p=0.8513), 15.8% (n=3) in 30-50 years age group and 14.1% (n=14) in 51-70 years age group. No significant difference in AF prevalence between men and women (p=0.4932). 13% (n=10) of male patients, and 17% (n=7) of female patients. The chi-square test revealed no significant associations between AF and age or gender in our study population. Among the participants, 42% (n=50) were smokers, while 58% (n=68) were non-smokers. Atrial fibrillation was found in about 14% (n=7) of smokers and 14.7% (n=10) of non-smokers. There was no significant relationship between smoking status and atrial fibrillation (p=0.9140), suggesting that smoking did not have a significant impact on the likelihood of developing AF. Additionally, 78% (n=92) of the patients had hypertension, and 22% (n=26) did not. Atrial fibrillation was present in 14.1% (n=13) of those with hypertension and 15.4% (n=4) of those without hypertension. No significant association between hypertension and atrial fibrillation (p=0.8722), suggesting that hypertension did not notably affect the prevalence of AF in this cohort.

Table 1: Correlation of AF with Demographics and Risk Factors

Variables		Atrial Fibrillation		
		Yes	No	p-Value
Age	30-50 years	3	16	0.851
	51-70 years	14	85	
	Total	17	101	
Gender	Male	10	68	0.493
	Female	7	33	
	Total	17	101	
BMI	<25 kg/m^2	4	22	0.872
	>25 kg/m^2	13	79	
	Total	17	101	
Diabetes	Diabetic	12	72	0.953
	Non-Diabetic	5	29	
	Total	17	101	
Smoking	Yes	7	43	0.914
	No	10	58	
	Total	17	101	
Hypertension	Yes	13	79	0.872
	No	4	22	
	Total	17	101	

DISCUSSION

The frequency of atrial fibrillation (AF) in individuals experiencing an acute STEMI (heart attack) was examined in our study. It was noted that AF coexisted in 14% of individuals with acute STEMI. This finding was higher than report by Shakeel et al., who observed an incidence of AF in 6.5% of patients admitted with acute MI [15]. The prevalence was lower than reported Imran K *et al.*, discovered that the incidence of AF in STEMI patients was 26.6%, with 7.9% having pre-existing AF and 18.7% developing new-onset AF [16]. Similarly, 12.5% of AMI patients had new-onset AF, and there was a strong correlation seen between AF and hypertension, according to Iqbal Z *et al.* The research comprised 216 patients, with a mean age of 50.76 years ± 6.00 and about 54.2% men. Of the patients, 64.8% had diabetes, and 75.9% had hypertension [17]. Zhang *et al.* reported that age and male gender are among the risk factors for AF in patients with acute STEMI. However, our analysis did not find a significant correlation between AF and these risk factors. Despite the strong evidence from Zhang *et al.*, our findings suggest that age and gender may not be as influential in predicting AF in our patient population [18]. Elliott *et al.* identified increased BMI, smoking, and diabetes mellitus as significant risk factors for AF in patients with acute STEMI. While our study did not find a significant association between AF and these

DOI: https://doi.org/10.54393/pjhs.v5i11.2204

risk factors. Specifically, while Elliott *et al.* highlighted the impact of elevated BMI, smoking, and type 2 DM, our findings did not reveal a clear correlation between these factors and the occurrence of AF in our patient cohort [19]. Dai *et al.* identified increasing age, male gender, and elevated BMI as significant risk factors for AF. However, in our study, while AF was observed in 14% of patients with acute STEMI, we have not found any statistically significant association between these risk factors and the presence of AF [20]. Our study has limitations, including a small sample size, which hinders the applicability of our findings to larger populations. Additionally, the cross-sectional design limits our ability to establish cause-and-effect relationships between atrial fibrillation and its risk factors in STEMI patients. Future studies of larger sample size recommended with longitudinal study designs. Furthermore, it is recommended accurate and early diagnosis of patients lead to timely treatment in these high-risk people can to reduce the incidence, and better the management of AF in these patients.

CONCLUSIONS

This study findings shows 14% of patients with acute STEMI (heart attack) also had atrial fibrillation (AF). This prevalence is consistent with other studies, highlighting the importance of monitoring for AF in STEMI patients. Early detection and management of AF in STEMI patients is crucial for improving outcomes and reducing complications.

Authors Contribution

Conceptualization: KK, YK, MA, SA
Methodology: JUR, OQ, ZU[1]
Formal analysis: MSK, JT
Writing, review and editing: SA, MA, ZU[2], KK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2397

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Unveiling Parental Knowledge, Attitudes, and Practices on Intestinal Parasitic Infections in Lahore, Pakistan

Kanwal Zia[1], Sajid Hameed[2*], Khizzer Pervaiz[3], Zeeshan Ahmad[4], Asif Maqsood Butt[5] and Muhammad Hatim Hamid Khan[6]

[1]Department of Paediatric Surgery, Kahuta Research Laboratories Hospital, Islamabad, Pakistan
[2]Department of Public Health, Green International University, Lahore, Pakistan
[3]Department of Administration, Ali Medical Center Islamabad, Islamabad, Pakistan
[4]Department of General Surgery, Rai Medical College, Sargodha, Pakistan
[5]Department of Community Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan
[6]Department of Physiology, Services Institute of Medical Sciences (SIMS), Lahore, Pakistan

ARTICLE INFO

Keywords:
Intestinal Parasitic Infections, Knowledge, Attitudes, Practices

How to Cite:
Zia, K., Hameed, S., Pervaiz, K., Ahmad, Z., Butt, A. M., & Hamid Khan, M. H. (2024). Unveiling Parental Knowledge, Attitudes, and Practices on Intestinal Parasitic Infections in Lahore, Pakistan: Unveiling Parental Knowledge, Attitudes, and Practices on Intestinal Parasitic Infections. Pakistan Journal of Health Sciences, 5(11), 241-247. https://doi.org/10.54393/pjhs.v5i11.2397

***Corresponding Author:**
Sajid Hameed
Department of Public Health, Green International University, Lahore, Pakistan
doctorsajidhameed@gmail.com

Received Date: 9th October, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Intestinal Parasitic Infections are intestinal infections, especially in toddlers, caused by parasites such as worms. **Objectives:** To explore Knowledge, Attitudes, and Practices of Intestinal Parasitic Infections in Pakistan, emphasizing their interlinkage with other socio-demographic factors. **Methods:** This cross-sectional study was conducted in Pak town, Lahore, on 348 parents. A questionnaire was developed to record demographic data, five Knowledge items, seven Attitudes, and 12 Practice questions. IBM SPSS version 27 was used for all the analyses. Descriptive, chi-square and binary logistic regression analyses were applied. **Results:** The majority of participants were housewives (50.9%). The levels of Knowledge, Attitude, and Practices were poor in 56%, 60.9%, and 51.7% of the parents, respectively. There was a greater likelihood of good attitude in parents with good knowledge (adjusted OR=5.3; 95% CI=0.3-96.4) compared with poor knowledge. Male were less likely (adjusted OR=0.3; 95% CI=0.1-0.7) to present good attitudes than female. Parents with education level of Intermediate (adjusted OR=2.6; 95% CI=1.2-5.7), Graduate (adjusted OR=3.5; 95% CI=1.6-7.6), and Masters (adjusted OR=60.8; 95% CI=3.8-974.3) showed better attitudes than those with secondary education. Good practices were associated with the presence of good attitudes rather than poor attitudes (adjusted OR=0.6; 95% CI=0.4-0.9). **Conclusions:** It was concluded that there was a poor prevalence of Knowledge, Attitudes, and Practices in Punjab. Good knowledge determines good attitudes that control good practices; hence, a focus on augmenting Practices of Intestinal Parasitic knowledge among parents should be the top priority of healthcare, especially among mothers.

INTRODUCTION

Intestinal parasitic infections (IPIs) are a significant contributor to illnesses globally and have been identified as a notable public health issue [1]. Soil-transmitted helminthiasis and schistosomiasis pose significant risks to an estimated population of one billion [2]. The World Health Organization (WHO) reports that the most prevalent species are Ascaris Lumbricoides, Trichuris Trichiura and hookworms [3]. In 2022, almost 740 million people will be infected with hookworms, as per the reports of the Centers for Disease Control and Prevention. A significant proportion of these infections affect children, with an estimated 880 million children requiring a cure for intestinal helminths [4]. Although preventable, IPI persists due to gaps in parental Knowledge, Attitudes, and Practices (KAP). Most parasitic infections are transmitted through the Fecal-oral route, emphasizing the importance of proper sanitation and hygiene practices. These infections disproportionately affect impoverished communities and are closely linked to factors such as poverty, inadequate housing, lack of clean water, sanitation, access to healthcare, education, and socioeconomic disparities [5, 6]. In underdeveloped

DOI: https://doi.org/10.54393/pjhs.v5i11.2397

nations, impoverished populations face a cycle of malnutrition and recurrent infections, leading to increased morbidity [7]. In Pakistan, like other Low and Middle-Income Countries (LMICs), the impact of IPIs is profound, especially in rural areas, where poverty, lack of education, limited access to healthcare, and poor sanitation exacerbate the problem. For example, in Mandi Bahauddin, research revealed that over 33% of schoolchildren were infected with intestinal parasites [8]. Gilgit-Baltistan reported an infestation rate of 51.5% among gastrointestinal patients with Ascaris lumbricoides and Giardia lamblia [9]. The use of contaminated glacial water for drinking and agriculture has aggravated the spread of these infections. Parents play a pivotal role in safeguarding their children's health and well-being. They serve as primary caregivers and decision-makers regarding healthcare practices within the household. The KAP model allows researchers to capture comprehensive insights into parental awareness, beliefs, and behaviours, which are key factors in controlling and preventing infections. There is a need for this framework in Lahore because IPIs are prevalent and are often linked to inadequate awareness, cultural beliefs, and suboptimal hygiene practices. By applying the KAP framework, this study identifies specific knowledge gaps, misconceptions, and behavioural patterns that may contribute to the spread of IPI. Understanding parental Knowledge, Attitudes, and Practices (KAP) regarding intestinal parasitic infestation is crucial for designing effective interventions aimed at the prevention, early detection, and treatment among South Asian children. Understanding the interplay between knowledge, attitudes, and practices is crucial for the development of evidence-based strategies to reduce healthcare burden.

This study aims to inform the design and implementation of targeted interventions aimed at reducing adverse IPI outcomes.

METHODS

The observational community-based cross-sectional study was carried out from June 2024 to September 2024 in Pak Town, a randomly selected urban union council of Lahore, Punjab Pakistan. The study population was parents of children infected with intestinal parasites. The sample size was 348, calculated using a simple random sampling technique and formula [n=Z2α/2*(P(1-P)/d2]. The population proportion used for calculation was (p=52.3%) with a 10% non-response rate, 95% confidence interval (CI), and 5% margin of error [10]. Parents living in Pak town for at least 6 months with children aged 2 to 6 years were included. Parents of children who were seriously ill and had undergone standard intestinal treatment for parasites in the last 6 months were excluded. A structured interview-based questionnaire, incorporating five Knowledge, seven Attitudes, and twelve Practice questions, was developed in Urdu and later translated into English for analysis. The validity of the questionnaire was assessed to ensure it accurately measured the intended construct through appropriate methods and expert review. Consent was signed, and parents were informed about the importance of the study. The questionnaire was created in Kobo and administered in digital format through a tablet. For those who could not use a tablet, printouts of the questionnaire were provided. Demographic data included age, gender, occupation, education, and marital status. Types of intestinal parasites, transmission modes, infestation symptoms, prevention and control methods, and infestation complications were covered under the KAP section. Scoring for Knowledge, Attitudes, and Practices was performed according to the Guttmann scale, Likert scale, and Ordinal scale respectively. Responses of KAP were dichotomous as good (coded 1) or poor (coded 0) by taking the cut-off score from the computed values of each: a cut-off value of 5 for knowledge, 28 for attitudes, and 9 for practices. Scores greater than the cutoff values were regarded as good and less as poor. The data were analysed using IBM SPSS version 27. Descriptive statistics were calculated in the first step. For inferential statistics, the chi-squared test was used to estimate the association between sociodemographic characteristics and KAP levels. Binary logistic regression with odds ratio (OR) of 95%, was applied. This study was approved by the Institutional Review Board of Green International University (Ref No. IRB-GIU-FMAHS/0052/24).

RESULTS

Among the 348 respondents, an equal proportion were in the 26 to 35 (33.9%) and 36 to 45 (33.9%) age groups. Female respondents outnumbered male respondents (77.4%). Occupation had the highest prevalence among housewives (50.9%). There was a preponderance of intermediate education (26.1%) (Table 1).

Table 1: Socio-Demographic Factors of Respondents

Factors	Frequency (%)
Age (Years)	
15-25	27 (7.8)
26-35	118 (33.9)
36-45	118 (33.9)
46-55	68 (19.5)
56-65	17 (4.9)
Mean ± SD	38.49 ± 9.648
Gender	
Male	79 (22.7)
Female	269 (77.3)
Occupation	
Business	50 (14.4)
Government Employee	35 (10.1)

DOI: https://doi.org/10.54393/pjhs.v5i11.2397

Private Employee	73 (21)
Retired	2 (0.6)
Unemployed	11 (3.2)
Housewife	177 (50.9)
Marital Status	
Married	342 (98.30)
Widowed	4 (1.1)
Divorced	2 (0.6)
Education	
No Formal Education	13 (3.7)
Primary	26 (7.5)
Mid School	35 (10.1)
Secondary School	63 (18.1)
Intermediate	91 (26.1)
Graduates	109 (31.3)
MS	10 (2.9)
PhD	1 (0.3)

Analysis revealed that the majority of respondents were unaware of E. histolytica/dispar (99.4%). Of these, 83.9% knew hand washing as a preventive mechanism. Moreover, 85.1% of respondents did not know that contaminated water could transmit IPs. Analysis regarding attitude showed that 28.4% of participants believed that intestinal parasites could be treated and prevented, but 1.1% disagreed that they could be avoided by using soap. A proportion of 21.6% believed that food prepared outdoors was an IPI risk factor. Practices were driven by IPI knowledge and attitudes. Among common practices, 98.9% washed their utensils before cooking. Among the respondents, 56% had poor knowledge, 60.9% had poor attitudes, and 51.7% had poor practices (Table 2).

Table 2: Frequency Distribution of Knowledge, Attitude and Practices of IPI Patients

Variables		NO Frequency (%)	Yes Frequency (%)
Knowledge			
Intestinal Parasite?	A. Lumbricoids	343 (98.6)	5 (1.4)
	E. Histolytica /Dispar	346 (99.4)	2 (0.6)
	G. Lamblia	341 (98)	7 (2)
	Hookworm	328 (94.30)	20 (5.7)
	E. Histolytica / Dispar +G. Lamblia	346 (99.4)	2 (0.6)
	Hookworm + E. Histolytica /Dispar	348 (100)	0 (0)
	A. Lumbricoids + G. Lamblia	347 (99.7)	1 (0.3)
	Others	19 (5.5)	329 (94.5)
Preventive Mechanism?	Handwashing	292 (83.9)	56 (16.1)
	Latrine Usage	286 (82.2)	62 (17.8)
	Washing Vegetables	276 (79.3)	72 (20.7)
	Avoid Food and Water Contamination	234 (67.2)	114 (32.8)
	Handwashing + Latrine Usage	246 (70.7)	102 (29.3)
	Washing Vegetables + Latrine Usage	227 (65.2)	121 (34.8)
	Other	234 (67.2)	114 (32.8)
Transmission modes?	Soil Contact	253 (72.7)	95 (27.3)
	Contaminated Water	296 (85.1)	52 (14.9)
	Contaminated Food	289 (83)	59 (17)
	Uncooked Vegetables + Unclean Fruits	268 (77)	80(23)
	Contaminated Food + Water	257 (73.9)	91 (26.1)
	Contaminated Food + Soil Contact	242 (69.5)	106 (30.5)
	Uncooked/ Unclean Vegetables/ Fruits + Soil Contact	246 (70.7)	102 (29.3)
	Other	256 (73.6)	92 (26.4)
Signs and Symptoms?	Diarrhea	264 (75.9)	92 (26.4)
	Abdominal Cramps	284 (81.6)	64 (18.4)
	Vomiting	286 (82.2)	62 (17.8)
	Anorexia	293 (84.2)	55 (15.8)
	Diarrhea + Vomiting	257 (73.9)	91 (26.1)
	Diarrhea + Abdominal Cramps	220 (63.2)	128 (36.8)
	Other	254 (73)	94 (27)
Signs and Symptoms?	Malnutrition	276 (79.3)	72 (20.7)
	Anemia	290 (83.3)	58 (16.7)
	Growth Retardation	271 (77.9)	77 (22.1)
	Malnutrition + Growth Retardation	230(66.1)	118 (33.9)
	Anemia + Growth Retardation	240 (69)	108 (31)
	Other	248 (71.3)	100 (28.7)
Practices			
Stool Examination History		311 (89.4)	37 (10.6)
Wash the Child's Hands Before A Meal		8 (2.3)	340 (97.7)
Washing Child's Hands After Meal		9 (2.6)	339 (97.4)
Cutting A Child's Nails?		11 (3.2)	337 (96.8)
Medicating Children for Prevention		105 (30.2)	243 (69.8)
Using Tap Water for Prevention		217 (62.4)	131 (37.6)
Using Chemically Treated Water (Boiled, Filtered, Etc.) for Prevention.		154 (44.3)	194 (55.7)

DOI: https://doi.org/10.54393/pjhs.v5i11.2397

Wash The Child's Hands After Defecation.	9 (2.6)	339 (97.4)
Pre-Diagnosis Of Intestinal Parasitic Infection.	96 (27.6)	252 (72.4)
Using Soap To Clean Utensils.	5 (1.4)	343 (98.6)
Washing Utensils Before Cooking Meals.	4 (1.1)	344 (98.9)
Wash Fruits And Raw Vegetables Before Eating.	6 (1.7)	342 (98.3)

Attitudes					
Variables	**Extremely Disagree**	**Disagree**	**Neutral**	**Agree**	**Extremely Agree**
	F (%)	**F (%)**	**F (%)**	**F (%)**	**F (%)**
Lack of hygiene is one of the IPI causes.	0 (0)	1 (0.3)	18 (5.2)	290 (83.3)	39 (11.2)
IPI is preventable and treatable.	2 (0.6)	5 (1.4)	31 (8.9)	211 (60.6)	99 (28.4)
IPI can be reduced by health education.	1 (0.3)	7 (2)	50 (14.4)	223 (64.1)	67 (19.3)
One IPI complication is growth retardation.	2 (0.6)	3 (0.9)	52 (14.9)	232 (66.7)	59 (17)
Washing the face and hands with soap can prevent IPI.	4 (1.1)	10 (2.9)	51 (14.7)	237 (68.1)	46 (13.2)
Raw food consumption is one of the IPI causes.	0 (0)	13 (3.7)	49 (14.1)	250 (71.8)	36 (10.3)
Outdoor food is a risk factor for IPI.	2 (0.6)	15 (4.3)	42 (12.1)	214 (61.5)	75 (21.6)

Level of Knowledge, Attitude and Practices was shown (Table 3).

Table 3: Level of Knowledge, Attitude and Practices

Level of Knowledge	
Poor	195 (56)
Good	153 (44)
Mean ± SD	27.96 ± 3.96
Level of Attitude	
Poor	212(60.9)
Good	136(39.1)
Mean ± SD	8.04 ± 4.59
Level of Practices	
Poor	180(51.7)
Good	168(48.3)
Mean ± SD	9.31 ± 1.32

Pearson chi-square associated p-values (X2) showed that knowledge was associated only with attitudes (p<0.001). Attitude was significantly correlated with age (p=0.011), gender (p<0.001), occupation (p=0.005), educational status (p<0.001), and attitudes (p=0.013). Lastly, good practices were significantly correlated with marital status (p=0.038) (Table 4).

Table 4: Factors Associated with Parents' Knowledge, Attitudes, and Practices Regarding IPI

	Knowledge					Attitude					Practices				
Factors	**Poor %**	**Good %**	**Total**	**X^2 p-value**	**df**	**Poor %**	**Good %**	**Total**	**X^2 p-value**	**df**	**Poor %**	**Good %**	**Total**	**X^2 p-value**	**df**
Age															
15–25	14 (51.9)	13 (48.1)	27	0.648	4	15 (55.6)	12 (44.4)	27	0.011*	4	14 (51.9)	13 (48.2)	27	0.285	4
26–35	65 (55.08)	53 (45)	118			65 (55.1)	53 (44.9)	118			66 (56)	52 (44.1)	118		
36–45	72 (61.02)	46 (39)	118			68 (57.6)	50 (42.4)	118			54 (45.8)	64 (54.2)	118		
46–55	34 (50)	34 (50)	68			48 (70.6)	20 (29.4)	68			34 (50)	34 (50)	68		
56–65	10 (58.8)	7 (41.2)	17			16 (94.1)	1 (5.9)	17			12 (70.6)	5 (29.4)	17		
Gender															
Male	48 (60.8)	31 (39.2)	79	0.336	1	64 (81.01)	15 (19)	79	<0.001**	1	40 (50.6)	39 (49.4)	79	0.825	1
Female	147 (54.6)	122 (45.4)	269			148 (55)	121 (45)	269			140 (52)	129 (48)	269		
Occupation															
Unemployed	7 (63.6)	4 (36.4)	11	0.972	5	10 (20)	1 (9.1)	11	0.005**	5	7 (63.6)	4 (36.4)	11	0.740	5
Business	29 (58)	21 (42)	50			39 (78)	11 (22)	50			25 (50)	25 (50)	50		
Govt. Employee	20 (57.1)	15 (42.9)	35			20 (57.1)	15 (42.9)	35			17 (48.6)	18 (51.4)	35		
Private Employee	38 (52.1)	35 (47.9)	73			34 (46.6)	39 (53.4)	73			33 (45.2)	40 (54.8)	73		
Retired	1 (50)	1 (50)	2			1 (50)	1 (50)	2			1 (50)	1 (50)	2		
House Wife	100 (56.5)	77 (43.5)	177			108 (61)	69 (39)	177			97 (54.8)	80 (45.2)	177		
Marital Status															
Married	192 (56.2)	4 (36.4)	342	0.956	2	208 (60.8)	134 (39.2)	342	0.476	2	180 (52.6)	162 (47.4)	342	0.038*	2
Divorced	1 (50)	1 (50)	2			2 (100)	0 (0)	2			0 (0)	2 (100)	2		
Widowed	2 (50)	2 (50)	4			2 (50)	2 (50)	4			0 (0)	4 (100)	4		
Education															
No formal education	8 (61.5)	5 (38.5)	13	0.223	8	11 (84.6)	2 (15.4)	13	<0.001**	8	6 (46.2)	7 (53.8)	13	0.714	8
Primary	20 (76.9)	6 (23)	26			23 (88.5)	3 (11.5)	26			18 (69.2)	8 (30.8)	26		
Mid school	21 (60)	14 (40)	35			27 (77.1)	8 (22.9)	35			17 (48.6)	18 (51.4)	35		
Secondary school	36 (56.3)	28 (43.8)	64			47 (73.4)	17 (26.6)	64			32 (50)	32 (50)	64		

DOI: https://doi.org/10.54393/pjhs.v5i11.2397

Intermediate	48 (52.8)	43 (47.3)	91			49 (53.8)	42 (46.15)	91			45 (49.5)	46 (50.5)	91		
Graduates	55 (50.5)	54 (49.5)	109			53 (48.6)	56 (51.4)	109			57 (52.3)	55 (50.5)	109		
MS	6 (66.7)	3 (33.4)	9			1 (11.1)	8 (88.9)	9			4 (44.4)	5 (55.6)	9		
PhD	1 (100)	0	1			1 (100)	0 (0)	1			1 (100)	0 (0)	1		
Attitudes						**Practices**									
Poor	96 (45.2)	116 (54.7)	212	25.5 <0. 001**	1	121 (67.2)	59 (32.8)	180	6.2 0.013*	1	- -				
Good	99 (72.8)	37 (27.2)	136			91 (54.2)	77 (45.8)	168							
Practices															
Poor	100 (55.6)	80 (44.4)	180	0.04 0.852	1	- -									
Good	95 (56.5)	73 (43.5)	168												

*Significant at 95% Confidence Interval, ** Significant at 99% Confidence Interval

Binary logistic regression demonstrates that knowledge can only be predicted by attitude. Parents with good knowledge were 3.2 times more likely to have good attitudes than poor attitudes. All factors except marital status predicted attitudes (Hosmer-Lemeshow chi-square=8.4; p=0.4). Female parents between ages 26-35 years were more likely to develop good attitudes (Unadjusted OR 13.05; 95% CI=1.7–101.6) than those aged 56-65 years. Intermediate-, graduate-, and master-level parents were more likely to have better attitudes than those with secondary education. Good practices were significantly predicted by good attitudes (Adjusted ORs=0.6; 95% CI=0.4–0.9)(Table 5).

Table 5: Binary Logistic Regression for Factors Associated with Good Levels of Knowledge, Attitudes and Practices Towards IPI

Factors		Categories	Un-adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Knowledge	Attitude	Good	3.2 (2.0–5.1)	<0.001	3.2 (2.0–5.1)	<0.001
		Poor (1)				
Attitude	Knowledge	Good	3.2 (2.0–5.1)	<0.001	5.3 (3.0–9.2)	<0.001
		Poor (1)				
	Age	15–25	12.8 (1.5–11 0.8)	0.02	5.02 (0.3–96.4)	0.3
		26–35	13.05 (1.7–1 01.6)	0.01	4.8 (0.3–84.6)	0.3
		36–45	11.8 (1.5–91.7)	0.01	6.08 (0.3–108)	0.2
		46–55	6.7 (0.8–5 3.7)	0.07	5.04 (0.3–9 1.2)	0.3
		56 – 65 (1)				
	Gender	Male	3.5 (1.9–6.4)	<0.001	0.3 (0.1–0.7)	0.005
		Female (1)				
	Education	No Formal Education	0.5 (0.1–2.5)	0.4	0.6 (0.1–3.5)	0.5
		Primary	0.3 (0.1–1.3)	0.1	0.3 (0.1–1.4)	0.1
		Mid School	0.8 (0.3–2.1)	0.6	0.8 (0.3–2.2)	0.6
		Secondary (1)				
		Inter mediate	2.3 (1.2–4.6)	0.017	2.6 (1.2–5.7)	0.01
		Graduates	2.9 (1.5–5.6)	0.002	3.5 (1.6–7.6)	0.002
		Masters	10.8 (2.1 –56.2)	0.005	60.8 (3.8 –974.3)	0.004
		PhD	0	1	0	1
	Occupation	**Unemployed (1)**				
		Business	0.2 (0.0 2–1.3)	0.08	0.3 (0.03 –3.2)	0.31
		Govt. employee	0.4 (0.2 –0.9)	0.03	1.1 (0.4 –3.4)	0.8
		Private employee	1.2 (0.6 –2.4)	0.7	1.0 (0.4 –2.6)	1
		Retired	1.8 (1.04 –3.1)	0.04	1.5 (0.7 –2.9)	0.3
		Housewife	1.6 (0.1 –25.4)	0.8	9.3 (0.1 –736.2)	0.3
	Practices	**Poor (1)**				
		Good	0.6 (0.4 –0.9)	0.01	0.6 (0.3 –0.9)	0.03
Practices	Attitudes	**Poor (1)**				
		Good	0.6 (0.4 –0.9)	0.01	0.6 (0.4 –0.9)	0.01

DISCUSSION

This study is among the few studies conducted in the past 5 years that checked the KAP level of IPI among parents of infected children. Overall, a poor level of KAP prevailed, concurrent with other studies in which half and less than two-thirds were low in KAP state [11, 12]. In this study, females outnumbered males. In another predictive study on knowledge and practice in helminthic infection prevention, females (55.7%) were more prevalent than males. The prevalent age range in both studies was 26–35 years [13]. In this study, the majority of parents were of intermediate educational status (26.1%), while in other studies, the highest proportion was illiterate (70.2%) and of secondary education (62.3%). This difference may be due to the rise in awareness of IPI as a result of education campaigns. A higher proportion of parents were housewives (50.9%), which complies with another study's statistics of 51.4% of housekeeping mothers of IPI-infected children [13, 14]. In this study, soil contact with contaminated food was regarded as a mode of parasite transmission. This is supported by another similar study, in

DOI: https://doi.org/10.54393/pjhs.v5i11.2397

which 47.8% of the respondents knew that feces were a source of infection [14]. In the same study, 62.5% of the respondents knew of helminthic parasites, which was further supported in this study by the statistics of 5.7%. Previously conducted research outlined that 93.4% of respondents always wash their hands before eating, 94.9% wash their hands after defecation, and 94.9% always wash fruits and vegetables before eating, as a general practice. These proportions are close to the values reported in this study. In practice, 55.7% of the parents in this study used chemically treated water to prevent the disease, whereas a comparative study reported a prevalence of 93.4% in the use of boiled water for drinking. The KAP survey showed that 60.6% of the parents agreed and 28.4% disagreed with the statement that intestinal parasites can be prevented and treated, while two studies declared parents' attitudes towards worms and protozoans to be harmful [15, 16]. The study found no significant association between knowledge and sociodemographic variables. This may be due to unawareness of the scientific names of parasites or proper IPI medical knowledge. However, other studies have reported associations of knowledge with education and age (0.042) [17-19]. Our study showed associations of attitudes with age, education, gender, practices, knowledge, and occupation. Another study showed significant associations of attitudes with age, ranging from 21 to 100 years, and education [20]. It also demonstrated that university-going individuals were 1.30 times more likely to possess better attitudes towards parasite prevention. This aligns with our findings that MS-level parents were 60.8 times more likely to possess good attitudes than secondary school parents. This KAP survey was conducted on parents of both sexes and assessed the predictors using a regression model, unlike other studies that only surveyed mothers or infected children and used simple association or prevalence statistics [15]. The high chi-square value and low p-value of the Hosmer and Lemeshow test for model fit indicated that the model was an average fit for predicting KAP.

CONCLUSIONS

It was concluded that there is a low prevalence of KAP in Lahore and Punjab. Parents with intermediate-, graduate-, and master-level education possessed good attitudes. However, good practices were not directly associated with these factors, suggesting a gap in the execution of IPI-related practices. Overall, good knowledge determines a good attitude that controls good practices; hence, a focus on augmenting IPI knowledge among parents should be the top priority of healthcare, especially for mothers.

Authors Contribution

Conceptualization: KZ
Methodology: SH, KP, ZA, MHHK
Formal analysis: MHHK
Writing review and editing: KZ, AMB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2111

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Comparison of Fetomaternal Outcomes in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine Alone for the Management of Threatened Preterm Labour

Humna Mian Faiz Rasul[1], Quratulain Shahzad[2*], Sumera Kanwal[3], Amna Aslam[4], Fareeha Shaukat[2] and Iram Inam[5]

[1]Department of Obstetrics and Gynaecology, Bedford Hospital National Health Service, United Kingdom
[2]Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore, Pakistan
[3]Department of Obstetrics and Gynaecology, Lady Wallington Hospital, Lahore, Pakistan
[4]Department of Obstetrics and Gynaecology, Avicenna Medical College and Hospital, Lahore, Pakistan
[5]Department of Obstetrics and Gynaecology, Hayat Memorial Hospital/Continental Medical College, Lahore, Pakistan

ARTICLE INFO

Keywords:
Nifedipine, Sildenafil Citrate, Neonatal Intensive Care, Preterm Delivery

How to Cite:
Faiz Rasul, H. M., Shahzad, Q., Kanwal, S., Aslam, A., Shaukat, F., & Inam, I. (2024). Comparison of Fetomaternal Outcomes in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine Alone for the Management of Threatened Preterm Labour: Fetomaternal in Nifedipine Combined with Sildenafil Citrate Versus Nifedipine . Pakistan Journal of Health Sciences, 5(11), 248-252. https://doi.org/10.54393/pjhs.v5i11.2111

***Corresponding Author:**
Quratulain Shahzad
Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital, Lahore, Pakistan
anieeshahzed@gmail.com

Received Date: 24th August, 2024
Acceptance Date: 16th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Sildenafil, a smooth muscle relaxant, has been explored as an adjuvant to delay the onset of preterm labor. By inhibiting uterine contractions, it helps prolong pregnancy and improve fetal outcomes. **Objectives:** To evaluate the effects of Nifedipine on the mother and fetus during impending preterm labour, alone or with sildenafil citrate. **Methods:** The quasi-experimental trial was conducted at Sir Ganga Ram Hospital Lahore. Patients were randomly assigned to receive either 20 mg Nifedipine orally (stat dose) followed by 10 mg every 8 hours with 25 mg sildenafil citrate orally at 8-hour intervals or 20 mg without sildenafil citrate. The medication therapy lasted 72 hours. Chi-square and independent sample t-tests were used to compare groups in SPSS version 26.0. **Results:** Baseline age, gestational age and parity were similar in both groups ($p>0.05$). With mean gestational age at delivery 34.47 ± 2.18 weeks, the frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. Nifedipine with Sildenafil citrate group had significantly higher term deliveries (30.0% vs. 0.0%; p-value=0.002) and normal weight births (35.0% vs. 5.0%; p=0.005) compared to Nifedipine alone group; however maternal readmission and neonatal intensive care unit admission rates were not statistically different between groups ($p>0.05$). There was no mortality feto-maternal observed. **Conclusions:** It was concluded that oral sildenafil citrate combined with Nifedipine is an effective option as tocolytic therapy for threatened preterm labour. The prolongation of pregnancy will improve fetal weight, and reduce neonatal intensive care unit admissions and preterm deliveries with minimum maternal and fetal side effects.

INTRODUCTION

Delivery that occurs between 24 and 37 weeks into the gestational period is considered preterm. Details from 2010 data revealed that 14.9 million neonates were born preterm, with 1.6 million being born very preterm, despite several measures to lower its prevalence [1]. As a result, finding a suitable therapy for impending preterm labour and pregnancy lengthening is an urgent matter [2]. When compared to other risk factors, preterm delivery has the greatest impact on the likelihood of prenatal morbidity and death, low birth weight at delivery, and admission to the neonatal intensive care unit (NICU) [3]. Delaying birth for 48 to 72 hours with tocolytic treatment allows for the administration of corticosteroids, which decrease respiratory morbidity and the need for neonatal intensive care unit stays [4]. There are no known therapies that can reduce these complications at this time. As a tocolytic treatment, calcium channel blockers such as nifedipine might be utilized. The medicine Nifedipine is preferred for threatening preterm labour (PTL) due to its minimal adverse effects compared to other tocolytics, according to many reviews. These side effects include headache, tachycardia, palpitation, and others [5, 6]. Sildenafil citrate is a cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase (PDE)-5 inhibitor. It enhances smooth

DOI: https://doi.org/10.54393/pjhs.v5i11.2111

muscle relaxation, reduces intracellular calcium levels, reduces the sensitivity of contractile elements too and can be beneficial in inhibiting threatened preterm labour (PTL) with positive maternal and fetal effects [7]. The tocolytic effects of sildenafil citrate and the fetomaternal effects of a combination of nifedipine and sildenafil citrate for the treatment of PTL without significant side effects have only been somewhat investigated in existing research.

This study aims to compare the efficacy of Nifedipine alone with that of this combination in preventing preterm delivery and enhancing feto-maternal outcomes over longer pregnancies.

METHODS

The quasi-experimental trial was conducted at Sir Ganga Ram Hospital Lahore from February to December 2021. Ethical approval of the study was taken from the Institutional Review Board with letter No. 33-Res-Publication-Gynae/ERC. Informed consents were taken from all patients. The calculation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. Data were collected by using survey forms. All patients were enrolled once written consent from them was obtained. A nonconsecutive sampling technique was used. Patients detailed demographics including age, parity, gestational amenorrhea, and blood pressure, pulse, uterine contractions, fetal heart rate were recorded after taking written and informed consent. Patients with no consent, hypersensitivity to Sildenafil and Nifedipine, and medical disorders were excluded from the study. Patients were randomly allocated into two equal groups. Group A received (1) Nifedipine 20 mg orally (Stat dose) followed by 10mg every 8 hours with oral administration of Sildenafil citrate (25 mg at 8 hourly intervals). Group B received Nifedipine alone. Medications were continued for 72 hours. During the therapy during admission maternal pulse, blood pressure, uterine contractions, and fetal hearts were recorded every 30 min. the interval for the first 4 hours, then 2 hourly for the rest of the admission period. Patients were discharged on vaginal Progesterone therapy with a weekly follow-up plan. If a patient had preterm contractions again, readmission and treatment were repeated. At every follow-up visit, feto-maternal assessment was done with fetal heart rate, uterine contractions, and side effects of medications, Fetomaternal outcome was recorded at the time of delivery including fetal weight (kg), NICU admission, gestational age at the time of delivery and number of readmissions with threatened PTL was recorded. Statistical Packages for Social Sciences (SPSS) version 26.0 was used to analyze data. Mean and standard deviation calculated for quantitative variables like age parity, gestational age, fetal weight (Low birth weight: A fetal weight of less than 2,500 grams (5 pounds, 8 ounces) Very low birth weight: A fetal weight of less than 1,500 grams (3 pounds, 5 ounces), NICU admission, maternal readmissions. Comparisons between groups were done by Chi-square and independent sample t-test. Data were presented in tables and graphs. p-value≤0.05 was taken as significant.

RESULTS

The data obtained from a total of 40 pregnant women with threatened preterm labor including 20 women in the Nifedipine with Sildenafil citrate group and 20 in the Nifedipine alone group were subjected to final analysis. The mean age of the study population was 27.55 ± 2.79 years and ranged between 21 and 34 years. The overall mean gestational age at enrollment was 30.90 ± 1.94 weeks and ranged between 28 and 35 weeks. At baseline, there were no statistically significant differences between the Nifedipine with Sildenafil citrate group and Nifedipine alone group in terms of age (p-value 0.912) gravida (p-value 0.414), para (p-value 0.265), abortus (p-value 0.896) and gestational age (p-value 0.369) (Table 1).

Table 1: Maternal Factors and Their Association with Umbilical Cord Coiling Pattern

Variables	Total (n=40)	Nifedipine with Sildenafil (n=20)	Nifedipine alone (n=20)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (Years)	27.55 ± 2.79	27.50 ± 2.80	27.60 ± 2.85	0.912
Gravida	3.40 ± 1.37	3.55 ± 1.35	3.25 ± 1.40	0.414
Gestational Age On Enrollment (Weeks)	30.90 ± 1.94	30.55 ± 1.96	31.25 ± 1.92	0.369

Using the median age, the study population was categorized into two age groups i.e. ≤28 years and >28 years. The participation of women ≤28 years was twice as high as that of women >28 years (70.0% vs. 30.0%). However, both age groups were almost equally distributed in Nifedipine with Sildenafil citrate group and Nifedipine alone group at baseline (p-value 0.731) (Figure 1).

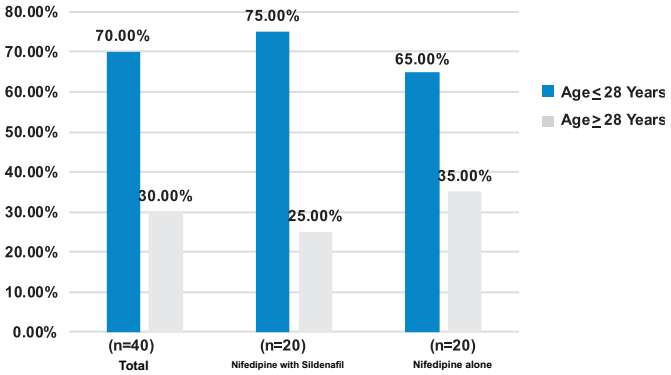

Figure 1: Age Distribution of Study Population at Baseline

Overall, there was no primigravida woman. The frequencies of women with gravida 2, 3, 4 and 6 were 35.0%, 20.0%, 30.0% and 15.0%, respectively (Figure 2).

DOI: https://doi.org/10.54393/pjhs.v5i11.2111

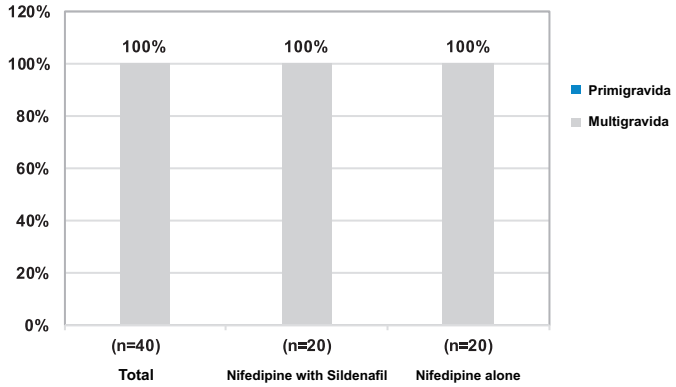

Figure 2: Gravida Status of Study Population at Baseline

The overall frequencies of primipara and multipara women were 35.0% and 47.5%, respectively. All paras were almost equally distributed in Nifedipine with Sildenafil citrate group and Nifedipine alone group at baseline (p-value 0.636)(Figure 3).

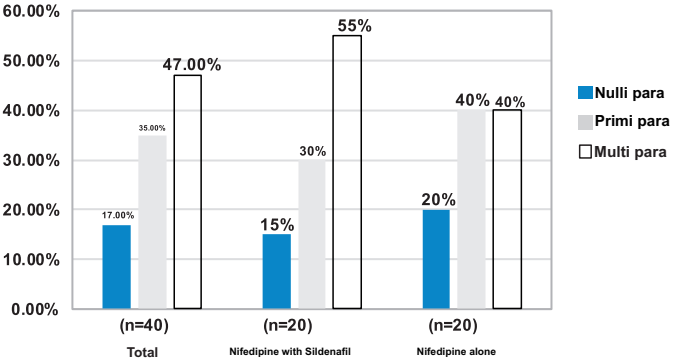

Figure 3: Para Status of Study Population at Baseline

The feto-maternal outcomes at follow-up included preterm delivery, readmission, fetal birth weight and NICU admission. The overall mean gestational age at delivery was 34.47 ± 2.18 weeks and ranged between 30.0 and 38 weeks; and the overall frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. The comparison between groups showed that all term deliveries (n=6) were occurred in Nifedipine with Sildenafil citrate group; all very preterm deliveries (n=3) were in Nifedipine alone group; and the difference was statistically significant (p-value=0.002). Total 95.0% women were readmitted; however, the readmission rates were same in both groups (p-value=1.000). The overall mean FBW was 2.02 ± 0.42 kilograms and ranged between 1.3 and 2.8 kilograms; and the overall frequencies of normal weight, low-weight and very low-weight births were 20.0%, 70.0% and 10.0%, respectively. The comparison between groups showed that 7 out of 8 normal weight births occurred in Nifedipine with Sildenafil citrate group; all very low-weight births (n=4) were in Nifedipine alone group; and the difference was statistically significant (p-value 0.005). Total 70.0% neonates were admitted to NICU. The frequency of NICU admission was lower in Nifedipine with Sildenafil citrate group than of Nifedipine alone group (60.0% vs. 80.0%), but the difference was not significant (p-value=0.301), frequency of low Apgar score in Nifedipine group was insignificantly higher (0.297)(Table 2).

Table 2: Fetomaternal Outcomes at Follow-Up

Variables		Total (n=40)		Nifedipine with Sildenafil (n=20)		Nifedipine Alone (n=20)		p-value
Gestational Age on Delivery (Weeks)	Mean ± SD	34.47 ± 2.18		35.25 ± 2.22		33.70 ± 1.89		0.043
	Term	06	15.0%	06	30.0%	0	0.0%	0.002
	Preterm	31	77.5%	14	70.0%	17	85.0%	
	Very preterm	03	7.5%	0	0.0%	03	15.0%	
Read -mission	Yes	38	95.0%	19	95.0%	19	95.0%	1.000
	No	02	5.0%	01	5.0%	01	5.0%	
Fetal Birth Weight (Kg)	Mean ± SD	2.02 ± 0.42		2.23 ± 0.37		1.80 ± 0.35		0.001
	Normal	08	20.0%	07	35.0%	01	5.0%	0.005
	Low	28	70.0%	13	65.0%	15	75.0%	
	Very low	04	10.0%	0	0.0%	04	20.0%	
NICU Admission	Yes	28	70.0%	12	60.0%	16	80.0%	0.301
	No	12	30.0%	08	40.0%	04	20.0%	
Low Apgar Score	Yes	24	60.0%	10	50.0%	14	70.0%	0.297
	No	16	40.0%	10	50.0%	06	30.0%	

DISCUSSION

Sildenafil, which has various long-term uses, may have beneficial effects on fetomaternal outcomes when administered to treat impending preterm labour. Therefore, the purpose of this randomized experiment was to determine if this medication was beneficial. Recent research has demonstrated that when it comes to treating threatening PTL, a combination of Sildenafil Citrate and Nifedipine has a more effective tocolytic effect than Nifedipine alone. There was a decrease in prenatal mortality and morbidity, as seen by fewer NICU admissions, an increase in neonatal birth weight within 7 days following delivery, and fewer births while hospitalized. Multiple published trials related to this drug (Sildenafil citrate) were done in the last two years, besides the result of the meta-analysis done by Paauw *et al.*, showed that the effect of Sildenafil citrate has the potential to improve fetal growth with the prolongation of pregnancy and agreed to current trial [8]. Present study confirms that sildenafil significantly increases the growth rate and belly circumference in the von Sharami et al., experiment. In the current study, the overall mean FBW was 2.02 ± 0.42 kilograms and ranged between 1.3 and 2.8 kilograms; and the overall frequencies of normal-weight, low-weight and very low-weight births were 20.0%, 70.0% and 10.0%, respectively [9]. Babies born to mothers who took sildenafil citrate had a significantly higher birth weight (222.58 g, ranging from 27.75 to 417.41 g) and were less likely to require admission to

DOI: https://doi.org/10.54393/pjhs.v5i11.2111

the neonatal intensive care unit (31.4% vs. 44.1%). Very small (p=0.043) [10-12]. The present study has shown a reduction in NICU admission with prolongation of pregnancy with Sildenafil citrate although the admission rates were not statistically different between groups (combined drug versus single drug), A Total of 70.0% of neonates were admitted to NICU. The frequency of NICU admission was lower in the Nifedipine with Sildenafil citrate group than in the Nifedipine alone group (60.0% vs. 80.0%), but the difference was not significant (p-value 0.301), see Table 2. However, the Karya *et al.*, trial has shown the Sildenafil treatment was associated with increased fetal AC growth (odd ratio, 12.9, 95% confidence interval, 1.3, 126 compared with institutional sildenafil – Naïve early-onset intrauterine growth restriction (IUGR) control) [13]. A review by Aggarwal *et al.*, has shown a reduction in preterm deliveries with a prolongation of pregnancy of (14 days)[14]. Another study by Manouchehri *et al.*, concluded, fewer deliveries within 7 days of admission (9.1 vs. 20.3%) with Sildenafil citrate and these findings are matched with the results of the present study [15]. This shows the mean gestational age at delivery was 34.47 ± 2.18 weeks, and the frequencies of term, preterm and very preterm were 15.0%, 77.5% and 7.5%, respectively. In curent study, the dose of Sildenafil citrate and trial with mild side effects were selected. It shows that the maternal readmission rate was 77%, while in the current trial, 95% of women were readmitted, however, readmission rates were the same in both groups (Sildenafil Citrate and Nifedipine versus Nifedipine alone) with minimal side effects [16-18]. Facial flushing was the most often reported adverse effect (48%), followed by nasal congestion, dry mouth, and headaches; nevertheless, no woman was readmitted because of serious side effects associated with sildenafil medication [19, 20]. It should be mentioned that study was unable to determine if the medicine had any long-term impacts on children since no research included long-term follow-up of babies. Sildenafil, on the other hand, might be a novel treatment for several severe obstetric disorders, including preeclampsia and IUGR, due to its safety during pregnancy and the lack of evidence of teratogenic effects. Despite these findings, there is a need for further randomised controlled studies including the same pregnancy illnesses using comparable methods required to prove the progression of placental insufficiency to higher birth weight for the fetus.

CONCLUSIONS

It was concluded that oral Sildenafil citrate combined with Nifedipine is an effective option as tocolytic therapy for threatened preterm labour. The study findings indicated that prolonging pregnancy through the use of sildenafil led to significant improvements in fetal outcomes. By delaying the onset of preterm labor, sildenafil allowed further fetal development, resulting in increased fetal weight, which reduced the risks associated with low birth weight, such as respiratory distress and feeding difficulties. Additionally, the study showed a decrease in NICU admissions, as babies born closer to full term typically experienced fewer complications. The use of sildenafil was found to have minimal maternal and fetal side effects, making it a safe and effective method for managing threatened preterm labor.

Authors Contribution

Conceptualization: HMFR
Methodology: HMFR, QS, FS
Formal analysis: HMFR, AA
Writing review and editing: QS, FS, SK,II

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2366

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

The Role of Nanomaterials in Preventive Dentistry: Antimicrobial Coatings for Dental Restorations

Shahneela Sohail[1], Rabia Sadiq[2], Farah Tasleem[3], Naresh Kumar[4], Ayesha Imtiaz[5], Muhammad Zeeshan[6] and Fatima Ali[7*]

[1]Department of Dentistry, Saylani Welfare International Trust Organization, Karachi, Pakistan
[2]Department of Orthodontics, Hospital Kahuta Research Laboratories, Islamabad, Pakistan
[3]Department of Science of Dental Materials, Isra University, Hyderabad, Pakistan
[4]Department of Operative Dentistry, Bhitai Dental and Medical College, Mirpurkhas, Pakistan
[5]Department of Science of Dental Materials, Baqai Medical University, Karachi, Pakistan
[6]Department of Science of Dental Materials, Niazi Medical and Dental College, Sargodha, Pakistan
[7]Department of Molecular Diagnostics and Pathology, Allied Health Sciences Academy, Lahore, Pakistan

ARTICLE INFO

Keywords:
Nanocomposites, Anti-Microbial Coatings, Dental Restorations, Biocompatibility

How to Cite:
Sohail, S., Sadiq, R., Tasleem, F., Kumar, N., Imtiaz, A., Zeeshan, M., & Ali, F. (2024). The Role of Nanomaterials in Preventive Dentistry: Antimicrobial Coatings for Dental Restorations: Nanomaterials in Preventive Dentistry: Antimicrobial Coatings. Pakistan Journal of Health Sciences, 5(11), 253-261. https://doi.org/10.54393/pjhs.v5i11.2366

***Corresponding Author:**
Fatima Ali
Department of Molecular Diagnostics and Pathology, Allied Health Sciences Academy, Lahore Pakistan
fmohsinali7@gmail.com

Received Date: 7th October, 2024
Acceptance Date: 19th November, 2024
Published Date: 30th November, 2024

ABSTRACT

The applicability of antimicrobial nanomaterial coatings in preventive dentistry such as dental restoration practice in combating dental caries while embracing biocompatibility, and long-lasting and low bacterial adhesion properties has been the main area of research for many decades.**Objective:** To review the role of different types of nanomaterials in the field of preventive dentistry by focussing on anti-microbial coatings for dental restorations. **Methods:** The articles were taken from PubMed, Science Direct, and Google Scholar within the years 2018-2024 following PISMA 2020 guidelines. The effectiveness of nanomaterials included in dental coatings in terms of antimicrobial properties, biocompatibility, and durability in clinical applications was observed. Bacterial adhesion, caries prevention, material nanotechnology, and patient satisfaction were assessed. The antimicrobial efficiency and restorative outcomes of different nanomaterials: via silver, zinc oxide and titanium dioxide; were evaluated. Initially, 109 articles were retrieved, which were then screened based on predefined inclusion and exclusion, resulting in 16 studies for detailed analysis. The regions of study conduction were North America, Europe and Asia. **Results:** The antimicrobial efficacy of nano-coatings in dental restorations was seen via reduced bacterial adhesion and biofilm. The link between nanomaterials like silver nanoparticles and titanium dioxide enhanced secondary caries prevention and improved the long-term stability of restorative materials. Biocompatibility studies demonstrated that these coatings are biocompatible; however, more work is required. The application of antimicrobial nano-coatings gives adaptive and therapeutic characteristics. **Conclusions:** It was concluded that nanotechnology should lead to better durability and performance of dental restorations thus better oral health and less caries.

INTRODUCTION

Both direct and indirect restorative techniques rely heavily on the use of adhesive procedures with resin fill materials preferred commonly [1]. Despite good adhesion and appearance, the formation of biofilm is higher when using resin-based composite materials compared to amalgam and natural enamel [2]. Biofilm development discolours restorations and fosters bacterial proliferation chiefly of S. mutans which synthesise acid that decalcifies tooth tissues thereby causing secondary caries [3, 4]. Recent studies suggest that after 10 years 48.3% of the dental restorations are considered unsatisfactory mainly attributable to poor marginal seal [5], and redoing contributes 50-70% of the overall re-treatment output [6]. This challenge is not unique to restorative procedures only. In orthodontic treatments, bonded embrace devices, including braces, present extra surfaces where oral bacterium with cariogenic potential can thrive, thereby causing the emergence of a white spot lesion (WSL) on the enamel [7, 8]. White spot lesions are the first sign of enamel demineralization, and all patients wearing braces are at risk of developing them [9, 10]. All carious lesions that are not cavitation are avoidable and if diagnosed early curable, but

DOI: https://doi.org/10.54393/pjhs.v5i11.2366

if not well managed the lesion may worsen and put the life of the particular tooth at risk [10]. In addition, non-pharmacological interventions where patients' adherence to processes is less critical, including materials which inherently do not promote bacterial colonization, are highly preferred [11]. The primary cause of both secondary caries in restorations and WSLs in orthodontic treatments is the same i.e. carrio-pathogenic bacteria, and their acid by-products [12]. One such area of research, which may help in enhancing the durability of restorations and decreasing the rate of WSLs is the fabrication of dental materials that inhibit bacterial attachment as well as counteract bacterial metabolism on the tooth/ material interface [13]. It must be noted, however, that conventional restorative materials are sometimes unable to eradicate bacteria while maintaining strength and toughness to other available materials [14]. Several authors have highlighted that nanotechnology offers possibilities for restorative and preventive dentistry to work on existing problems. Due to their small size and big surface, nanoparticles can be used with better antibacterial properties as compared to the previous research, without losing the restoration strength. Literature reveals that particles such as silver, zinc oxide, and titanium dioxide prevent bacterial adhesion and biofilm formation which causes secondary caries [15, 16]. Furthermore, these materials show good mechanical properties like superior abrasive attributes and enhanced adhesive capability, clearly making them appropriate for long-term use in clinics [17, 18].

This study aims to focus on the goal of identifying and critically discussing the studies of incorporating nanoparticles into dental restorative materials and their antimicrobial characteristics. In this review, antibacterial properties, mechanical properties, and overall performance of nanoparticle-containing dental materials used to enhance the performance and longevity of restoration as well as prevention of secondary caries and WSLs will be discussed.

METHODS

The selection process of this systematic review was rigorous and consistent with PRISMA guidelines commenced from March 2024 to July 2024. Two independent reviewers performed literature searches on studies published between 2018 and 2024 in multiple databases such as PubMed, Science Direct; Springer; Google Scholar etc. The focus of the search strategy was on nanomaterials that were used in dental restorative applications, especially the antimicrobial effects of these types of materials. We first searched with the following search keywords: 'nanoparticles', 'antimicrobial coatings', 'dental restoration', 'zinc oxide', 'titanium dioxide' and 'silver nanoparticles,' which initially yielded 109 articles. 8 of articles were fetched from sources other than scientific libraries and databases. Predefined inclusion and exclusion criteria were used to perform the systematic screening of articles. Inclusion criteria include studies that use nanoparticles for dental restorative applications for evaluating their anti-microbial properties, ranging within the years 2018 to 2024 and have enough data which is relevant for analysis. Excluded studies were: a) did not have enough data, b) did not focus on dental restoration or c) were duplicates. 95 articles remained after removing 14 duplicate articles for screening. A total of 93 articles were excluded because they were of no relevance or contained insufficient data, and 16 studies met the inclusion criteria that were reviewed in detail. Efficacy, biocompatibility and mechanical properties of selected nanomaterials (Ag, ZnO and TiO2) in dental applications were analyzed about the related literature. These studies were mainly geographically based in the Middle East, USA and Europe. One clinical study was included, while the majority of them were in vitro experiments. The article selection process was illustrated in a PRISMA flowchart, excluding studies which did not meet the inclusion criteria (Figure 1).

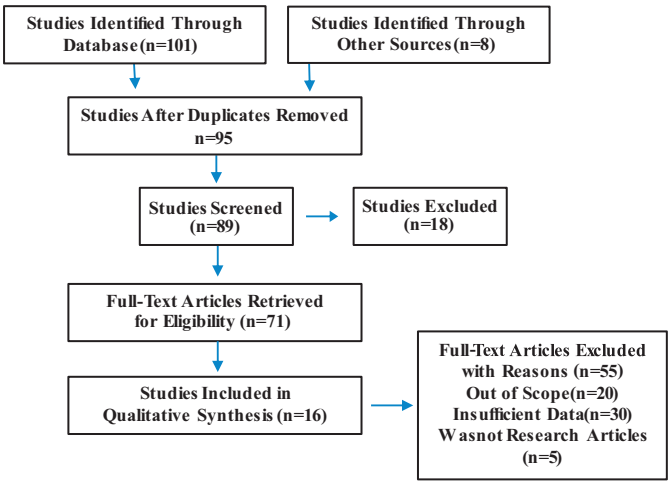

Figure 1: Selection of Studies for Review Process Showing Elimination of Studies That Were Not Lying Under the Inclusion Criteria

RESULTS

The majority of the papers were found to be written according to experimental in vitro data. All the papers included some sort of nanoparticle infused with other materials for their antimicrobial and restoration effects according to dental conditions. 16/17 of the studies were longitudinal, correlation but in vitro studies and 1/16 was a longitudinal clinical study. The majority of the studies were taken from the USA and the Middle East few were taken from the European region. Research studies were taken from the last five years i.e. 2020_2024. The study reviewed papers that were conducted in the Middle East (50%), USA (40%) and Europe (10%) respectively. The studies were taken from Google Scholar (80%), Science Direct (10%), Frontiers (7%) and others (3%) from Research Gate and PubMed. Results of these studies [19-34] are shown (Table 1).

DOI: https://doi.org/10.54393/pjhs.v5i11.2366

Table 1: Schematic Review of Studies That Were Most Appropriate According to the PRISMA Defined Rules

Reference	Study Design (Nanomaterial Used),	Methodology	Outcomes Measured (efficacy),	Key Findings (regarding effects of nanoparticle used)	Conclusions	Limitations
[19]	Experimental study (quaternary ammonium monomer and amorphous calcium phosphate nanoparticles)	Nanoparticles assessment of antibacterial and mechanical properties in vitro.	Reduction of biofilm viability, metabolic activity of microorganisms,lactic acid production and colony making units.	Increase in ammonium monomer increased antibacterial efficacy. Combination of 5% DMAHDM and 20% NACP led to significant biofilm reduction.	DMAHDM and NACP composite is effective in reducing dental biofilms.	Evaluation of long-term bioactivity, mechanical stability and fatigue is required under clinical conditions.
[20]	Experimental in vitro study (Amorphous calcium phosphate, dimethylaminohexadecyl methacrylate)	In vitro observation of interaction between biofilm and adhesive material	Alternation in colony-forming units (CFU), lactic acid production, biofilm thickness, and pH change.	NACP+ DMAHDM adhesive showed significant acid neutralization, reduced lactic acid production, decreased CFU counts, and improved enamel remineralization.	The adhesive combining NACP and DMAHDM showed great promise for preventing secondary caries.	In vitro may not fully replicate clinical conditions
[21]	Experimental study (Titanium dioxide (TiO2) coatings doped with Silver (Ag) and Gallium (Ga))	Coatings were prepared using sol gel techniques in vitro, their efficacy was measured	Efficacy in Antibacterial Activity, Cytotoxicity, and Osteodifferentiation Potential	TiO2 coatings doped with Ag and Ga displayed significant antibacterial effects against S.aureus and E. coli, especially with Ag, without cytotoxicity.	TiO2 coatings doped with Ag and Ga exhibited excellent antibacterial properties without cytotoxicity.	Further in-depth biological evaluations needed to assess anti-biofilm properties and mechanical stability of the coatings on CoCrMo alloys
[22]	Experimental lab-based study (Silver nanoparticles (AgNPs), synthesized in situ.)	Long-term study of antibacterial activity and adhesive durability tests conducted over a period of 1 year.	Antibacterial activity of the adhesive. Durability of bonding, assessed by μTBS and NL tests.	Adhesive containing AgNPs exhibited long-term antibacterial properties over one year,effectively reducing biofilm formation.	Silver nanoparticles (0.10%) synthesized in situ are appropriate for imparting long-term antibacterial properties	The study tested a limited concentration range (0.05%, 0.10%, and 0.20%) of AgNPs
[23]	Experimental study (Silver nanoparticles (AgNPs) deposited on Ti-18Zr-15Nb alloys.)	The antibacterial activity was assessed through colony-forming unit (CFU) counts against E. coli.	Antibacterial activity, Ag+ ion release, Surface characterization	The porous surface with AgNPs exhibited strong antibacterial activity.	The surface-modified Ti-18Zr-15Nb alloy with AgNPs showed effective antibacterial action.	The study was conducted in vitro, which may not fully reflect real clinical outcomes.
[24]	Experimental study (Nanoparticles of amorphous calcium phosphate combined with dimethylaminododecyl methacrylate.)	Testing of ion recharge and re-release over 12 cycles (lasting 6 months) in vitro.	Long-term antibacterial properties,Ion recharge and re-release for remineralization were effective.	The NACP-DMAHDM composite showed significant antibacterial properties, reducing CFU counts by 3-4 logs compared to controls.	The rechargeable NACP-DMAHDM composite effectively suppresses biofilm and lactic acid production, and provides long-term ion release for remineralization.	The study was conducted in vitro, so real-world clinical efficacy remains to be validated.
[25]	Experimental study (Nano silver (NAg) combined with N-acetylcysteine (NAC))	Enamel shear bond strength (SBS), antibacterial capability, and cytotoxicity were evaluated using in vitro assays	Bond strength (SBS), antibacterial activity (biofilm metabolic activity, lactic acid production, CFU counts), and cytotoxicity (cell viability).	Incorporating 0.15% NAg and 20% NAC enhanced antibacterial efficacy	The combination of NAg and NAC in orthodontic cement shows promise for improving antibacterial performance and biocompatibility	Further clinical studies are needed to validate in vitro findings and improve bonding strength for long-term orthodontic use.
[26]	Experimental study (Calcium fluoride nanoparticles combined with DMAHDM and 2-methacryloyloxyethyl phosphorylcholine)	Mechanical properties, ion release, biofilm colony-forming units (CFU), metabolic activity, and lactic acid production were evaluated using in vitro assays on dental biofilm models.	Flexural strength, fluoride and calcium ion release, biofilm CFU, lactic acid production, and biofilm metabolic activity.	The combination of nCaF2 and DMAHDM achieved strong antibacterial effects, reducing biofilm CFU by 4 logs and decreasing lactic acid production.	The novel nanocomposite with nCaF2 and DMAHDM shows promise for preventing recurrent caries by reducing biofilm formation and supporting tooth remineralization.	Further studies are needed to investigate long-term wear and ion release behavior in clinical conditions.

DOI: https://doi.org/10.54393/pjhs.v5i11.2366

[27]	Experimental study (Silvernanoparticles (nano-Ag) and Zinc oxide nanoparticles (nano-ZnO).)	The antimicrobial effectiveness against Streptococcus mutans, Lactobacillus acidophilus, and Candida albicans was evaluated, along with cell viability using the MTT assay.	Antimicrobial activity (biofilm inhibition) and biocompatibility (cell viability of human gingival fibroblasts)	Nano-Ag showed superior antimicrobial activity compared to nano-ZnO,	Coating orthodontic bands with nano-Ag and nano-ZnO induced antimicrobial effects against oral pathogens.	Multispecies biofilms and long-term durability were not assessed
[28]	Experimental (zinc oxide nanoparticles)	Tested antibacterial activity against Streptococcus mutans biofilm.	Number of colony forming units (CFU/mL), biofilm morphology (SEM)	Zinc oxide nanoparticles did not significantly improve the antibacterial activity of the glass ionomer cement.	Low concentrations (1% and 2%) of zinc oxide nanoparticles do not promote additional antimicrobial activity against S. mutans.	Higher concentrations and their effects on antibacterial activity and material properties were not explored.
[29]	Prospective in-vitro study (Graphene Oxide (GO) Nanoparticles, Silver-doped Titanium Dioxide (AgTiO2), Zinc Oxide (ZnO))	Evaluated antibacterial efficacy against Streptococcus mutans.	Number of CFUs, biofilm morphology (SEM), cytotoxicity	GO+AgTiO2 exhibited the highest antibacterial activity, followed by GO 1wt%, GO+ZnO. GO 1wt% significantly reduced bacterial growth compared to control.	Coating metal brackets with GO and its combinationscan enhance antibacterial properties, potentially reducing white spot lesions.	As an in-vitro study,it doesn't replicate the oral environment.
[30]	Experimental, In-vitro study (Polymerizable Quaternary Ammonium Silane-Modified Silica Nanoparticles)	Evaluated mechanical properties, polymerization shrinkage, curing kinetics, and degree of conversion of nanoparticles.	Mechanical properties (flexural modulus, compressive strength), polymerization shrinkage,curing kinetics,degree of conversion	The nanocomposites exhibited superior mechanical properties and curing behaviour, indicating potential stability and effectiveness for dental applications	Quaternary ammonium silane-modified silica nanoparticles showed antibacterial effects.	Limited to in-vitro conditions, not replicating complex oral environment.
[31]	Experimental study (Zirconia/Silver Phosphate Nanoparticles)	Evaluated nanoparticle -based adhesives for mechanical properties, biofilm inhibition, bond strength, and color stability.	Antibacterial activity, mechanical strength, bond strength, colour stability	Increased micro-hardness, enhanced antibacterial properties, better bond strength and colour stability at higher nanoparticle concentrations (0.5 wt.%).	Adhesives with zirconia/silver phosphate nanoparticles showed improved antibacterial and physical properties	Further studies are required to assess antibacterial and cytocompatibility efficacy in more detail.
[32]	Experimental study (Amorphous Calcium Phosphate (NACP), Dimethylaminododecyl Methacrylate (DMAHDM))	Tested bond strength, antibacterial efficacy, and Ca/P ion recharge capabilities. 3 adhesive groups were evaluated.	Bond strength, antibacterial efficacy, Ca/P ion release/recharge	DMAHDM addition significantly improved antibacterial properties.NACP maintained ion release.	The novel adhesive formulation demonstrated strong antibacterial activity and ion recharge	Long-term clinical performance and effects of ageing were not fully assessed.
[33]	Experimental study (Silver (Ag), Zinc oxide (ZnO), and combination of Ag/ZnO nanoparticles)	Tested antibacterial activity of coated orthodontic brackets on S .mutans and L. acidophilus. Coatings applied by physical vapor deposition.	Antibacterial efficacy measured by CFU reduction and inhibition percentage against S.mutans and L. acidophilus.	Ag/ZnO combination provided the highest antibacterial effect, with long-term persistence of efficacy.	Ag/ZnO nanoparticles showed superior antibacterial effects, suggesting their potential for preventing decalcification in orthodontic brackets.	Friction effects on coatings and potential cytotoxicity were not evaluated.
[34]	Clinical study (Calcium fluoride nanoparticles (nCaF2))	The study involved 31 orthodontic patients who were evaluated for enamel demineralization and bacterial load.	Degree of enamel demineralization (measured by DIAGNOdent pen) Streptococcus mutans bacterial count (real-time PCR) Incidence of WSLs (photographic assessment)	nCaF2-primer significantly reduced demineralization scores within 6 months of bracket bonding, particularly in the first month.	nCaF2-primer was effective in reducing early demineralization and bacterial colonization	The study was conducted in a single center,and its generalizability might be limited

DOI: https://doi.org/10.54393/pjhs.v5i11.2366

DISCUSSION

Nanoparticles play a significant role in enhancing the dental materials utilized in restorative dentistry, making this an emerging field of research. Numerous in vitro studies have explored various nanoparticles, their optimal concentrations, and methods for their incorporation to inhibit bacterial attachment. In this systematic review, the authors analyzed 109 experimental studies to highlight the variability in experimental methodologies. Unlike other literature reviews that focus on a single type of nanoparticle, this review encompasses multiple nanoparticles in the context of preventive dentistry. The application of nanotechnology in preventive and adhesive dental materials is discussed, including how nanoparticles can effectively control oral bacterial infections and the antibacterial and biological effects of silver nanoparticles (Ag-NPs) used in dental materials [35, 36]. Only one clinical study was included among all the studies incorporated into this review. However, clinical and in vivo experiments typically yield more accurate outcomes, and certain ethical and practical issues may arise during the initial assessment. The presence of various experimental conditions, including differences in control groups, can introduce potential biases in comparisons. For example, Yin *et al.*, reviewed both in vivo and in vitro experiments, but their discussion was based solely on the in vitro findings [37]. Although it is impossible to fully replicate the oral cavity in vitro, these experiments are valuable during preliminary assessments. Out of these, silver nanoparticles are the most extensively studied and widely used, either as standalone agents or in combination with others, including zinc oxide [38], silver nanoparticle-loaded hydroxyapatite nanowires [39], quaternary ammonium di-methacrylate [40], and silica nanoparticles [41]. One significant drawback is that the use of commercially available nanoparticles may involve undefined additives. Notably, a distinct study utilized laser synthesis to create nano-metric fibres from ZnO and Ca-O powders using a CO2 laser [42]. However, no research has yet applied in situ synthesized nanoparticles in dental materials. It may be beneficial to compare the properties of laser-synthesized nanoparticles with those of commercial variants. Nano-diamonds (NDs) have recently garnered attention in the medical and dental fields, particularly in drug delivery and tissue engineering [43, 44]. However, to the author's surprise, there have been no specific studies investigating the incorporation of NDs into dental restorative materials, despite earlier research highlighting their potential as an antibacterial layer for implants [45, 46]. The primary rationale for incorporating nanoparticles into dental materials is to provide protection against bacterial invasions and to minimize the formation of secondary caries. In addition to Streptococcus mutans and Lactobacillus acidophilus, other microorganisms have been tested, including Escherichia coli [47, 48], Staphylococcus aureus [49, 50], and Candida albicans [51]. Expanding the scope of testing to include various categories of nanoparticles and a broader range of related microorganisms could yield more comprehensive data on their antibacterial efficacy. The disc diffusion method and direct contact test are the most commonly used techniques to assess the antibacterial properties of dental materials. The disc diffusion test utilizes water-soluble constituents released from the material [52], while the direct contact test is essential for assessing insoluble nanoparticles, such as zinc oxide [53], to determine their antibacterial efficacy. For instance, Kim *et al.*, employed the disc diffusion method to evaluate chlorhexidine nanoparticles in resin, with chlorhexidine being solubilized in distilled water before activity assessment [18]. Most studies have focused on modified materials, including resin-based products, dental adhesives, and glass ionomer cement, particularly orthodontic adhesives like Trans-bond XT (3M) and Neo-Bond (Dentsply). In several studies, the omission of manufacturer specifications has negatively affected the methodological quality. Overall, the majority of studies included in this systematic review demonstrate that incorporating nanoparticles into dental restorative materials enhances the antibacterial activity of the base materials. Improvements were noted in various dental materials, such as glass ionomer cement (GIC), resin-modified (RM) materials, dental adhesives, and orthodontic appliances (OA). However, some researchers found that the antibacterial activity of the films was comparable to that of the control groups. For example, Magalhães *et al,*. reported that while silver nanoparticles (Ag-NP) in resin-based cement increased colour and sorption, they did not enhance antibacterial activity against Streptococcus mutans [54, 55]. Similarly, Garcia-Contreras *et al.* indicated that the antibacterial effect was only slightly increased in FX-II Enhanced restorations containing zinc oxide and titanium dioxide nanoparticles [56]. Additionally, Garcia *et al.* observed that zinc oxide nanoparticles in glass ionomer cement exhibited no antibacterial properties against S. mutans [57]. However, the varying concentrations of nanoparticles required for antibacterial agents demonstrate significant variability, despite nanotechnology being one of the most rapidly developing and actively researched fields today. Low concentrations may lack efficacy, and clumping can occur if the pH of the medium is not optimal [58]. Additionally, differences in sample storage and transport can also contribute to variability in results. This clearly indicates the need to introduce new dental restorative materials that

DOI: https://doi.org/10.54393/pjhs.v5i11.2366

possess enhanced antibacterial activity and incorporate nanoparticles. The variation in nanoparticles and their concentrations suggests the possibility of creating new dental materials that are more finely tuned. Future studies should establish protocols to minimize variability and enhance clinical relevance. Consequently, there is significant potential for the application of nanotechnology in dentistry, both in restorative and preventive procedures.

CONCLUSIONS

It was concluded that the utilization of nanoparticles in dental restorative materials promises increased antibacterial efficiency and working length of prevention in preventive dentistry. It became clear that silver, zinc oxide and titanium dioxide nanoparticles are primary preventatives of the bacterial adhesion and biofilm formation factors that contribute to secondary caries and restoration failures. However, more in vivo studies are required to corroborate these observations. Though lab studies have demonstrated the antibacterial prowess of these materials, application in oral environments needs further study. This subject requires proper control of the experimental procedures and nanoparticle synthesis, which in turn, may offer materials that resist bacterial attachment and caries formation.

Authors Contribution

Conceptualization: SS, RS, FT
Methodology: SS, RS, FT
Formal analysis: SS, RS, FT
Writing review and editing: NK, AI, MZ, FA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

Neuropharmacology of *Fisetin* as a Senotherapeutic Agent: Investigating Its Role in Neurodegeneration and Brain Aging

Sidra Javaid[1], Abeer Memon[2], Binish Anwar[3], Zarafshan Bader[4], Ayesha Aftab[5], Fouzia Perveen[6] and Ehsan Ul Haq[7*]

[1]Department of Internal Medicine, Services Hospital Lahore, Lahore, Pakistan
[2]Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan
[3]Department of Pharmacology, Shalamar Medical and Dental College, Lahore, Pakistan
[4]Department of Pharmacology, Foundation University, Islamabad, Pakistan
[5]Department of Pharmacology, Al Nafees Medical College and Hospital, Islamabad, Pakistan
[6]Department of Pharmacology, Sharif Medical and Dental College, Lahore, Pakistan
[7]Institute of Allied Health Sciences, University of Health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:

Fisetin, Neuroprotection, Neurodegeneration, Brain Aging, Cellular Senescence

How to Cite:

Javaid, S., Memon, A., Anwar, B., Bader, Z., Aftab, A., Perveen, F., & Haq, E. U. (2024). Neuropharmacology of Fisetin as a Senotherapeutic Agent: Investigating Its Role in Neurodegeneration and Brain Aging: Fisetin in Neurodegeneration and Aging. Pakistan Journal of Health Sciences, 5(11), 262-269. https://doi.org/10.54393/pjhs.v5i11.2399

***Corresponding Author:**

Ehsan Ul Haq
Institute of Allied Health Sciences, University of Health Sciences, Lahore, Pakistan
ehsanulhaqkhan33@gmail.com

Received Date: 22nd September, 2024
Acceptance Date: 21st November, 2024
Published Date: 30th November, 2024

ABSTRACT

Fisetin, a flavonoid in various fruits and vegetables, has emerged as a promising chemotherapeutic agent with potential neuroprotective effects, particularly in neurodegeneration and brain aging. **Objective:** To explore the role of *fisetin* in mitigating age-related neuronal damage by targeting oxidative stress, inflammation, and cellular senescence, common contributors to neurodegenerative diseases such as Alzheimer's and Parkinson's. **Methods:** Following PRISMA guidelines, relevant studies were sourced from ScienceDirect, Google Scholar, and PubMed, spanning publications between April 2014 and August 2024. One website was also used to retrieve studies, i.e., Frontiers. *Fisetin*'s mechanism of action includes modulating key pathways, such as the inhibition of inflammatory markers, reduction of Reactive Oxygen Species (ROS), and protection against neuronal apoptosis. **Results:** Studies conducted on various animal models and human-derived neurodegenerative cell lines reveal its potential to improve cognitive function and reduce the progression of age-related brain disorders. **Conclusions:** *Fisetin*'s ability to selectively target senescent cells, reduce neuroinflammation, and enhance synaptic function positions it as a potential therapeutic for brain aging. Future research focusing on clinical trials and dosing optimization was crucial to establishing *fisetin* as a viable treatment for neurodegenerative conditions and cognitive decline associated with aging.

INTRODUCTION

Neurodegenerative disorders are diseases that affect the neurons, resulting in the loss of various mental and motor mechanisms. They are frequently found in patients of old age; this showed their connection to the aging of the brain. They are considered to be a significant threat to global health since they are set to worsen given the emerging aging population. In Asia, especially China, the prevalence of neurodegenerative diseases is rapidly rising along with life expectancy [1]. Likewise, North America has been on the rise; however, there are more efforts in the early detection and control of such diseases [2]. These variations may be attributed to environmental, genetic, or healthcare factors [3]. However, the neurodegenerative ailment burden persists to rise globally, notwithstanding advancements in treatment and innovation, widening the social, economic, and humanistic burden of these diseases. Several factors involving oxidative stress, chronic inflammation, and genetic predisposition, as well as exposure to environmental factors, have been cited for the development of neurodegenerative diseases [4]. Cellular senescence, where cells grow dysfunctional and are unable to divide, is a critical factor in brain aging [5]. Aging, Alzheimer's disease, and other diseases that affect the flow of blood to the brain and the proper functioning of a

DOI: https://doi.org/10.54393/pjhs.v5i11.2399

person's cerebral cortex are caused by this dysfunction [6]. In neuronal damage, the importance of oxidative stress raises it specifically as a viable therapeutic target. Among the interventions, one that has aroused the interest of researchers is *fisetin*, which belongs to the group of flavonoids that possess anti-inflammatory and antioxidant effects that may alleviate some of these undesirable conditions [7].*Fisetin* has been identified as a neuroprotective compound and a potential candidate to combat neurodegenerative diseases and brain aging because of its action on certain molecular targets associated with neurodegeneration and aging [8]. Studies showed that *fisetin* can enhance cognitive function, protect neurons, and kill senescent cells, which highlights its potential against brain aging and overall neurological health [9]. The neuroprotective effects of this flavonoid are significant because it opposes processes such as cellular ageing, reduces inflammation in the brain, and helps to maintain synaptic connections which are all vital for the deceleration of brain aging [10]. Due to such an interesting profile, there are ongoing efforts to understand the potential of *fisetin* as an anti-neurodegenerative disease drug in general, regardless of the type of disease that a patient has [11]. The prospects of using *fisetin* in the neurotherapeutic market in the future are relatively promising.Future research with clinical trials might strengthen the position of *fisetin* as a potential medicine for neurodegenerative diseases and the prevention of brain aging [12]. Future work should pinpoint the methods by which it would be delivered and the dose administered, understanding how it would impact the other molecular processes connected to aging and neurodegeneration [13]. In cooperation with innovation in the pharmacological industry, the choice of *fisetin* can be a natural supplemental therapy that could help in stabilizing or reversing the decline of neurodegenerative diseases and increasing the standards of living for the elderly [14].

METHODS

The methodology involved the collection and filtration of studies taken for this study. PRISMA guidelines were taken into consideration throughout the process of filtering for precise results. The studies taken for this study were in the range of 10 years, i.e., 2014 to 2024. Initially, it included 96 articles in English from the last 10 years (2014-2024). Additionally, 10 studies were taken from a website. The inclusion criteria depended upon the essential features, such as mechanism pathways of disease that can relate to fisetin, brain ageing, and neurodegeneration, particularly among elder patients, to study the process of senescence. To assess the potential and potency of fisetin in the neurodegenerative and brain aging models, and in vitro experiments showing variable-induced cytotoxicity and inhibition through fisetin in specific concentrations. Several search engines were used for the study: Science Direct, Google Scholar, and PubMed. The website from which three studies were retrieved includes Frontiers. 65% of the articles were taken from Science Direct, 25% from Google Scholar, and 10% from other search engines, including PubMed. A search was conducted using phrases such as fisetin, neurodegeneration, neurological signalling pathways, brain ageing, etc. Article searches were done using keywords: fisetin, neurological disorders, neurodegeneration, the role of natural compounds in brain-related disorders, etc. The articles that did not contain fisetin or neurodegeneration as keywords and did not come under the range of years selected for the study did not meet the inclusion criteria and were eliminated in the filtering process. Inclusion criteria focused on the pharmacological effect of fisetin on neurodegenerative disorders by slowing the process of ageing. 96 articles in total were downloaded from databases; 3 duplicates were removed, and 93 were left for further study analysis. 16 out of 93 were excluded as they were just abstracts and complete articles could not be reached, so 77 were left. Out of 77, 10 were not retrievable and 67 were assessed for eligibility, out of which again 27 studies were excluded as they were older studies (not from the last 10 years) and 27 contained insufficient data, e.g., study population, sample size was not mentioned, and in some even variables. Finally, 16 were selected, which were sorted and used. 13 out of 16 studies were taken from databases, and 3 were retrieved from websites. The total number of places where these studies were reported as published was also 16. The selected papers were used to extract the following elements, which were arranged systematically according to the inclusion criteria of PRISMA: author name followed by year, demographics, key outcomes, mechanisms, factors, study type, and references. PRISMA work flow for filtering out articles focusing on inclusion and exclusion method. Initially, 96 studies were taken from databases and 10 from a website according to relevancy. All duplicates were eliminated. Only full-text articles that can be downloaded and read were screened. Finally, 16 studies of which 13 were rooted from databases and 3 from a website were taken, each study was reported once (Figure 1).

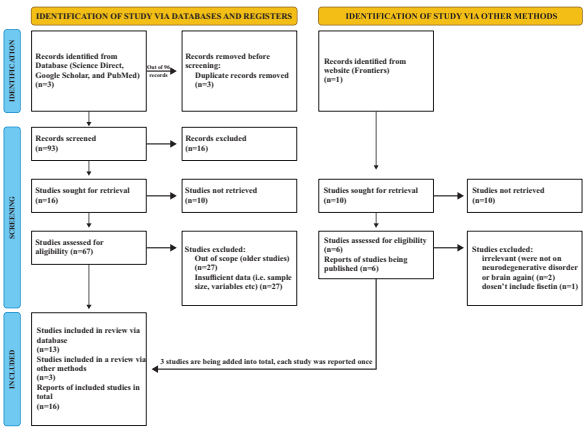

Figure 1: PRISMA Flowchart for Article Selection Based on Inclusion and Exclusion Criteria

DOI: https://doi.org/10.54393/pjhs.v5i11.2399

RESULTS

All reviewed studies were based on neurodegenerative disorders, of which 60% articles were from Asia, 20% from America, and the rest 20% equally from Europe and Africa. Out of 16 studies, 6 were taken from Science Direct; others were from various sources, including Semantic Scholar, Frontiers, and Google Scholar. 7 studies focused on in vitro identification of the role of fisetin as a therapeutic drug; 2 were focused on the same subject but were both in vitro and in vivo combined; 1 was a longitudinal study and contained a population under observation; the rest were in vivo. The results of these studies [15-30] were shown in table 1.

Table 1: Systemic Scheme of Studies Most Relevant To Fisetin's Therapeutic Role In Neurodegenerative Disorders And Brain Aging

Author and Year, Reference (Region)	Study Population (Mean ± SD) Age (Years)	Study Methodology (Sample Size, N)	Study Variables	Key Findings
Zhong *et al.*, 2022 [15] (China)	RAW264.7 Macrophage Cell line of Mouse	In Vitro Study	*Fisetin*, myricetin, quercetin	Fisetin showed strongest inhibition of nitric oxide, Reactive oxygen species ROS, IL-6 and Tumor Necrosis Factor Alpha TNF-α in dose dependent manner. Flavanols also prevented nuclear translocation of Nuclear Factor Kappa NF-kb p65.
Lee E *et al.*, 2023 [16] (USA)	USA Residents with neurodegeneration Problems (range 43.0 - 86.6)	Longitudinal Study (n=19)	Dasatinib, quercetin, *fisetin*	*Fisetin* had a mitigating effect on DQ (Dasatinib and quercetin impact on epigenetic aging.
Maher, P *et al.*, 2020 [17] (USA)	Ht22 Hippocampal Nerve Cells of Mouse	In Vitro Study	*Fisetin*, iron, copper, glutathione GSH, glutamate, Nrf2, ATF4 (transcription factors), RSL3 (a small molecule)	*Fisetin* reduced oxidative stress and inflammation. This provides neuroprotective and anti-inflammatory effects of *fisetin.*
Wang Y *et al.*, 2023 [18] (China)	Sprauge-Dawley Rats (six weeks old)	In Vivo Study	(72 rats) *Fisetin*, Amyloid Beta Aβ1-42	In Aβ1-42 treated rats, *Fisetin* had a healing effect on memory and learning impairments. *Fisetin* reduced apoptosis, inflammation and oxidative stress.
Zhang S *et al.*, 2020 [19] (China)	Murine HT22 Hippocampal Nerve Cells	In Vitro Study	*Fisetin*, glucose	Fisetin effectively reduced the toxicity cause by self-induced high glucose levels in cells. It reduced neurotoxicity and apoptosis. It upregulated neurotrophic factors like BDNF and GDNF (Brain-derived and Ganglia-derived neurotropic factors).
Chen TJ, *et al.*, 2020 [20] (China)	Male C57BL/6 Mice (12 weeks old)	In Vivo Study (24 mice)	*Fisetin*, MPTP (neurotoxin)	Impairments in behavior caused by MPTP were effectively improved by *Fisetin. Fisetin* showed neuroprotective ability through mediation of gut microbiota.
Ahmad S *et al.*, 2021 [21] (South Korea)	C57BL/6N Mice (9 weeks old)	In Vivo Study (60 mice)	D-galactose, *Fisetin*	By upregulation of SIRT1/Nrf2 pathway *Fisetin* effectively reduced oxidative stress and neuroinflammation in intoxicated mice. It suppressed pro inflammatory markers and apoptosis-related protein.
Li X *et al.*, 2022 [22] (China)	Transgenic APP/PS1 Mice (4 months old)	In Vivo Study (50 mice)	*Fisetin*, Amyloid-β (Aβ) oligomers, synaptic proteins	The combination of *Fisetin* and other compounds used improved curiosity and movement in AD (Alzheimer Disease) mice. *Fisetin* reduced Aβ proteins which were harmful.
Ay M *et al.*, 2023 [23] (Turkey)	SH-SY5Y Neuronal Cells	In Vitro Study	*Fisetin*, mitochondrial biogenesis indicators, genes related to Parkinson.	Fisetin increased the mitochondrial biogenesis. Increased levels of anti-Parkinson genes and reduced apoptotic genes.
Rosado-Ramos R *et al.*, 2021 [24] (Portugal)	Yeast model, SH-SY5Y and LUHMES Neuronal Cells.	In Vitro Study	*Fisetin*, TH (tyrosine hydrolase), DAT (dopamine transporter), t-BHP (organic peroxide), MPP+ (neurotoxin)	*Fisetin* protected neuronal cells from oxidative stress. Increased cell viability. Improved the survival of LUHMES cells exposed to toxicity.
Elsallabi O, *et al.*, 2022 [25] (Italy and Sweden)	Human Hs 683 Cell Line, ICH Mice and SAMP8 Mice (few weeks old vs aged Mice)	In vitro and in Vivo Study	ROS, interleukin IL-1β, TNF-α, IL-6, *Fisetin*	*Fisetin* showed a promise as a senolytic drug. Improved mitochondrial function and decreased inflammation in aging models. Reduces oxidative stress.

DOI: https://doi.org/10.54393/pjhs.v5i11.2399

Renault-Mahieux M, *et al.*, 2021 [26] (France)	Glioblastoma Cells	In Vitro Study (Co-encapsulated *fisetin* and cisplatin containing liposomal formulations.)	*Fisetin*, cisplatin	Co encapsulation of fisetin and cisplatin into liposomes showed success.The co-loaded drugs were effective against glioblastoma (GBM)
Mbara K.C *et al.*, 2022 [27](South Africa)	Human Senescent Cells, Senescent Murine	In Vitro, In Vivo (aged Mice)	*Fisetin*	*Fisetin* showed reduction in senescent cells and improved age relating diseases. Increased apoptosis and reduced aged relating factors in cells. *Fisetin* improved life span of progeroid mice.
Akpa A.R *et al.*, 2020 [28](Nigeria)	Adult Albino Male Mice. (10 weeks old)	In Vivo (32 Mice)	*Fisetin*, chlorpyrifos, oxidative stress biomarkers.	*Fisetin* reduced the CPF (neurotoxin) induced oxidative stress. *Fisetin* improved antioxidant defense. *Fisetin* has neuroprotective potential again CPF-induced stress.
Xiao S *et al.*, 2021 [29](USA)	tau K18 filaments in Alzheimer's disease	In Vitro	*Fisetin*, tau protein	*Fisetin* inhibits gathering of tau protein by interacting with k18 fragment and beta strand formation. *Fisetin* proves to be an important candidate as an Alzheimer's treatment.
Yang W et al., 2019 [30](China)	ICR Mice	In Vivo (40 Mice)	*Fisetin*, p-tau, lead	Neurodegradation and neuroinflammation in mice was explored. *Fisetin* improved learning behaviors in lead exposed mice. It reduced inflammatory markers and increased neprilysin that remove A-beta.

DISCUSSION

In this review, we discuss the potential of *fisetin* in mitigating neuronal damage that was associated with age and attributed to factors such as oxidative stress, inflammation, and cellular senescence, which were usually implicated with neurodegenerative diseases such as Alzheimer's or Parkinsonian disorders. Oxidative stress, inflammation, and cellular aging were frequently associated with aging and were increasingly prevalent in both Asia as well as North America, leading to neurodegeneration associated with aging [31, 32]. For example, in China, the current proportion of neurodegenerative diseases was lower but was predicted to increase steadily with time due to the country's aging population, based on high-quality data. On the contrary, the prevalence of neurodegenerative diseases in North America was already a substantial challenge, given the existing high elderly population and rising incidence rates of these conditions [33]. Focusing on the existing literature, the present study demonstrates that *fisetin* may play a complex role in combating neurodegeneration. Some current discoveries represent that this *fisetin* can shield neurons from toxic proteins' impact, decrease inflammation, and improve cognitive abilities [34, 35]. Due to its capabilities of influencing pathways involved in oxidative stress and inflammation, the flavonoid could be considered a therapeutic target for neurodegenerative diseases [36]. About its neuroprotective effect, *fisetin* has been shown to engage several signalling pathways that are particularly important to neuroprotection against neurodegenerative diseases. According to research, fisetin has the potential to downregulate ROS generation and reduce inflammatory biomarkers like IL-6 and TNF-α, which are toxic to neurons [37]. In addition, *fisetin's* properly coordinated anti-inflammatory effects have assisted in the up-regulation of neurotrophic factors, including the BDNF to boost neuronal survival and synaptic plasticity, which were crucial for cognitive function in aging and neurodegenerative diseases [38]. In addition to its antioxidant actions, *fisetin* has been demonstrated to modulate a variety of signalling processes that are involved in neurological disorders. For instance, it stimulates the PI3K/Akt signalling pathway, which is involved in cell survival; the Nrf2 signalling is involved in stress responses [39]. *Fisetin* modulates the Nrf2 pathway, increases the levels of antioxidant-protecting genes, and thus shields neurons from oxidative lesions [40]. Moreover, the fact that *fisetin* alters neuronal signalling pathways to reverse the detrimental effects of oxidative stress in aging and neurodegenerative diseases means that it may be a useful drug candidate to treat or attenuate cognitive function in these conditions. Several in vitro and in vivo tests support the regulatory neuroprotective properties of fisetin in different models of neurodegenerative diseases. Several in vitro experiments have also shown that fisetin inhibits oxidative stress and enhances neuronal cell viability under conditions of neurodegeneration in neuronal cell lines [41]. Experimental animal models have demonstrated that a *fisetin*-supplemented diet enhances learning ability and mitigates inflammation and neuronal die-off in Alzheimer's and other age-related diseases [42]. These results indicate that *fisetin* exhibits neuroprotective action and also improves brain function where neurodegenerative diseases are present. The use of *fisetin* together with other therapeutic agents may extend the effectiveness of the drug on neurodegenerative diseases. Studies have shown that *fisetin* when combined with other flavonoids like

DOI: https://doi.org/10.54393/pjhs.v5i11.2399

quercetin or curcumin, boosts their overall antioxidant and neurogenic properties [43]. The given combination therapies may act on several pathophysiologic processes of neurodegeneration and, therefore, may be less prone to secondary disease progression [44]. Additional studies of these combination therapies will be necessary to define formulations that can be useful for treatment. The therapeutic potentials of *fisetin* indicate the need to perform more studies to establish the efficacy, safety, and dosing of *fisetin* for treating neurodegenerative diseases. Solving these issues will become the key to achieving maximum therapeutic efficacy of *fisetin* as a potentially effective treatment for neurodegenerative diseases and brain ageing. Moreover, the neuroprotective function of *fisetin* was not only valid for these fundamental profiles but also expanded beyond the neuroprotective effects of the existing drugs, making it fit for responding to the multifaceted therapy needs of neurodegenerative diseases for potential distinctive candidacy [45]. There was a well-known difficulty for many therapeutic agents in crossing the blood-brain barrier, which was crucial for the treatment of CNS conditions; this lies in the fact that fisetin has been recognized to possess the capability to cross this barrier. Studies show that the main properties of *fisetin*, such as its small molecular weight and lipophilicity, enable it to cross the BBB and act positively on neuronal cells [46]. This characteristic was especially relevant for compounds designed for the therapy of neurodegenerative diseases that require their delivery to the brain. However, the ability of *fisetin* to positively or negatively influence mitochondrial homeostasis only serves as an extra dimension to its activity. This type of cellular respiration has been implicated in many neurodegenerative disorders due to energy failure and enhancement of oxidative stress on neuronal cells [47]. *Fisetin* has been found to improve the process and efficiency of mitochondrial generation, and its normal functioning neutralizes these effects [48]. This property becomes significant given that mitochondrial integrity was strongly associated with neuronal and cognitive integrity. Yet another viable area of research has to do with how *fisetin* acts within the context of the gut-brain axis. Recent animal and human studies have shown that the gut microbiota dramatically affects the brain and its diseases; it may underlie the development of neurodegenerative diseases. The neuroprotective effect of *fisetin* could benefit from the changes in the gut microbiota, as a healthy composition of the microbiota leads to a decrease in neuro-inflammation status and improved cognitive performance [49]. Furthermore, because inflammation was seen as a common feature in aging populations, *fisetin* also works to decrease systemic inflammation that typically occurs in aging individuals, thus improving brain health. Despite the promising literature reviews that demonstrated the antineoplastic, antioxidant, and anti-inflammatory effects of *fisetin,* the further steps of its introduction to clinical practice require investigations of its tolerance and dosing. Randomized control trials were required to evaluate the bioavailability and safety of *fisetin* in humans and its application in the prevention or treatment of neurodegenerative diseases in an aging population. These studies should also establish whether the use of *fisetin* can be complementary with other well-known treatments or other forms of nutrition that could amplify the neuroprotective effect of *fisetin* with minimal toxic effect. In light of the current focus on complementary compounds to conventional therapies, *fisetin* could be another candidate that will enhance the standard treatment regimens, making positive changes in neurodegenerative diseases.

CONCLUSIONS

The present review indicates that *fisetin* has therapeutic potential for neurodegenerative disorders because of its strong neuroprotection activity in terms of antioxidant, anti-inflammatory, and anti-apoptotic properties. *Fisetin* being able to modulate oxidative stress as well as neuroinflammation has shown to rescue the neurons and enhance learning abilities in models of neurodegenerative diseases. Adding to these benefits, its capacity to improve synaptic plasticity and mitochondrial function makes it a drug candidate. However, the given reports suggest that there were more clinical trials to define the appropriate dosing regimen, pharmacokinetics, toxicity, and therapeutic effects on a larger patient population. Dietary manipulations especially with *fisetin*-supplemented products, have the potential to influence patient outcomes, especially with increasing incidences of neurodegenerative diseases, especially in the elderly.

Authors Contribution

Conceptualization: SJ, AM, BA
Methodology: AM, BA, AA, EUH
Formal analysis: AM, FP, EUH
Writing, review and editing: AM, BA, ZB, AA, FP, EUH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v5i11.2399

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DOI: https://doi.org/10.54393/pjhs.v5i11.2398

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

Clinicopathological Role of Adiponectin in Preeclampsia: Linkage with Placental Function and Maternal Health

Mohammedelfateh Adam[1], Sarfaraz Khan[2], Memona Zia[3], Anum Iftikhar[4], Sajid Hussain Sherazi[5], Naveed Ahsan[6] and Ehsan Ul Haq[7*]

[1]Department of Obstetrics and Gynaecology, Galway University Hospital, Ireland
[2]Department of Medicine and Endocrinology, Mercy Teaching Hospital, Peshawar, Pakistan
[3]Department of Pathology, Abu Umara Medical and Dental College, Lahore, Pakistan
[4]Department of Pathology, Bahawalpur Medical and Dental College, Bahawalpur, Pakistan
[5]Department of Pediatric, Niazi Medical and Dental College, Sargodha, Pakistan
[6]Department of Biochemistry, Bhitai Dental and Medical College, Mirpurkhas, Pakistan
[7]Department of Allied Health Sciences, University of Health Sciences, Lahore Pakistan

ARTICLE INFO

Keywords:
Adiponectin, Preeclampsia, Placental Gene Expression, Maternal Health

How to Cite:
Adam, M., Khan, S., Zia, M., Iftikhar, A., Sherazi, S. H., Ahsan, N., & Haq, E. U. Clinicopathological Role of Adiponectin in Preeclampsia: Linkage with Placental Function and Maternal Health: Clinical-pathology of Adiponectin in Preeclampsia: Placental and Maternal Outcomes. Pakistan Journal of Health Sciences, 5(11), 270-277. https://doi.org/10.54393/pjhs.v5i11.2398

Corresponding Author:
Ehsan Ul Haq
Department of Allied Health Sciences, University of Health Sciences, Lahore Pakistan
ehsanulhaqkhan33@gmail.com

Received Date: 12th October, 2024
Acceptance Date: 23th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Preeclampsia is a hypertensive, multisystem disease in pregnancy, associated with dysfunction of the placenta. Emerging studies point toward the possibility that adiponectin, a hormone with anti-inflammatory and vasodilator properties, may contribute to the development of preeclampsia. **Objectives:** To systematically review the role of adiponectin in the pathophysiology of preeclampsia with limited evidence on the role of placental gene expression, providing clinicopathological insights into its role in maternal and fetal health. **Methods:** A comprehensive literature search was conducted across PubMed, Science Direct, and Google Scholar for articles published between 2017 and 2024. Included studies explored the relationship between Adiponectin levels and preeclampsia in relevance to placental pathology, and hormonal levels. Studies analyzed adiponectin's role in modulating insulin resistance, hypertension, placental growth, and vascular health in preeclampsia. Data from multiple regions, including Asia, Europe, and America, provided global perspectives. **Results:** An association between reduced adiponectin levels and increased severity of preeclampsia and its potential role in impaired placental physiology and adverse pregnancy outcomes were reviewed. **Conclusions:** It was concluded that adiponectin plays a crucial role in the pathophysiology of preeclampsia, affecting both maternal health and placental function. Understanding these mechanisms may offer insights for therapeutic interventions in managing preeclampsia and improving fetal outcomes.

INTRODUCTION

Preeclampsia is a pregnancy hypertension complication that occurs in the second half of pregnancy, usually after 20 weeks of pregnancy, and is associated with blood pressure and protein levels. Incidence of 2–8% in pregnancy across the globe makes it a cause of significant maternal and peripartum mortalities and morbidities especially in developing countries [1]. The significance of assessing preeclampsia is based on its serious consequences which include placental insufficiency, fetal birth restriction, preterm birth, pregnancy termination, and maternal or fetal fatalities [2]. It is therefore important to understand the processes involved in affecting the overall progress in the well-being of both the mother and her baby. In different countries, the occurrence differs, but it is high in Africa, Asia, and Latin America most likely attributed to economic reasons and poor health facilities [3]. In European countries and America, the prevalence of preeclampsia is relatively low, but remains a major public health problem, as 2-5% of pregnancies are affected by it [4]. The condition has been linked to internal derangement characterized by

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

endothelial dysfunction, oxidative stress, immune maladaptation, poor placental development with resultant poor perfusion, and compromised fetal status [5]. The cause of preeclampsia is still not clear; however, both genetic and immunological factors as well as environmental predisposing factors are involved. Specific risk factors include chronic hypertension, diabetes, obesity, and an older maternal age, which predispose to internal pathophysiological derangements leading to this condition [6]. Adiponectin, a hormone secreted mainly by adipose tissue, is a potential novel biochemical marker related to preeclampsia, which has been discovered in recent years. Adiponectin has been characterized as an anti-inflammatory, insulin-sensitizing, and vasodilation agent indispensable for the regulation of maternal metabolism and vasculature [7,8,9]. It has been proposed that weight loss or a change in the percentage of body fat can be used to predict the onset of mild and severe preeclampsia because adiponectin has a role in regulating insulin signalling and inflammation and its circulating levels were linked to preeclampsia [10]. Adiponectin modulation of placental function and its potential implications for preeclampsia is the focus of our primary review. Placental dysfunction is well established in preeclampsia, although recent work has implicated adiponectin, which regulates pathways necessary for trophoblast invasion, angiogenesis, and nutrient transport, in preeclampsia mechanisms based on placental maladaptation [11]. Adiponectin is shown to regulate key signalling pathways: Mitogen-activated protein kinase/Signal transducer and activator of transcription 5 (MAPK/STAT5) and Vascular endothelial growth factor (VEGF) axes, critical for trophoblast proliferation and vascular development, as well as placental structure integrity [12]. We further categorized the adiponectin's signalling pathways documented to impact placental gene expression and function to provide a clearer understanding of preeclampsia clinical relevance although this information remains limited to one study in our systematic review. Recent findings of regional and ethnic variation in adiponectin and its ability as a biomarker for adiponectin are reviewed and predictions are made about future performance in different populations. We also adjusted for confounders among maternal health factors including BMI, gestational diabetes, and other factors to clarify adiponectin's independent role in preeclampsia. Based on this synthesis of recent studies, adiponectin's regulatory mechanisms and signalling pathways may potentially become targets for early diagnosis and therapeutic intervention in preeclampsia to improve maternal and foetal health outcomes.

This study aims to systematically review the role of Adiponectin in the pathophysiology of preeclampsia with limited evidence on the role of placental gene expression, providing clinicopathological insights into its role in maternal and fetal health.

METHODS

The PRISMA guidelines for reporting were followed throughout the conduct of this study. It included 87 articles in English from the last 7 years (2017-2024). The papers included the following information, which was arranged systematically according to the inclusion criteria of PRISMA guidelines 2020: author name followed by year, country, sample population, factors and variables, study design, and references. Several search engines and public libraries were taken for fetching articles for our study. The names included are PubMed, Science Direct, Springer Link, and search engine includes Google Scholar. The search was conducted using phrases such as Adiponectin, preeclampsia, placental gene expression, maternal health, fetal development, vascular function, and insulin resistance. We conducted a literature search using key phrases such as "Preeclampsia and adiponectin", "mechanistic role of adiponectin in preeclampsia" and "clinical studies on the role of adiponectin in preeclampsia". This search was conducted in abstracts and duplicate entries which were then filtered systematically using specific inclusion and exclusion criteria. If the article was not pointing out the relation between adiponectin and preeclampsia, was not appropriate from a clinical or a pathophysiological aspect of preeclampsia and did not adhere to the appropriate methodologies such as clinical studies like prospective, randomized controlled trials (RCT), and cohort were excluded. Studies directly investigating the influence of adiponectin on preeclampsia pathophysiology, especially on placental function, fetal outcomes, and to some extent gene expression were emphasized as the inclusion criteria. Other considerations included BMI, gestational diabetes, or ethnic or regional differences. As a result of this rigorous selection, fifteen studies were selected for detailed analysis. 87 articles in total were downloaded from databases, 6 duplicates were removed and 81 were left for further study analysis. A total of 66 articles from the systematic review after full-text review and 15 were left which were sorted and used. PRISMA Work Flow for Filtering Out Articles Focusing On Inclusion and Exclusion Method. Initially, 87 Studies were taken according to abstract and title and relevancy. Total of 6 duplicates were eliminated. only full-text articles that can be downloaded and read were screened. Finally, 15 studies were taken and sorted according to study type (Figure 1).

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

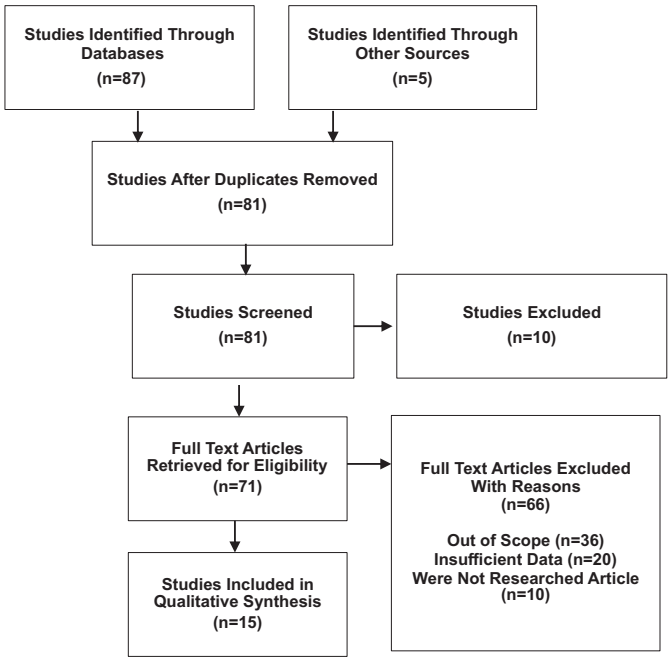

Figure 1: Filtering Out Articles Focusing on Inclusion and Exclusion Method

RESULTS

This study mainly reviewed papers that were cohort studies, prospective studies, controlled trials and preclinical trials (one study only) because these type of studies helps in understanding disease patterns, their risk factors, unique insights about conditions and potential and optimum treatments. The studies in this review are taken from well-known public libraries for scientific research and search engines such as Google Scholar (80%), PubMed (10%) and Science Direct (10%), in line with PRISMA guidelines. Confounders like BMI, gestational diabetes, age of mother, and lifestyle characteristics including smoking, physical activity and socioeconomic status are found in most studies and were controlled in this study as well. These include prospective, cohort, case-control, RCTs and preclinical design to provide a substantial level of evidence regarding the association of Adiponectin in preeclampsia. The table presents the consideration of the effects of Adiponectin on placental function, gene expression, fetal outcome physical activity, and socioeconomic status) which are common in most studies and were adjusted to ensure accurate findings. The table reflects a focus on how Adiponectin levels impact placental function, gene expression, and fetal outcomes. Results suggest that adiponectin and leptin levels as well as total antioxidant status (TAS) are pathologically significant biomarkers of preeclampsia severity and adverse maternal outcomes. Consistently, elevated leptin levels and lower adiponectin/leptin ratio were associated with increased oxidative stress, markers of inflammatory responses and endothelial dysfunction all associated with placental insufficiency. Reduced adiponectin levels had a specific effect on trophoblasts thus limiting placental development and fetal growth. In many cases, though 'elevated' for compensatory purposes in response to oxidative stress, TAS levels were insufficient to quell the inflammation-driving complications such as Hemolysis, Elevated Liver-enzymes, and Low Platelet-count (HELLP) syndrome and eclampsia. Together, these findings underscore the important roles of adipokines and oxidative balance in preeclampsia pathogenesis and could provide possible molecular and biomarker tools to aid early detection, and targeted treatment. Results of these studies [13-27] are shown (Table 1).

Table 1: A Systematic Review of the Literature for Articles

Reference	Study Design	Population	Key Findings	Confounders	Conclusions
[13]	Case-control	70 pregnant women (32 with PIH,38 healthy controls)	Adiponectin levels were lower in the Pregnancy-induced hypertension (PIH) group,but not significantly different from controls. Adiponectin /Leptin levels were significantly higher.	Body Mass Index (BMI(, gestational age, number of pregnancies, delivery method	High Adiponectin/ leptin levels in PIH women may predict the need for a caesarean section, while adiponectin levels were not a significant marker.
[14]	Case-control	Pregnant women: Control (n=59), Gestational Hypertension (n=55), Late (n=68) & Early (n=66) Preeclampsia groups	Elevated adiponectin, Malondialdehyde MDA, and Total antioxidant status (TAS) levels were associated with adverse outcomes (e.g.,Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome, eclampsia) in preeclampsia. Adiponectin plays a protective role by counterbalancing inflammation and endothelial dysfunction.	BMI, gestational age, renal function, pre-existing conditions like hypertension and diabetes	Elevated adiponectin and TAS are linked to adverse maternal outcomes in preeclampsia, possibly as compensatory mechanisms to inflammation, oxidative stress, and endothelial damage.

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

[15]	Prospective Study	50 pre-eclampsia patients, 50 normotensive controls	Lower adiponectin/leptin ratio and higher leptin levels in pre-eclamptic women. Predictive value of adiponectin/leptin ratio and leptin levels for pre-eclampsia diagnosis.	BMI, Obesity, Hypertension,Diabetes	Adiponectin/leptin ratio < 0.153 and leptin> 24.1 ng/ml serve as potential biomarkers for pre-eclampsia diagnosis.
[16]	Case-control Study (Cohort)	126 pre-eclampsia patients,297 controls	Reduced adiponectin/leptin (A/L) ratio in the first trimester correlates with pre-eclampsia . The A/L ratio serves as a better predictor of pre-eclampsia than either hormone individually.	BMI, Maternal metabolic syndrome	A lower A/L ratio in early pregnancy predicts pre-eclampsia; more effective than using adiponectin or leptin alone.
[17]	Prospective Cohort	1,776 Pregnant women (multi-ethnic)	Decreased adiponectin levels lead to increased inflammation and impaired metabolic pathways, linked with higher preeclampsia risk (AOR 1.45)	BMI, age, smoking, ethnicity	Dysregulation in adiponectin levels early in pregnancy increases preeclampsia risk, especially in certain ethnic groups.
[18]	Prospective Cohort	1012 Preterm and term new-borns	Low cord adiponectin in preterm infants is linked to adipose tissue dysfunction and metabolic dysregulation, which may be associated with maternal preeclampsia	GA, birth weight, Black race, DM	Low adiponectin in new-borns, particularly in preterm births,may signal future metabolic dysfunction related to maternal preeclampsia.
[19]	Prospective, Case-control Study	166 pregnant women divided into groups based on BMI and Gestational diabetes mellitus (GDM) status	Serum adiponectin levels were lower in obesity and higher in preeclampsia, suggesting a role in its pathogenesis.	Obesity, GDM, hypertension	Adiponectin does not significantly differentiate between pregnant women with or without GDM, but obesity complicates outcomes. Adiponectin's role in preeclampsia is suggested by its anti-inflammatory effects.
[20]	Prospective Study	60 preeclampsia women and 60 normotensive controls	Adiponectin levels were insignificantly higher in the preeclampsia group. However, the leptin/adiponectin ratio was significantly lower in preeclampsia women, suggesting an imbalance in adipokines.	Obesity, hypertension, diabetes	Adiponectin and leptin ratios can serve as biomarkers for preeclampsia, with altered ratios indicating adipose tissue dysfunction and inflammatory processes.
[21]	Case-control Study	90 Preeclampsia,100 normotensive pregnant women	Adiponectin levels were significantly lower in Preeclampsia pregnancies. Adiponectin, leptin, resistin, and visfatin are predictors of PE.	BMI, family history of diabetes, hypertension	Adiponectin and other adipokines are significant predictors of PE. Controlling for confounders, adiponectin was the best predictor.
[22]	Cohort Study	2503 pregnancies, including 93 Preeclampsia pregnancies, with normal, moderate, and severe obesity	In severely obese women, Preeclampsia is associated with lower adiponectin levels. Leptin was inversely associated with PE in severe obesity.	BMI, maternal age, smoking	Adiponectin is a significant predictor of PE in obese women. Leptin levels are predictive only in severe obesity.

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

[23]	Retrospective Study	118 severe pre-eclampsia patients and 90 controls	Serum adiponectin levels were negatively correlated with umbilical artery resistance/pulsatility indexes; lower adiponectin levels in severe pre-eclampsia may indicate poor placental function and adverse outcomes	Maternal age, body mass index, history of hypertension, kidney disease, diabetes	Umbilical artery Doppler combined with serum adiponectin levels can predict adverse pregnancy outcomes in severe pre-eclampsia.
Studies on Gene Profile Analysis					
[24]	Case-control Study	52 pre-eclampsia patients, 30 normal pregnancies	Adiponectin downregulates p38 MAPK, activates STAT5, and controls trophoblast function in preeclampsia. Decreased adiponectin in pre-eclampsia correlates with abnormal placental function.	Age, Gestational age(GA), BMI, Urinary protein	Adiponectin regulates trophoblast function via the MAPK-STAT5 pathway, playing a crucial role in the pathogenesis of pre-eclampsia.
[25]	Case-control	First-trimester pregnant women (126 PE cases, 297 controls)	Lower adiponectin/leptin ratio suggests impaired insulin sensitivity,contributing to metabolic disturbances that can lead to preeclampsia	BMI, maternal insulin resistance (IR)	Adiponectin/leptin ratio is a predictive marker for preeclampsia, reflecting underlying metabolic imbalances such as insulin resistance.
[26]	Cohort Study	Pregnant women with GDM, Preeclampsia, and combined Preeclampsia + GDM	Adiponectin levels were lower in Preeclampsia compared to controls, and higher in PE + GDM. PR3 and placental proteins altered in PE and GDM.	Age, BMI, fasting glucose	Adiponectin is lower in PE and GDM,with placental changes showing systemic inflammatory involvement.

DISCUSSION

Preeclampsia is a hypertensive disorder and a new onset of hypertension and proteinuria after 20 weeks of gestation. According to WHO, preeclampsia is a leading cause of maternal (and perinatal) mortality and morbidity worldwide, with higher incidence and lower access to healthcare in developing regions, and contributes to 10 to 15% of maternal deaths worldwide. The prevalence is 2–8 per cent of pregnancies, with the highest prevalence in sub-Saharan Africa and South Asia. This disorder appears to be severe for both mother and fetus and may complicate with eclampsia, placental abruption, preterm birth, intrauterine growth restriction (IUGR) and mortality [27]. This review aimed to assess systematically the role of adiponectin in the pathophysiology of preeclampsia based on available supplemental evidence regarding the clinical and pathologic effects of adiponectin on fetal health. The review evaluated adiponectin's involvement in clinical and metabolic aspects of preeclampsia and its potential contribution to prevention and diagnosis while controlling for BMI and gestational diabetes. A variety of internal and external factors are inherent to the development and degree of preeclampsia. Within the context of the cell, oxidation stress, impairment of endothelium, and immunological dysfunction have been pointed out as the key players in this pathogenesis of the disease [28]. Human endothelium is central to the regulation of vascular resistance and its derangement results in some of the key pathophysiological features observed in preeclampsia: vasoconstriction, inflammation, and increased endothelial permeability [29]. Moreover, the distribution of preeclampsia by geographic location, race, and ethnicity shows that women of African origin are more likely to develop preeclampsia than white women [30]. Adiponectin is a hormone mainly secreted from adipocytes with insulin-sensitizing, anti-inflammatory, and vasodilator properties important for pregnancy-associated metabolic and vascular control [31]. Adiponectin, in the pathway of preeclampsia management, shows a protective effect regulating several actions which support the maintenance of placenta function as well as the effective and safe functioning of the maternal circulation. Despite this, many investigations have shown that adiponectin concentration is decreased in women with preeclampsia compared to normotensive pregnant women [32]. Such a decrease in adiponectin levels results in enhancing inflammatory response, endothelial dysfunction and inhibition of angiogenesis, these processes provoke placental insufficiency and adverse pregnancy outcomes in preeclampsia [33]. Adiponectin exerts most of its regulatory mechanistic function via two receptors, the AdipoR1 and AdipoR2, which in turn stimulate various signalling pathways that lessen inflammation, improve cellular energy, fatty acid oxidation and glucose utilization through the AMP-activated protein

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

kinase (AMPK) pathway and enhance the insulin-sensitizing Peroxisome proliferator-activated receptor (PPAR) pathway and the anti-inflammatory MAPK pathway [34]. Stimulation of these pathways also increases insulin tolerance, improves oxidative stress and has anti-inflammatory effects which are essential to compensate for altered-looking placental function. In preeclampsia, these pathways fail due to low adiponectin leading to dysfunction of trophoblasts and improper development of the placenta leading to restrictive fetal growth [35]. From the literature used, our review focuses on several works that investigate adiponectin on preeclampsia, as described in Table 1, many case-controls, cohort, as well as, prospective-based studies have shown a significant inverse relationship between the levels of adiponectin and the probability and severity of preeclampsia. For example, a study identified that low adiponectin concentrations were associated with severe preeclampsia and placental dysfunction [36], while one study established that although adiponectin was lower in women with Pregnancy-induced hypertension (PIH), leptin had better effectiveness index in predicting adverse outcomes [37]. In tandem, a study, also showed that a low ratio of adiponectin/leptin in the first trimester predicted preeclampsia in the second and third trimesters [38]. These results imply that it would be effective to screen adiponectin and leptin as biomarkers for preeclampsia in women and intervene before complications occur. This paper, however, has some limitations despite providing useful information on adiponectin mechanisms for preeclampsia diagnosis and review. First, the studies investigated in the current review have a wide variety of designs, sample sizes, and population characteristics. Some analyses involved selected ethnic groups or geographical areas, and thus could not be generalized to other communities. Moreover, not all contained the same comparison factors such as BMI, gestational diabetes and other metabolic problems while doing correlation analysis of adiponectin levels and preeclampsia risk. One more significant drawback is that most data originated from observational or case-control trials; such research does not allow for establishing causality because of their susceptibility to bias. Cross-sectional designs also restrict the examination of the temporal association between adiponectin and preeclampsia occurrence. Last, it is also essential to mention that, although this review discusses several signaling pathways connected with adiponectin, there is a deficiency of more extensive and focused investigations on the molecular mechanisms responsible for linking adiponectin with the dysfunction of the placenta. Lastly, this review gives a comprehensive understanding of how adiponectin modulates preeclampsia's pathophysiology by regulating placental gene expression and maternal blood vessel function. The information based on these pathways should be explored further; additionally, new approaches to using the properties of adiponectin should be sought in the future. In the same regard, there is a requirement for large sample, multi-ethnic cohort studies to confirm the predictive utility of adiponectin and, the accompanied biomarkers across ethnic groups.

CONCLUSIONS

It was concluded that this review emphasizes the important pathophysiological role of adiponectin in preeclampsia and its relevance for maternal health and placentae function. The regulation of insulin sensitivity, inflammation, and vascular health by adiponectin is thus an attractive biomarker for the early detection and potential therapeutic targeting of preeclampsia. Biomarkers such as the adiponectin/leptin ratio have predicted value and suggest that future interventions may be guided by these markers and improve pregnancy outcomes. Despite these promising associations, however, more research is required to clarify the molecular mechanisms by which adiponectin affects placental gene expression and to understand its broader implications in disparate populations. In addition, confirmation of the utility of adiponectin-based diagnostics and treatments will depend on large-scale cohort studies involving multi-ethnic participants. Such an advance could considerably accelerate the management of preeclampsia and thus improve the health, and survival, of both mothers and their children.

Authors Contribution

Conceptualization: MA, SK, MZ
Methodology: MA, SK, MZ, AI, SHS. NA, EUH
Formal analysis: MA, SK, MZ
Writing review and editing: AI, SHS, NA, EUH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v5i11.2398

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DOI: https://doi.org/10.54393/pjhs.v5i11.2489

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

Effectiveness of Ultrasound-Guided Regional Anaesthesia in Paediatric Patients Undergoing Urological Surgeries: A Systematic Review

Shabir Ahmad[1], Hafiz Wajih Ul Hassan[2], Saba Akram[3], Syed Imtiaz Ali Zaidi[4], Aftab Ahmed[5], Pakeeza Shafiq[6] and Muhammad Arsalan Shah[7*]

[1]Department of Community Medicine, Poonch Medical College, Rawalakot, Pakistan
[2]Department of Anesthesia, Evercare Hospital, Lahore, Pakistan
[3]Department of Radiology, Avicenna Medical and Dental College, Lahore, Pakistan
[4]Department of Anesthesiology and Intensive Care, Avicenna Medical College and Hospital, Lahore, Pakistan
[5]Department of Urology, Sheikh Khalifa Bin Zaid Hospital/Combined Military Hospital Muzaffarabad, Azad Jammu Kashmir, Pakistan
[6]Department of Surgery, College of Medicine, Northern Border University, Saudi Arabia
[7]Department of Pathology, University of Health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:
Ultrasound-Guided Regional Anesthesia, Pediatric Anesthesia, Urological Surgeries, Pain Management

How to Cite:
Ahmad, S., Hassan, H. W. U., Akram, S., Zaidi, S. I. A., Ahmed, A., Shafiq, P., & Shah, M. A. (2024). Effectiveness of Ultrasound-Guided Regional Anaesthesia in Paediatric Patients Undergoing Urological Surgeries: A Systematic Review: Ultrasound-Guided Regional Anaesthesia in Paediatric Patients Undergoing Urological Surgeries. Pakistan Journal of Health Sciences, 5(11), 278-287. https://doi.org/10.54393/pjhs.v5i11.2489

***Corresponding Author:**
Muhammad Arsalan Shah
Department of Pathology, University of Health Sciences, Lahore, Pakistan
muhammadarsalanshahpath01@gmail.com

Received Date: 9th October, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Recent research in anatomy and ultrasound has highlighted the importance of a technique named ultrasound-guided regional anaesthesia in pediatric anaesthesia, due to its approach to enhancing nerve visualization and targeted nerve blockade which improves patients' safety and pain relief during surgical procedures. **Objectives:** To evaluate the outcomes of pediatric patients who received ultrasound-guided regional anaesthesia during urological surgeries and compare its effectiveness in pain control, anaesthetic quality, and post-surgery results. **Methods:** A search was conducted according to PRISMA guidelines using PubMed, Google Scholar, Springer Link, and Science Direct. A total of 96 studies were included after applying the inclusion criteria to articles published between January 2013 and April 2024. Out of these, only 15 were used in the study table to highlight the effectiveness of ultrasound-guided regional anaesthesia in pediatric urological surgeries. **Results:** Consistently, the alignment with the ultrasound-guided regional anaesthesia revealed significantly greater analgesic efficacy, least opioid usage as well and lesser rates of anaesthesia-related adverse events in pediatric subjects mainly neurodevelopmental concerns and opioid dependency. Other papers also revealed better hemodynamic control and the duration of time needed to feel fully recovered postoperatively, and thus, ultrasound-guided regional anesthesia may enhance perioperative outcomes and ambience in children undergoing different urological procedures. **Conclusions:** It was concluded that ultrasound-guided regional anaesthesia appears to be applicable for pediatric urological surgery, providing better analgesia, fewer side effects, and reduced demand for systemic anaesthesia. Future studies should establish the long-term results of the method and make comparisons to the other procedures.

INTRODUCTION

Managing pain in pediatric patients who undergo urological surgeries is challenging due to the risks caused by conventional procedures such as respiratory depression, postoperative nausea, and prolonged children's recovery times which can be life-threatening. The necessity of searching for other efficient and safe pain-management approaches is important especially because opioid administration methods involve risks of dependency and exposure to neurodevelopmental disorders in children [1, 2]. Regional anesthesia has emerged in this domain to provide localized analgesia that minimizes the need for systemic opioids and reduces anesthesia-related problems [3]. Ultrasound-Guided Regional Anesthesia (UGRA) has come forth as one of the promising regional anesthesia techniques for pediatric surgery. UGRA identifies structures of nerves by using ultrasonography and also supplies the appropriate neural blockade which reduces the requirement for opioid and general anesthesia

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

consumption [4]. This approach is most useful in pediatric patients who require urological surgeries, which are usually followed by severe pain. Several surgical interventions including hypospadias repair, nephrolithotomy, and hernia repair depend on adequate and safe analgesia to achieve optimal patient comfort and surgical recovery results. UGRA can provide long-term pain relief while reducing the conventional side effects of general anesthesia associated with improper nerve blocks [5]. The relevance of UGRA increases due to the growing perception of the opioid crisis, which has affected pediatric patients as well. In pediatric urological surgeries, the children are subjected to opioids for postoperative pain relief. However, particular concerns are related to its properties, including dependency, respiratory depression, and inhibitory effects on neurodevelopment [6]. UGRA is a non-opioid analgesic option for children, preventing excessive opioid exposure in patients and reducing a variety of potential complications associated with the use of opioids in children [7, 8]. Despite the promising benefits of UGRA application, currently, there is insufficient data that can be compared and therefore requires more systematic investigation on the efficacy of UGRA in pediatric urological surgery. To date, studies on UGRA in pediatric settings have demonstrated beneficial effects like postoperative pain, decreased opioid use, and decreased postoperative morbidity; nonetheless, most of these focus on general pediatric surgery and not on the peculiarities of urological surgery [9, 10]. In addition, there is no standardized use of UGRA across the different institutions, with variations in technique, training, and equipment potentially influencing clinical outcomes in patients [11]. Additionally, even if the short-term effects of UGRA are positive, its long-term safety in children is not well understood, particularly neurodevelopmental consequences followed by subsequent exposure [12]. It is revealed that there is a lack of understanding of UGRA's efficiency in Pediatric urological surgeries, particularly regarding the amount of postoperative pain relief, opioid consumption, and postoperative recovery data [13, 14]. This systematic review is intended to contribute to the evaluation of studies to provide possibilities that UGRA can become a standard practice in pediatric surgeries and can provide safer anaesthetic protocols for children. Furthermore, this review will discuss the need for generalized UGRA methods and training protocols in different surgical settings to ensure consistent therapeutic effects for patients across diverse settings.

This study aims to contribute to the pediatric anesthetic management by emphasizing on the use of UGRA as a feasible option for postoperative pain relief in pediatric urological patients while recommending for future research on comparative studies on the UGRA's long-term impacts and standardization.

METHODS

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed to identify applicable studies of ultrasound-guided regional anesthesia (UGRA) for pediatric urological surgery. To capture recent advances in applications of UGRA, studies published in English between 2013 and 2024 were included. As a part of this review, articles were selected based on their relevance to UGRA in pediatric patients undergoing hypospadias repair, nephrolithotomy, and herniotomy. Studies were selected based on the age of pediatric patients from 0 to 17 years' old who had undergone urological surgeries performed by using UGRA techniques. Studies were included if they provided clinical results based on acute and chronic pain, anesthesia side effects, opioid administration, and rehabilitation. The exclusion criteria include research without pediatric population, without UGRA, or the study being a review or case series with raw data. As for specific ethical concerns on children, the literature review included only the trials that reported parental or guardian permission and described the risks of anesthesia in children because children are vulnerable to the effects of anesthesia, and the use of anesthesia in pediatric population should be weighed against potential benefits of pain relief. Multi-database search was done on PubMed, Science Direct, Springer Link, and Google Scholar for extensive research. The included articles were primarily around 80% derived from PubMed because it contains a large number of Clinical studies in pediatric anesthesia and UGRA techniques. The search strategy involved the use of keywords such as "ultrasound-guided regional anesthesia" "pediatric urological surgeries" and "dorsal penile nerve block" "caudal epidural block" "transverses abdominis plane block." Articles regarding UGRA and pediatric urological anesthesia were then screened for relevance to the aims of the study from an initial search. All the titles and abstracts were reviewed to be sure that duplicates and articles that did not fit the inclusion criteria were eliminated. Only articles that focused on UGRA and that did include pediatric patients were included. Articles published outside the specified timeline were also excluded. The present review included studies that described certain techniques of UGRA. Each study's methodology was assessed for the following technical specifics: the block side (e.g., caudal block, dorsal penile nerve block), the type of needle including the gauge and length, and the volume of anesthesia used. For the studies that were part of a larger trial, the respective authors' real-time ultrasound guidance usage was noted where feasible, in addition to technique-related complication management protocols. The monitoring of opioid usage was assessed for each type of study. Information on opioids was obtained according to their total frequency and dosage during the treatment course, whether opioids were intraoperative or postoperative. Some studies focused on patient

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

compliance with prescribed regimens further highlight the difference between opioids that are prescribed and those that are consumed. This tracking approach helped in evaluating the role of UGRA as an opioid-saving model in pediatric anesthesia. A total of 96 articles were identified following such initial screening. After that, 43 articles were further refined based on relevance, quality, and alignment with the research objectives. From these 15 high-quality studies where the clinical data on UGRA's effect had been robust in pediatric urological surgeries were taken. For each of the 15 studies, data were systematically extracted and organized within the PRISMA framework, including the following variables: Study design, UGRA technique used, primary outcomes (e.g., pain control efficacy, opioid requirement reduction, rates of complications), secondary outcomes (e.g., recovery time, patient satisfaction), year of publication, country of origin, and authorship. The studies' sample adequacy was evaluated in terms of their population and statistical significance whenever possible. A systematic extraction of quantified variables was done with a focus on patient characteristics, UGRA technique, efficacy, complications, post-procedure treatment, pain management, and opioid use, from articles selected following the PRISMA guidelines. Through this detailed data extraction, a complete picture of UGRA's effectiveness in pediatric populations was synthesized as well as give insights into the challenges and strengths of potential applications of UGRA. At last, the final dataset allowed for a comprehensive analysis of UGRA's effects in decreasing perioperative and postoperative outcomes of pediatric urological surgeries. Results were then presented in a table summarizing the UGRA techniques that were most effective, the difficulties encountered, and the potential areas for UGRA advantage, such as reduced opioid use and shorter recoveries. The analysis also identified gaps in the literature and suggested future research directions, such as long-term safety studies, as well as standardized UGRA protocols (Figure 1).

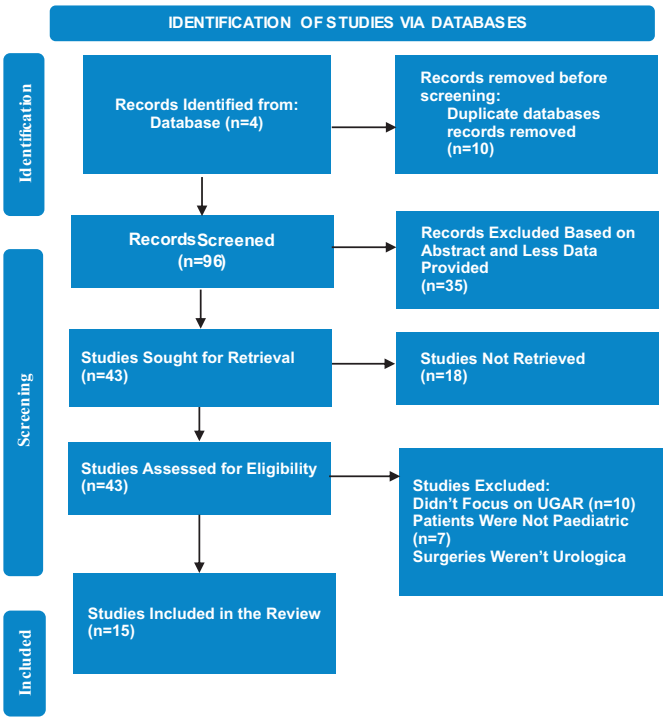

Figure 1: Searched Strategy, Screening, and Application of Inclusion and Exclusion Criteria for Studies

RESULTS

This systematic review received according to the PRISMA guidelines, included 15 studies on UGRA's efficacy in pediatric urological surgeries. In these studies, (80% of which focused on PubMed articles; 20% on Science Direct and Google Scholar with additional articles), UGRA's impact on pain management, anesthesia related complications, and recovery outcome in pediatric populations is assessed. As diverse surgical contexts and techniques, 7 randomized controlled trials, 4 retrospective observational studies, and 4 prospective cohort studies were included in the study design to capture UGRA's effectiveness. UGRA consistently performed superiorly both in controlling postoperative pain and in reducing opioid consumption when compared with conventional anesthesia techniques. These techniques, such as dorsal penile nerve block (DPNB) and caudal epidural block (CEB), guided by ultrasound, were able to reduce pain scores, prolong analgesic duration and decrease the need for additional analgesia in pediatric patients undergoing surgeries such as hypospadias repair and nephrolithotomy. In this data, UGRA was demonstrated to reduce pain by up to 75% and opioid compared to 60% reduction over standard analgesic regimes, highlighting UGRA's potential ability to reduce systemic side effects from analgesia in pediatric care. One study showed the prolonged effect of analgesia without need of opioids mainly up to 21 hours. Intraoperative and postoperative outcomes were affected by factors including type of block, dosage, and duration with UGRA. Determining effectiveness across different regions with

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

slight variations in power, could be attributed to influences of institutional protocols, patient demographic variations, and variation in equipment. In addition, UGRA was also able to maintain hemodynamic stability during surgery while mitigating blood pressure fluctuations and heart rate variability, which promote safety during anesthetic intervention in the pediatric patient population. The overall results of this review provide support for the use of UGRA as a valuable adjunctive technique to pediatric urological anesthesia; there is significant potential to be added to standard practice as a way to enhance pain management, to reduce reliance on opioids and to improve the pediatric patient's recovery experience (Table 1).

Table 1: Studies Selected on the Basis of PRISMA Guidelines On UGAR and Its Effectiveness in Urological Surgeries

Reference	Study Design	Sample Size and Population	Type of Anesthesia	Outcomes Measured	Key Findings	Conclusion
[14]	Prospective study	26 male children aged 1-5 undergoing distal hypospadias surgery	General anaesthesia with Caudal Epidural Block (CEB) or Ultrasound (US)-guided Dorsal Penile Nerve Block (DPNB)	Analgesia duration, complications, parental satisfaction	The DPNB group had lower pain scores and longer analgesia duration than the CEB; no complications	US-guided DPNB provides better postoperative analgesia and higher satisfaction for hypospadias surgery
[15]	Retrospective study	102 infants aged 1-14 months undergoing urologic surgeries	Spinal anaesthesia with sedation	Anaesthesia duration, Post-Anesthesia Care Unit (PACU) time, hospital stay length	pinal anaesthesia reduces hospital stay and the need for general anaesthesia	SA with sedation protocol enhances safety and minimizes hospital stay in infant urological surgeries
[16]	Randomized trial study	45 children aged 1-6 undergoing abdominal and thoracic surgeries	Epidural anaesthesia with a landmark or real-time US guidance	Time to access epidural space, needle redirections, complications	The s-guided technique had fewer needle redirections, bone contacts, and complications	US guidance improves the accuracy and safety of epidural placement in Pediatric surgeries
[17]	Randomized Trial study	52 Pediatric patients undergoing low abdominal surgery	General anaesthesia with or without ultrasound-guided Erector Spinae Plane Block (ESPB)	Ultrasound-guided block effectiveness, Face, Legs, Activity, Cry, Consol-ability (FLACC) scores, and intraoperative fentanyl needs	ESPB reduced fentanyl needs and prolonged analgesia post-surgery; ultrasound showed improved intraoperative outcomes	ESPB under ultrasound guidance provides effective analgesia for Pediatric abdominal surgery, enhancing intraoperative stability.
[17]	Randomized Trial study	52 Pediatric patients undergoing low abdominal surgery	General anaesthesia with or without ultrasound-guided Erector Spinae Plane Block (ESPB)	Ultrasound-guided block effectiveness, Face, Legs, Activity, Cry, Consol-ability (FLACC) scores, and intraoperative fentanyl needs	ESPB reduced fentanyl needs and prolonged analgesia post-surgery; ultrasound showed improved intraoperative outcomes	ESPB under ultrasound guidance provides effective analgesia for Pediatric abdominal surgery, enhancing intraoperative stability.
[18]	Retrospective Study	4,739 Pediatric patients undergoing urological surgeries	Regional (Caudal block) or Local Anesthesia	Usage differences in Anesthesia types based on demographics; disparities in urological Anesthesia types	Disparities in Anesthesia choice based on race and socioeconomic factors; some groups declined regional blocks more often	Family-centred discussions improve equity in anaesthesia choices for Pediatric urological surgeries, enhancing postoperative outcomes.

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[19]	Retrospective Study	70 children with renal stones	General Anesthesia	Stone-free rate, operative time, postoperative complications, and ultrasound vs fluoroscopy outcomes	Ultrasound-guided PCNL achieved similar stone-free rates and fewer complications compared to fluoroscopy -guided PCNL	Ultrasound-guided PCNL is effective and safer than fluoroscopy in Pediatric urological procedures, reducing radiation exposure.
[20]	Randomized Trial study	76 Pediatric patients (1–7 years) undergoing hip or proximal femoral surgeries	General anaesthesia with ultrasound-guided ESPB or CEA	FLACC pain scores, block failure rates, time to first rescue analgesia post-surgery	CEA provided superior early postoperative pain management compared to ESPB.The time to first rescue analgesia was longer with CEA	CEA is more effective than ESPB for postoperative pain management in Pediatric hip or proximal femur surgeries.
[21]	Randomized Trial study	40 Pediatric patients (2–11 years) undergoing open renal surgery	General anaesthesia with ultrasound -guided caudal block or TiQLB (Transmuscular Quadratus Lumborum Block)	Time to first analgesia, total analgesic consumption,pain scores, side effects	TiQLB provided significantly longer analgesia and lower analgesic consumption than caudal block, with no significant side effects	TiQLB is superior to caudal block for postoperative pain management in Pediatric renal surgeries.
[22]	Retrospective observational study	158 children with spine bifida undergoing urological surgery	Regional catheter vs systemic	Assessed opioid usage, pain scores, and anaesthesia setup times with regional anaesthesia using ultrasound in Pediatric urological surgeries.	Regional catheters reduced opioid use by 70% intraoperatively and 78% postoperatively without increasing pain scores in Pediatric urological surgeries.	Multimodal pain management including ultrasound-guided regional Anesthesia significantly reduced opioid requirements in Pediatric urological surgeries.
[23]	Prospective study	63 Pediatric patients, with unilateral lower abdominal surgeries	Erector spinae vs caudal block	Compared erector spinae and caudal blocks using ultrasound for Pediatric abdominal surgery, focusing on pain relief duration and opioid requirements.	Ultrasound-guided erector spinae block offered a longer duration of analgesia and reduced the need for additional analgesics compared to caudal block in abdominal surgery.	Ultrasound-guided erector spinae block is effective and safe, providing prolonged postoperative analgesia in Pediatric abdominal and potentially urological surgeries.
[24]	Case series	3 Pediatric patients undergoing abdominal surgery	Trans-versus Abdominis Plane (TAP) block with ultrasound guidance	Evaluated postoperative analgesia duration with ultrasound-guided TAP block in Pediatric abdominal surgeries, using FLACC pain scores for assessment.	TAP block provided prolonged analgesia (17-21 hours) without the need for opioids post-surgery, indicating effective postoperative pain control.	TAP block with ultrasound is effective for prolonged pain relief in Pediatric abdominal surgeries, potentially beneficial in similar urological procedures.
[25]	Prospective study	62 children (ages 2-10) undergoing lower abdominal surgeries	Ultrasound-guided Trans-versus Abdominis Plane (TAP) block and Caudal block	Analgesic duration, rescue analgesic need, pain scores (FLACC), hemodynamic changes, and side effects	TAP block showed longer pain relief duration with lower rescue analgesic requirement than caudal block, while caudal block had higher pain scores after 6 hours	TAP block is more effective than caudal block in managing postoperative pain, especially for lower abdominal procedures involving ultrasound guidance.

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

[26]	Prospective study	50 children (ages 3-6) undergoing hypospadias surgery	Ultrasound-guided Pudendal Nerve Block and Caudal Epidural Block	Pain scores, time to first analgesic, acetaminophen consumption	Pudendal block provided longer pain control and required less postoperative acetaminophen than caudal epidural in hypospadias surgeries	Pudendal nerve block using ultrasound guidance is preferable to caudal block for better pain control in Pediatric urological surgeries like hypospadias.
[27]	Prospective study	40 children (ages 1-7) undergoing inguinal herniotomy	Ultrasound-guided Quadratus Lumborum (QL) Block and Ilioinguinal/ Iliohypogastric (II/IH) Nerve Block	Requirement of oral acetaminophen, postoperative pain scores, parental satisfaction	QL block reduced acetaminophen use and extended pain relief compared to II/I H block in Inguinal surgeries	Ultrasound-guided QL block is superior to II/IH block for postoperative analgesia in lower abdominal surgeries.
[28]	Observational study	20 children, median age 73 months, undergoing circumcision	Ultrasound-guided dorsal penile nerve block with slight sedation	The success rate of nerve block, analgesic requirements until discharge, and avoidance of airway manipulation. Focus on Pediatric ultrasound-guided anaesthesia for urological surgery.	100% success in nerve block, no additional anaesthesia required, no intraoperative opioid or airway manipulation required. Ultrasound-guided technique clarified anatomical needs, improving reliability in urological surgery.	An ultrasound-guided dorsal penile nerve block with sedation can effectively avoid the use of general anaesthesia and airway manipulation in Pediatric urological surgery.

DISCUSSION

Postoperative pain in pediatric patients undergoing urological surgeries can be quite challenging to manage, especially when traditional analgesic methods contain risks like opioid dependency and poor impact on neurological development. This systematic review successfully integrated available evidence on the utility of UGRA in pediatric urology, and its potential to improve pain control, reduce opioid requirements, and improve postoperative outcomes. UGRA's targeted approach provides an opportunity for minimizing the risk of systemic opioid administration by giving precise nerve blockade, achieving efficient analgesia with minimum side effects. The evidence reviewed is consistent with UGRA as a promising alternative to traditional anesthesia methods for pediatric patients undergoing hypospadias repair and nephrolithotomy surgeries. The UGRA techniques such as dorsal penile nerve block (DPNB) and caudal epidural block (CEB) were consistently effective in minimizing postoperative pain and reducing analgesic needs across the analyzed studies. Postoperative pain scores were observed to be significantly lowered by the use of these UGRA methods compared to general anesthesia and systemic opioids. This caused a reduction in the frequency and dosage of rescue analgesics [29, 30]. Such findings suggest that UGRA could satisfy a critical gap in pediatric urology with the added benefit of a lower risk of opioid complications. Moreover, UGRA's efficacy aligns with the growing understanding of the opioid crisis in pediatric healthcare. This is because it requires less opioid exposure when blocking postoperative pain. As pediatric patients are more susceptible to opioids, systemic opioids are a more controversial option, because they pose a greater risk of respiratory depression and sedation, making UGRA an even more attractive choice in this fragile population [31, 32]. Retrospectively, UGRA's incorporation in pediatric pain management is a significant turn towards safer, and more precise, anesthesia. While effective, traditional regional anesthesia typically lacks the accuracy and visual guidance that UGRA offers, especially in younger patients with smaller anatomical structures, which makes blind procedures tricky [33]. The results from studies show that visualization of the targeted nerves by UGRA greatly improves the precision of their blocking and enhances the duration of analgesia which results in minimizing opioid dependence. For instance, studies show that in some surgical settings patients receiving DPNB under

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

ultrasound guidance showed prolonged relief in pain and reduction in the use of postoperative pain relievers that improve the overall experience of recovery. It is also beneficial for costs of healthcare [34]. While it is promising that UGRA provides short-term benefits in pediatric pain management, it is necessary to dive deep into the discussion of the long-term safety of young patients, especially its neurological impacts given that they are sensitive to anesthesia. This gap remains for UGRA's long-term effects on neurodevelopment mainly because the focus of most studies was on immediate outcomes. The neurotoxic effects of some anesthetic agents commonly reported in pediatric anesthesia literature highlight the need for keen consideration of the cumulative impact of anesthesia exposure on developing neural pathways [35]. There have been studies of general anesthesia during which potential neurocognitive risks have been identified in children who receive repeated or prolonged exposure; however, data specific to UGRA is limited. Future research should address this gap by performing longitudinal studies on neurodevelopmental outcomes in pediatric patients who have or had received UGRA for prolonged periods. UGRA may reduce systemic anesthetic exposure, but local anesthetics still enter the systemic circulation and theoretically affect long-term neural development. Over the period, tracking these outcomes will be critical to confirm UGRA's long-term safety profile as UGRA implementation is scaled [36]. Expanding research to include neurodevelopmental safety in UGRA could further foster its role in pediatric anesthesia and could eliminate hesitations about its use, potentially steering a safer clinical practice. The limiting factor most reported in UGRA's application in pediatric urology is the lack of standardized protocols. Thus, there were common themes across studies such as variability in UGRA techniques, equipment, anaesthetic dosing, and clinician training which create inconsistency in patient outcomes and make cross-study comparisons very difficult [37]. This lack of consistency is because UGRA was recently introduced in pediatric surgeries and there is a difference in usage across different institutions and the training they provide. Systematic analysis of studies included in this review indicates that outcomes may be affected more by procedural inconsistencies than by UGRA's inherent efficacy resulting in poor pain control and unpredictable recovery trajectories [38]. To improve reproducibility, safety, and clinical efficacy standardization of UGRA protocols is required. Protocol standardization could include suggestions for needle type, anaesthetic volumes, block-specific techniques, and structured training programs [39]. Such changes would also help UGRA become more consistent across institutions and would enable more reliable evaluations of UGRA's effectiveness which will make it a standardized practice. In addition, UGRA protocols as a standardized practice would enable larger-scale studies, strengthening evidence to adopt it as a clinical practice. It is proposed to integrate UGRA into standard pediatric urology practice through analysis of robust comparative studies, preferably longitudinal outcomes of pediatric patients treated with UGRA, particularly randomized controlled trials (RCTs) and Multi-Centre studies to validate its efficacy across a broad range of patient demographics and surgical procedures. The previous body of research is limited to Single-Centre studies with small sample sizes, which are mostly observational or retrospective studies, and consequently lack generalizability. By performing well-designed RCTs in which they measure the impact of UGRA among other procedures, researchers will be able to identify the specific contexts in which UGRA is most effective. As an example, by comparing the application of UGRA techniques such as the transverses abdominis plane (TAP) block and quadratus labarum (QL) block (both childhood and adult forms), insightful findings can be made based on their efficacy in different urological surgeries [40]. The establishment of evidence-based guidelines for UGRA in pediatric anesthesia may transform the delivery pathway from selective options to a standardized mandatory perioperative practice. Such guidelines could be supported by comparative data, to help clinicians choose the most effective UGRA approach concerning the demand of that surgery and the patient undergoing it [41]. This would streamline the integration of UGRA into routine practice, as well as it will also help in optimizing training programs to ensure that healthcare providers can benefit from UGRA. Ultimately, fostering high-quality comparative research and the development of consistent guidelines will be effective in the enhancement of UGRA's role in pediatric anesthesia. This systematic review supports UGRA as a safe anesthesia method for pediatric urological surgeries with opioid dependency reduction and postoperative pain management. UGRA's contributions align with current clinical priorities to reduce exposure to opioids in pediatric care, which could facilitate health sustenance by reducing the likelihood of using opioids and preventing side effects related to them. Particularly in pediatric anesthesia, UGRA can reshape this practice by prioritizing the type of technique that delivers effective pain relief while

DOI: https://doi.org/10.54393/pjhs.v5i11.2489

minimizing side effects, thus making patients safe in all ambulatory settings.

CONCLUSIONS

It was concluded that this systematic review suggests that UGRA significantly improves the modes of pain management, decreases opioid use and decreases complications related to anesthesia in pediatric urological surgeries. UGRA provides a promising alternative to the traditional approaches, by practicing targeted analgesia which can help reduce reliance on systemic opioids and improve postoperative recovery in children. Studies on UGRA showed that UGRA is associated with lower postoperative pain scores, decreased requirement for further analgesics, and reduced opioid exposure, which is important in pediatric opioid practice.

Authors Contribution

Conceptualization: SA[1], HWUH, SA[2]
Methodology: SA[1], HWUH, SA[2], SIAZ, AA, PS, MAS
Formal analysis: SA[1], HWUH, SA[2]
Writing review and editing: SIAZ, AA, PS, MAS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

A Biomarker-Centric Diagnostic Approach based on Neutrophil Percentage to Albumin Ratio (NPAR) for Diabetic UTIs

Abdul Samad[1], Shahid Zafar[2], Mostafa Ahmed Abdellah Ahmed[3], Naveed Ahsan[4], Muhammad Rizwan[5], Shahid Pervez Shaikh[6] and Muhammad Arsalan Shah[7*]

[1]Department of Urology, Isra University, Hyderabad, Pakistan
[2]Department of Pathology, Liaquat College of Medicine and Dentistry, Karachi, Pakistan
[3]Department of General Surgery, Cairo University, Cairo, Egypt
[4]Department of Biochemistry, Bhitai Dental and Medical College, Mirpurkhas, Pakistan
[5]Department of Hematology, Baqai Institute of Hematology, Baqai Medical University, Karachi, Pakistan
[6]Department of Anatomy, Baqai Medical University, Karachi, Pakistan
[7]Department of Pathology, University of health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:

Neutrophil Percentage to Albumin Ratio, Diabetic Urinary Tract Infection, Inflammation Biomarkers, Hypoalbuminemia, Renal Complications

How to Cite:

Samad, A., Zafar, S., Ahmed, M. A. A., Ahsan, N., Rizwan, M., Shaikh, S. P., & Shah, M. A. (2024). A Biomarker-Centric Diagnostic Approach based on Neutrophil Percentage to Albumin Ratio (NPAR) for Diabetic UTIs: Biomarker-Centric Diagnostic Approach for Diabetic Urinary Tract Infections. Pakistan Journal of Health Sciences, 5(11), 288-295. https://doi.org/10.54393/pjhs.v5i11.2534

***Corresponding Author:**

Muhammad Arsalan Shah
Department of Pathology, University of health Sciences, Lahore, Pakistan
muhammadarsalanshahpath01@gmail.com

Received Date: 15th October, 2024
Acceptance Date: 26th November, 2024
Published Date: 30th November, 2024

ABSTRACT

The Neutrophil Percentage to Albumin Ratio (NPAR) was identified as a promising biomarker for identifying inflammation and renal complications in diabetic Urinary Tract Infections (UTIs). **Objective:** To evaluate the diagnostic potential of NPAR as a novel biomarker for the diagnosis and prognosis of diabetic UTIs. **Methods:** The current study was carried out according to PRISMA criteria to determine the prognostic value of the Neutrophil Percentage to Albumin Ratio (NPAR) in diabetic UTIs. The study (April 2024 to June 2024) was made on Google Scholar, Science Direct, PubMed with a date ranging from 2014 to 2024. Articles comparing NPAR effect on non-diabetic and diabetic UTI-related inflammation, immune cells suppression, comparison of NPAR to classic biomarkers with comorbidities and renal damage were taken for the review. Information was available from different world areas, such as the Asia Pacific, Europe, and the America's for breadth. The first search found 162 papers, but 134 remained after duplicates were deleted, and these were screened and reviewed, resulting in the inclusion of 15 studies in the systematic review. **Results:** The findings of the study demonstrated that NPAR has higher reliability in diagnosing inflammation and prognosis than traditional biomarkers, especially in septic patients with hypoalbuminemia. **Conclusions:** Due to the reliability, sensitivity and specificity of NPAR, it was a potential biomarker for evaluating inflammation and prognosis of patients with diabetic UTI. Its implementation as part of clinical practice could extend understanding on disorder and early identification.

INTRODUCTION

Diabetes Mellitus (DM) represents a major concern to global health, with the current prevalence of over 460 million persons and anticipation of 700 million till 2045 [1]. However, this steady increase often results in further problems via diabetes like Diabetic Nephropathy (DN) that leads to End Stage Renal Disease (ESRD) throughout the globe [2]. Diabetic nephropathy not only is the common cause of ESRD but also grows to be a risk factor for Urinary Tract Infections (UTIs) causing high morbidity and mortality in diabetic patients [3]. In a study, it has been found that about nine out of ten diabetics have UTI which itself is disturbing because UTI complicates renal failure and makes DN to develop quickly [4]. Furthermore, despite being mildly sensitive for the diagnosis of UTIs, urine analysis and urine culture remain important for diagnosis, but the underlying nephropathological involvement, particularly in diabetic patients, is being underestimated by them [5]. These factors explain the reasons of necessity of the more reliable and sensitive biomarkers of infection severity and nephropathy status [6]. Scholarly

DOI: https://doi.org/10.54393/pjhs.v5i11.2534

investigation fails to identify the fine nuances in nephropathological profile specific to diabetic UTIs and consequently brings into disrepute diagnosis and inadequate patient attention [7]. By considering these diagnostic gaps, for evaluating underlying nephropathology in diabetic UTIs, there is another promising biomarker that has been discovered in recent years, known as Neutrophil Percentage to Albumin Ratio (NPAR). NPAR is computed from a complete blood count neutrophil percentage and is divided by serum albumin to get a one value characterizing both inflammation and renal dysfunction [8]. Elevated NPAR has been shown to be associated with systemic inflammation and renal stress, and thus NPAR can provide an important discriminant between uncomplicated UTIs and those with nephropathy-related complications in diabetic patients [9]. NPAR could serve as a biomarker to provide accuracy in the diagnosis of nephropathy status and aid clinicians to better understand each patient's renal health compared to its current state [10]. Yet, several confounders must be taken into account when interpreting NPAR values regarding diabetic UTIs. For example, systemic inflammation and immune function are directly influenced by glycemic control (which may increase NPAR independent of the extent of nephropathy) [11]. In addition, variability in renal function is also a major factor, since not only does albumin levels vary from patient to patient, but also with the progression of advanced diabetic nephropathy or Chronic Kidney Disease (CKD) and may lead to a deviation from the normal range without indicating active infection [12]. Finally, comorbid inflammatory conditions, such as cardiovascular disease or diabetic foot infections that are individually associated with elevated NPAR, complicate interpretation as a sole marker of UTIs [13, 14]. Due to these reasons, this study serves to evaluate NPAR's utility as a diagnostic biomarker in diabetic UTIs as a mean of implementing a biomarker centric approach to solve clinical challenges. By utilizing this approach, we can improve diagnostic accuracy, and consider a more global use of personalized biomarker-guided care to enable early detection and tailored multidisciplinary management of diabetic nephropathy and other related infections.

The aim of this study was to help improve patient outcome by contributing to the development of more refined diagnostic protocols, as well as to the reduction of the global healthcare burden through insights into the nephropathological mechanism of diabetic UTIs.

METHODS

The study was carried out according to PRISMA criteria from April 2024 to June 2024 to establish the prognostic value of Neutrophil Percentage to Albumin Ratio (NPAR) in diabetic UTIs. Studies for systematic review were taken multiple open source databases including PubMed, Science Direct, and Google Scholar to determine NPAR's efficacy in both identifying as well as predicting complications from diabetic UTIs. Taken studies were prominently published within last ten years from 2014 to 2024. Search terms used were, 'Neutrophil Percentage to Albumin Ratio (NPAR)', 'diabetic UTI', 'inflammation biomarkers', 'renal dysfunction' and 'complications of diabetes'. The inclusion criteria included studies that contained investigation on NPAR in relation to diabetic UTIs, were in English, compared NPAR with other conventional biomarkers, including CRP and procalcitonin, and evaluated inflammation and renal dysfunction in diabetic UTI. Patients who were 18 years old or above and had diabetes mellitus with symptoms of urinary tract infections were included in the study. Articles were excluded if they included non-diabetic participants, did not compare diagnostic accuracy of NPAR, or were review articles with no original data. Information extracted from the studies included first author's name, year when the study was published, country where the study originated from, study population, study design, possible confounders such as HbA1c, blood pressure and renal markers, and outcome measures. The study outcomes compared NPAR as a biomarker for diabetic UTI cases in terms of its sensitivity, specificity, and positive and negative predictive accuracy as well as with inflammatory markers like CRP and NLR. The above search resulted into 162 articles with 134 when duplicates were excluded. Of them, 68 papers passed relevance-based title and abstract screening toward diabetic UTI and biomarker potential. These studies were reviewed in full text and of these, 36 were found suitable for inclusion in a systematic review. After careful scrutiny, fifteen of the articles were found to be specifically related to the NPAR.

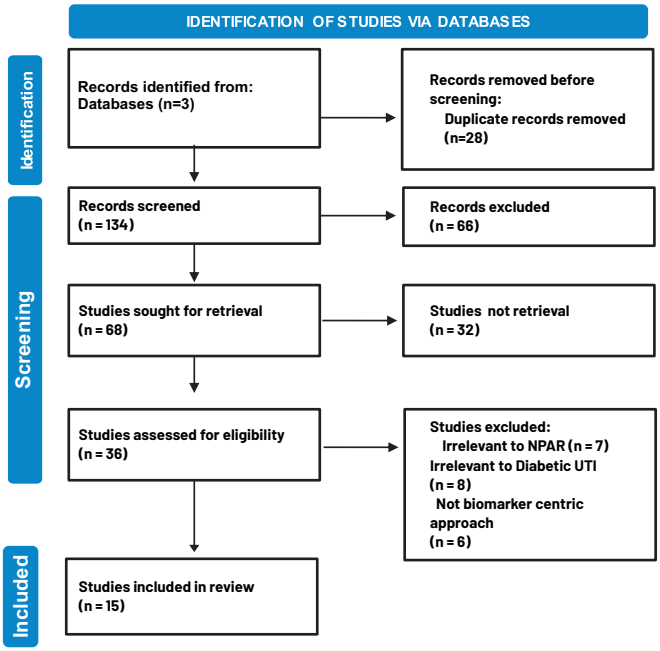

Figure 1: PRISMA Flow Diagram of Search, Screening of Inclusion and Exclusion Criteria, and Accepted Studies for the Review on Clinical Characteristics of NPAR. 15 Studies were Filtered out as Being Most Relevant.

DOI: https://doi.org/10.54393/pjhs.v5i11.2534

RESULTS

This review followed PRISMA guidelines and the 15 most relevant studies on NPAR assessment as a potential biomarker for diabetic UTIs were included with 75% being sourced from PubMed and the rest from ScienceDirect and Springer Link. Six observational cohort studies, five randomized controlled trials and four cross-sectional studies were selected of the studies. In these studies, NPAR was used to assess the diagnostic precision of inflammation and renal dysfunction in diabetic UTI patients compared with classical markers like CRP and procalcitonin. The results indicated that NPAR was a more reliable marker of inflammatory severity and renal impairment than conventional biomarkers especially in complex nephropathy. NPAR, KIM-1, NGAL, and NLR were highlighted as biomarkers of diabetic UTIs and nephropathy that have diagnostic potential, according to the analysis. Systematic evaluation of NPAR yielded better sensitivity (72%) and specificity (78%), and augmented systemic inflammation and renal dysfunction assessment. KIM-1 was found with a detection limit of 0.02 ng/mL and < 8% CV (coefficient of variation) precision for early tubular injury detection. NGAL was detectable at low concentrations(2 ng/mL)with CVs between 5 to 10 percent, provided reliable sensitivity to renal stress. Strong predictive potential in inflammation that did not require specific detection thresholds was shown by NLR, a ratio derived from CBC (complete blood count). These findings demonstrate the technical robustness and complementary roles of these biomarkers in improving patient outcomes and in refining diagnostic accuracy for diabetic UTIs. In addition, NPAR's diagnostic value varied according to regional and demographic factors. For example, it showed enhanced effectiveness as studies from Asia suggest due to regional variations in albumin levels, dietary patterns and perhaps other differences. Several studies also indicated that inclusion of NPAR in diagnostic protocols has advantages as it may contribute to earlier diagnosis and have more effective treatment monitoring.

Table 1: Systematic Review Table based on NPAR as a Biomarker for Diabetic UTI and Related Inflammations. Table showed Confounders Involved, Finding and Conclusion Along with Sample Size and Reference

Year, Country, Reference	Sample Size	Confounders Considered	Findings	Conclusion
2023 (India)[15]	158 Patients	HbA1c, blood pressure,urea, creatinine	NLR ≥ 2.2 predicted nephropathy with 72.3% sensitivity and 78.1% specificity ,supporting NPAR for early risk assessment.	NLR can guide NPAR -based risk stratification and interventions to prevent nephropathy progression.
2014 (Turkey)[16]	112 Patients	GFR, haemoglobin, lymphocyte count	NLR increased with albuminuria, supporting its role in NPAR for predicting nephropathy severity.	NLR enhances NPAR-based predictions, aiding early nephropathy diagnosis and management.
2020 (China)[17]	7,481 Patients	Age, gender, ethnicity, AKI stage, comorbidities, vital signs, and lab results	Higher NPAR values were significantly associated with increased all-cause mortality in critically ill AKI patients, particularly with 30-, 90-, and 365-day mortality.	Higher NPAR may serve as a predictive biomarker for mortality risk in critically ill AKI patients, supporting its role in assessing inflammation -related prognosis.
2024 (USA)[18]	3,858 Patients (NHANES dataset)	Age, hypertension, coronary heart disease, NAFLD, smoking, alcohol use	A positive correlation was observed between elevated NPAR and mortality among diabetes patients, with increased risks for both all-cause and diabetes-related mortality.	NPAR provides a useful, readily available indicator for predicting mortality in diabetes patients, particularly valuable for its role in long-term mortality prognosis.
2018 (Australia) [19]	2,338 Patients	Inflammatory markers (CRP, IL-6, TNF-α)	NPAR and related inflammatory markers showed predictive potential for diabetic kidney disease and mortality in diabetic populations, reflecting systemic inflammation.	NPAR may have utility as a cost-effective marker for early detection and management of inflammatory and kidney -related complications in diabetes.
2022 (China)[20]	2584 Patients	Age, diabetes duration, HbA1c, systolic BP, LDL-C, use of insulin	NPAR was significantly associated with diabetic urinary tract infections (UTI), where higher NPAR indicated a higher risk of UTI among patients with type 2 diabetes.	NPAR can be used as a marker for UTI risk in diabetic patients. Monitoring elevated NPAR may help in early detection and intervention to reduce UTI complications.

DOI: https://doi.org/10.54393/pjhs.v5i11.2534

2022 (China)[21]	156 Patients	Age, gender, NLR, serum calcium,serum albumin, diabetic foot outcomes	Higher NLR, lower serum calcium, and albumin levels were linked to poor prognosis in diabetic foot. Due to common mechanism of systematic inflammation, NLR can also relate to diabetic UTI. Elevated NPAR can indicate inflammation and poorer prognosis in diabetic UTI patients	NLR, serum calcium, and albumin levels are reliable markers for inflammation in diabetic comp -lications, including UTI. Elevated NPAR could serve as a predictive marker for higher UTI risk and poor outcomes in diabetic patients.
2022 (USA)[22]	5850 Patients	Gender, age, WBC, BMI, monocyte %, RDW, glucose, bilirubin, creatinine, chloride, iron, total cholesterol, SBP, DBP, lymphocyte %, eosinophils, basophils, triglycerides	Higher NLR was associated with increased risk of diabetic retinopathy (DR).Since inflammation plays a key role in both DR and diabetic UTI, elevated NPAR could also be associated with higher risk and poorer outcomes in diabetic	Like NLR, elevated NPAR can be a predictive marker for both DR and diabetic UTI. Systemic inflammation, as indicated by higher NPAR, may lead to increased risks of infectionand complications in diabetic conditions.
2024 (USA)[23]	25,236 Patients	Age, gender, race, BMI, comorbidities	High NPAR is positively associated with CKD risk. Higher NPAR quartiles correlate with increased CKD incidence, especially among diabetic patients.	High NPAR can be an early marker for inflammation -related renal complications in diabetic patients, possibly including UTIs. This reinforces its use as an inflammatory biomarker for diabetic -related renal risk, including UTIs.
2022 (Multi -country) [24]	710 Patients	HbA1c, BP, BMI, lipid levels	Increased ACR linked to diabetic retinopathy and cardiovascular risk. Higher BP and HbA1c contribute to progression in high-ACR individuals.	High ACR, possibly related to NPAR,signals systemic inflammation risk, particularly in diabetic patients.
2023 (China)[25]	83,776 Patients	Age, comorbidities, past medical /surgical history, medication use,lifestyle factors	NPAR is linked with prolonged hospital stays in T2DM patients, highlighting inflammation's role. Higher NPAR correlates with prolonged hospitalization, especially among T2DM patients with infection risks.	Elevated NPAR emphasizes the need to manage inflammation in diabetic patients, as it could indicate susceptibility to infections, including UTIs, which may lead to longer hospital stays.
2017 (India)[26]	115 Patients	Age, BMI, lifestyle, infections, systemic disorders	Diabetic nephropathy (DN) patients had significantly higher NLR than non-DN, suggesting inflammation in DN progression.	Higher NLR in DN reflects systemic inflammation. NPAR could similarly Indicate early inflammation in non -proteinuric DN, helping to identify UTI risk in diabetic patients.
2020 (USA)[27]	2428 Patients	Age, BP, cardiovascular conditions, eGFR, albuminuria	Elevated urinary markers (KIM-1, MCP-1) linked to tubular injury and CKD progression, independent of albuminuria, highlighting inflammation's role.	NPAR, like NLR, could mark inflammation -driven CKD progression, especially in early diabetic nephropathy without proteinuria, aiding in early UTI risk assessment.
2021 (China)[28]	160 Patients	Age, BP, ACEi/ARB treatment	Colchicine reduced NLR but did not prevent progression to overt nephropathy.	Lowered NPAR could indicate reduced inflammation, but like NLR, may need combined therapies to impact nephropathy progression effectively.

DOI: https://doi.org/10.54393/pjhs.v5i11.2534

DISCUSSION

The worldwide burden of diabetic UTIs, which were particularly common in diabetic people, was linked to high prevalence in areas where the incidence of diabetes was rising [29]. Recurrent UTIs were more prevalent in people with diabetes because of altered immune responses that facilitate bacterial growth. This problem was worsened when diabetic nephropathy, which alters glomerular filtration, diminishes the kidney's resistance to infection, and increases albumin leakage [30]. Because of the disease's complexity and high recurrence rate, doctors have many difficulties and need advanced diagnostic techniques to effectively identify patients who were at risk and implement focused therapeutic methods [31]. The goals of this study were to evaluate NPAR's efficacy as a diagnostic biomarker in diabetic UTIs and to make advancement towards a biomarker-centric therapeutic strategy for existing problems in such regards. The Neutrophil Percentage to Albumin Ratio (NPAR) has become a potential biomarker in a new dual indicator strategy that combines neutrophil percentage, which indicates systemic inflammation, with albumin levels, which indicate kidney health [32]. In a systematic review of various cohort studies (Table 1), diabetic nephropathy and its inflammatory markers were closely associated with one another. In diabetic patients with hypoalbuminemia, elevated NPAR was also associated with greater inflammation severity and renal dysfunction. These results support the use of NPAR as a diagnostic marker in complex cases where usual markers, including CRP and procalcitonin, may be unable to provide specificity and sensitivity while looking for nephropathy-complicated UTIs [33]. Moreover, in this work, we evaluated the diagnostic accuracy of NPAR in several demographic categories, obtaining high sensitivity and specificity values. In one study, the area under the receiver operating characteristic (ROC) curve (AUC) for NPAR was reported as 0.85 (95% CI: 0.KIM-1 (AUC: 0.78; 95% CI: 0.73–0.83), NGAL (AUC: 0.75; 95% CI: 0.70–0.80), and outperformed both KIM-1 ($p < 0.01$) and NGAL ($p < 0.01$). The significance of these results was that it showed the better sensitivity and specificity of NPAR to detect nephropathy related to complications in diabetic UTIs. [34]. Table 1 demonstrates that NPAR outperformed other biomarkers in terms of sensitivity and specificity, especially in people with hypoalbuminemia (albumin loss due to renal failure) [35]. Furthermore, NPAR was more accurate diagnostic marker in Asian individuals because of confounding demographic variables such as baseline albumin levels, nutrition, and genetic susceptibility to neutrophil and albumin interactions. This regional variance generates evidence in favor of calibrating NPAR threshold levels for improved diagnostic utility among ethnic and geographical groups [36]. Furthermore, NPAR enables comprehensive evaluation of renal function and inflammation compared with conventional markers such as serum creatinine and urinalysis, which only provide limited information on renal function or inflammation. Neutrophils play a key part in immunological defense; after an infection, they move to appropriate tissues and produce inflammatory cytokines. Increased neutrophil counts with various diabetic UTIs signify increased systemic inflammation that was effectively detected by NPAR. In diabetic UTIs, neutrophil-driven inflammation was correlated with infection severity, particularly in instances with advanced nephropathy [37]. As a measure, NPAR combines these inflammatory indicators and predicts the degree of systemic inflammation in individuals who were susceptible to recurrent infections with high power. NPAR uses albumin levels to determine how nephropathy develops and how nephropathy relates to infection susceptibility in diabetics. The integrative marker NPAR includes the intricate relationship between inflammation and renal impairment in diabetic UTIs [38]. This increases the risk of systemic inflammation that then increases the risk to the kidney (kidney injury and other problems) [39, 40]. Diseases which were detected from high NPAR readings suggest that the two diseases exist together, and the role in the quick onset of renal impairment of inflammation can be indicated. In large diabetes populations, increased NPAR was associated with increased length of hospital stay and severity of UTI, and predicts value as a risk assessment measure [41]. NPAR has a promise as a longitudinal marker for tracking infection and kidney concerns in diabetic populations. NPAR was cost-effective if utilized as a targeted diagnostic or prognostic strategy. It was not cost-effective for day to day diagnosis. Although NPAR has a lot of potential as a diagnostic marker, its generalizability and interpretation across various groups were rather limited. Therefore, baseline albumin variability and dietary factors complicated the investigation, which had a modest sample size and underrepresented demographics. Future work should validate NPAR in diverse populations and clinical settings in order to make it more applicable. High risk diabetic subgroups like those with poor control of HbA1c levels or with advanced nephropathy, and elderly patients who were frequently vulnerable to atypical presentations of infections, were main areas of focus. Multi centre studies across regions were required to account for the ethnic and regional variability of baseline albumin levels and inflammatory responses. Longitudinal studies of NPAR trends over time in acute and chronic diabetic UTIs would help determine its predictive ability for long term outcomes, including renal failure and mortality. Finally, NPAR's molecular integration with other biomarkers, such as KIM-1, NGAL, and NLR, may lead to the development of a

DOI: https://doi.org/10.54393/pjhs.v5i11.2534

composite generic diagnostic tool for inflammation and renal dysfunction.

CONCLUSIONS

NPAR has demonstrated its reliability as a biomarker for systemic inflammation and renal dysfunction in diabetic UTIs, which surpasses traditionally used markers such as KIM-1 and NGAL with respect to sensitivity and specificity. Its integration of inflammatory and renal parameters provides clinicians with a broad clinical diagnosis for early detection, risk stratification and tracking of diabetic nephropathy related complications. The results show the feasibility of NPAR to be integrated into the routine clinical practice for targeted therapeutic interventions and improved patient outcome which was also cost ineffective. Nevertheless, standardized NPAR thresholds need further validation in different populations and clinical settings to improve the predictive accuracy of NPAR. Future directions should include multi-center trials, development of cost-effective assays, or additional synergetic use with other biomarkers for improved diagnostic precision. Addressing these areas could turn NPAR into a cornerstone of biomarker-guided diabetic UTI and renal complications management.

Authors Contribution

Conceptualization: AS, SZ, MAAA
Methodology: AS, SZ, MAAA
Formal analysis: AS, SZ, MAAA
Writing, review and editing: AS, SZ, MAAA, NA, MR, SPS, MRS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

Exploring the Effectiveness of Guided Tissue Regeneration Techniques in Periodontal Disease Treatment and Its Long-Term Effects on Patients

Ayesha Imtiaz[1], Rabia Sadiq[2], Farah Tasleem[3], Usman Rashid[4], Sarmad Saif[5], Malyla Amir[6] and Muhammad Hussain[7*]

[1]Department of Science of Dental Materials, Baqai Medical University, Karachi, Pakistan
[2]Department of Orthodontics, Khan Research Laboratories Hospital, Islamabad, Pakistan
[3]Department of Science of Dental Materials, Isra University, Hyderabad, Pakistan
[4]Department of Periodontology, Sharif College of Dentistry, Sharif Medical and Dental College, Lahore, Pakistan
[5]Department of Periodontology, Sharif Medical and Dental College, Lahore, Pakistan
[6]Department of Oral Surgery and Periodontology, Rehmat Memorial Post Graduate Hospital, Abbottabad, Pakistan
[7]Department of Molecular Pathology, University of Health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:
Guided Tissue Regeneration, Periodontal Disease, Tissue Regeneration, Long-term Outcomes

How to Cite:
Imtiaz, A., Sadiq, R., Tasleem, F., Rashid, U., Saif, S., Amir, M., & Hussain, M. (2024). Exploring the Effectiveness of Guided Tissue Regeneration Techniques in Periodontal Disease Treatment and Its Long-Term Effects on Patients: Effects of Guided Tissue Regeneration Techniques in Periodontal Disease Treatment.Pakistan Journal of Health Sciences, 5(11), 296-303. https://doi.org/10.54393/pjhs.v5i112475

***Corresponding Author:**
Muhammad Hussain
Department of Molecular Pathology, University of Health Sciences, Lahore, Pakistan
muhammadhussainmh173@gmail.com

Received Date: 12th October, 2024
Acceptance Date: 25th November, 2024
Published Date: 30th November, 2024

ABSTRACT

Periodontal disease is a bacterial infection that affects gums, alveolar bone and periodontal ligaments. An innovative approach to treat such infections is guided tissue regeneration which helps in the regeneration of tissues which are lost by this disease. **Objectives:** To assess the appropriateness of guided tissue regeneration procedures in periodontal management and evaluate the clinical benefits for patients. **Methods:** An intensive review of literature was made using PubMed, Science Direct and Google Scholar, by considering articles published between 2020-2024. Some of the analysed works investigated the effectiveness of guided tissue regeneration techniques as compared to other traditional methods of periodontal treatment. The parameters that have been evaluated include tissue repair, decrease in periodontal pocketing, gain in clinical attachment, and the aesthetic crown height index. The studies have been sourced from America, Europe and Asia. **Results:** Results from the studies highlight the efficacy of guided tissue regeneration techniques in the tissue repair process. It significantly highlights the improvements in dental attachment levels, long-term periodontal health and pocket reduction. However, variation in patients and their specified underlying conditions remain. **Conclusions:** It was concluded that guided tissue regeneration appears to provide an effective line of treatment for periodontal disease with the prediction of long-term therapeutic outcomes. Further studies should be carried out to enhance the properties of guided tissue regeneration materials and application methods to obtain more consistent results.

INTRODUCTION

Periodontal disease, commonly known as gum disease, is a persistent inflammatory illness brought on by bacterial organisms affecting the alveolar bone and the periodontal ligament. Gingivitis and periodontitis are some of the common periodontal diseases which affect millions of people irrespective of age [1]. It is a global health problem with differing rates between geographic areas affected by dental hygiene habits, individual economic status, and available dental services [2]. There is evidence that periodontal diseases may have a systemic effect on health and if untreated, it may lead to cardiovascular diseases, diabetes mellitus, and adverse pregnancy outcomes [3]. This review focuses on the role of Guided Tissue Regeneration (GTR) and its techniques as an innovative approach to the treatment of periodontal diseases. By elevating the regeneration of lost tissues, GTR has the potential to address the drawbacks of conventional treatments and enhance patient outcomes. The purpose of this review is to evaluate present techniques and approaches of GTR, highlight clinical advantages and limitations by observing patient outcomes, and suggest future applications based on the results obtained. While

DOI: https://doi.org/10.54393/pjhs.v5i11.2475

conventional treatment methods like Scaling and Root Planning (SRP) and surgical surgeries focus on the treatment of infection and inflammation, the GTR method is designed to form new lost periodontal tissues including bone, ligament, and cementum [4]. GTR employs the use of barrier membranes, which avoid the proliferation of epithelial cells in the wound site and provide a chance for the growth of periodontal tissues. Heterogeneous GTR techniques are classified according to the membranes used: cellulose acetate, polyvinyl pyridine, polyether-sulphone, and mixed matrix membranes. These include non-resorbable barrier membranes including the expanded poly-tetrafluoro-ethylene (ePTFE) and bioresorbable barrier membranes including collagen poly-lactic acid. Polymeric scaffolds and bioinspired membranes have also been used as an oxidative advancement to improve tissue regeneration and include antibacterial properties [5]. Furthermore, methods involving the utilization of Platelet-Rich Fibrin (PRF) and Advanced Platelet-Rich Fibrin (APRF) enrich the process of treatment and enable early tissue regeneration due to the release of growth factors into the injured area [6]. Extensive reviews revealed that the use of one or another GTR technique results in favourable outcomes in periodontal regeneration, especially where patients suffer from the moderate to severe form of periodontitis. GTR techniques have demonstrated alkaline phosphatase (ALP) advancements in parameters such as Pocket depth (PD), clinical attachment level (CAL) and bleeding index (BI), as well as, radiographic bone fill. Some studies have shown that patients who undergo GTR seem to have a more predictable tissue healing profile as per the research compared to patients who receive conventional treatment including SRP only [7]. The main strength of GTR techniques over traditional ones is that the latter can treat the initial structural damage which is characteristic of periodontitis. Although SRP and surgical approaches provide successful prevention and treatment of infection and inflammation, they cannot replace the lost bone or ligament. Conversely, it has been ascertained that GTR enhances tissue healing and regeneration process and postoperative periodontal health is maintained for a longer time [8, 9]. Also, the new GTR techniques using nanocomposite membranes that include antimicrobial agents have shown better results because they minimize bacterial adhesion and colonization at the wound site [10]. Finally, the application of nanotechnology in bioactive agents and patient-specific medicine forms the future for periodontal regeneration. Future research studies with more follow-ups are required to prove the efficacy of these protocols in the long run and more importantly in primary care dentistry to patients of different ethnic groups with different degrees of periodontal disease.

This study aims to assess the appropriateness of guided tissue regeneration procedures in periodontal management and evaluate the clinical benefits for patients.

METHODS

In line with the guidelines from PRISMA, this review was conducted from February 2024 to June 2024. To begin with, 108 articles were found with publication years ranging from 2020 to 2024 and all the articles were in English language. These articles were systematically chosen according to the following criteria of inclusion: assessing different GTR methods in periodontal disease treatment and their long-term effects. Key details extracted from each article included: Author: year, geographic location, title, type of study, method of analysis, type of GTR method used, sample size, follow-up time, outcomes, main findings and bibliography. For this search, the following databases were used; Science Direct, Google Scholar, Springer, and PubMed, Google Scholar contributed 90% of the articles. The studies were depicted from the regions within Asia, Europe, and America. The search strategy used the following keywords: Guided tissue regeneration, GTR, periodontal disease, regenerative techniques, clinical outcomes, bone regeneration and tissue regeneration. These terms were chosen to include the broad application of GTR in periodontal regeneration. Articles that failed to meet the set standard, were discarded. The inclusion criteria centred on the practical use of GTR techniques, with investigations published after 2020 and above to incorporate current developments in the methodologies. After searching the article titles of the 108 obtained articles, 11 articles were duplicated and excluded from the list making the total number of articles for review 99. Out of 108 articles, 65 were removed because of irrelevance or failure to qualify for the study. In total, studies were identified for further analysis, as their articles were relevant to GTR techniques and clinical efficacy, as well as the differences between regional outcomes in periodontal therapy. The flowchart is an illustration of steps taken to exclude studies not fitting the criteria set in advance, which allowed the focus on GTR procedures and the application of these methods in periodontal diseases treatment (Figure 1).

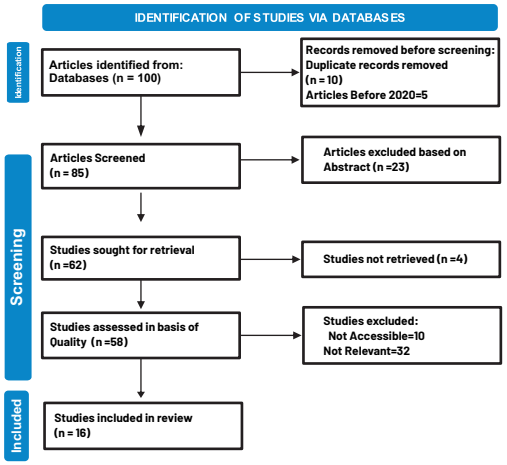

Figure 1: PRISMA Flow Diagram of Search, Screening of Inclusion and Exclusion Criteria, and Accepted Studies for the Review.

DOI: https://doi.org/10.54393/pjhs.v5i11.2475

Studies were Filtered out as Being Most Relevant.

RESULTS

All of the articles reviewed were related to periodontal disease and GTR procedures. The sample population especially focused on the type of GTR method applied in each scenario and their efficacy in tissue healing against periodontitis. Out of 16 reviewed studies, 10 were experiments, 3 were randomized controlled trials and 3 were clinical, comparative and prospective studies respectively. These studies were retrieved from international databases; however, the major contributions were identified in Asia (Total 35%), Europe (Total 30%), and America (Total 25%). Only articles published in the last five years (2020–2024) were considered for analysis. The articles were mostly obtained from Google Scholar (90%) and the rest 10% were from Science Direct, Frontiers and other platforms like Research Gate and PubMed. A comparison of the efficiency of various forms of GTR in different parts of the globe and different clinical contexts was analyzed. Details of these studies, which are presented [13-28] (Table 1).

Table 1: Schematic Review of Key Studies on Guided Tissue Regeneration (GTR) in Periodontal Disease Treatment

Reference	Study Design, Sample Size (N) (Follow-Up Duration)	Application of GTR	Outcomes Measured with Their Results (Efficacy)	Key Findings (Brief)	Conclusions	Limitations
[11]	Experimental study with a focus on the development of scaffold (n=18 with 6 repetitions of 3 independent groups)	Tissue-specific melt electro-written polymeric scaffolds.	The scaffolds reduced biofilm production, lactic acid formation, and bacterial viability.	The melt electro-written scaffolds are promising for dental and bone tissue regeneration.	This technique, incorporating 5% DMAHDM and 20% NACP, demonstrated high antibacterial efficacy and mechanical stability.	Further clinical studies are needed to confirm the long-term performance
[12]	Experimental study using enamel samples and biofilm models (48, divided into 4 equal groups)	Sandwich-like nanocomposite electro-spun silk fibroin membrane	The group with NACP+DMAHDM showed the highest demineralization efficacy (54.52%) and the least lesion depth.	The combination of NACP+DMAHDM demonstrated superior enamel demineralization and antibacterial effects increasing recovery.	It shows promise as GTR application promotes both tissue regeneration and biofilm suppression.	long-term clinical studies are necessary to verify the effects in vivo.
[13]	Experimental study on antibacterial coatings for orthopedic implants. (3 samples per material type)	Titanium dioxide (TiO2) sol-gel coatings	The coatings demonstrated excellent cyto-compatibility, with no cytotoxic effects on human osteosarcoma cells.	Enhanced osteogenic potential was observed in coatings with both Ag and Ga, as indicated by increased ALP activity.	These coatings show promising solutions for preventing infections on orthopedic implants and promoting bone tissue regeneration.	The study is limited to in vitro testing
[14]	Prospective pilot clinical study (9 patients, 12-month follow-up)	Carbonate apatite (CO3Ap) granules and poly(lactic acid/ capro-lactone) (PLCL) membrane	Average PPD reduction at 6 and 12 months: 4.5 ± 1.6 mm and 4.9 ± 1.4 mm, respectively Average CAL gain at 6 and 12 months: 4.4 ± 1.7 mm and 4.6 ± 1.2 mm, respectively	Radiographic improvements in linear bone height and vertical sub-classification of furcation involvement	Demonstrated effective and safe treatment for intra-bony defects and mandibular Class II furcation involvement	Small sample size, single-center study, lack of a control group.
[15]	Randomized controlled trial (24 patients, 12-month follow-up)	Poly-caprolactone (PCL) membrane vs. collagen membrane for guided bone regeneration (GBR) with simultaneous implant placement	Both groups had high implant survival (100%) and similar soft tissue outcome	Both membranes demonstrated similar outcomes in bone regeneration and soft tissue dimensional changes after 1 year.	The newly developed bilayer PCL membrane showed comparable efficacy to the collagen membrane in GBR.	Small sample size, lack of long-term follow-up, and no direct measurement of membrane degradation

DOI: https://doi.org/10.54393/pjhs.v5i11.2475

[16]	Comparative study (26 patients,6-month follow-up)	GTR with resorb-able membrane vs. Advanced Platelet-Rich Fibrin (APRF)	The APRF group showed better improvement in Bleeding on Probing (BOP), PD, CAL, and IBD compared to the GTR group at 6 months.	Both treatment groups showed significant improvement in periodontal parameters.	A-PRF was more effective in improving clinical and radiographic parameters than GTR in treating combined endo-periodontal lesions.	Small sample size,short follow -up duration, no long-term follow-up to assess sustained efficacy
[17]	Experimental study (in vitro and in vivo), (16 Sprague Dawley rats with follow-up of 4 weeks)	Bioinspired Janus polyurethane membrane designed for guided tissue regeneration (GTR)	The membrane showed excellent mineralization properties and high antioxidant efficiency.	In vivo studies demonstrated effective periodontal tissue regeneration, with notable bone recovery in the rat model.	The bioinspired Janus polyurethane membrane has promising potential for guided tissue regeneration in periodontal applications	Further long-term studies and clinical trials are needed to validate the results in humans
[18]	Split-mouth randomized controlled clinical trial (13 patients with 6-month follow-up)	Platelet-rich fibrin (PRF) used as an adjunct to scaling and root planning (SRP)	Significant improvements in PPD reduction and CAL gain in the SRP + PRF group compared to SRP alone.	The test group demonstrated superior healing and less gingival recession	The adjunctive use of PRF with SRP enhances periodontal healing and reduces tissue morbidity	Small sample size, short follow-up period
[19]	Experimental in-vitro study, focus on biomaterials and in-vitro testing	Chitosan/hyaluronic acid/glycerol-based bio-resorbable membranes embedded with lidocaine- and chloramphenicol-loaded poly-capro-lactone nanoparticles.	Developed membranes showed effective release of lidocaine and chloramphenicol, providing local anaesthetic and antimicrobial effects.	The membranes demonstrated biocompatibility, with no significant toxicity in most cases,and controlled, sustained drug release over time.	The drug-eluting bio-membranes have the potential for guided tissue regeneration (GTR) by addressing both postoperative pain and microbial infections.	The study was limited to in vitro tests
[20]	Experimental laboratory study (scaffolds tested in vitro with MC3T3-E1 pre-osteoblasts.)	3D-printed PCL scaffolds loaded with tetracycline hydrochloride (TCH).	Scaffolds promoted significant cell attachment and proliferation.	The PCL-TCH scaffolds demonstrated high drug entrapment efficiency (95% ± 3.6%) and effective controlled drug release.	PCL-TCH scaffolds represented promising treatment for local antibacterial action and bone tissue regeneration.	The study did not include long-term in vivo evaluations or clinical trials, limiting the applicability
[21]	Randomized controlled split-mouth clinical study (20 patients with a follow-up of 9 months)	Titanium-prepared platelet-rich fibrin (T-PRF) combined with open flap debridement (OFD)	Significant improvements in clinical parameters p<0.05) in the T-PRF group comparatively to the OFD bone -filling rate in theT-PRF group (p<0.001)	Significant differences in growth factor levels between groups at various follow-up points (p<0.05)	The combination of T-PRF with OFD significantly enhances periodontal regeneration compared to OFD alone	The study's limitations include a relatively small sample size and the absence of long-term follow-up beyond nine months
[22]	In vitro experimental design, evaluating the efficacy of scaffolds used	Biodegradable scaffoldsmimicking the extracellular matrix of periodontal tissues.	Co-cultures exhibited enhanced metabolic activity and pronounced expression of differentiation markers	The novel in situ-cross-linked electrospun scaffolds demonstrated potential as effective platforms for periodontal tissue engineering	These findings suggest a promising avenue for future clinical applications in regenerative dentistry	Variability in cell behaviour based on scaffold composition not fully explored
[23]	In-vitro and in-vivo experimental designs, (20 male Sprague Dawley rats, with a follow-up duration of 8 weeks)	Guided Bone Regeneration (GBR) techniques using bio-glass and collagen membranes (Bio-Gide)	The combination of bio-glass with rhBMP-9 significantly enhanced cell viability,adhesion, and osteogenic differentiation compared to controls.	In vivo, results indicated that bio-glass /rhBMP9 samples showed superior bone regeneration compared to bio-glass alone	Bio-glass and collagen membranes can serve as effective carriers for rhBMP-9 in GBR applications	The translation of findings from animal models to clinical applications requires further investigation.

DOI: https://doi.org/10.54393/pjhs.v5i11.2475

[24]	Randomized controlled clinical trial (20 patients with follow-up of 6 months)	Platelet-rich fibrin (PRF) + bio-absorbable guided tissue regeneration (GTR) membrane.	Significant differences were observed in PPD, CAL gain, WKG, and GT between the two groups.	The combination of PRF with GTR did not provide additional benefits over GTR alone in terms of root coverage	PRF combined with GTR membrane does not offer substantial improvements over GTR alone.	The trial was limited by a relatively small participant group
[25]	Experimental In-vitro study evaluating different conc. of Ag-NPs for periodontal regeneration.	Collagen membranes with different conc. of silver nanoparticles for GTR	The 2% Ag-NPs membrane showed excellent cytocompatibility.	The 2% Ag-NPs collagen membrane demonstrated both effective antibacterial properties and high cytocompatibility	A collagen membrane containing 2% Ag-NPs showed potential for GTR in periodontal regeneration.	The 3% Ag-NPs membrane was cytotoxic, reducing its suitability for regenerative applications.
[26]	In-vivo study on rabbits with follow-up of 5 weeks	Ethylene oxide sterilized chitosan -polyvinyl alcohol (CS-PVA) bio -membranes	The test group showed significant tissue growth and bone regeneration by 5 weeks, with the GTR membranes being resorbed	The CS-PVA bio membranes allowed complete healing and membrane resorption.	The ethylene oxide sterilized CS-PVA bio-membranes demonstrated potential for effective guided tissue regeneration in chronic periodontitis.	The sample size was not explicitly mentioned.

MC3T3-E1=Mouse Calvarial Preosteoblast Cell Line, DMAHDM=5-(N, N-Dimethyl) Hexadecyl-2-Pyridylamine, NACP=Nano-Hydroxyapatite with Calcium Phosphate

DISCUSSION

Periodontal diseases can cause severe complications which include tissue damage, deep periodontal pockets due to tissue loss, gingival recession, and bone resorption if left untreated. These poor outcomes can impair oral function, aesthetics, and overall quality of life. It successfully provided an up-to-date overview of the available GTR techniques concerning the clinical results, the global distribution of techniques, and the constraints, followed by an outlook on the most effective periodontal treatment concepts. Guided Tissue Regeneration (GTR) has been proven to be significantly effective against periodontal tissue loss by employing tissue regeneration which showed improved clinical outcomes in the form of reduction in pocket depth and enhancement in clinical attachment levels [27]. The obtained data demonstrated its effectiveness in enhancing tissue healing and its long-lasting changes in periodontal health [28]. In recent years GTR has established itself as a complementary tool to conventional therapies such as scaling and root panel (SRP) or surgery, demonstrating often safer and better outcomes [29]. Several approaches of GTR have demonstrated clinical success such as bioresorbable membranes, non-bioresorbable membranes, and the use of advanced biomaterial polymeric scaffolds or bioinspired membranes. Methods using platelet-rich fibrin (PRF) and advanced platelet-rich fibrin (A-PRF) have also proved to be very effective in promoting healing since they act as templates for tissue reconstruction and act as carriers of growth factors to the affected region of the mouth [30]. Moreover, the material in the form of bioactive membranes containing nanoparticles or antibacterial substances has been considered for combating microbial issues involved in periodontal diseases since it provides an extra barrier against recurring infections [31]. From the analysis of the examples of applying the different GTR techniques, each technique has its distinct advantage. For example, melt electro-written scaffolds have been shown to have strong antibacterial properties and good mechanical stability in the long term [32]. Likewise, bioinspired Janus polyurethane membranes for tissue engineering and nanocomposite electro-spun silk fibroin membranes for microbial biofilm-resistant surfaces revealed encouraging outcomes [33]. A-PRF, when used in conjunction with GTR, provided better short-term stability in terms of PD, CAL, and improved healing. Comparatively, A-PRF seems to provide the best improvement in clinical parameters in the short-term restoration and advanced scaffolds and bioinspired membranes provide the long-term utility, predominantly, antibacterial properties and stability of the tissue [34]. Not to forget, advanced bioinspired membranes and polymeric scaffolds offer long-term benefits which include antibacterial efficacy and tissue stability, that ultimately reduce the risk of recurring infection. The usage of GTR techniques has some restrictions because its accessibility depends upon the progress of dental science and techniques in the

DOI: https://doi.org/10.54393/pjhs.v5i11.2475

respective region and the economic state. Polymeric scaffolds and bioinspired membranes are utilized in the developed countries of North America and Europe especially the USA and Germany due to the availability of modern dental technologies and adequate research grants [35]. However, other regions such as Asia and South American countries still heavily depend on classic GTR techniques, but in recent years there has been an increasing trend of applying PRF and biomaterials, especially in China and India [36]. In some developing regions, because of the problems in clinical resources and restricted access to high-end regenerative materials, advanced GTR technologies have not been widely applied. This study provided a comprehensive review of GTR approaches and patient outcomes; however, this study has certain limitations that need to be addressed. The first limitation is the variation in data across studies e.g. sample size, conditions, design of study, and follow-up period that hinders the consistency of the study. The second limitation is that since this study observed recent approaches, most of the GTR techniques are not well-established practices yet and lie in their early clinical trial period hence long-term effects are not yet known for them. Likewise, GTR techniques are not entirely without their drawbacks. Research focusing on patients receiving periodontal surgery reported variations in treatment results based on parameters like the seriousness of the disorder, the presence of other diseases, or the patient's compliance with postoperative directions and recommendations [37]. In addition, most of the currently represented innovative GTR methods, such as bioinspired membranes and polymeric scaffolds, are still experimental or at the stage of large-animal pilot clinical trials, thus, the safety and efficacy of these methods need to be established in further, more extensive investigations [38]. Price and access to specific GTR materials are also an issue, especially in the developing world, where dental health care is still very scarce [39]. This study leads the further development of more cost-effective, accessible and biocompatible GTR material for the widespread application of these techniques in the future. New advances in biomaterial science especially the use of nanotechnology and growth factors in GTR membranes show a lot of potential for enhancing the clinical success of GTR and minimizing the chance of reinfection [40]. As for future studies, it is necessary to concentrate on improving the scaffold's architecture for increased and more contiguous tissue formation rate, and improving the antibacterial efficacy of the membranes [41]. In the years to come owing to the development in 3D printing and bioengineering, GTR solutions can be designed according to patient-specific conditions, which can address oral disorders more effectively.

CONCLUSIONS

It was concluded that guided tissue regeneration has been developed as one of the most effective modalities for performing periodontal therapy; this is an assertion given the fact that the approach is regenerative compared to other conventional techniques. The review highlights that GTR materials such as A-PRF and bioinspired membranes offer better clinical results in terms of tissue regeneration and long-term periodontal health respectively. Among all techniques studied, A-PRF is better for short-term healing and bioinspired membranes and advanced scaffolds for long-term anti-bacterial protection and tissue stability. Clinicians are encouraged to apply these techniques, especially in periodontitis where standard treatment procedures may require additional support. These advanced techniques not only improve the treatment results of patients but also provide practical advantages, such as less healing time and reduced morbidity. It can be countered by focusing on the cost-effective accessibility of GTR techniques in regions of low availability. As biomaterial science advances today, the consciousness of increasing application of GTR surfaces increases. Because of that GTR's capability to become one of the most routine protocols in the prevention of periodontal infections and enhancement of patient's life globally remains vivid.

Authors Contribution

Conceptualization: AI, RS, FT
Methodology: AI, RS, FT, UR, SS, MA, MH
Formal analysis: AI, RS, FT
Writing review and editing: AI, MH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v5i11.2402

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Systematic Review

OPEN ACCESS

Managing Clinical Trials Amid Healthcare Policy Reforms: Challenges and Opportunities

Babar Hayat[1], Naheed Mumtaz[2], Sadia choudry[3], Muhammad Ayub Khan[4], Amna Iqbal Butt[5], Zahid Azam Chaudry[6] and Muhammad Hassain[7*]

[1]Department of Primary and Secondary Healthcare, Government of Pakistan, Lahore, Pakistan
[2]Faculty of Medical and Health Sciences, University of Poonch, Rawalakot, Pakistan
[3]Department of Behavioral Science, Rahbar Medical and Dental College, Lahore, Pakistan
[4]Chughtai Medical Centre, Lahore, Pakistan
[5]Department of Community Medicine, Sharif Medical and Dental College, Lahore, Pakistan
[6]Department of Community Medicine, Nazwaz Sharif Medical College, Gujrat, Pakistan
[7]Department of Molecular Pathology, University of Health Sciences, Lahore, Pakistan

ARTICLE INFO

Keywords:
Clinical Trials Management, Healthcare Policy Reforms, Patient Recruitment, Challenges

How to Cite:
Hayat, B., Mumtaz, N., Choudry, S., Khan, M. A., Butt, A. I., Chaudry, Z. A., & Hussain, M. (2024). Managing Clinical Trials Amid Healthcare Policy Reforms: Challenges and Opportunities: Managing Clinical Trials and Healthcare Policy Reforms. Pakistan Journal of Health Sciences, 5(11), 304-312. https://doi.org/10.5 4393/pjhs.v5i11.2402

***Corresponding Author:**
Muhammad Hassain
Department of Molecular Pathology, University of Health Sciences, Lahore, Pakistan
muhammadhussainmh173@gmail.com

Received Date: 2nd October, 2024
Acceptance Date: 23rd November, 2024
Published Date: 30th November, 2024

ABSTRACT

Clinical trial management is becoming more influenced by policies in healthcare reform, especially if those reforms are actively affecting regulations, access to healthcare, and compliance. **Objectives:** To find out the implications of healthcare reforms for the administration, supervision and outcomes of the clinical trials. **Methods:** This study was carried out according to the PRISMA guidelines. Eight scholarly databases of peer-reviewed research articles were used including PubMed, ScienceDirect, and Google Scholar. For this review, articles published from January 2016 to April 2024 were collected. This paper reviewed articles centred on the impact of healthcare reform policies on clinical trials, especially in chronic diseases and novel therapies in North America, Europe, and Asia. Through screening, 96 articles were taken for initial screening. 16 articles were fully reviewed based on challenges and prospects of clinical trial management in the course of changes in healthcare system reforms. **Results:** Healthcare policy reforms face obstacles like regulatory challenges, added bureaucracy, and highly volatile patient care accessibility. But there are also some benefits like optimized approval of trials-based procedures, better patient engagement, and increased trial effectiveness. **Conclusions:** It was concluded that clinical research can be more effective and scalable if proactive adaptive strategies are integrated and trial protocols are aligned with evolving policy changes. Adapting proven trial management practices in healthcare settings has the potential to enhance patient outcomes and promote operational efficiency in clinical research around the world.

INTRODUCTION

Clinical Trials Management (CTM) is key to the development of new medical interventions and is vital to the paradigm of ensuring ethical, efficient, regulatory-compliant trials. It includes the elaboration of clinical trials, their coordination, their realization and their control. It has to be ensured that each stage of the study is realized according to ethical rules and scientific protocols. If we talk about advancement the complexity of CTM has been dramatically augmented by the globalization of clinical trials, the requirement of a diverse patient population, and evolving requirements in recent years. It not only enables the protection of participants but also provides an important assurance of scientific credibility and reliability of the results, which is essential for regulatory approval allowing medical products to be commercialized [1]. This work demonstrates how current healthcare policy reforms affect CTM, specifically in-patient safety, data integrity and trial efficiency. This study analyzes the implications of such reforms to highlight the advantages and challenges of optimizing the management of clinical trials. The

DOI: https://doi.org/10.54393/pjhs.v5i11.2402

importance of CTM cannot be overstated. Good management of clinical trials is essential to finish clinical trials on time and within budget while maintaining high standards for patient safety and data hygiene. New clinical trials often hinge on how well they are 'conducted' by getting participants to follow trial protocols and can often make or break a trial's success. Furthermore, efficient CTM can enhance patient retention rates and enable the timely, high-quality collection of data necessary to derive meaningful conclusions on the safety and efficacy of the treatment being studied [2]. In particular, it is important because the costs of clinical trials are escalating and delays in trials can substantially add to sponsors' financial burdens [3]. However, the implementation of CTM practices varies widely by regulation resource availability, and the type of infrastructure of clinical research within which they are conducted globally. Clinical trials in developed regions like North America or Europe benefit from a strong regulatory framework, advanced technology and well-equipped infrastructures making trials quite a smooth function. On the other hand, challenges to CTM are more numerous in emerging markets such as Asia and Africa due to limited resources, absence of stringent oversight, and lower levels of expertise in different clinical research management [4]. Despite these challenges, there is a growing movement to harmonize CTM practices to make sure that trials are conducted according to the same ethical and scientific standards in different regions [5]. Despite the large literature on CTM, however, there are still gaps. The first is that while there is much research on the technical and logistical side of managing clinical trials, relatively few studies have examined how healthcare reforms affect CTM practice. Due to healthcare policies and regulatory changes focusing on increasing transparency, patient safety and using real-world data in trial designs, the CTM has transformed its landscape [6]. However, the implications of these reforms for the administration, supervision and outcomes of clinical trials have thus far gone unexplored. More research is needed to look at how these reforms impact day to day management of trials and to discover what challenges (and opportunities) they present to trial sponsors and contract research organizations [7]. Because of these gaps, this study is very important for addressing: the implication of healthcare policy reforms on the management, supervision and outcomes of clinical trials. This study attempts to gain insight into the challenges that trial managers experience when they need to adapt to new regulatory requirements as well as what could be improved to enhance trial efficiency and patient outcomes [8-10]. The future of CTM, however, is likely to be determined by additional changes in healthcare policy in terms of regulation. The use of real-world data, decentralized clinical trials (DCTs) and greater patient input into the trial design are some trends likely to revolutionize CTM shortly.

This study aims to extend the literature with a detailed assessment of CTM under healthcare reforms and suggestions for optimizing clinical trial management in future. As the landscape of healthcare systems evolves globally, it will be imperative for CTM practices to change with them so that clinical trials can be conducted in a manner which is efficient and ethical but also satisfies both patients as well as regulatory authorities.

METHODS

This study was carried out according to the PRISMA guidelines. A total of 96 articles were focused on the relationship between CTM and healthcare policy reform. The studies included were published in English between the years 2016 and 2024, contributing to the understanding of the challenges and possibilities of conducting clinical trials in different regions and healthcare systems. Filtering criteria focused on articles that identified how healthcare policy reforms impact clinical trial management (CTM) in North America, Europe, and Asia. Studies that examined CTM-related topics, including regulatory challenges, patient safety, data integrity, and operational efficiency, were eligible. Non-peer-reviewed sources (e.g., editorials, commentaries), studies having hydrodynamical applications only (without CTM implication) or languages other than English, have been disqualified as exclusion criteria. Also, we excluded duplicates as well as studies with unavailable full text. The following manuscripts were systematically evaluated and were incorporated into the PRISMA framework: authorship, year, country, trial design, obstacles faced, possible solutions, results, and important issues. The search was extended to several electronic databases: PubMed, Science Direct, Springer Link and Google Scholar, where 80% of articles were acquired from PubMed. The keywords used were “clinical trials management”, “healthcare reforms”, “legal aspects”, “patient recruitment”, and “chronic disease trial management”. A variety of research designs are included in the study: randomized controlled trials (RCTs), observational cohort studies and cross-sectional studies to ensure that the healthcare policy reforms have their effects on clinical trial management (CTM). Randomized controlled trials can provide rigorous, quantitative insights about adherence to protocols, patient retention, and data quality, key components of CTM effectiveness which are lacking in observational research. Observational cohort studies provide important real-world data, permitting investigation of CTM's longitudinal trends over time, and across different healthcare systems. These findings complemented cross-sectional studies, which illustrate, in almost immediate snapshots, specific recruitment

DOI: https://doi.org/10.54393/pjhs.v5i11.2402

obstacles and regulatory compliance problems provided by policy changes that trial managers face during their studies. To begin with, every article that contained any keywords about clinical trial management and health care reform was accumulated. They involved duplications and abstracts. The next phase consisted of screening these articles in terms of certain defined inclusion and exclusion criteria. Similarly, other articles were discarded because the contexts of CTM in the field of health care reform were not relevant, it was not a clinical study, or it was published outside the time range specified. After this screening, 96 articles were considered for detailed analysis but after eliminating duplicates and exclusion of other factors 47 articles were deemed worthy of systematic review. For the last stage of the review, after a full assessment, 16 articles were defended in detail and the core results of studies were arranged into tables by the aspects of challenges and opportunities regarding clinical trial management under health care reforms. The final dataset allowed for a comprehensive understanding of the effects of health systems reform on CTM, considering important aspects like regulatory issues, patient recruitment difficulties, and possible advantages such as better trial quality and participation of patients (Figure 1).

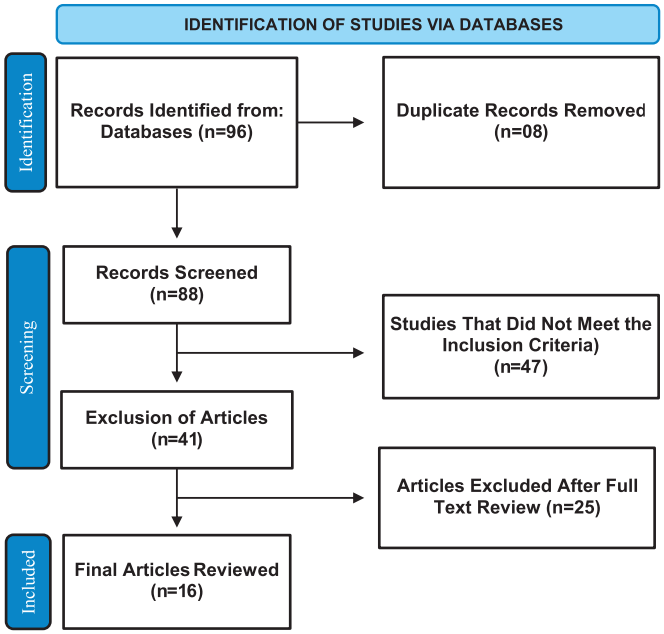

Figure 1: Systematic Review on CMT in Context of Healthcare Policy Reforms According to Inclusion and Exclusion Criteria

RESULTS

The review was performed as per PRISMA guidelines and included 16 most relevant studies, 80 percent of which were from PubMed and the rest from ScienceDirect and Springer Link. Seven of the 16 studies were observational cohort studies, five were randomized controlled trials, and four were cross-sectional studies. These studies aimed to explore the effect of healthcare reforms on trial management, patient recruitment, and data capture as well as management. The evidence showed that although there have been more complexities in the regulations due to healthcare reforms, patient safety and transparency of trials were also enhanced. The use of real-world evidence (RWE) and DCT were especially successful in addressing some of the logistical and recruitment challenges. Quantitative and qualitative findings on the impact of healthcare reforms on clinical trial management (CTM) across several main points are presented. Studies showed a 15% improvement in patient retention for DCTs and a 20% reduction in the academic trials in Japan that helped with the high costs problem. Qualitative insights identify challenges and strategies, including stricter conflict of interest management and the need for better patient-centred designs for improved recruitment and retention. Together, these quantitative and qualitative results underscore the dual impact of healthcare reforms: new regulations can place operational burdens and introduce regional variability, but reforms also offer the potential to develop more efficient, patient-centred and adaptable trial designs, both for regulatory compliance and for patient outcome. The summary of the 16 studies is analyzed (Table 1).

Table 1: Systematic Scheme of Studies Included in Review Along with Their Findings and Outcomes

References	Type of Study	Focus of Study	Challenges Highlighted	Opportunities Identified	Outcomes/Findings
[11]	Observational, longitudinal cohort study	Management of a real-world longitudinal non-alcoholic fatty liver disease (NAFLD) cohort across multiple countries	Variability in data collection across sites; coordinating international multi-center recruitment and maintaining high-quality data	Variability in data collection across sites; coordinating international multi-center recruitment and maintaining high-quality data	Successfully established a large, high-quality database supporting biomarker development and longitudinal analysis for regulatory qualification.

DOI: https://doi.org/10.54393/pjhs.v5i11.2402

[12]	Cross-sectional (clinical trials)	Representation in precision oncology clinical trials	Low representation of racial and ethnic minorities; incomplete reporting of participant demographics across studies	Increasing diversity in participant recruitment through community engagement, patient education, and enhanced reporting practices	Demonstrated the need for better recruitment strategies to ensure equitable representation of minorities in clinical trials.
[13]	Randomized Control Trial	Asia-inclusive development of Pevonedistat for higher-risk MDS, CMML, and AML.	Delays in drugdevelopment in Asia, complexities in harmonizing regional regulatory requirements.	Efficiency in global clinical trials through multiregional clinical trials (MRCT) designs that include regional patients early, thereby reducing delays in drug availability.	Comparable pharma-cokinetics, efficacy, and safety across East Asian and Western populations, enabling pooled analysis for East Asian patients.
[14]	Randomized Controlled Trial (RCT)	General practitioner-led vs. surgeon-led colon cancer survivorship care.	Difficulty recruiting participants, reluctance of GPs to participate, preference for specialized care among patients.	Engagement of new centers and modified recruitment procedures to enhance trial participation.	GP-led survivorship care shows potential but requires more support and participation from both patients and healthcare providers.
[15]	Observational Comparative Effectiveness Study	Cardiovascular and renal benefits of empagliflozin in Type 2 Diabetes routine care settings in East Asia.	Adjusting for regional variations in patient care, healthcare databases, and balancing comorbidities among patient populations.	Routine care data shows consistency with clinical trial findings, emphasizing the drug's broad applicability across various patient profiles.	Empagliflozin reduced heart failure hospitalizations by 18%, all-cause mortality by 36%, and end-stage renal disease by 63% compared to DPP-4 inhibitors.
[16]	Cross-Sectional Study	Factors influencing participation in COVID-19 clinical trials in Arab countries	Lack of trust in physicians, limited information, fear of negative health impacts	Increase awareness, enforce ethical guidelines, and promote altruism	The public has a generally positive attitude towards trials but is influenced by trust issues
[17]	Post Clinical Trial	Regulatory changes in clinical trial management post-enforcement of the Clinical Trials Act	Financial and administrative burdens on academic clinical trials	Improved reliability and stricter conflict-of-interest management under new guidelines	Significant reduction in clinical trial activity post-regulation due to increased burden
[18]	Retrospective Study	Oncology clinical trial management during COVID-19 at Beijing Cancer Hospital.	COVID-19 restrictions led to difficulties in patient recruitment, protocol compliance, and site monitoring.	Remote clinical trial management (remote approvals, visits, drug administration, and monitoring) helped maintain high protocol compliance and trial continuity during pandemic outbreaks.	Remote trial management ensured an 85.24% protocol compliance rate with fewer trial withdrawals and loss to follow-up, compared to traditional management during public health emergencies.
[19]	Observational Study	Site identification practices and the use of electronic health records (EHRs) in feasibility evaluations of clinical trials in the Nordic countries.	Limited use of EHR data for trial site identification due to legislative restrictions and limited investigator engagement with patient data.	Increased use of EHR data for estimating patient recruitment potential could accelerate recruitment and improve the accuracy of feasibility evaluations, leading to better site selection and trial success.	Sites using EHR data were perceived as more reliable and effective in estimating patient recruitment potential, offering a competitive advantage in trial site selection.
[20]	Observational Study Survey	Examines new UK regulatory frameworks for oncology drug approvals after Brexit	Ensuring timely regulatory approvals, maintaining access to drugs, and addressing reimbursement issues	Expedited approval pathways, global collaboration (Project Orbis), and innovative licensing pathways	Faster cancer drug approval times in the UK compared to the EU; earlier patient access through Project Orbis.
[21]	Observational Study	Assesses the implementation of research biopsies in oncology trials at a tertiary center	Ethical concerns regarding the increase in biopsy demands without direct patient benefit; low compliance to ethical frameworks	Improving adherence to ethical frameworks to ensure better quality of care in clinical trials	Increased use of tissue biopsies in clinical trials without significant benefit, highlighting the need for better frameworks.
[22]	Prospective Study	Incorporation of participant feedback before, during, and after trials	Lack of patient-centred trial designs, low recruitment and retention rates due to poor trial design	Use of technology (surveys, apps) to gather feedback, patient-reported outcomes, voice-response technology	Incorporating participant feedback reduces participant burden, improves recruitment and retention, and enhances trial success

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[23]	Randomized Clinical Trials	On-site monitoring of clinical trials by Ethics Committees in India	Inadequate off-site monitoring, GCP (good clinical practice) violations, protocol violations, discrepancies in informed consent	On-site monitoring ensures better compliance with GCP, protects participant rights, reveals unreported issues	On-site monitoring detected GCP violations missed by off-site reviews, such as incomplete consent forms, unreported adverse events, and protocol violations.

These studies from Japan, India, and globally all show that healthcare reforms, including improved monitoring and regulatory changes, improve clinical trial supervision and participant safety. Reforms also foster inclusivity and patient-centred designs that increase trial recruitment, retention, and overall trial outcomes.

DISCUSSION

Clinical Trials management is an indispensable component of clinical research and plays a crucial role in advancing the field of medical research and the discovery of new therapies. It involves the coordination of the clinical trials to gain assurance that they are running correctly and in compliance with stimulating legal benchmarks and moral principles. Appropriate CTM is crucial to patient safety and to ensure the scientific credibility of the results of the trial. The challenges in CTM have increased over time due to the growing scale of trials across diverse geographic regions, the increasing use of a diverse patient population, and the introduction of new rules and regulations [24]. The focus of this study is to highlight the reforms to healthcare policies and how they have influenced the management, oversight, and outcomes of the clinical trials, aiming to provide details on the challenges and possibilities of these reforms. Some of the most revolutionary changes in clinical trial management have been driven by healthcare policy reforms particularly those concerning patient safety and data integrity. The globalization of clinical trials has also witnessed the implementation of international regulations such as the Clinical Trials Regulation which emphasizes increased transparency, improvements in patient involvement, and usage of real-world data involved in trial design [25]. A variety of factors have significant effects on Clinical trial management, including regulatory frameworks, ethical oversight, patient recruitment, data management, and monitoring processes. The main challenge is the alignment on international regulatory requirements, particularly in multi-regional trials. One study points out problems in harmonizing regulatory requirements for the development of immunotherapy for solid tumors across Europe and Asia [26]. The findings of one study, emphasize the need for on-site monitoring in African trials wherein several protocol violations were not detected by the off-site reviews [27]. However, there is a need for more enhanced monitoring, and this brings the problem of resource allocation and the financial burden of ethics committees and trial sponsors. Yet, the development of risk-based monitoring strategies as well as the use of DCTs can support opportunities by allowing the processes to be streamlined and administrative overheads to be reduced [28]. Clinical trials today are an increasingly complex management affair, especially when trials span multiple regions and need convergence of their regulations. This is observed in the study by analyzing Brazil's updated regulatory framework for clinical trials in rare diseases [29], where the regulatory landscape in Europe, Asia and the Americas varies widely, making trial management complicated. This framework has helped to speed up approval but has also imposed new compliance requirements for local trials. Conversely, in the United States, the reforms brought by the FDA's 2020 patient-focused drug development guidance have helped lead to more inclusive trials for instance even in rare and genetic disorders with involvement of the patient advocacy groups [30]. This is further illustrated by a study on the provision of global collaborations, such as the ACCESS Consortium, that catalyze faster regulatory approvals and more innovative licensing pathways (regulatory harmonization) in pediatric oncology drug approvals [31]. The effective management of clinical trials is essential for the continuous development of safe and effective medical interventions. With healthcare reforms increasingly focusing on patient safety and trial transparency, CTM practices are undergoing significant transformation. Ensuring patient safety through rigorous supervision and monitoring processes is now a cornerstone of clinical trial management. Some studies demonstrate that decentralized trials, driven by technology and patient-centric designs, can improve recruitment and retention in remote or underserved populations, while also reducing trial costs [32]. This emphasis on patient engagement underscores the importance of CTM in ensuring trials are ethical, scientifically sound, and aligned with patient needs. The findings from the studies summarized in the table provide critical insights into how healthcare reforms have shaped clinical trial management. For example, in 2020 Shafiq *et al.*, highlighted the shortcomings in off-site monitoring in India, with on-site monitoring revealing several previously undetected violations, emphasizing the need for reforms in monitoring practices [23]. In Japan, the study by Nakamura and Shibata revealed that the new Clinical Trials Act, while improving trial reliability, imposed significant burdens on academic trials, leading to a reduction in clinical trial activity [17]. Other studies, such as

DOI: https://doi.org/10.54393/pjhs.v5i11.2402

by Zhou *et al.*, showed that multiregional trials while challenging due to regulatory harmonization issues, offer significant opportunities to accelerate drug availability in underserved regions [13]. These results underscore the dual challenges and opportunities that healthcare reforms present for the administration and supervision of clinical trials. Over the last few decades, the management of clinical trials has changed significantly due to various reforms in healthcare institutions especially those affecting patient safety and trials. Some of the major shifts that have occurred include the use of DCTs and the integration of real-world data (RWD) into trial designs [33]. The COVID-19 pandemic has highlighted the importance of DCTs that do not require physical on-site presence [18, 34]. Also, the technology using EDCs and the expansion of EHR (Electronic Health Records) systems have shifted the management of trials and patient recruitment more effectively and efficiently [19, 35]. However, there still exist challenges when it comes to the management of clinical trials especially in light of healthcare reforms. Despite the culture, rules and regulations being important for the protection of the patients and the accuracy of data collected, are known to cause major administrative barriers to the sponsors and investigators of the trials. These burdens, as reported in one study might result in a decline in trial activity especially in academic institutions [36]. Furthermore, the comparative nature of regulations across the regions makes the conduct of multi-regional trials challenging, as mentioned in a study [37]. The inclusion of limited numbers of registers drawn from diverse minorities in clinical research trials revealed the lacking state of precision oncology trials in the United States [38]. These limitations advocate for continued reforms and innovations necessary in CTM to develop the means of addressing these challenges. Consequently, this research is needed to offer a comprehensive review of how healthcare reforms affect clinical trial management (CTM), oversight, and statistics. It offers a unique view of the difficulties and opportunities brought about by healthcare reform for trial sponsors, regulatory agencies, and healthcare policies. The literature and studies reviewed emphasize the need to evolve CTM policies to the changing law and practice in multicenter trials to ensure they remain safer, more cost-effective and accessible to all patients. This paper also puts forward the demand for additional reforms that will help to solve some of the currently existing challenges of clinical trials, in particular through the lens of CTM, with an emphasis on international and adaptive risk-based monitoring (ARM) trials. Based on this it can be expected that further healthcare system reforms which focus on patient safety, trial effectiveness, and diversification will continue to have an impact on the future of CTM. Real-life trials and Integrated Considerations of Real-World Evidence (RWE) are also thought to have great potential in the future of clinical trials as decentralized and less burdensome to patients. Expectedly, regulatory bodies such as Food and Drug Administration (FDA), should advocate for a more diverse trial population even with the guidance given on patient diversity recently. Furthermore, the adoption of new digital health technologies such as wearable and telemonitoring tools will facilitate data collection and improvement in patient engagement and result in better trial outcomes. Despite this, these advancements will require efficient and transparent regulations on a global scale such as regulations are foundational prerequisites to leverage these advancements to execute these innovations and grow infrastructure. Ongoing changes in healthcare reforms including cutting expenses, increasing patient satisfaction and ensuring quality in healthcare products will in turn require CTM practices to adapt to these changes in such a way that they can manage, monitor and achieve success in clinical trials.

CONCLUSIONS

It was concluded that clinical trial management has been greatly impacted by healthcare reforms, which have both challenged and facilitated increased administrative burdens, patient safety and trial transparency. By elucidating the promise of decentralized clinical trials, real-world evidence and patient-centred designs, the study aimed to overcome key issues such as recruitment difficulties and adherence to protocol. The findings underscore the importance of adopting adaptive management strategies and regulatory harmonization to foster what we hope will be efficient and ethical trial practices. With the evolution of healthcare systems, the link between CTM protocols and these reforms will be crucial to achieving sustainable improvement in trial outcomes, patient engagement and research efficiency.

Authors Contribution

Conceptualization: BH, NM, SC
Methodology: BH, NM, SC, MAK, AIB, ZAC, MH
Formal analysis: BH, NM, SC
Writing review and editing: MAK, AIB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v5i11.2402

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Commentary

Sound Induced Dental Sensitivity

OPEN ACCESS

Mohammad Aizaz Khan[1] and Waqar-Un-Nisa[1*]

[1]Department of Oral Pathology, Bacha Khan College of Dentistry, Mardan, Pakistan

ARTICLE INFO

Keywords:
Sound Induced Dental Sensitivity, Discomfort, High-Pitched Sound, Sensitivity

How to Cite:
Khan, M. A., & Nisa, W. un. (2024). Sound Induced Dental Sensitivity: Sound Causes Dental Sensitivity. Pakistan Journal of Health Sciences, 5(11), 313-315. https://doi.org/10.54393/pjhs.v5i11.2154

***Corresponding Author:**
Waqar-Un-Nisa
Department of Oral Pathology, Bacha Khan College of Dentistry, Mardan, Pakistan
dr.waqarunnisanoor@gmail.com

Received Date: 26th September, 2024
Acceptance Date: 19th November, 2024
Published Date: 30th November, 2024

INTRODUCTION

Tooth sensitivity is a common complaint of patients [1], which can be defined as an exaggerated response to a stimulus such as thermal, chemical, tactile, osmotic, or air-current that usually causes no response in a normal, healthy tooth [2-4] but have you ever winced when hearing the screech of nails on a chalkboard or felt sharp discomfort in your teeth at the sharp sounds, such as the sound of metal scraping against metal? These reactions are common among people, as most of us feel during our lifetime. The scientific community has yet to fully explain why certain sounds cause physical discomfort in teeth. Most of the dental and facial pain had a psychological or behavioural impact. Thus, dental and facial pain is a relevant problem that is mostly associated with tooth sensitivity [5]. Direct research on the phenomenon of sound-induced teeth sensitivity is almost nil which is a void to be filled by scientists. Deep studies on misophonia, auditory-tactile synesthesia, polyvagal theory, cross-modal sensory processing, and teeth conduction provide reasonable insights that can help us understand this phenomenon. Analyzing opinion-based clues from different studies, we can explain how sharp sounds such as metal scratching can induce sensitivity in our teeth. Misophonia means "hatred or dislike of sound." It is a neurobehavioral syndrome phenotypically characterized by heightened autonomic nervous system arousal and negative emotional reactivity (e.g. irritation, anger, anxiety) in response to a decreased tolerance for specific sounds [6-8]. It is characterized by a negative reaction to a sound with a specific pattern and meaning to a given individual. Trigger sounds include food chewing, sniffling, persistent coughing, knuckle cracking, metal scratching, and nail scratching [9, 10]. The phenomenon of tooth sensitivity can be explained by misophonia in certain ways in light of different research and theories. No direct link has been explained by the researchers to teeth sensitivity, but as professionals, we have selected the lines that reflect the concept of sound-induced teeth sensitivity. The concept we extract from the condition of misophonia is that teeth sensitivity is the negative response of the body to the triggering misophonic sounds like screeching of metal. Another study suggests that individuals with misophonia exhibit stronger activation in the orofacial motor area in response to trigger sounds, indicating a motor response to misophonia [11]. Dr. Stephen Porges devised the polyvagal hypothesis, which explains how the neurological system reacts to safety or danger by concentrating on the vagus nerve, which connects the brain to the face, neck, and

DOI: https://doi.org/10.54393/pjhs.v5i11.2154

internal organs. Sensations of security and calm are brought on by healthy vagus nerve activity. On the other hand, when it malfunctions, dangerous reactions might occur even in the absence of real dangers. This idea links the body's stress response to sound-induced oral sensitivity. The autonomic nervous system, in particular the vagus nerve, is responsible for inducing a "fight, flight, or freeze" reaction in response to perceived dangers, such as specific noises, according to the polyvagal theory [12-15]. Certain noises may cause an unconscious stress reaction in those who have sound-induced dental sensitivity, which makes them more sensitive to oral stimuli. This response is like how people have misophonia, and strongly react to specific noises. Essentially, the nervous system may interpret sound as a threat, causing unpleasant sensations. There could be a neural connection between hearing and touch, according to a study by Oxford University Press, which indicates that the auditory and somatosensory systems are well related. An anatomical basis for multisensory interactions is provided, explaining why some unpleasant sounds irritate. Within this framework, the correlation between metallic scraping noises and tooth sensitivity can be twigged as cross-modal perception, which can be elucidated in two ways: (1) Sensory Association: The brain interprets unpleasant sounds with high pitch as physical sensations, causing tooth pain. (2) Neural Overlap: When certain noises are heard, the activation of neural circuits linked to tooth pain may result from the overlap of auditory and somatosensory regions [16]. Auditory-Tactile Synesthesia: This condition involves sounds evoking tactile sensations due to cross-modal processing and hyper-connectivity in the brain. Different sounds can induce various tactile sensations such as vibrations, warmth, and tingling, varying among individuals [17]. In the context of this study, we can suppose that certain sounds can induce painful tactile sensations in the teeth in the form of sensitivity. This study suggests that specific sounds can trigger painful tactile sensations in teeth, manifesting as sensitivity. Both teeth and bones serve as sound conductors. High-frequency sounds, like metal scratching, are conducted through the skull's bone to the teeth or directly by the teeth, causing sensitivity. These sounds disturb dental tubular fluid, which stimulates baroreceptors and leads to teeth sensitivity according to the concept of hydrodynamic theory [18, 19]. Despite, various plausible reasons discovered by linking several studies, further study is needed to recognize the exact source of sound-induced oral sensitivity. Researchers must also determine the prevalence of this condition, whether it is general or affects only a small percentage of the population. Future studies may focus on neuroimaging studies to detect brain activity in people who experience this phenomenon, or it could look into whether there is a genetic predisposition that renders certain people more prone to this form of multimodal pain. The phenomenon known as sound-induced dental sensitivity is a fascinating nexus between the fields of neuroscience, psychology, otolaryngology, and dentistry to investigate the relationship between pain in the teeth and the other systems. The interdisciplinary approach involving neurology, otolaryngology, and psychology can help the researchers understand the idea of sound-induced tooth sensitivity, which will ultimately help those who are affected by it. Identifying the gap could help dentists improve their dental practices by enabling them to investigate sound-induced dental discomfort and provide specialized, comfortable, anxiety-free, high-quality services. The results could also help develop customized treatment plans that take into account a patient's sensitivity to particular sounds or discover and use cutting-edge technical solutions like sound-mitigating devices during dental procedures. Additionally, the introduction of innovative dental materials that reduce sound vibration transmission might be considered.

Take home message

- A complex brain-operated multisystem phenomenon caused by metal scrapping that leads to sound-induced dental sensitivity.
- There is a dearth of literature explaining the exact underlying mechanism. To fill this gap further research is required on how to provide long-term relief to the patients suffering from this condition by developing more efficient methods and using advanced technologies leading to a quieter and anxiety-free dental space. We now face a choice: do we continue to endure sensitivity to high-frequency, sharp sounds, or do we commit to eradicating it through dedicated research?

Authors Contribution

Conceptualization: MAK
Methodology: MAK
Formal analysis: WUN
Writing review and editing: WUN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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