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Original Article

Trends of Hepatorenal Variations in Hepatitis-C Patients Visiting THQ Level Hospital in Arifwala Punjab

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ABSTRACT

Hepatitis C virus (HCV) is a source of kidney illness and liver pathogenesis such as cirrhosis and hepatocellular carcinoma (HCC). **Objective:** To evaluate variations in hepatic and renal profile of hepatitis-C patients. **Methods:** For this purpose, blood samples of 94 participants were collected. Out of which 64 were hepatitis-C patients and 30 were healthy controls. All the participants were enlisted from Tehsil Headquarter (THQ) Hospital, Arifwala. Both males and females were included in the HCV Patients group. The serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) urea, creatinine, albumin, bilirubin, glucose and gamma-glutamyl transferase (GGT) were estimated by chemistry analyzer. Unpaired Student "t" test was applied to analyze the data of biochemical variations in hepatitis-C patients as compared to normal persons with significance level of $p \leq 0.05$. For statistical interpretation, Graph pad prism version 6.0 software was utilized. **Results:** Significant elevation in the levels of glucose ($p = 0.0002$), ALP ($p = 0.01$), ALT ($p = 0.0009$), AST ($p = 0.002$) and GGT ($p < 0.0001$), whereas, non-significant increase in the levels of creatinine ($p = 0.9$) and bilirubin ($p = 0.51$) was evidenced in hepatitis-C patients as compared to healthy controls. While, significant decrease in the level of albumin ($p = 0.0008$) was observed in hepatitis-C patients as compared to healthy controls. **Conclusions:** The fluctuations in these parameters suggest that HCV has a significant impact on hepatic health markers.

INTRODUCTION

Hepatitis C virus (HCV) is a pronounced reason of chronic liver infection, causing almost 400,000 deaths annually worldwide [1]. HCV, a single stranded RNA based virus with its eight established genotypes that are subdivided into 86 confirmed subtypes differing by only 15%–25% [2, 3]. Different estimations have documented that 130-170 million individuals are infected annually with the hepatitis C infection. Hence, HCV is considered as significant general medical problem [4]. The highest incidence of HCV infection is reported in Egypt, where it goes up to 15% [5]. There are six comprehensive genetic variants of HCV that differ in their disease-causing ability, output of interpretation/duplication and receptiveness to anti-viral treatment. Genotype 1, 2 and 3 are the significantly observed in Western Europe, North America and Japan. Whereas, genotype 4 has been found in the Middle East, Northern and in Central Africa. While, genotype 5 has been documented in South Africa and Genotype 6 in Southeast Asia, respectively [6]. Mostly the spread of HCV infection is through percutaneous contacts of blood transmission, replacement of diseased organs and infusing medications. Perinatal transmission happens at lower rate and the chance of sexual transmission is disputable [7]. In 20–30% of diseased people, HCV causes intense infection, but in most patients, it causes a long-term chronic illness. Persistent infection with HCV is associated with the

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development of chronic hepatitis, hepatic steatosis, cirrhosis and hepatocellular carcinoma (HCC) [8]. Chronic hepatitis C (CHC) is the chief sources of hepatic demise and most well-known sign for liver transplantation in the United State of America [4]. It should be noticed that more than 350,000 diseased persons die due to HCV-related liver illnesses [9]. From 10% to 20% of HCV-tainted patients develop cirrhosis over a time of 15 to 30 years. When cirrhosis develops, exhaustion, muscle shortcoming and squandering, liquid maintenance with edema and ascites, simple wounding, dull pee, jaundice, tingling and upper gastrointestinal discharge can happen [10]. The fundamental site of HCV multiplication is in hepatocytes, which clarifies the huge liver harm that it manifests. Most of the injury in the liver is brought about by a cell-intervened response against contaminated liver cells [9]. In HCV conditions cryoglobulins are regularly produced causing organ damage through either a hyper viscosity condition or immune mediated mechanism [11]. Though, cryoglobulinemia are produced in numerous diseased conditions, however, these are significantly associated with HCV patients [12, 13]. Clinical indications of liver illness will in general at first be vague, and irregular, with exhaustion depicted as torpidity, discomfort, absence of energy, anorexia, sickness, arthralgia, myalgia and weight loss [14]. Many pathological conditions are attributed with the hepatitis conditions. A few clinical investigations have documented a relationship between chronic HCV disease, insulin resistance and diabetes mellitus (DM) [15]. The epidemiological data have depicted that type 2 diabetes mellitus (T2DM) developed in 14.5-33% of patients with CHC [16]. Type 2 diabetes mellitus was predominant in patients infected with HCV-related cirrhosis of the liver than in those with cirrhosis of the liver coming about because of other liver infections [17]. HCV infection is an autonomous indicator of stroke and cerebrovascular [18]. Patients with CHC have indicated a pronounced danger of cardiovascular disorders [19]. HCV infection is correlated with different thyroid illness like chronic thyroiditis, hypothyroidism, and hyperthyroidism [20]. Idiopathic pulmonary fibrosis (IPF) is a condition related with HCV contamination. It is clinically portrayed by dyspnea and interstitial irritation with thick collagen fibrosis [21]. Renal association is one of the most widely recognized extreme indications of mitochondrial cytopathy (MC). Studies have demonstrated that patients with HCV contamination are 40% bound to develop end stage renal infection than the general population [22]. Kidney is an important target of HCV disorder, other than liver, musculoskeletal, hematopoietic system and skin [23]. HCV may induce kidney infection in different ways (a) glomerular complications (b) direct intrusion to the renal parenchyma; (c) nephrotoxicity of medications utilized for its treatment [24]. Persistent HCV exposure can bring about a huge danger for renal health acute kidney injury (AKI) in patients with lack of hydration, sepsis, or progressed liver injury [25]. This is a well-established fact documented in <5% -15% of HCV positive subjects [26]. The purpose of present study was to assess the fluctuations in glycemic, renal and hepatic profile of hepatitis-C patients as compared to healthy controls. Hence, the result would help out to do better in therapeutic management of hepatitis-C patients in these regions.

METHODS

This study plan was endorsed by the Institutional ethical review committee of Institute of Zoology, University of the Punjab, Lahore in 2021. Phlebotomy of total 94 subjects was carried out for this study. Among these, diseased group comprised of 64 hepatitis-C patients and 30 healthy controls. Both males and females were included in the HCV Patients group. Thirty-nine females and twenty-five males were recruited for hepatitis-C group. Whereas, control group contain twelve females and eighteen males. Random sampling technique was done for this case control investigation. Subjects having confirmed biochemical investigation of HCV were included in the diseased group. However, patients having condition like hepatocellular carcinoma or any type of cancer were excluded from this investigation. Blood samples of all the subjects were taken from Tehsil Headquarter Hospital (THQ) Hospital Arifwala, Punjab, Pakistan. All studied participants were informed about the significance of the study. Initially, a proforma was designed to note complete data of the clinical record of controls and patients. It included the fundamental attributes like age, sex, habit of smoking or addiction, family history of any ailment and BMI (kg/m^2). The motivation that clinical information gathered during this investigation would assist our medical professionals for future management of hepatitis patients was explained to each participant of the study. Moreover, written informed consent form was also signed by each of the participant before study. Subjects having hepatitis-C infection were included in the study as diseased group. Whereas, participants not having any hepatic ailment were considered as control group. A registered health technician was hired for the process of blood sampling. All the protective measures were taken as human subjects were engaged in the study. Before sampling, health condition of each person was confirmed. Three mL blood sample was drawn from each individual in separate tubes. Collected samples were then centrifuged at 3000 rpm for 15 minutes. Serum was separated from the clot in another acid washed test tube after 3-4 hours of blood compilation. The serum samples were then stored at -20 ºC in the

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labeled plastic vial. Within four hours of sampling, biochemical test of blood samples of control and hepatitis-C patients was done. Both control and HCV Patients' sample were analyzed using commercially available kits. Clinical chemistry analyzer (microlab 300) was used to measure the concentration of Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Urea, Creatinine, Albumin, Bilirubin, Glucose, Gamma-Glutamyl Transferase (GGT). Determination of all studied parameters was performed in Physiology/Endocrinology Laboratory, Institute of Zoology, University of the Punjab, Lahore. Graph Pad Prism (version 6.0) software was used for statistical analysis. Unpaired student "t" test was applied to assess mean and SEM of biochemical variations in hepatitis-C patients as compared to normal persons.

RESULTS

Table 1 showed the glucose, blood urea, creatinine, albumin, ALP, AST, ALT, GGT and bilirubin level in control and affected participants.

Table 1: An overall comparison of renal and hepatic profile in controls and hepatitis-C patients

Parameters	Mean ± SEM		p-value	Percentage difference
	Control (N=30)	Diseased (N=64)		
Glucose (mg/dL)	100.5 ± 2.64	164.3 ± 11.28	0.0002	63↑***
Blood Urea (mg/dL)	29.45 ± 1.83	44.73 ± 7.03	0.1	52↑
Creatinine (mg/dL)	0.86 ± 0.03	1.05 ± 0.13	0.3	22↑
Albumin (g/dL)	4.09 ± 0.104	3.51 ± 0.10	0.0008	14↓***
ALP (U/L)	91.00 ± 4.34	115.3 ± 6.66	0.01	27↑*
AST (U/L)	27.20 ± 2.56	37.36 ± 1.90	0.002	37↑**
ALT (U/L)	21.57 ± 1.59	30.17 ± 1.54	0.0009	40↑***
Bilirubin (mg/dL)	0.52 ± 0.05	0.59 ± 0.07	0.5	14↑
GGT (U/L)	24.13 ± 2.84	48.59 ± 3.46	< 0.0001	101↑***

***, **, * indicate level of significance at p< 0.001, 0.01, 0.05, respectively; Ns: Not Significance; ↑Increase; ↓Decrease; mg/dL: milligram per deciliter; g/dL: gram per deciliter; U/L: units per liter

Glucose: Our investigation showed a significant increase ($p < 0.0002$) of 63% in glucose level of hepatitis-C patients as compared to control subjects (Fig; 1A). Urea: No significant difference was observed in urea level of hepatitis-C patients in comparison to controls. However, the hepatitis-C patients demonstrated a mild increase of 52% in urea level as compared to controls (Fig; 1B). Creatinine: The creatinine value demonstrated non-significant increase of 22% in hepatitis-C patients as compared to controls (Fig; 1C). Albumin: The level of albumin was significantly ($p < 0.0008$) lowered by 14% in hepatitis-C patients in comparison to controls (Fig; 1D). Alkaline Phosphate (ALP): There was significant increase ($p < 0.01$) of 27% in the level of alkaline phosphate in hepatitis-C patients as compared to controls (Fig; 1E). Aspartate Transaminase (AST): Hepatitis-C patients showed significant ($p < 0.002$) rise of 37% as compared to controls (Fig; 1F). Alanine aminotransferase (ALT): The results indicated a significant increase ($p < 0.0009$) of 40% in hepatitis-C patients as compared to controls (Fig; 1G). Bilirubin Total: The Bilirubin value increased non-significantly ($p < 0.51$) by 14% in patients of hepatitis-C in comparison to controls (Fig; 1H). Gamma-Glutamyl Transferase (GGT): Hepatitis-C patients presented a significant increase ($p < 0.0001$) of 101% as compared to controls (Fig; 1I).

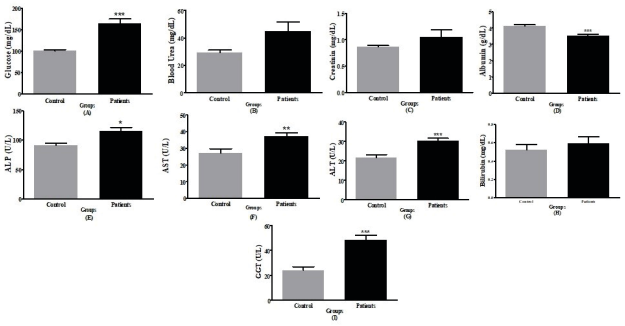

Figure 1: (A-I): An overall presentation of Glucose, Urea, Creatinine, Albumin, ALP, AST, ALT, Bilirubin and GGT in Control and HCV patient's groups
Values are Mean ± SEM. ***, **, * indicate levels of significance at p < 0.001, 0.01, 0.05, respectively

DISCUSSION

Extrahepatic ailments manifested by chronic HCV illness possess serious threats to the status of the diseased subjects [22]. Numerous epidemiological investigations have documented that active HCV is attributed to a greater incidence of chronic kidney disease (CKD) in these subjects. Moreover, it is recommended that patients with HCV should be screened for CKD even without symptom of any kidney dysfunction [27]. HCV is one of the pronounced reasons for hepatic disorder because of fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Exosomes derived from infected hepatocytes manifest hepatic fibrosis. Initial screening of HCV can reverse the fibrosis. Whereas, lack of initial screening may lead to end stage liver injury. For this reason, in time identification establishment of HCV diagnosis is a key to reduce pathogenesis of the disease [28]. Our findings have shown a significant increase in glucose, alkaline phosphate, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase, whereas, non-significant increase in the levels of creatinine and bilirubin was evidenced in hepatitis-C patients as compared to healthy controls. Significant decrease in the level of albumin was observed in hepatitis-C patients as compared to healthy controls. As far as albumin level is concerned, hepatitis-C patients depicted significant reduction in their levels as compared to healthy controls. These findings are in accordance with the investigation of Nagao and Sata [29]. Reduced serum concentration of albumin predicts poor hepatic activity.

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The well-established reason behind a reduced albumin is chronic hepatic injury manifested by cirrhosis. The deranged serum albumin concentration indicates the onset of liver cirrhosis and huge liver damage. In hepatic cirrhosis condition, serum albumin level might be below 3.5 g/dL. Moreover, reduced concentration of albumin van result in ascites and edema in hepatitis C patients [30]. Our investigation has depicted an increase in bilirubin in hepatitis C patients in comparison to controls. The findings of Ashraf-uz-Zaman *et al.*, [31] and Anand and Velez [32] documented similar trends of fluctuations in serum bilirubin levels of hepatitis C patients. In this study, the concentration of AST was raised in HCV subjects, however, it does not establish the diagnosis of hepatic ailment as documented by Hajarizadeh *et al.*, [33]. It is well known fact that AST is generally present in major tissues including heart, liver parenchyma, brain, kidney and muscles. Hence, it can easily seep in serum when any of these organs are damaged [34]. In this study the concentration of ALT in hepatitis-C subjects was documented pronouncedly high than the controls. These findings are in accordance with the research of Hajarizadeh *et al.*, [35]. In that investigation it was interpreted that, high ALT levels were associated with the presence of HCV virus in serum, especially in intense of hepatitis patients, which could be related with up-regulation of inflammatory cytokines and chemokines. Biosynthesis of ALT occurs in liver cells from there it is delivered into the systemic circulation due to hepatic injury. Additionally, elevated ALT concentration is characteristic of hepatocellular injury and is used as a marker of hepatic damage. Few investigations have established that raised ALT is a prominent indicator of liver fibrosis in HCV infection regardless of HCV RNA levels [33]. In our study, the GGT level was prominently raised in hepatitis-C patients as compared to control. These finding are in agreement with the results of Thamer *et al.*, [36] who established that raised serum GGT is attributed with manifestation of metabolic disorder ultimately leading to cardiovascular events and chronic hepatic malfunctioning. Moreover, raised serum GGT levels indicate presence of bile duct soreness in subjects with HCV infection [37]. As far as blood sugar level is concerned our study documented prominently high glucose levels in infected individuals as compared to control. These results found connection with the findings of Asaduzzaman *et al.*, [38] who presented that HCV affect glucose metabolism through setting off a response against the β-cell of islet that prompts diabetes. The relationship among hepatitis C disease and diabetes have been validated by various investigations in the previous twenty years. In the current study, there was non-significant elevation of creatinine as compared to controls. These findings are in accordance with the work of Dalrymple *et al.*, [39]. Their investigation found that HCV infection was related with a greater incidence of renal disorder characterized by a serum creatinine ≥1.5 mg/dL. Moreover, the chances of renal inefficiency were 40% more noticed among subjects having positive HCV test as compared to the individuals presenting negative test. This study witnessed that hepatitis-C patients have significant elevation in ALP levels. These findings are in consistent with the study of Ijaz *et al.*, [40]. They explained that the higher level of alkaline phosphate suggests that there are chances of liver metastasis, extra-hepatic bile obstruction, cirrhosis and liver inflammation. Higher value of ALP may be an indication of advanced disease progression. A few investigations have indicated that treatment of chronic HCV infection can improve the capacity of influenced organs, hence, reducing the chances of mortality. Moreover, patients with significant HCV signs need to have interferon-free treatment (IFN). Additionally, remedial improvements in the handling of HCV can possibly wipe out or improve HCV extrahepatic alterations in these subjects [22]. Increased glucose level in blood of hepatitis C patients is the main cause of diabetes. Similarly, higher amount of urea, creatinine, albumin, and alkaline phosphate show that kidney is not properly working. The variations of these parameters are the source of renal illnesses which is the prime reason of renal failure in hepatitis C patients. Similarly, uneven concentrations of ALT, AST, bilirubin and GGT may interrupt the normal functioning of liver. As a result, different types of hepatic diseases may occur in hepatitis-C patients.

CONCLUSIONS

The outcomes of these fluctuations suggest that HCV not only affect liver which is the main infection site of hepatitis C virus, but also this virus affect different organs of diseased persons and alter the normal efficiency of these organ.

Authors Contribution

Conceptualization: NR
Methodology: AUR, UJ, MAI
Formal Analysis: MHN, MAI
Writing-review and editing: KM, UJ, NR

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

Conflicts of Interest

The authors declare no conflict of interest.

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