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Association of Low Serum Ferritin Levels with Melasma: A Case-Control Study at a Tertiary Care Hospital

Raheel Tahir[1], Muhammad Khurram Shahzad[2*], Aliya Akhtar[1], Sadaf Badar[1] and Chamman Farooq[1]

[1]Department of Dermatology, Nishtar Medical University, Multan, Pakistan
[2]Department of Dermatology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan

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***Corresponding Author:**
Muhammad Khurram Shahzad
Department of Dermatology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan
dr.khuram178@gmail.com

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ABSTRACT

Melasma is a common acquired hyperpigmentation disorder with multifactorial etiology, including hormonal influences, genetic predisposition, and environmental factors. Yet the relationship between serum ferritin levels and melasma remains unclear. **Objective:** To determine the association between low serum ferritin levels and melasma among patients presenting at a tertiary care hospital. **Methods:** This case-control study was conducted in the Department of Dermatology, Nishtar Hospital, Multan, from June 3, 2024, to December 2, 2024. A total of 114 participants were included, with 57 melasma cases and 57 age- and gender-matched controls. Serum ferritin levels were measured and compared between groups. Data were analyzed using SPSS version 23.0, with odds ratios (ORs) and p-values were calculated. **Results:** The mean age of participants was 24.67 ± 5.27 years and the mean BMI was 24.22 ± 2.17 kg/m^2. Low serum ferritin levels were significantly associated with melasma (p=0.002, OR=5.20). The association was stronger in males (p=0.002, OR=24.00), but not statistically significant in females (p=0.142, OR=2.81). Among participants with Fitzpatrick Skin Type III, the association was significant (p=0.001, OR=19.50), but not in those with Skin Type IV (p=0.490). A significant association was also observed in individuals older than 30 years (p=0.015, OR=2.66), and in non-obese participants (p=0.003, OR=4.85). **Conclusions:** This study demonstrates a strong association between low serum ferritin levels and melasma, particularly in male and individuals with Fitzpatrick Skin Type III, suggesting that iron storage depletion may play a role in melasma pathogenesis. Future studies should explore whether iron supplementation influences melasma severity or treatment outcomes.

INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder that primarily affects the face and carries a significant psychosocial impact. It is more prevalent in women and is influenced by multiple factors, including genetic predisposition, ultraviolet (UV) radiation, hormonal fluctuations, and oxidative stress [1]. Beyond these established causes, recent studies have explored the possible involvement of iron metabolism, particularly serum ferritin levels, in the pathogenesis of melasma [2, 3]. Ferritin, the primary intracellular iron-storage protein, is involved in regulating oxidative stress, inflammatory pathways, and melanogenesis [4]. Since iron is a cofactor for enzymes like tyrosinase, crucial in melanin biosynthesis, iron deficiency may impair normal pigment regulation [5]. Moreover, reduced serum ferritin levels may contribute to increased oxidative stress and inflammatory responses, both of which have been implicated in the development and exacerbation of melasma [6, 7]. A study evaluated the link between serum ferritin and melasma. For instance, some researchers have reported significantly lower serum ferritin, iron, and transferrin saturation levels in female melasma patients compared to healthy controls, which may indicate a potential role of iron storage depletion in melasma pathophysiology [8]. Another study found an inverse correlation between serum ferritin levels and melasma severity as assessed by the Melasma Area

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and Severity Index (MASI) [9]. However, not all evidence supports this association; some studies found no significant relationship, underscoring the need for further investigation [10]. The idea of correcting iron deficiency as an adjunct to standard melasma treatment has also been proposed. While a few reports suggest clinical improvement following iron supplementation, robust evidence from randomized controlled trials is still lacking [11–13].

Despite increasing interest in the role of iron metabolism in dermatological disorders, evidence regarding the association between serum ferritin levels and melasma remains inconsistent and limited, particularly in the Pakistani population. Most previous studies have focused on serum iron or anemia rather than ferritin as a marker of iron storage, and subgroup analyses based on gender, age, or skin type are scarce. This lack of localized and stratified data limits a clear understanding of whether iron depletion independently contributes to melasma pathogenesis. Therefore, further investigation is required to clarify this association in our setting. This study aims to investigate the association between low serum ferritin levels and melasma among patients presenting to a tertiary care hospital. By comparing ferritin levels between melasma patients and matched controls, we seek to clarify whether iron deficiency may play a contributory role in melasma development.

METHODS

This case-control study was conducted in the Department of Dermatology, Nishtar Hospital, Multan, from June 3, 2024, to December 2, 2024. A total of 114 patients were included in the study, with 57 cases (patients with melasma) and 57 controls (healthy individuals without melasma). The sample size was determined using EPI-Info software based on a melasma prevalence of 33% in cases and 9.8% in controls, with a 95% confidence interval [14]. The sampling technique employed was non-probability consecutive sampling. Written informed consent was taken from all the patients. The inclusion criteria for cases comprised male and female patients aged 18 to 45 years, having Fitzpatrick skin types III, IV, or V, and diagnosed with melasma for more than six months. The controls were also selected from both genders, aged 18 to 45 years, and having Fitzpatrick skin types III, IV, or V. Patients were excluded if they had been under melasma treatment within the last month, had a history of hirsutism or menstrual dysfunction, were pregnant, had Hepatitis C, or were using oral contraceptives. The study was approved by the institutional ethical committee, as shown by the reference number 7062. The subjects who met the inclusion criteria were selected from the outpatient department (OPD) of the Dermatology Department. All participants gave informed consent, and their anonymity was ensured. They were informed that the study posed no potential risks. Some of the control factors, including age, obesity, and skin type, were measured. All participants were requested to provide 3 ml of venous blood in a sterile tube for serum ferritin level determination, conducted in the hospital laboratory. The information was recorded in a pre-designed proforma. SPSS version 23.0 was used to analyze the data. Continuous variables such as age, serum ferritin levels, and BMI were summarized using mean and standard deviation. Categorical variables such as gender, obesity, skin type, and ferritin status were presented as frequencies and percentages. The odds ratios (OR) for the association between low serum ferritin levels and melasma were calculated, with values greater than 1 considered significant. Age, gender, skin type, and obesity were controlled as potential confounding factors through stratification. Ferritin levels were also analyzed after adjustment of ORs with post-stratification.

RESULTS

This study included a total of 114 participants, with a mean age of 24.67 ± 5.27 years and a mean body mass index (BMI) of 24.22 ± 2.17. The study demonstrates the association between low serum ferritin levels and melasma. Among the 57 melasma cases, 19 (33.3%) had low serum ferritin levels, compared to only 5 (8.8%) in the control group. In contrast, 38 (66.7%) melasma cases and 52 (91.2%) controls had normal ferritin levels. A statistically significant association was found between low serum ferritin levels and melasma (p=0.002). The odds ratio (5.20) indicates that individuals with low serum ferritin levels are approximately 5 times more likely to have melasma compared to those with normal ferritin levels (Table 1).

Table 1: Association of Low Serum Ferritin Levels with Melasma among Study Participants (n=114)

Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Yes (n=24, 21.1%)	19 (33.3%)	5 (8.8%)	5.20	0.002
No (n=90, 78.9%)	38 (66.7%)	52 (91.2%)		
Total	57 (100%)	57 (100%)		

This study presents the stratification of gender concerning low serum ferritin levels. Among male participants (n=32), 9 (28.1%) cases and only 1 (3.1%) control had low serum ferritin levels, with a statistically significant odds ratio of 24.00 (p=0.002). This finding suggests that males with low serum ferritin levels are 24 times more likely to develop melasma compared to those with normal ferritin levels. Conversely, among female participants (n=82), 10 (12.2%) cases and 4 (4.9%) controls had low serum ferritin levels, yielding an odds ratio of 2.81 (p=0.142), which was not statistically significant. These findings indicate that low serum ferritin levels are significantly associated with

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melasma in male but not in female. Results illustrate the stratification of age concerning low serum ferritin levels and melasma. Among participants up to 30 years old (n=92), 13 (14.1%) cases and 5 (5.4%) controls had low serum ferritin levels, with an odds ratio of 3.41 (p=0.036), indicating a statistically significant association. Among participants older than 30 years (n=22), 6 (27.3%) cases and 0 (0%) controls had low serum ferritin levels, with an odds ratio of 2.66 (p=0.015), which was also statistically significant. These findings suggest that low serum ferritin levels are significantly associated with melasma across different age groups, with a stronger association in individuals older than 30 years (Table 2).

Table 2: Stratification by Gender and Age

Variables	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Gender					
Male (n=32)	Yes (n=10)	09 (28.1%)	01 (3.1%)	24.00	0.002
	No (n=22)	06 (18.8%)	16 (50.0%)		
Female (n=82)	Yes (n=14)	10 (12.2%)	04 (4.9%)	2.81	0.142
	No (n=68)	32 (39.0%)	36 (43.9%)		
Age Group					
Up to 30 Years (n=92)	Yes (n=18)	13 (14.1%)	5 (5.4%)	3.41	0.036
	No (n=74)	32 (34.8%)	42 (45.7%)		
More than 30 Years (n=22)	Yes (n=6)	6 (27.3%)	0 (0%)	2.66	0.015
	No (n=16)	6 (27.3%)	10 (45.4%)		

The findings present the stratification of skin type concerning low serum ferritin levels. Among participants with Fitzpatrick Skin Type III (n=64), 13 (20.3%) cases and 1 (1.6%) control had low serum ferritin levels, yielding a statistically significant odds ratio of 19.50 (p=0.001). This suggests that individuals with Skin Type III and low serum ferritin levels are 19.5 times more likely to have melasma than those with normal ferritin levels. In contrast, among participants with Fitzpatrick Skin Type IV (n=50), 6 (12.0%) cases and 4 (8.0%) controls had low serum ferritin levels, with an odds ratio of 1.83 (p=0.490), which was not statistically significant. These findings indicate that low serum ferritin levels are strongly associated with melasma in individuals with Skin Type III but not in those with Skin Type IV (Table 3).

Table 3: Stratification Concerning Skin Type

Skin Type	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Type III (n=64)	Yes (n=14)	13 (20.3%)	1 (1.6%)	19.50	0.001
	No (n=50)	20 (31.2%)	30 (46.9%)		
Type IV (n=50)	Yes (n=10)	6 (12.0%)	4 (8.0%)	1.83	0.490
	No (n=40)	18 (36.0%)	22 (44.0%)		

The findings present the stratification of obesity concerning low serum ferritin levels. Among obese participants (n=7), 2 (28.6%) cases had low serum ferritin levels, whereas none of the controls had low levels. The odds ratio of 1.66 (p = 0.290) suggests no statistically significant association between obesity and low serum ferritin levels in melasma cases. Among non-obese participants (n=107), 17 (15.9%) cases and 5 (4.7%) controls had low serum ferritin levels, with a statistically significant odds ratio of 4.85 (p = 0.003). These findings indicate that low serum ferritin levels are significantly associated with melasma in non-obese individuals, but not in obese individuals (Table 4).

Table 4: Stratification Concerning Obesity

Obesity	Low Serum Ferritin Levels	Cases	Controls	Odds Ratio	p-Value
Yes (n=7)	Yes (n=2)	2 (28.6%)	0 (0%)	1.66	0.290
	No (n=5)	3 (42.9%)	2 (28.6%)		
No (n=107)	Yes (n=22)	17 (15.9%)	5 (4.7%)	4.85	0.003
	No (n=85)	35 (32.7%)	50 (46.7%)		

DISCUSSION

This case-control study demonstrated a significant association between low serum ferritin levels and melasma. Participants with low ferritin were approximately five times more likely to have melasma (OR=5.20, p=0.002). This association was particularly marked in males (OR=24.00, p=0.002) but not statistically significant in female (OR=2.81, p=0.142). Stratified analysis further revealed significant associations among individuals over 30 years of age, non-obese individuals, and those with Fitzpatrick Skin Type III. These findings suggest that iron storage depletion may contribute to the pathogenesis of melasma, especially in certain subgroups. Our findings are in line with several previous studies. For instance, Goodarzi *et al.*, reported significantly lower serum ferritin and iron levels among melasma patients, supporting the link between iron metabolism and pigmentation disorders [14]. Similarly, Qazi *et al.*, observed an inverse correlation between serum ferritin and melasma severity, reinforcing the idea that diminished iron stores may exacerbate pigmentation [15]. However, contrasting evidence exists. Deshpande *et al.*, did not find a significant association between serum ferritin and melasma, and Behrangi et al., reported lower iron levels in melasma patients without statistical significance [16, 17]. Such discrepancies may reflect differences in sample sizes, ethnic backgrounds, sun exposure patterns, hormonal status, or dietary iron intake. Thus, while there is growing support for an association between iron deficiency and melasma, larger multicenter studies are needed to clarify these relationships. Prakash *et al.*, also found deranged iron profiles, including reduced ferritin levels, in 100% of melasma cases studied [18]. These results support the hypothesis that impaired iron storage could contribute to melasma development. Biologically, iron is a key cofactor for tyrosinase, the enzyme responsible for melanin

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production. Iron deficiency may impair tyrosinase activity, leading to altered melanogenesis and pigmentation abnormalities [19]. Furthermore, iron depletion increases oxidative stress by elevating reactive oxygen species (ROS), which can stimulate melanocyte activity and lead to hyperpigmentation [20]. Ferritin serves as a long-term storage form of iron, and its depletion can be an early marker of subclinical iron deficiency. Therefore, low ferritin levels may influence pigmentation even before serum iron levels drop [21]. An interesting aspect of our study is the significant association seen in males but not in female. This is consistent with the findings of Kiayani *et al.,* who found no link between iron deficiency anemia and melasma in women [21]. One possible explanation is that women, due to regular menstrual blood loss, are more physiologically adapted to lower iron levels. In men, however, a sudden or significant drop in iron stores may have a more noticeable effect on melanocyte function and pigmentation.

This study has certain limitations, including its single-center design, relatively small sample size, and use of non-probability sampling, which may limit generalizability. Additionally, serum ferritin was assessed at a single time point without evaluating other iron profile parameters or inflammatory markers that may influence ferritin levels. Future multicenter studies with larger cohorts, comprehensive iron profiling, and longitudinal follow-up are recommended to better elucidate causal relationships and to determine whether iron supplementation may improve melasma severity or treatment outcomes.

CONCLUSIONS

This study found a significant association between low serum ferritin levels and melasma, particularly in males, individuals older than 30 years, non-obese participants, and those with Fitzpatrick Skin Type III, suggesting that iron storage depletion may contribute to melasma pathogenesis. While previous studies have primarily focused on serum iron levels, our findings highlight the importance of ferritin as a long-term marker of iron status and its potential role in skin pigmentation regulation. The observed gender- and age-based differences indicate that iron metabolism may affect melasma development differently across populations, warranting further investigation. Given the potential role of iron deficiency in melasma, assessing serum ferritin levels in affected individuals could serve as a useful diagnostic and therapeutic consideration.

Authors' Contribution

Conceptualization: RT, MKS
Methodology: RT, MKS, AA, SB, CF
Formal analysis: RT, MKS, AA, SB, CF
Writing and Drafting: AA, SB, CF
Review and Editing: AA, SB, CF, RT, MKS

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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