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Evaluating the Role of Thyroid Stimulating Hormone and Ferritin Levels with Hair Loss among Patients with COVID-19: Case-Control Study

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Abstract:

Background: The emergence of COVID-19 has led to many clinical manifestations, including post-infection hair loss. The objective of this study is to investigate the association between thyroid function, iron levels, and the probability of hair loss after COVID-19 infection.

Materials and Methods: 100 female patients who recovered from COVID-19 participated in a cross-sectional case-control research. Utilizing cutting-edge immunoassay technology, thyroid-stimulating hormone (TSH) and ferritin levels were evaluated biochemically. Through the use of a standardized questionnaire, information on the patient's demographics, hair loss duration, and chronic illnesses was gathered.

Results: TSH levels were significantly different between patients with hair loss and controls ($p < 0.001$), suggesting a possible link between high TSH and post-COVID-19 hair loss. On the other hand, ferritin levels between the two groups did not differ significantly ($p = 0.492$). TSH was identified as a viable predictor for hair loss patients by ROC-curve analysis (AUC = 0.737, sensitivity = 84%, specificity = 46%), although ferritin had only a little ability to predict hair loss (AUC = 0.519).

Conclusion: This study indicates that thyroid function may play a role in hair loss after COVID-19 infection by showing a possible correlation between higher TSH levels and hair loss. However, ferritin levels did not exhibit a significant correlation, highlighting the need for additional study to fully comprehend the underlying mechanisms.

Keywords: COVID-19, TSH, Ferritin, alopecia areata, androgenic alopecia, hair loss.

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Introduction

In Wuhan, China, in December 2019, an unidentified pneumonia outbreak appeared. The

pneumonia-causing virus was discovered to be a brand-new coronavirus in January; it was later

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known as the illness of coronavirus disease 2019 (COVID-19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1-4).

In the first two to three months following the infection, 25% of COVID-19 cases experience acute classic telogen effluvium (TE), with women being more susceptible than men. However, less than two months after COVID-19 infection, particularly in patients with more severe COVID-19 infections, an early onset TE after COVID-19 has been seen (5).

Research is still being done to determine the relationship between COVID-19 and numerous autoimmune conditions that affect the thyroid gland and other bodily systems. In a previous investigation, three cases of autoimmune thyroid illness, including subacute thyroiditis, Graves' disease, and profound hypothyroidism, were found 6 and 8 weeks following COVID-19 infection (6).

It is generally recognized that iron deficiency anemia and hair loss are related, and people who suffer from these conditions can gain from taking an oral iron supplement. Although evidence suggests benefits, it is controversial if an iron supplement is also advantageous in cases of TE who do not have iron-deficient anemia. Serum ferritin levels in individuals with post-COVID-19 alopecia should be assessed to determine iron stores, and oral iron prescription may promote hair regrowth when blood ferritin measures fall below the reference threshold (7).

Materials and Methods :

Sample collection and study design:

This investigation was carried out in the laboratories of the Colleges of Medicine and Pharmacy-University of Babylon. There were 100 people in this cross-sectional case-control research. 500 participants with COVID-19 made up the patient group at first; 50/500 of these individuals were then chosen because they had experienced hair loss as a result of their COVID-19 infection. The control group included healthy volunteers who had previously suffered from COVID-19 but had never before experienced any abnormal hair loss during or after the illness.

The samples were collected between November 20, 2022, and May 20, 2023. Patients were collected from those who went to the outpatient clinics at Merjan Medical City and A-Imam Al-Sadiq Teaching Hospital. Specialist physicians and dermatologists made the patient diagnosis and selected the control groups based on selection criteria. The following aspects were used to approve the diagnosis of COVID-19: the patient's medical history, physical examination, radiological findings, serology, positive PCR results from the patient's archive obtained during the infection, or positive antibody (IgG, IgM) results obtained after the infection.

Any girl between the ages of 17 and 45 who has experienced hair loss following COVID-19 infection is included in the patient group. The control group included any female between the ages of 17 and 45 who had never experienced hair loss following COVID-19 infection. Any subjects who fulfilled even one of the following criteria were excluded from the study. Other well-known illnesses that might result in hair loss, besides pressure-induced alopecia areata, include chronic sickness, immunological disorders, hereditary hair loss, and known instances of hormone imbalance.

After drawing venous blood samples, the sera were subjected to biochemical testing. TSH and ferritin levels were evaluated using Fluorescence Immuno Assay Technology (FIAT) from Finicare® (China). The COVID-19 serological test (IgG, IgM) was measured using the Enzyme-Linked Immuno Sorbent Assay (ELISA) from Elabscience® (USA). Complete blood counts from whole blood were performed during the blood tests using a Fully Automated Haematology Analyzer DYMIND®-DH-36 (3 Parts).

The study questionnaire contained questions about age, height, weight, duration of post-COVID-19 hair loss, history of any chronic diseases, and medications.

Ethics approval:

All study contributors were informed and given the chance to verbally consent before being included. The study procedure, individual information, and consent form were revised and permitted by a local college and hospital ethical

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committee using the document number [IRB: 5-25,18/10/2022].

Statistical analysis

Statistical analysis was finalized using SPSS IBM, ver-24. Data distribution normality was examined using the Shapiro-Wilk tests and Kolmogorov-Smirnov. Continuous, normally distributed, data were reported as mean/SD. The Mann-Whitney-U-test and Student's t-test were applied to match the means of the groups for non-normal and normally distributed data, respectively. Partial coefficients were used in binary correlations. To

determine analytic performance and classify a patient's sickness status as positive or negative based on test results, the ROC curve was used. A 0.05 p-value was deemed statistically significant.

Results

Table 1 shows an overview of numerous factors and their associated values in a particular population. It is possible to comprehend the distribution and ranges of the variables by using the mean values, standard deviations, and minimum and maximum values observed for each variable.

Table 1: The study variables' general demographic characteristics

Variables	Total Mean \pm SD	Min - Max
Age/years	29.7 \pm 8.7	17 – 45
Age categories N0. (%)		
17 – 24	34	33.3%
25 – 35	40	39.9%
36 – 45	28	27.4%
TSH	1.88 \pm 1.1	0.11- 4.8
Ferritin	36.2 \pm 31.1	1.5-198.6
BMI (kg/m²)	25.7 \pm 3.5	19 – 35
WBCs (10³/uL)	7.3 \pm 2.2	2.5 – 13.9
Hb (10⁶/uL)	12.4 \pm 1.2	9.9 – 14.7
Platelets (10³/uL)	296.2 \pm 3.2	103 – 661
Duration/months since		
Infection	8.2 \pm 3.3	3 – 15
Hair loss	5.6 \pm 3.3	1 – 12
Hair loss after infection	2.6 \pm 1.2	1 – 7
Marital state No (%)		
Married	52	51%
Unmarried	50	50%
Menstrual regularity		
Regular	86	84.3%
Irregular	16	15.7%

Several variables are compared between patients and controls in Table 2. The mean age of the patients is younger than that of the control group. In addition to having higher TSH levels than the

controls, patients also show non-significant differences in ferritin levels between them and the controls.

Table 2: Comparison of demographic and biochemical variables between the two study groups

Variables	Patients Mean \pm SD	Control Mean \pm SD	P. Value
Age/Years	27.58 \pm 8.6	31.9 \pm 8.3	0.011
TSH	2.37 \pm 1	1.49 \pm 0.98	0.001

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Ferritin	38.296 ± 35.8	43.0 ± 25.4	0.492
BMI (kg/m²)	25.67 ± 3.2	25.8 ± 3.9	0.830

TSH and age also show non-significant associations, as do TSH and ferritin. There is little correlation between TSH and BMI. According to this study, there was a negative non-significant

correlation between ferritin and age and ferritin and BM, as well as a positive significant association between age and BMI ($r=0.309$ and $p=0.002$), Table 3.

Table 3: Correlations among the variables of the study

Variable	Age	TSH	Ferritin
Age			
TSH	$r=-0.015$ $P=0.884$		
Ferritin	$r=0.106$ $P=0.291$	$r=0.084$ $P=0.403$	
BMI	$r=0.309$ $P=0.002$	$r=0.084$ $P=0.399$	$r=0.096$ $P=0.337$

Analysis of the research operation's character demonstrated that TSH can distinguish between COVID-19 patients who have hair loss and those

who do not. The capacity of ferritin to distinguish between COVID-19 patients with and without hair loss was found to be poorly predictive.

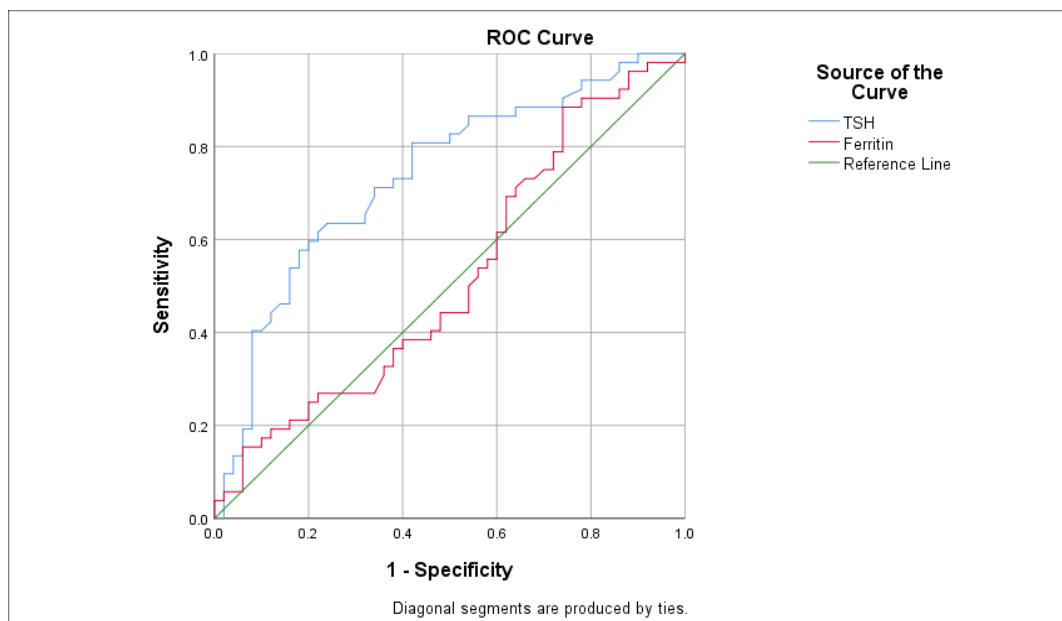


Figure 4: ROC-curve analyses of TSH and ferritin to predict patients with hair loss from those without hair loss

Table 4: ROC-curve analyses of TSH and ferritin to predict patients with hair loss from those without hair loss

Variable	AUC	Sensitivity	Specificity	P-Value	95% CI
TSH	0.737	84%	46%	0.001	0.640-0.834
Ferritin	0.519	60%	40%	0.735	0.406-0.633

Discussion:

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In this study, the effects of TSH, ferritin, and hair loss were estimated in women with COVID-19 in the province of Babylon. The primary findings of this study were high TSH levels in patients and non-significant variations in ferritin levels between patients and controls.

According to a current study, long-lasting COVID-19 features include malaise, headache, hair loss, dysosmia/dysgeusia, dyspnea, and insomnia. It is noteworthy that cortisol levels and FT4 are strongly linked with the manifestation. Additionally, patients with generalized fatigue had lower plasma GH and higher serum FT4 concentrations. Additionally, cases with relatively high levels of circulatory antibodies revealed lower ratios of FT4/TSH and ACTH/cortisol, indicating the possibility of reduced ACTH response and a latent state of hypothyroid. Prolonged COVID-19 with initially severe manifestations were also more likely to develop hypothyroidism (8).

Another study displayed that in 98.1% of cases, the TSH concentration was within normal ranges, while it declined in one (1.8%) patient. In one healthy person, the TSH concentration was lower, while in one healthy person, it was higher. Within the control group, 96.4% of healthy people had normal blood TSH measures ($p = 0.56$) (9).

Human hair follicle activities such as anagen extension and promotion of both proliferation of hair keratinocytes and hair color are directly impacted by thyroid hormones, which have a substantial impact on hair growth (10). The growth cycle can be altered by hypothyroidism without causing inflammation (prolongation of the telogen phase) (11). As a result, hypothyroid and hyperthyroid individuals have hair loss and changes in texture and color (12).

Given that TSH is necessary for follicular development and maintenance, alopecia may be a symptom of a thyroid condition (1). There are various levels of approaches to the thyroid gland panel for hair loss. One way to categorize the function of TSH at the skin's level is according to their paracrine, endocrine, and autocrine functions. Instead, gonadal status and related pathologies to thyroid disorders themselves, such as insulin resistance, androgen concentrations, metabolic issues, vitamin D deficiency, etc., in

addition to the link with autoimmune thyroid disease, may contribute to the development of alopecia (13). A growing level of interest in vitamin D's broad-spectrum immunoregulatory role has lately surfaced (14-19).

The hypothalamic pituitary thyroid axis, which regulates numerous metabolic pathways, has a significant impact on human skin, particularly the hair follicles. The hypothalamus releases thyrotropin-releasing hormone (TRH, thyroliberin), which stimulates the hypophysial gland to release thyroid-stimulating hormone (TSH). The thyroid gland then secretes the thyroid hormones triiodothyronine (T3) and thyroxine (T4) as a result of the TSH effect. Human hair follicles are among the peripheral tissues where circulating T4 mostly activates after deionizing to T3. Thyroid hormones are crucial in controlling skin function because they directly increase gene expression by acting on nuclear receptors. Thyroid hormones, TSH (anterior pituitary gland product), and even TRH, (hypothalamus product), all have specific receptors in skin cells. The nipple and the hair root outer sheath may both contain thyroid hormone receptors (20).

A few weeks following COVID-19's clinical manifestation, the hair loss symptom started to appear. According to Di Landro et al. findings, all patients' vitamin B12, ferritin, iron, and thyroid function results were within the normal range. However, hair thinning and hair loss were their main complaints (13). As a result, it is consistent with the theory that the post-COVID-19 problem is connected to the dermatologic manifestation (21)

In contrast to prior research, no significant alteration in blood ferritin levels between female COVID cases and the healthy controls was found. According to a Turkish study, patients had mean blood ferritin levels between 14.72 and 25.30 ng/ml while healthy individuals had levels between 10.70 and 204 ng/ml ($p = 0.001$). 43 (79.5%) people had normal serum ferritin levels, while 11 (20.4%) patients had levels that were dropping (22).

Serum ferritin had a cut-off value of 40 ng/mL for the diagnosis of iron deficiency, with a specificity and sensitivity of 98% (23-25). In the present study, healthy individuals' mean blood ferritin

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levels were 45.55 ng/mL, which ruled out menstruation as the source of TE occurrence. The optimal cut-off value for patients with TE was 24.5ng/mL, which was substantially less than the levels of the control participants. The average ferritin level in these patients was 24.27ng/mL. One cause of TE is the source of iron consumption, which has decreased as a result of the development of the vegetarian régime for weight loss. However, a lot of other things, such as high-dose contraceptives, anticonvulsants, anticoagulants, etc., also have an impact on the hair follicle cycle. Previous research has shown that serum ferritin, with a sensitivity and specificity of 64.2% and 73.8%, might be employed as a biomarker for the diagnosis of TE. Serum ferritin had a specificity and sensitivity of 59.6% and 64.2% once used to distinguish between AGA and TE suggesting that additional biomarkers may be required to increase the diagnostic utility of this method (26).

It deserves to be cited that the complex phenomenon known as hyper-ferritinemic syndrome, which was observed in a prior study, may promote cellular death. The occurrence of metabolic iron disarray in COVID-19 infection might not only be due to direct and indirect metabolic stimulation by virus infection but also secondary to hemoprotein digestion with subsequent iron cell leakage (27).

Recent research indicates that the viral-induced rise in cytokines like IL-6 and IL-1 β coincided with an increase in serum ferritin levels in response to inflammation (28). This is probably because these molecules stimulate the production of hepcidin, a protein that regulates the influx of iron into the bloodstream in mammals. It's interesting to note that current research claims SARS-CoV2 possesses intrinsic hepcidin-mimetic activity that worsens hyperferritinemia (29).

Serum ferritin is a sign of inflammation as well as a measure of the body's iron reserves (23-25). The degree of the infection coincides with hyperferritinemia brought on by severe inflammation. It is a biomarker that allows us to assess how well the infection is responding to therapy. Death rates are linked to high ferritin levels. The serum ferritin level, which is cited as a separate risk factor in evaluating the severity of

the disease, is shown in another study to have a negative link with thyroid function tests, and the drop in fT4 and fT3 levels gets more pronounced as the disease severity grows (30).

As the severity of the disease develops, the drop in fT4 and fT3 levels becomes more pronounced, as seen in our study, where thyroid function tests exhibit a negative connection with serum ferritin levels, which are considered to be independent risk factors (31).

The findings of the present study demonstrated a significant correlation between age and the incidence of hair loss following COVID-19. According to a similar study, the majority of people with hair loss (36.9%) were between the ages of 36 and 45. 49.6% of those with hair loss were between the ages of 15 and 25. Meanwhile, Individuals 45 and older experienced significantly less hair loss than individuals in other age groups as described by other academics (32). A rigorous meta-analysis of several studies found that after COVID-19, 80% of the population, aged 17 to 87, had long-lasting effects. Because COVID-19 infections in children are less common and their symptoms are milder than those in adults with COVID-19, the majority of cases of hair loss occur in adults (33).

Hair density begins to decrease after peaking at 27 years old or before. An observer cannot perceive hair loss until there is less than 250/Cm² of hair, according to research. This discrepancy between one's experience of hair loss and their actual hair density implies that perception is impacted by factors other than hair density. Up until around age 30, hair diameters increase, and then they begin to decrease. The hair density is comparable to this. Studies have shown that low hair density was related to a larger reduction in large-diameter hair when compared to hairs of other diameters (34).

In a study on the relationship between androgenic alopecia (AGA) and BMI in Turkey, 12% of males and 20% of females were obese, while 38% of women and 46% of men were overweight. BMI was not substantially different across groups in this study, and the change in BMI had no impact on hair loss following COVID-19. However, neither gender's AGA frequency nor severity was correlated with BMI (35). AGA and BMI were

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only linked in one of the four preceding case-control research (36). As well, Another study that included 100 healthy controls and 116 males with AGA indicated that the patient's BMI was higher than that of the control group (36). Furthermore, it is widely acknowledged that obesity plays a role in immunoregulation (37).

Although these signs may vary as the disease progresses, investigations have shown that the study's hematological results were equivalent to normal or slightly reduced WBCs in the early stages of COVID-19 disease when persons do not exhibit characteristic symptoms. 68.1% of the 140 COVID-19 patients studied by Zhang et al. who were hospitalized had leukocyte counts that were within normal ranges, 12.3% had increased, and 19.6% had decreased (38). Dermatologists in Karbala found 30 samples of patients with hair loss similarly; the same findings were also found in 10 samples of healthy individuals used as controls (39). Recent research on mice revealed that certain macrophages, a type of white blood cell, can direct skin cells to develop hair. Anti-inflammatory medication administration to mice has an impact on their hair development, according to research. Researchers were able to get the macrophages to become active again and develop hair by medicating them (39).

New animal research suggests that certain macrophages, a subtype of white blood cell, can instruct skin cells to grow hair. Anti-inflammatory medicine administration in mice was shown to affect hair growth. By medicating the macrophages, researchers were able to induce hair growth in the cells (40). In contrast, 38% of the patients had hemoglobin levels that were lower than what Huang et al. had found. In contrast, 38% of the patients had hemoglobin levels that were lower than what Huang et al. had found (41).

Haemoglobin is discovered to be affected by COVID-19 in the bone marrow and erythrocytes. Furthermore, research has found enhanced RDW in COVID-19 patients, which suggests primary erythroid myelodysplasia because RDW was higher at the time of immature cell production (42). Viral endocytosis results from the virus's interaction with erythrocytes and/or blood cell precursors via ACE2, CD147, CD26, and other receptors. Therefore, the virus would target the

heme on the hemoglobin's 1-beta chain, resulting in hemolysis and the formation of a combination with the freed heme that would produce a large amount of defective hemoglobin (43).

The platelet count is a vital criterion in many classifications that assess the severity of an illness, like in the case of multi-organ dysfunction syndrome (44). Thrombocytopenia, a symptom of consumption coagulopathy in the presence of COVID-19 infection, is correlated with the severity of the sickness. According to research on SARS and MERS infection, it is present in roughly 60% of severe cases (45).

Only a tiny number of study participants had irregular periods; the majority had regular menstrual cycles. The proportion of married individuals was over half. An investigation carried out in Jordan and Iraq revealed a connection between menstrual irregularities and COVID-19 infection. Nearly half of the women's menstrual cycles changed after contracting COVID-19, either in the number of days between cycles, the amount of bloodshed, or the length of the menses. Stress, depression, and other mental diseases can frequently alter these fluctuations in the menstrual cycle. These changes are acknowledged as chronic COVID-19 infection symptoms (46).

As the medical community continues to unravel the multifaceted effects of COVID-19 on various physiological systems, this study contributes to the growing body of knowledge that can guide medical professionals in addressing the unique challenges posed by post-infection symptoms. Further research, larger sample sizes, and more extensive investigations are required to comprehensively understand the interplay between COVID-19, thyroid function, and hair loss, ultimately leading to better preventive and treatment strategies for those affected by this novel health concern.

Conclusion

The findings suggest that high TSH levels may play a role in hair loss following COVID-19 infection, highlighting the importance of thyroid function in maintaining healthy hair growth. However, the study did not find a significant association between ferritin levels and hair loss, indicating that the connection between iron levels

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and post-COVID-19 hair loss might be more complex than initially thought. Additionally, the study emphasizes the need for continuous monitoring of thyroid function and ferritin levels in individuals recovering from COVID-19 to identify potential risk factors for post-infection hair loss.

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