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ORIGINAL ARTICLE

Study the Effect of Inflammatory Cytokines on Hair Loss

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ABSTRACT

Background: *Hair loss, a frequently reported problem, severely impacts the quality of life of patients; diffuse hair loss (DHL) is nonscarring reversible hair that falls out all over the scalp and is distressing to patients and affects both females and males at any age; Most of the time, the reason for hair loss is unclear, several studies have shown cytokine causes inflammation in the hair follicles promotes the shift from the growth phase to the resting phase and has been linked to the advancement of hair loss.* ***Objectives:*** *We aimed to assess the association between inflammation and diffuse hair loss by measuring inflammatory cytokines IL-6 and TNF-α in DHL and healthy controls.* ***Methodology:*** *Serum concentrations of IL-6 and TNF- α were evaluated in 96 patients with DHL and 53 healthy controls aged between 16-42 years.* ***Results:*** *Patients with diffuse hair loss showed considerably higher blood concentrations of IL-6 and TNF-α compared to healthy controls. (mean IL-6: 20.339±2.893 vs 18.122±4.395 pg/ml p value=0.001*; TNF-α: 48.902±12.987 vs 25.616±7.083 pg/ml p value=0.001*). There were significant positive correlations between serum IL-6, TNF-α, and diffuse hair loss.* ***Conclusion:*** *Our study shows a statistically significant positive with a role of immune system activation in DHL pathogenesis.*

INTRODUCTION

Human hair, a significant aspect of the human body, reflects one's appearance and uniqueness. It is often associated with youth, beauty, good health, and success. The diversity of human hair is influenced by genetics, demographics, hair grooming, and sociocultural practices[1,2]. Hair is a filamentous biomaterial derived from follicles in the dermis, composed of 65-95% keratin proteins, the remainder being water, lipids, pigments, and trace elements[3]. Hair is a byproduct of the epidermis and consists of two unique structures: the follicle in the dermis layer of the skin and visible hair shafts on the body surface[4]. Scalp hair undergoes cyclical growth, with each follicle going through 10-30 cycles throughout its lifespan[5].

Hair growth is a continuous process with four phases: (the growth phase, which can last from 2 to 8 years), catagen (the regression phase, often lasting 4 to 6 weeks), and telogen (the resting period, which normally lasts 2 to 3 months). Exogen, the process of shedding dead hair, occurs during the final phase of the telogen period[5,6]. The average person has over 100,000 hairs on their scalp, with 10% to 15% in the telogen phase. After telogen, hair is released and shed, and the next cycle begins. It is common to lose up to 100 telogen hairs daily. Hair loss is not noticeable due to the simultaneous growth of new hair, as hair follicles are the most rapidly developing tissue in the human body[6-8].

As hair covers the scalp, strong and dense hair is associated with beauty and has psychological importance in our society. The most common hair disorder is termed alopecia[2]. There are three main kinds of hair loss: non-cicatricial (possibly reversible), irreversible Cicatricial, and due to hair shaft abnormalities[9]. Diffuse hair loss (DHL) is a nonscarring, reversible hair loss that affects both males and females of any age. It is characterized by consistent and uniform hair loss across the entire scalp[6], often resulting in an increase in hair found on pillows, brushes, or shower drains. However, females have a higher incidence rate due to their tendency to be more distressed by hair shedding and thus require more medical attention[10].

Telogen effluvium is a common form of diffuse hair loss, categorized as acute or chronic. Acute telogen effluvium (ATE) involves continuous hair shedding for less than six months, while chronic telogen effluvium (CTE) lasts for more than six months[11]. Anagen effluvium is less common and associated with chemotherapy radiation and pesticides[12]. Diffuse hair loss occurs when there is a disturbance in one phase of the hair cycle, leading to shedding more than 200 hairs daily. Patients may notice a decline in hair volume after hair density decreases by 30% to 50%[6,9,13]. Physiological stressful events, Chronic diseases, chronic disorders of the thyroid, chronic malnutrition and chronic anemias can all trigger diffuse hair fall[13,14].

Hair follicles are immune-privileged structures, including the hair matrix and the bulge region, which protects hair stem cells. They generate and maintain an interfollicular plexus (IP) to isolate harmful substances in anagen phases, but disappear during regression and telogen phases[4,15]. The hair bulb's ability to evade immune system reactions against self-keratinocyte and melanocyte peptides is due to a variety of factors[16,17]. Hair follicle collapse can be explained by abnormalities or failures of the immune system[4]. Cytokines, soluble proteins secreted by immune cells, play a crucial role in regulating cell functions. Epithelial cells produce pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)[18], the abnormal release of TNF-α and IL-6 cytokines has a role in the pathophysiology of various diseases in the human body like hair loss[19,20].

This cytokine causes inflammation in hair follicles, promoting the transition from growth to the resting phase and contributing to hair loss. It influences various types of hair loss, including stress-induced hair loss, Alopecia areata, and male- and female-pattern hair loss. Each type has a reduced ratio of anagen to telogen. Chronic, systemic inflammatory diseases can lead to telogen effluvium, characterized by the premature transition from anagen to telogen phase[5,11]. The purpose of this study is to look at the effect of inflammatory cytokines on diffuse hair loss patients by measuring the levels of TNF-α and IL-6 markers in diffuse hair loss patients and healthy control.

METHODOLOGY

Sampling & Data collection

This study was A case-control study carried out at the Privet Dermatology Clinic of Doctor Firas Fakhir Altameemi at AL Basra City, Iraq. The research was carried out between November 2023 and April 2024. The current research comprised a case-control study involving 149 samples: (96) patient samples suffered more than 6 months of diffuse non-scarring hair loss (50 females and 46 males) with ages between 16-42, mean of age was (27.145±7.572) and (53) healthy control samples. (26 females and 27 males) aged between 17-41 years with a mean of age(26.849±6.171) was taken for control had no exclusion criteria and healthy individual.

A systematic questionnaire was created to select individuals for a study. Patients and controls were asked to fill out a self-reported questionnaire to obtain sociodemographic information. Demographic data included age, gender, weight, height, BMI, family history, smoking, and stress state. Laboratory data included TNF-α (pg/ml)and IL-6 (pg/ml) measurements. All patients underwent a full history-taking and general examination.

Patient inclusion criteria

The patients were selected according to the following criteria:

1. Sex both female and male
2. Ages 16-45
3. No comorbidity condition

For every patient, a clinical history, an examination, and relevant laboratory tests were done. The clinical conditions of hair loss were diagnosed by physicians using recent clinical practice guidelines.

Exclusion criteria

The exclusion criteria of our study were: aged more than 45 years old, pregnancy, autoimmune disorders, alopecia areata, androgenic alopecia and no surgery and no immunosuppressive therapy were taken

Blood sampling

Aseptically, a 5 mL venous blood sample was obtained from each participant in the trial and transported to the Clinical Biochemistry Laboratory in basic test tubes with no anticoagulant (gel tube). After coagulation, samples were centrifuged (at 2000 g for 10min). Each serum sample was divided for analysis using ELISA and then transferred into separate Eppendorf tubes. Consequently, each serum sample from both patients and controls was separated into two equal parts. To limit the number of freezing-thawing cycles, serum samples were frozen deep freeze at a temperature of -80 degrees Celsius until the start of the investigation, for subsequent assay of IL-6 and TNF- α.

At the time of the study, samples from both the patients and control groups had been taken out from deep freeze and kept in the laboratory room until they reached room temperature. Afterward, they were mixed thoroughly using vortex techniques and made ready for analysis. The assays were carried out using an enzyme-linked immunosorbent assay (ELISA) technique.

Assay principle

The kit was based on the indirect ELISA detection method. In this type of ELISA, an antigen is immobilised in the plate's well, and the antibody specific to that antigen in the sample interacts with it to produce an Ab-Ag complex (Antigen-Antibody complex).

The presence of a primary antibody is detected by adding a secondary antibody coupled to an enzyme, which creates a signal in the form of a coloured product when substrate is added. The Stop Solution changes the color from blue to yellow and the intensity of the color is measured at450 nm using a spectrophotometer

Assay procedure

Prepare all reagent before starting assay procedure. Add standard: set standard wells, testing sample wells, add standard 50µl to standard well, add sample: add testing sample 10 µl then add sample diluent 40 µl to testing sample well, blank well doesn't add anything.

Add 100µl of HRP-conjugate reagent to each well, cover with an adhesive strip and incubate for 60 minutes at 37°C. Aspirate each well and wash, repeating the process four times for a total of five washes. Wash by filling each well with wash solution (400µl) using an autowasher. Complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining wash solution by aspirating or decanting. Invert the plate and blot it against clean paper towels. Add chromogen solution A 50µl and chromogen solution B 50µl to each well. Gently mix and incubate for 15 minutes at 37°C, protect from light.

After 15 min, add 50µl stop solution to each well. The color in the wells should change from blue to yellow. If the color in the wells is green or the color change does not appear uniform, gently tap the plate to ensure thorough mixing. Read the Optical Density (O.D.) at 450 nm using a microtiter plate reader within 15 minutes.

ROC Analysis

TNF-alpha shows excellent diagnostic accuracy with an AUC = 0.914, indicating high sensitivity and specificity (Table 1) and (Fig. 1). IL-6 has moderate diagnostic accuracy with an AUC = 0.670, suggesting it may be less effective as a standalone biomarker (Table 1) and (Fig. 1). Both biomarkers have statistically significant AUC values ($p< 0.001$), confirming their potential utility in clinical diagnostics of hair loss. Still, TNF-alpha can be considered a primary biomarker for diagnosing inflammatory hair loss conditions due to its high sensitivity and specificity. IL-6, despite its moderate performance, may serve as a secondary marker or be used in combination with TNF-alpha to enhance diagnostic accuracy.

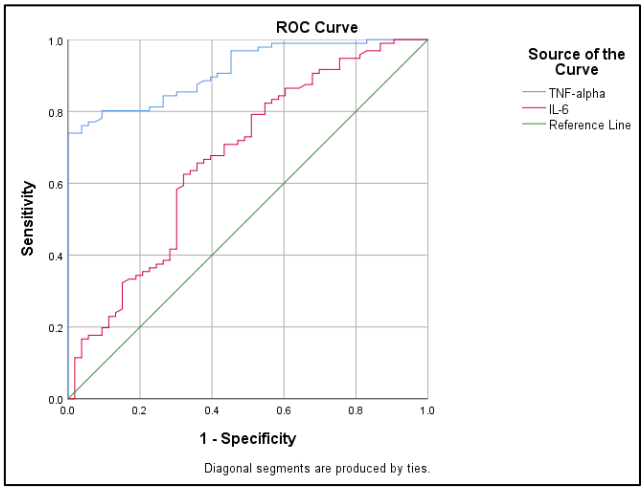

Fig. 1: ROC Curve for TNF-alpha and IL-6 Biomarkers in Diagnostic Evaluation

Table 1: Diagnostic Accuracy of TNF-alpha and IL-6 Using ROC Curve Analysis

Test Result Variable(s)	Area	Std. Error [a]	Asymptotic Sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
TNF-alpha	0.914	0.022	0.000	0.871	0.957
IL-6	0.670	0.047	0.001	0.577	0.764

Statistical analysis

The program used was the IBM SPSS Statistics 25.0 version. The constant data was presented as the mean ± standard deviation. The normality distribution of the groups was assessed using the Shapiro-Wilks test, which is a descriptive statistical procedure. The study of normally distributed values was conducted using the Independent Samples T-test. A significance level of $p< 0.05$ was considered statistically significant.

RESULTS

The study comprised a total of 149 individuals who met both the inclusion and exclusion criteria. Among them, 96 individuals were classified as the case group, exhibiting diffuse non-scarring hair loss, while the remaining 53 individuals were healthy control subjects. The case and control groups were matched based on age and gender. The main characteristics of descriptively analysed study samples are listed below in (Tables 2 and 3).

There was no statistically significant difference between the groups according to age, BMI, gender, family history, and smoking. The $p >0.05$. While there was a statistically significant difference in stress state between the groups $p< 0.05$. Independent samples parametric data, Student's t-test was used to test the difference for quantitative variables between two groups to compare between controls and patients.

Table 2: The clinical demographic features of both the patient and the healthy control groups. Crosstabs and Chi-sq. test

Parameters		Groups		P value
		Control N=53	Patients N=96	
Mean age	26.849±6.171		27.145±7.572	0.808
Mean BMI	24.862±4.554		24.9501±4.073	0.904
Gender	Female	26	50	0.723
	Male	27	46	
Family history	No	38	58	0.168
	Yes	15	38	
Stress state	No	33	43	0.041
	Yes	20	53	
Smoking	No	35	75	0.108
	Yes	18	21	

Table 3: Serum TNF- α and IL-6 in patients with diffuse hair loss and normal control

Parameters	Control Mean ± SD N=53	Patients Mean± SD N=96	T-value	*p*-value
IL6	18.122±4.395	20.339±2.893	3.702	**0.001***
TNF-alpha	25.616±7.083	48.902±12.987	12.087	**0.001***

p-value ≤ 0.05 significant; N: number; Mean ±SD is the mean value and standard deviation.

The difference in mean TNF- α and IL-6 Values between DHL patients and controls was found to be significantly higher ($p< 0.05$). Diffuse hair loss patients' mean levels of the TNF- α and IL-6 activity were higher than in the control group.

DISCUSSION

Hair issues are commonly seen by dermatologists in their daily practice. Hair loss has minimal or no physical effects, but it might result in psychological ramifications such as heightened levels of anxiety and sadness[21]. The various aetiology of the condition demands a complete history, clinical examination, hair microscopy, and evaluating laboratory testing to identify the underlying causes and give an idea for treatment DHL.

According to the findings of another studies[22-25], several demographic characteristics, including weight, body mass index (BMI), and family history of both patients and healthy control did not show any correlation with hair loss in our study.

The role of smoking in skin aging and hair loss has been a great topic of interest and research[26]. Smoking can cause microcirculation dysfunctions in the hair papilla, which decreases capillary blood flow in the dermal papilla of hair follicles[27,28]. In human hair follicles, smoking causes mitochondrial DNA mutations, Moreover, smoking-induced oxidative stress and anti-oxidant system disequilibrium may release pro-inflammatory cytokines from follicular keratinocytes, which decrease hair follicle growth[28,29]. Smoking may disrupt the hair follicle growth cycle by disrupting tissue remodelling protease/antiprotease systems[30].

Several studies show a positive correlation between androgenic hair loss and alopecia aerate with smoking in men[26,28,31,32]. However, there are few investigations on the effect of smoking on diffuse hair loss. In an study, there is no statistically significant role of smoking in DHL, and the sample size of male smokers in both the patient and control groups was small. In future sampling of smoker men could be increased.

The correlation between psychological stress and hair loss is complicated, and the experience can be distressing for patients. Previous reports of temporary hair loss due to severe stress have been confirmed[6]. This study also confirmed a positive correlation between stress and hair loss Stress can induce follicles to enter the resting phase, leading to hair falling out. Hair follicles have a life cycle, including growth, displacement, breakage, and hair shaft loss. Stress alters the proportion of hair in the growth and transition phase or telogen phase[33,34].

Most of the time, the reason for hair loss is unclear. It may relate to stressful events, chronic illnesses, major surgery, Febrile illnesses, long-term thyroid abnormalities, prolonged dietary deficiencies, and persistent anaemia[13,35]. In this study, we focus on inflammatory mediators to it is role in DHL. The current investigation showed a significant increase in

plasma levels of TNF- α and IL-6 in DHL patients when compared to healthy controls.

Hair follicles have a restricted range of responses to inflammatory damage, which are determined by the specific kind, location, intensity, and length of the inflammatory onslaught. The main range of reactions observed includes premature initiation of the catagen phase, dystrophic anagen and scarring[36]. In this inflammatory setting, the rise in the circulating level of cytokines promotes the premature and abrupt entry of hair follicles into the catagen phase[37].

Interleukin-6 (IL-6) is a common pleiotropic cytokine found in mammals, with enhanced production at inflammation sites[38]. It has both pro- and anti-inflammatory activities and has a role in the pathophysiology of all inflammatory diseases[20,39]. Elevated IL6 levels stimulate the anagen-to-catagen transition in the hair follicle, which results in hair growth suppression[40].It affects the hair follicle (HF) by causing the collapse of immune privilege; it predisposes and exacerbates hair loss by inhibiting the first phase of the hair growth cycle (anagen phase) and hair follicle proliferation, as well as causing inflammation in the surrounding area[41,42].

TNF-α is an inflammatory cytokine that plays a vital role in a healthy immune response. Nevertheless, uncontrolled release of TNF-α may be detrimental and can contribute to various diseases in the human body[19]. TNF-alpha modifies the immunological environment of the follicle. While it may not cause immediate damage to the follicle, it can disrupt the normal cycle dynamics and renewal of stem cells over time[43]. So TNF-alpha is considered a potent inhibitor of hair follicles and proliferation, which causes abnormal termination of the anagen phase and disturbs the normal hair development cycle, leading to excessive hair loss[44].

Cytokines, such as IL-6 and TNF-alpha, play a crucial role in the progression of widespread hair loss due to an immune-mediated inflammatory response that attacks hair follicles and disrupts the hair growth cycle.

CONCLUSION

Across the world, hair loss is a widespread issue, and to develop new therapeutic targets, the underlying molecular mechanisms of the problem need to be recognised. Our study shows a statistically significant positive with a role of immune system activation in DHL pathogenesis. The current study may be valuable in that it offers a body of evidence for potential future therapy recommendations. Despite our findings, more studies with a more robust approach are still required to advance our understanding of this field.

Ethical Approval Specification

This study lasted one year, and institutional ethical committee approval was secured well before it began. University of Basrah, college of Pharmacy approval number = EC45 IN 1/9/2023

Abbreviation

BMI: body mass index
DHL: Diffuse hair loss
HF: Hair follicle
IL-6: interleukin-6
TNF-α: Tumor necrosis factor-alpha

Conflict of Interest

The authors have declared that no conflict of interest exists.

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