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Study of the serum levels of lipocalin-2 as well as of metabolic and oxidative stress markers in alopecia areata patients of the Babil Province

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ABSTRACT

Rapid hair loss is caused by the chronic inflammatory disorder alopecia areata, which destroys the hair follicle. Alopecia areata often affects the scalp, although it can also affect other hairy areas such as the beard or the eyebrows. Metabolic abnormalities have been observed in patients with alopecia areata. The aim of this study was to investigate the potential roles of lipocalin-2, insulin, other associated metabolic markers, and oxidative stress in the pathophysiology of alopecia areata. In this case-control study, 90 individuals from the Babil Province of Iraq were recruited: 45 alopecia areata patients and 45 individuals with excellent hair health. Blood samples were collected from them between September 2023 and March 2024, in addition to the medical history and basic clinical measurements of all participants. In our study, alopecia areata patients presented with elevated serum levels of lipocalin-2, insulin, and C-peptide, together with elevated levels of important antioxidant enzymes and oxidative stress markers (as compared to those of age-matched healthy individuals), thereby suggesting a potential disease progression mechanism through metabolic dysregulation.

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1. Introduction

Alopecia areata is an autoimmune disease that manifests as a chronic inflammatory disease characterized by non-scarring patches of overface hair loss, the scalp, and the body. Different treatments can be administered for alopecia areata, but no curative ones exist and none can induce a state of remission. Approximately 1% to 2% of the general population may eventually be affected by the illness. According

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Table 1. Levels of metabolic and oxidative stress-related markers in patients with alopecia areata (patient group) and healthy individuals (control group). Abbreviations used: CAT, catalase; GSH, glutathione; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low density lipoprotein; MDA, malondialdehyde; SD, standard deviation; SOD, superoxide dismutase.

Variables	**Patient group** (mean ± SD)	**Control group** (mean ± SD)	**Significance** (*p*-value)
Lipocalin-2 (ng/mL)	308.0 ± 66.4	233.11 ± 28.08	<0.05
Total cholesterol (mg/dL)	185 ± 42	191 ± 23	0.08
LDL cholesterol (mg/dL)	112 ± 32	117 ± 27	0.09
HDL cholesterol (mg/dL)	69.0 ± 11.3	61.0 ± 13.7	0.07
Triglycerides (mg/dL)	89 ± 19	91 ± 13	0.11
Glucose (mg/dL)	91.0 ± 11.2	88.0 ± 13.9	0.06
Insulin (μIU/mL)	6.9 ± 1.9	4.2 ± 0.5	<0.05
HOMA-IR score	1.3 ± 0.5	0.9 ± 0.3	<0.05
C-peptide (ng/mL)	1.4 ± 0.4	1.3 ± 0.2	<0.05
CAT (ng/mL)	2.8 ± 1.1	1.5 ± 0.8	<0.05
SOD (μg/mL)	8.2 ± 3.1	5.2 ± 1.9	<0.05
GSH (μg/mL)	112.2 ± 59.2	84.7 ± 25.3	<0.05
MDA (nmol/mL)	1.7 ± 0.6	1.1 ± 0.5	<0.05

to skin biopsies from patients with alopecia areata, lymphocytes are present around the hair follicle bulb[1].

Currently, more than 600 adipokines with different biological properties within the human body have been identified; they are characterized by pro- and anti-inflammatory features[2]. Pro-inflammatory adipokine upregulation stimulates a low-grade chronic inflammatory state, which is involved in the dysfunction of the metabolism. In addition, adipokines have been shown to be active regulators of cutaneous inflammation. Their contribution has been shown in several dermatological cases, such as acne, rosacea, psoriasis, and atopic dermatitis, in addition to alopecia areata. The disease pathogenesis of the latter has not been fully elucidated[3]. Previous studies have shown that alopecia areata is related to autoimmunity, including notably elevated serum levels of several cytokines[4]. A number of skin diseases has been associated with insulin resistance (i.e., acanthosis nigricans, acne, and psoriasis), while others have been suggested to be probably related to insulin resistance (i.e., acrochorda, androgenetic alopecia, hidradenitis suppurativa, and hirsutism). Insulin has been assumed to contribute to the regulation of cutaneous androgen metabolism in addition to the hair growth cycle. However, the association between alopecia areata and insulin resistance remains controversial[5].

Lipocalin-2 is an adipokine that contributes to glucose regulation, homeostasis, and systemic inflammation. Its contribution to several inflammatory diseases, such as psoriasis, rheumatoid arthritis, atopic dermatitis, and alopecia areata, is well-known. Moreover, oxidative stress has been reported to significantly contribute to alopecia areata pathogenesis; an imbalance takes place among oxidative and antioxidant mechanisms when the production of reactive oxygen species (ROS) rises or when the antioxidant activity is decreased[6]. The purpose of this study was to investigate the potential roles of lipocalin-2, insulin, other associated metabolic markers, and oxidative stress in the pathophysiology of alopecia areata.

2. Methodology

In this case-control study, 90 individuals from the Babil Province of Iraq were recruited: 45 alopecia areata patients and 45 individuals with

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excellent hair health. Blood samples were collected from them between September 2023 and March 2024, in addition to the medical history and basic clinical measurements of all participants. Samples were obtained from patients who had visited dermatological clinics at the Hilla General Teaching Hospital, the Imam Al-Sadiq Teaching Hospital, and the Marjan Teaching Hospital. The patients were aged >25 years. Dermatologists assessed all participants and organised the study's groups. Individuals who were smokers, had received medication(s) within the previous 3 months, or were know to suffer from chronic conditions (such as diabetes, hypertension, and cancer) were excluded from the study.

After extracting the serum and placing it in Eppendorf tubes, the levels of lipocalin-2, insulin, and C-peptide were determined by using ELISA kits. The data were analysed by using the SPSS v. 26 software. Continuous variables are herein presented as mean ± standard deviation (SD), while group comparisons were performed using the independent *t*-test. Statistical significance was set at a *p*-value of <0.05. The ROC curve analysis was used in order to assess the diagnostic value of lipocalin-2.

This study was conducted following the ethical guidelines of the local health authorities, and its protocol was approved by the Institutional Review Board of the College of Pharmacy of the University of Babylon under protocol number 1345 (dated: 17-Jul-2023). Written informed consent was obtained from all participants prior to their inclusion in the study. This study adhered to the principles outlined in the Declaration of Helsinki.

3. Results and Discussion

The control and the alopecia areata groups did not differ significantly in terms of age and body mass index. However, alopecia areata patients presented with elevated serum levels of lipocalin-2, insulin, and C-peptide (Table 1). Lipocalin-2, also known as neutrophil gelatinase-associated lipocalin, is a 25-kDa glycoprotein released by adipocytes in addition to immune cells such as neutrophils; its expression is promoted by several proinflammatory cytokines, while studies have reported elevated serum levels of lipocalin-2 in inflammatory diseases such as psoriasis, atopic dermatitis, and rheumatoid arthritis[7]. In addition, it has been assumed that alopecia areata is probably related to an elevated risk of metabolic diseases, and that lipocalin-2 can significantly contribute to glucose homeostasis in addition to insulin sensitivity. In fact, alopecia areata patients have been previously shown to have significantly higher ($p<0.05$) fasting blood glucose serum levels, insulin levels, and C-peptide levels, besides a higher homeostatic model assessment of insulin resistance (HOMA-IR) score when compared to healthy controls[8]. Interestingly, serum glucose levels were also found increased in the alopecia areata patients of our study, but not to a statistically significant degree when compared to those of the control group (Table 1).

No significant variations were observed in terms of the serum levels of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides among the alopecia areata patients and the healthy participants of our study (Table 1). At the same time, we observed notably ($p<0.05$) increased catalase (CAT) and superoxide dismutase (SOD) activities, in addition to increased malondialdehyde (MDA) and glutathione (GSH) levels in the serum of alopecia areata patients (Table 1). Our understanding of the correlation between oxidative stress and alopecia areata has been limited[9]. Intracellular ROS generation, which causes oxidative cellular damage, is known to increase as a result of the infiltrating inflammatory cells and the synthesized cytokines.

4. Conclusion

Our study has shown that Iraqi alopecia areata patients are presented with elevated serum levels of lipocalin-2, insulin, and C-peptide, together with elevated serum levels of important antioxidant enzymes (such as CAT and SOD) and oxidative stress markers (such as GSH and MDA), thereby suggesting a potential disease progression mechanism through metabolic dysregulation. The latter also affected the patients' HOMA-IR score, but

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not their glucose, cholesterol (total, LDL, and HDL), and triglyceride levels (as compared to those of age-matched healthy individuals). Additional studies are required in order to determine the potential role of lipocalin-2 in alopecia areata diagnosis and disease progression tracking, while based on our findings, therapeutic strategies focusing on the management of metabolic derangements and oxidative stress show particular promise for the treatment of alopecia areata.

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Conflicts of interest

None exist.

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