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Serum level of calprotectin as a new inflammatory marker in patients with alopacia areata

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Abstract

Alopecia areata (AA) is an inflammatory and autoimmune, non-scarring condition. The exact mechanism that induces loss of immune privilege is unknown. Serum calprotectin (CLP) levels are a strong predictive factor and a unique inflammatory marker in several autoimmune disorders. This study aimed to evaluate CLP levels in alopecia areata patients and correlate them with various clinical characteristics of the disease, particularly severity, to identify any potential associations. The present study included 30 AA patients and 30 age and gender-matched volunteers as controls. Severity of AA was determined according to the Severity of Alopecia Tool (SALT) score. Serum CLP levels were measured in all participants by the Enzyme-Linked Immunosorbent Assay. The CLP serum levels were significantly higher in AA patients than in controls ($p< 0.0001$). A significant association was observed between CLP serum levels and age of patients, SALT score, and duration of disease ($p=0.048$, $p< 0.0001$ and $p< 0.0001$, respectively). Additionally, a significant association was present between CLP levels and type, severity of AA, and nail affection ($p<0.0001$, $p<0.0001$ and $p=0.003$, respectively). In conclusion, the present results demonstrated that AA was linked to systemic inflammation, and CLP could be a beneficial indicator of inflammation in AA patients.

Keywords: Alopecia areata, Calprotectin, Disease severity.

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Introduction

Alopecia areata (AA) is an autoimmune disease that causes hair loss without scarring. It is fairly common, affecting up to 2% of people worldwide.[1] In Egypt, however, according to a clinical trial study, included 100 patients in Sohag Governorate, the prevalence of AA represented 26% between all cases of hair loss. In another clinical study conducted in Egypt, the prevalence of AA was 3.1% between new dermatology outpatients.[2] While it can occur at any age, it seems to be more common in children and young adults, and slightly more likely to affect females than males.[1] People with genes that make them more likely to get AA, and who experience environmental triggers, may develop the disease because their immune system's signaling is malfunctioning.[3]

Hair follicles have a form of protective immunity, granting them privilege against the body's autoimmunity. However, in patients with AA, the immune system mistakenly attacks healthy hair follicles. This occurs because the body's normal defenses against attacking itself are weakened. Scientists believe that this attack might target proteins from melanocytes and keratinocytes within the follicle**.** Immune attack involves different types of immune cells and signaling molecules. Three types of helper T cells (Th1, Th2, Th17) are all involved, each secreting signaling molecules that influence the immune response. In particular, Th1 cytokines, interleukin-2, (IL-2), IL-12, and TNF and Th17 cytokines (IL-17 and IL-17E) seem to play a particularly important role in this attack.[4]

There are three main types of alopecia areata. Patchy alopecia areata: in this type, which is the most common, hair loss happens in one or more coin-sized patches on the scalp or other parts of the body. Alopecia totalis, people with this type lose all or nearly all of their hair on their scalp. Alopecia universalis, in this type, which is rare, there is a complete or nearly complete loss of hair on the scalp, face, and rest of the body. Although there are various treatments for AA, like steroids and newer injectable medications, none of them can permanently cure the condition or prevent persistent remission.[5] Several comorbidities are linked to AA, as metabolic syndrome, atopic diseases, lupus erythematosus, thyroid diseases, iron deficiency anemia, vitamin D deficiency, and psychiatric diseases.[6]

Calprotectin (CLP) is a protein complex made up of the S100 calcium-binding protein A9 (S100A9) and S100A8 proteins. These proteins are calcium and zinc binding cytosolic proteins produced by neutrophils and activated monocytes both in the circulation and inflamed tissues. CLP has been proposed as a possible biomarker for inflammation.[7]

CLP plays a role in inflammation by binding to its specific receptors on the cell surface, initiating subsequent signal transduction, and inducing the recruitment of leukocytes and cytokine production in inflammatory areas. Pro-inflammatory activities are mainly triggered by activated granulocytes in a calcium-dependent manner.[8] Serum CLP is a novel indicator linked to primary autoimmune disorders. Current research emphasizes the critical role of serum CLP in monitoring treatment for numerous autoimmune conditions.[9]

Instead of relying on acute-phase proteins, CLP levels could potentially serve as a better indicator of autoimmune diseases. Significant levels of CLP have been detected in two main categories of autoimmune diseases. The first group is systemic autoimmune illnesses, like vasculitis, myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus. The other group is organ-specific autoimmune diseases like Hashimoto's disease.[10]

CLP has been studied in multiple autoimmune diseases. However, to the best of our knowledge, serum CLP levels have not been investigated in AA. Therefore, this study aimed to evaluate serum CLP levels in AA patients and correlate them with disease severity.

Subjects and Methods

This hospital-based, case-control study recruited 30 patients with AA diagnosed with the standard clinical and dermoscopic characteristics. In addition, 30 normal subjects, matched for age and sex, served as controls. All subjects were selected from the Outpatient Clinic of the department of Dermatology and Venereology of Al-Zahraa University Hospital between January 2024 and April 2024.

Individuals younger than 18 years old, those suffering from chronic diseases, neoplastic conditions, or cystic fibrosis, and pregnant or lactating women were excluded from the study. Additionally, those suffering from other autoimmune or inflammatory diseases that may affect CLP levels were also excluded.

Clinical Assessment

All participants underwent a thorough history taking, a general health check-up, and a dermatological examination to identify any potential systemic disorders associated with AA. The Severity of Alopecia Tool (SALT) score system was used to clinically evaluate AA severity.[11] Patients were categorized based on the percentage of scalp hair loss: S0 (no hair

loss), S1 (<25% hair loss), S2 (25–49% hair loss), S3 (50–74% hair loss), S4 (75–99% hair loss), and S5 (100% hair loss).[12]

Clinically, the disease is classified as mild if the patient had 3 or fewer patches of alopecia with 3 cm or less maximum diameter, or when the illness only affected the eyebrows and eyelashes. Moderate if more than 3 patches were detected or when a patch over 3 cm in diameter was present without alopecia totalis/universalis, severe if alopecia totalis/universalis were present.[13] The body was examined for signs of alopecia, specifically looking for areas with hair loss. Additionally, the nails were examined to determine if they were also affected.

Collection of Blood Samples

A venous blood sample (3 ml) was collected from each participant in a serum separator tube under sterile conditions. The blood was then allowed to coagulate at room temperature for 10-20 minutes. Afterward, it was centrifuged at 698 xg at room temperature for 20 minutes. Finally, the serum was collected and preserved at -20°C until used.

Measurement of Serum CLP Level

Serum CLP level was measured using Enzyme-linked Immunosorbent Assay (ELISA) commercial kits "Catalog No: 201-12-5461B, Human calprotectin (CALPRO, Sun Red, Shanghai, China,), according to the manufacturer's instructions.

Statistical Analysis

Data were analyzed by the Statistical Package for Social Science (SPSS) Software (IBM, Ver. 27). The quantitative data are presented as mean, standard deviations and ranges for parametric data, and median, inter-quartile range (IQR) for non-parametric data. The qualitative variables are presented as numbers and percentages. Chi-square test was used to compare groups with qualitative data. The independent t-test was used to compare two independent groups with quantitative data and parametric distribution, while Mann-Whitney test was used for non-parametric data. Comparison between three groups regarding quantitative data and non-parametric distribution was done using Kruskall Wallis test. The correlation between two quantitative parameters in the same group was assessed by Spearman correlation coefficient. The receiver operating characteristic (ROC) curve was used to assess the best cut off point for CLP level and its specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and area under curve (AUC). The *p*-value was considered significant at the level of <0.05..

Results

This case–control study enrolled 30 AA patients and 30 controls. Out of 30 AA patients, 15 (50%) were males with an age ranged from 19 to 40 years old, with a mean of 27.1 ± 6.07 years, The AA duration ranged from 2-30 months, with a median of 8 months. There were 16 (53.3%) patients of AA focalis, 8 (26.7%) patients of AA multifocalis, 4 (13.3%) patients of AA totalis and 2 (6.7%) patients of AA universalis. The AA severity was assessed by SALT score which ranged from 2 to 100. Of the patients, 53.3%, 26.7% and 20% had mild, moderate and sever disease, respectively. Other characteristics of the studied patients were shown in Table 1.

There was no significant difference in the age and sex among patients and controls (p >0.05). However, CLP serum levels were significantly higher in AA patients compared to controls (p< 0.001, Table 2). The ROC curve analysis of AA patients showed that the serum CLP at a cut-off level of >123.5 the sensitivity was 90% and the specificity 96.67%, meaning that a person may be considered as healthy below this level (Figure 1).

Table 1. Demographic data and characteristics of the 30 alopecia areata (AA) patients studied.

Studied parameter		Data
Age	Mean ± SD	27.1 ± 6.07
	Range	19 – 40
Sex	Female	15 (50%)
	Male	15 (50%)
Duration/ month	Median (IQR)	8 (6 - 13)
	Range	2 – 30
Family history	No	27 (90%)
	Yes	3 (10%)
Type of AA	AAF	16 (53.3%)
	AAMF	8 (26.7%)
	AAT	4 (13.3%)
	AAU	2 (6.7%)
SALT score	Median (IQR)	23.6 (8 - 65.4)
	Range	2 – 100
Calprotectin	Median (IQR)	230.85 (173.8 – 289.3)
	Range	115.7 – 1178.2
Chronicity	Acute	10 (33.3%)
	Chronic	20 (66.7%)
Nail affection	No	26 (86.7%)
	Yes	4 (13.3%)
Severity	Mild	16 (53.3%)
	Moderate	8 (26.7%)
	Sever	6 (20%)
Recurrence	No	26 (86.7%)
	Yes	4 (13.3%)

SALT: Severity of Alopecia Tool

Table 2. Comparison of demographic data and calprotectin levels between alopecia areata cases and controls groups.

		Cases group	Control group	*p*-value
		No.= 30	No.= 30	
Age	Mean ± SD	27.1 ± 6.07	27.4 ± 5.7	NS•
	Range	19 – 40	19 – 40	
Sex	Female	15 (50%)	15 (50%)	NS*
	Male	15 (50%)	15 (50%)	
CLP	Median (IQR)	230.85 (173.8 – 289.3)	65.5 (55.5 – 109.8)	<0.0001≠
	Range	115.7 – 1178.2	40.1 – 340.1	

CLP: calprotectin; Chi-square test; •: Independent t-test; ≠: Mann-Whitney test. $p > 0.05$ is not significant (NS).

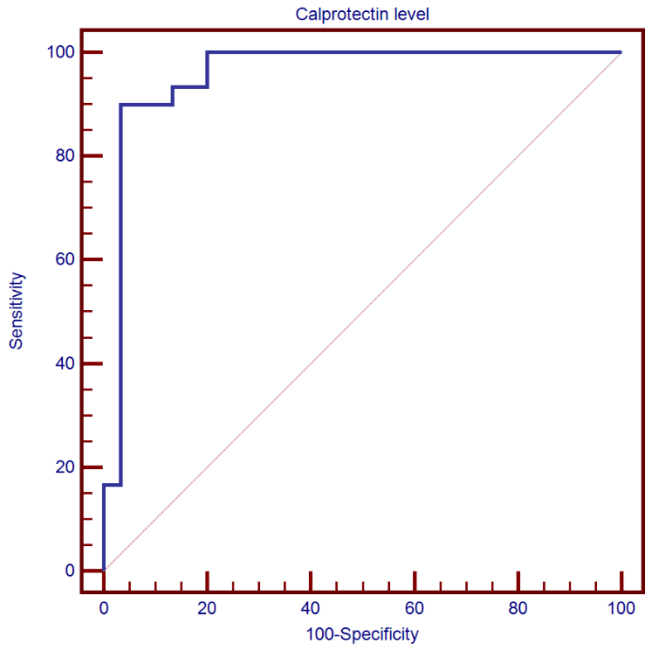

Figure 1. Receiver operating characteristic (ROC) curve for calprotectin level to differentiate between alopecia areata cases and controls groups

There was a significant positive correlation between the CLP levels and age of patients, SALT score and duration of disease (r = 0.365, r = 0.749, and r = 0.991, and $p = 0.048$, $p < 0.0001$ and $p<0.0001$, respectively) (Table 3).

Table 3. Correlation of calprotectin (CLP) levels with age, duration of disease and Severity of Alopecia Tool (SALT) score among alopecia areata cases group.

	CLP	
	r	*p* value
Age	0.365*	0.048
Duration/m	0.749**	<0.0001
SALT score	0.991**	<0.0001

Spearman correlation coefficients. $p \leq 0.05$ is significant.

Regarding the relationship between CLP levels and patient's parameters, a significant association was observed between CLP levels, type and severity of AA and nail affection (p< 0.01 for all). However, there was no significant relation between CLP levels and the other patients studied characteristics (Table 4).

Table 4. Relation between calprotectin (CLP) levels with the other parameters studied among alopecia areata cases group.

		CLP levels		*p*-value
		Median IQR	Range	
Sex	Female	211.3 (147.7 - 304.5)	115.7 - 379.7	NS•
	Male	231.8 (173.8 - 289.3)	115.7 -1178.2	
Family history	No	231.8 (173.8 - 304.5)	115.7 -1178.2	NS•
	Yes	173.3 (145.5 - 289.3)	145.5 - 289.3	
Type of AA	AAF	173.8 (138.3 - 193.3)	115.7 - 231.8	<0.0001≠
	AAMF	272.5 (257.5 - 285.8)	248.8 - 304.5	
	AAT	360.75 (345.5 - 374.8)	339.4 - 379.7	
	AAU	1172.05 (1165.9 - 1178.2)	1165.9-1178.2	
Chronic	Acute	209 (145.5 - 257.5)	115.7 - 339.4	NS•
	Chronic	257.45 (174.15 - 328.05)	115.7 - 1178.2	
Nail affection	No	209 (173.3 - 266.1)	115.7 - 1165.9	0.003•
	Yes	374.8 (354.65 - 778.95)	339.4 - 1178.2	
Severity	Mild	173.8 (138.3 - 193.3)	115.7 - 231.8	<0.0001≠
	Moderate	272.5 (257.5 - 285.8)	248.8 - 304.5	
	Sever	374.8 (351.6 - 1165.9)	339.4 - 1178.2	
Recurrence	No	209 (173.3 - 282.3)	115.7 - 1178.2	NS•
	Yes	285.3 (261.8 - 342.1)	257.5 - 379.7	

AA: Alopecia areata; •: Mann-Whitney test; ≠: Kruskal-Wallis test. $p > 0.05$ is not significant (NS).

From patchy AA to alopecia totalis/universalis, serum CLP levels increased gradually. When compared to patchy AA, the highest levels were linked to alopecia totalis/universalis p< 0.001 (Figure 2).

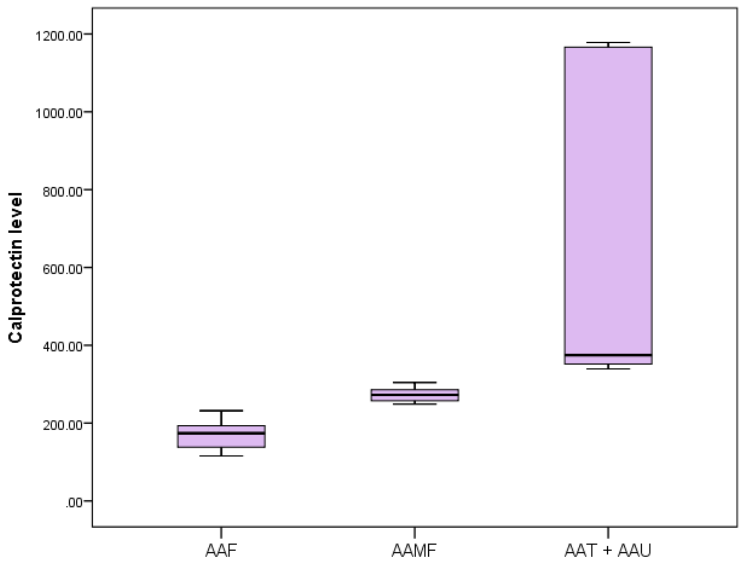

Figure 2. Relation between type of alopecia areata (AA) and calprotectin levels among alopecia areata cases group.

Discussion

AA is an autoimmune disorder in which T-cells release cytokines surrounding anagen-stage hair follicles.[14] The pathogenesis of AA involves the interaction of hereditary, psychological, environmental, and immune components; however, the precise variables are unclear.[15]

The association between CLP and autoimmune diseases may be due to its role in the innate immune system, contributing to local inflammation and the production of inflammatory cytokines and chemokine.[16] CLP may be implicated in the pathogenesis of several chronic inflammatory conditions, including Bechet's illness, juvenile chronic arthritis, Antineutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitis, and rheumatoid arthritis[17] by activation of immune cells like CD8 T cells and modulation of inflammatory responses.[18]

Up to our knowledge, little is known regarding the role of calprotectin in the alopecia areata. So, we conducted this study to get aware of the prospective function of CLP as a crucial element in AA, CLP serum levels were measured both in AA patients and normal controls. The results revealed that CLP serum levels were considerably increased in patients than the controls. In addition, this study is the first to assess the predictable value of serum CLP for diagnosis of AA using ROC curve analysis. At a cut-off level of >123.5, serum CLP showed a sensitivity of 90% and specificity of 96.67% in AA. Accordingly, calprotectin showed high specificity and sensitivity. These results demonstrated the significance of serum calprotectin as a reliable marker for disease identification and for differentiating between AA patients and controls indicating that CLP may have a role in the AA pathophysiology. This could be attributed to its potential involvement in the inflammatory process linked to AA. Understanding the inflammation caused by AA and the associated processes can open new therapeutic approaches for AA.

Also, according to our study, higher CLP levels of AA patients compared to controls indicate that CLP may be used to assess patient's response to therapy and to evaluate the severity of disease.

Few research has studied the role of inflammatory markers in AA, with conflicting observations. The study by Mustafa et al., 2021,[18] observed the CRP levels were increased in AA patients suggesting a potential connection between inflammation and activity of AA. So, that observation was against what was observed by Gao et al., 2021,[19] and Yousefi et al., 2014,[20] who found that there was no significant difference in CRP levels between AA patients and controls.

On reviewing literature, only one study by Soliman et al., 2024,[21] evaluated the serum CLP level in patients with AA compared to control. However, in contrast to our findings, they reported that serum CLP did not show a significant difference between AA and control. This could be attributed to the differences in sample size and patient characteristics. In addition, to the best of our knowledge, our study is the first to assess the serum CLP level in relation to AA severity. We found a significant positive correlation between CLP level and SALT score.

Considering all we know, this may be the initial inquiry to assess CLP's role in AA. It has been proven that a number of inflammatory and autoimmune disorders have elevated CLP levels. According to the study by Inciarte-Mundo et al., 2022,[16] CLP was found to be higher in synovia and plasma in patients with rheumatoid arthritis (RA) and showed a correlation with the disease activity, suggesting that CLP may be a useful marker of RA illness activity.

The study by Kopi et al., 2019,[22] reported that inflammatory bowel disease (IBD) patients had significant higher serum CLP levels than those of the controls, and there was a relationship between patients' CLP levels and the severity and activity of their diseases. Both IBD and RA are autoimmune conditions, and AA may share similar pathogenesis with other autoimmune diseases that were associated with AA in multiple epidemiological and genetic research studies.

Besides, the study by Ometto et al., 2017,[23] reported a significant correlation between

serum CLP concentrations and severity of disease, in certain autoimmune and inflammatory illnesses. High CLP levels are associated with severe rheumatic disease symptoms including lung fibrosis and glomerulonephritis. Similar results were reported in systemic lupus erythematosus,[24] rheumatoid arthritis,[10] and sepsis.[25] These studies agreed with the current observations of a significant relationship between serum CLP levels and severity of disease in AA patients. So, serum CLP level, as a new serum-based indicator, has been studied in many recent research studies, and it may serve as a better indicator of systemic inflammation.[22]

Our investigation reported a significant correlation between CLP, the age of patients, SALT score and duration of disease. However, there was no significant correlation with patients' sex. In line with Homa-Mlak et al., 2022,[24] reported that serum CLP was significantly related to the duration of diseases other than AA. In addition, our study found no significant correlation between serum CLP and other clinical parameters, including chronicity of disease.

Regarding the association between CLP levels and the severity of the illness, our research found that cases with alopecia areata totalis (AAT) and universalis (AAU) showed significantly higher CLP levels compared to alopecia areata focalis (AAF). Moreover, the study suggests that higher levels of CLP in the blood may be a sign of more severe AA. People with AA involving both the scalp and body had higher CLP levels than those with AA only on the scalp. CLP may be a marker indicating how serious the inflammation is in AA.

Similarly, the study by Stascheit et al., 2021,[26] reported that CLP is a marker of different diseases severity, including psoriasis, myasthenia gravis, rheumatoid arthritis, and inflammatory bowels diseases.

The restrictions of this research consist of the tiny sample size, the absence of additional salivary or fecal specimens for CLP evaluation, and the lack of follow-up of CLP levels in AA patients who received treatment afterward.

In conclusion, higher CLP levels in AA patients than in controls suggested a potential role for CLP in the pathophysiology of AA. These levels were positively correlated with age of patients, duration, and severity of disease. These findings might offer support for CLP's involvement in the pathology of AA, and it could be a useful marker for AA progression and severity.

Author Contributions

HME and BEMR; research idea, the design, conception of the study, literature review, manuscript preparation, editing and review; HME, BEMR, MSA and DAHP; the data collection, lab assessment, data analysis, statistical analysis, interpretation, writing, and editing of the final manuscript; EEM and FGY; laboratory procedures, and statistical analysis. All authors contributed to the interpretation of data, drafted the article or critically revised, and final approval of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; and all authors have read and approved the manuscript.

Declaration of Conflicting Interests

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Ethical approval

The research protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine for Girls, Al Azhar University (Approval no. 2245, dated January 2024).

Informed consent

All patients were provided with detailed information about the study, and they signed a written consent form.

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