Short Communication

Studying the Levels of Copeptin and Cortisol as a Stress Monitoring Biomarkers in the Patients with Alopecia Areata in Babylon Governorate

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Abstract

Background: Alopecia areata (AA) can manifest clinically as little areas of hair loss or as total loss of scalp and body hair. Stress is a common cause of hair loss. In response, the adrenal gland secretes glucocorticoids and catecholamines, which affect the immune system by preventing extensive activation, the metabolism by providing acute energy, and the vasculature by increasing blood pressure. **Objective:** The aim of this research is to investigate the potential role of stress in the pathophysiology of AA. Additionally, to elucidate the potential use of a stress monitoring biomarker as a diagnostic indicator for AA. **Materials and Methods:** An investigation using a case–control method involved 60 male patients with AA and 60 male controls in good condition. In addition, the individuals with AA were separated into two age groups: adults and non-adults. Blood samples were obtained to measure copeptin and cortisol. Age and body mass index were evaluated in addition to other variables. **Results:** This study found that copeptin and cortisol concentrations in both adult and pediatric patients increased significantly ($P < 0.05$) compared to the control group. The area under the curve (AUC) for adult copeptin was 0.841 and 0.759 in children, while the AUC for cortisol was 0.878 in adults and 0.872 in children. **Conclusions:** According to this study, copeptin and cortisol could be key players in the pathophysiology of AA .

Keywords: Alopecia areata, copeptin, cortisol, Iraq, ROC curve

Introduction

An autoimmune condition known as alopecia areata (AA) causes a person to temporarily lose their hair without leaving scars; however, the hair follicle itself remains intact. All parts of the body where hair develops can be affected by hair loss, which can present as well-defined patches, partial, or total.[1] According to skin biopsies from AA patients, approximately 1% to 2% of the general population may eventually be impacted by the illness. Lymphocytes are present in and around the bulb (the bottom portion) of the hair follicle during the anagen (hair growth) phase,. It is thought that a major contributing factor to AA is a disturbance in the immunological privilege of the hair follicle.[2] All age groups are thought to be affected by AA, which has an overall incidence of 2.3% among Saudi patients.[3] The hypothalamic-pituitary-adrenal (HPA) and brain-hair follicle (BHA) axes are triggered under psychological stress. Through the HPA axis, hypothalamic hormones corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) together regulate cortisol secretion.[4]

One well-known stress hormone involved in the body's reaction to both physical and mental stress is cortisol.[5] Increased cortisol concentrations harm glycosylated proteins called proteoglycans, which are essential for the healthy function and cycle of hair follicles and the surrounding tissue.[6]

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Copeptin, sometimes called CT-proAVP, is a 39-amino acid peptide produced from the pre-pro-hormone of arginine vasopressin (AVP) at the C-terminus.[7] The AVP gene codes for the hormone known as antidiuretic hormone (ADH), or AVP. Abnormal levels of AVP are linked to a number of disorders and are implicated in many renal and cardiovascular pathways. Therefore, measuring AVP would be helpful, but it is not frequently done in clinical practice because of its short half-life, which makes quantification challenging. Conversely, copeptin is a surrogate marker for vasopressin since it is easily examined immunologically.[8]

The purpose of this study is to investigate the role of stress in the pathophysiology of AA and to elucidate the potential use of a stress monitoring biomarker as a diagnostic criteria for AA.

Materials and Methods

In this case–control research, 120 individuals were included: 60 with AA, while the remaining 60 seemed to be in excellent health. Sample were collected between September 2023 and March 2024. Samples were obtained from patients who had registered visits to the dermatological clinics at the Hilla General Teaching Hospital, Imam Al-Sadiq Teaching Hospital, and the Marjan Teaching Hospital.

The patients were either less than 18 years old or older than 18 years old. A great deal of information was documented, such as the patient's history, height, weight, age, duration, and severity of symptoms. Dermatologists diagnosed patients and classified them based on various criteria, including smokers, those who had received medication within the previous three months, and those with chronic conditions such as diabetes, hypertension, and cancer, based on selection and exclusion criteria.

Every participant had venous blood sampling. The sample was centrifuged for 10 minutes at 3000 × g after the blood was gently pumped into a gel tube and allowed to coagulate for 10 to 15 minutes at room temperature. After extracting the serum and transferring it into Eppendorf tubes, the amounts of copeptin and cortisol were determined.

Serum concentrations of copeptin and cortisol were measured in the morning using commercially available enzyme-linked immunosorbent assay (ELISA) kits from Bioassay Technology Laboratory in accordance with the manufacturer's instructions.

Ethics approval

Before collecting samples, all study participants were informed and allowed to consent verbally. A local college and hospital ethics committee examined and approved the study protocol, subject information, and permission form by the document number [IRB: 1291, 16/8/2023].

Statistical analysis

The current study results compared the patient and control groups using the *t*-test and were statistically calculated to find the mean difference between the two groups (P-value ≤ 0.05), which is considered significant. Pearson correlation was also used to determine the correlation between the parameters under study. The International Business Machines Statistical Package for the Social Sciences (SPSS V. 26) was used to conduct the copeptin level receiver operating characteristic (ROC) curve analysis.

Results

The demographic characteristics of the study participants

The mean difference between the control and AA groups, as well as the correlation between the various patient parameters, were computed statistically using the *t*-test in the current comparative analysis of the patient and control groups. The study group included 60 adults and 60 children in all, divided into two control groups of 30 each.

Age

There was no statistically significant difference in the results ($P > 0.05$). Table 1 displays the age distribution and disease rate. The mean age of adult patients (27.30 ± 8.49) and child patients (12.17 ± 2.77) is compared to that of healthy controls (31.27 ± 9.14 for adults and 11.57 ± 3.39 for children), respectively.

Body mass index (BMI)

There was no statistically significant difference in the results ($P > 0.05$). Table 2 displays the BMI distribution and disease rate. The mean BMI of adult patients (22.40 ± 2.31) and child patients (19.767 ± 1.91) is compared to that of healthy controls (23.03 ± 1.90 for adults and 20.662 ± 1.81 for children), respectively.

Biochemical parameters

The patient group's copeptin and cortisol concentration in adults and children increased significantly ($P < 0.05$) in comparison to the control group, as shown in Table 3.

Table 1: Age means of the study groups

Study variable	Groups	*N*	Mean ± SD	*P* value
Age adult	Patient	30	27.30 ± 8.94	0.095
	Control	30	31.27 ± 9.14	
Age children	Patient	30	12.17 ± 2.77	0.456
	Control	30	11.57 ± 3.39	

Table 2: Body mass index means of the study groups

Study variable	Groups	*N*	Mean ± SD	*P* value
BMI adult	Patient	30	22.40 ± 2.31	0.252
	Control	30	23.03 ± 1.90	
BMI children	Patient	30	19.767 ± 1.91	0.068
	Control	30	20.662 ± 1.81	

BMI, body mass index

Table 3: Comparison of cortisol and copeptin levels between study participants

Variable	*N*	Patients (Mean ± SD)	Control (Mean ± SD)	*P* value
Copeptin (ng/mL) in adult	30	0.458 ± 0.161	0.303 ± 0.189	0.002
Copeptin (ng/mL) in children		0.414 ± 0.207	0.226 ± 0.111	0.001
Cortisol (ng/mL) in adult	30	1.535 ± 0.493	0.953 ± 0.281	0.000
Cortisol (ng/mL) in children		1.185 ± 0.640	0.459 ± 0.183	0.000

Table 4: Pearson correlation among the study variables in the adult patients group

Study variables		Cortisol	Copeptin	Age	BMI
Cortisol	*R*	—	−0.122	0.013	−0.115
	P value	—	0.519	0.945	0.544
Copeptin	*R*	−0.122	—	−0.146	0.214
	P value	0.519	—	0.441	0.257
Age	*R*	0.013	−0.146	—	0.291
	P value	0.945	0.441	—	0.119
BMI	*R*	−0.115	0.214	0.291	—
	P value	0.544	0.257	0.119	—

BMI, body mass index

Discussion

In comparison to the control group, the adult AA patients in this study had higher blood cortisol levels (1.535 ± 0.493 vs. 0.953 ± 0.281, *P*-value < 0.05). Table 3 shows that the pediatric patients had significantly higher blood cortisol levels (1.185 ± 0.640 vs. 0.459 ± 0.183) compared to the control group, with a *P*-value < 0.05. Numerous autoimmune disorders have been linked to chronic stress, and cortisol is a key player in the pathophysiology of these diseases.[9] Consequently, cortisol's function in the autoimmunity seen in AA is explained by its elevated levels in both adults and children. Many studies have discovered that prolonged cortisol production causes cortisol resistance, which reduces the anti-inflammatory benefits of cortisol and transforms them into negative effects, such as mast cell granulation, impeded hair development, and perifollicular inflammation, ultimately resulting in hair loss.[10]

The adult patient group and control group mean levels of copeptin differed significantly (*P* < 0.05) according to the results of this investigation. Furthermore, a significant difference (*P*-value < 0.05) was observed in the mean levels of copeptin between the pediatric patients and the control group. Table 3 demonstrates that the copeptin levels in ill children are higher than those of the control group. When comparing the adult patient group to the control group, serum copeptin levels were higher in the former. The AVP hormone and ACTH are closely related. High amounts of the hormone are transported to the pituitary portal system through a neuron secretory channel, where AVP and CRH cooperate to trigger the anterior pituitary's production of ACTH.[11]

The hypothalamus's "backup" system of two hormones for ACTH release emphasizes the physiological significance of the endocrine stress response.[12]

As indicated in Table 4, the results in the current study indicated that there was no link (*P*-value > 0.05) between copeptin and cortisol in the adult patient group. Furthermore, there was no association (*P*-value > 0.05) found between copeptin, age, and BMI. Table 5 also demonstrates a strong positive connection (*P*-value = 0.009, *r* = 0.468) between the levels of copeptin and cortisol in the pediatric group. On the other hand, copeptin, age, and BMI did not correlate (*P*-value > 0.05).

Table 6 and Figure 1 display the ROC curve analysis for the specificity and sensitivity of copeptin for the adult patient group compared to the control group at the cutoff point of 0.31 ng/l, with an AUC of 0.841. Copeptin is a useful marker to utilize for the diagnosis of adult patients with

Table 5: Pearson correlation among the study variables in the children patients group

Study variables		Cortisol	Copeptin	Age	BMI
Cortisol	*r*	—	**0.468****	0.034	−0.141
	P value	—	**0.009**	0.858	0.456
Copeptin	*r*	**0.468****	—	−0.003	−0.135
	P value	**0.009**	—	0.988	0.478
Age	*r*	0.034	-0.003	—	0.029
	P value	0.858	0.988	—	0.881
BMI	*r*	−0.141	−0.135	0.029	—
	P value	0.456	0.478	0.881	—

BMI, body mass index
P-value < 0.05 = significant (in bold)
**Significant correlation

Table 6: Area under the curve for copeptin between the adult patient and control group

AUC	Specificity	Sensitivity	SE	*P* value	95% confidence interval	
					Lower bound	Upper bound
0.841	74%	90%	0.057	**0.000**	0.729	0.954

SE: standard error, AUC: area under the curve
P-value < 0.05 = significant (in bold)

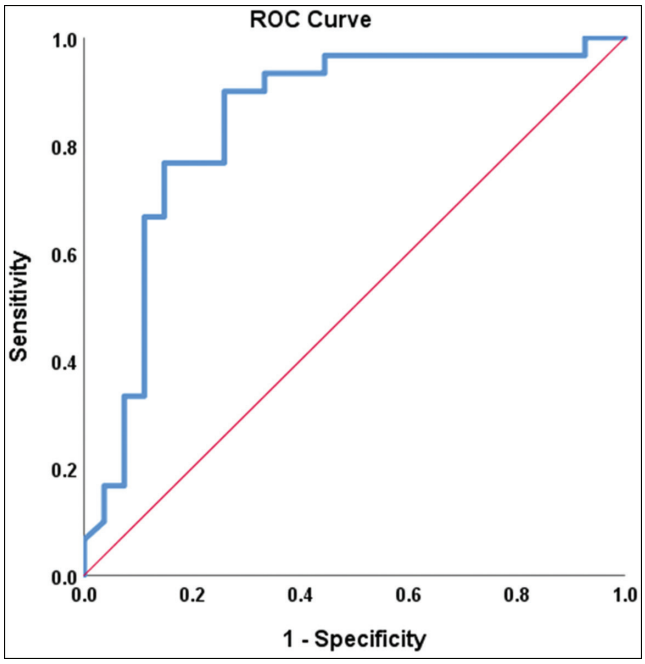

Figure 1: Receiver operating characteristic curve analysis for copeptin between the adult patients and control group

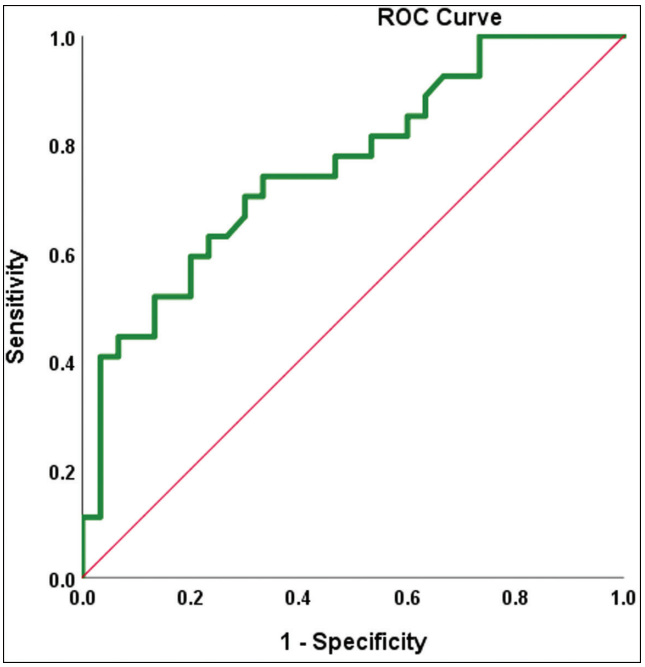

Figure 2: Receiver operating characteristic curve analysis for copeptin between the children patients and control group

Table 7: Area under the curve for copeptin between the children patient and control group

AUC	Specificity	Sensitivity	SE	*P* value	95% Confidence interval	
					Lower bound	Upper bound
0.759	67%	74%	0.063	**0.001**	0.635	0.883

SE: standard error, AUC: area under the curve
P-value < 0.05 = significant (in bold)

AA, according to the value of the AUC. The specificity and sensitivity of copeptin were 74% and 90%, respectively.

Moreover, the ROC curve study for the adult patient group showed that copeptin specificity and sensitivity were higher than those of the control group at the cutoff point of 0.25 ng/l, with an AUC of 0.759. Copeptin has a

specificity and sensitivity of 67% and 74%, respectively, as illustrated in Figure 2 of Table 7. Copeptin is a useful marker that may be utilized to diagnose AA in pediatric patients, as can be shown from the AUC value.

The ROC curve analysis for specificity and sensitivity for cortisol in the adult patient group in comparison to the control group at the cutoff point of 1.4 ng/l showed an AUC of 0.878. For cortisol, the corresponding values were 63% and 96%, respectively, as depicted in Figure 3 of Table 8. The AUC for cortisol indicates that it is a good marker that may be utilized for the diagnosis of adult patients with AA, based on the findings of ROC analysis; however, because of its greater specificity than sensitivity, it may not be helpful in validating the real positive results.

Furthermore, the AUC was 0.872 for the ROC curve study comparing cortisol specificity and sensitivity between the children's patient group and the control group at the cutoff point of 0.82 ng/l. For cortisol, the sensitivity and specificity were 67% and 100%, respectively, as shown in Figure 4 of Table 9. The AUC of cortisol indicates that it is a useful marker for the diagnosis of AA in pediatric patients; nevertheless, its low sensitivity (67%) and high specificity make it difficult to verify actual positive results.[13,14]

Conclusion

In adult participants, the current study found elevated levels of stress indicators in AA patients. In contrast, there was a strong positive link between copeptin and cortisol levels in the children's group and no correlation between copeptin and cortisol in the adult patient group. In

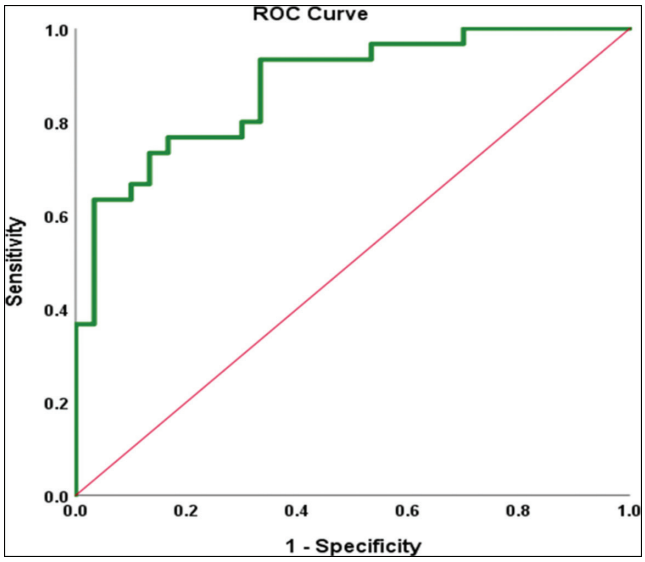

Figure 3: Receiver operating characteristic curve analysis for cortisol between the adult patients and control group

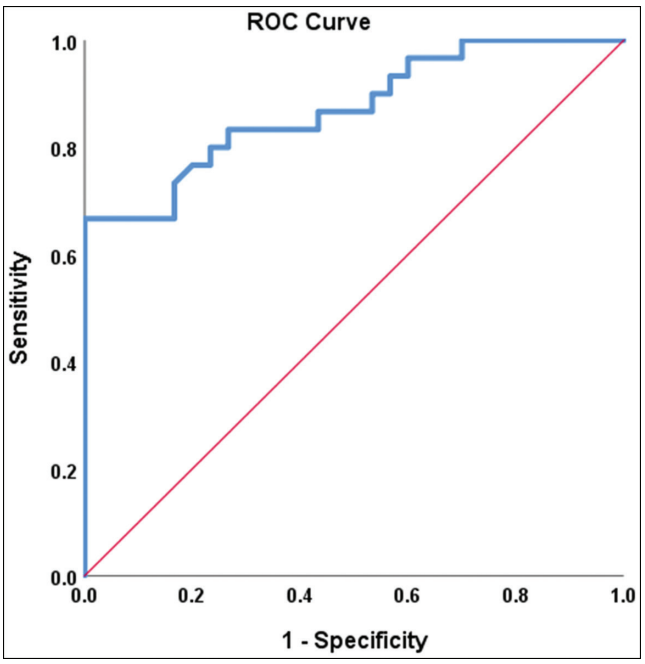

Figure 4: Receiver operating characteristic curve analysis for cortisol between the children patients and control group

Table 8: Area under the curve for cortisol between the adult patient and control group

AUC	Specificity	Sensitivity	SE	*P* value	95% Confidence interval	
					Lower bound	Upper bound
0.878	96%	63%	0.043	**0.000**	0.793	0.963

SE: standard error, AUC: area under the curve
P-value < 0.05 = significant (in bold)

Table 9: Area under the curve for cortisol between the children patient and control group

AUC	Specificity	Sensitivity	SE	*P* value	95% Confidence interval	
					Lower bound	Upper bound
0.872	100%	67%	0.045	**0.000**	0.783	0.96

SE: standard error, AUC: area under the curve
P-value < 0.05 = significant (in bold)

individuals with AA, copeptin and cortisol may be helpful as stress indicators.

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Conflicts of interest
There are no conflicts of interest.

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