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Association of Serum Copeptin Levels with Inflammatory Status and Disease Activity in Patients with Rheumatoid Arthritis

Rehab A.A. Alhamashi[1] and Ali H.A. Al-Jalibawi[2]

[1]*Department of Biology, College of Education for Pure Sciences, University of Wasit, Wasit, Iraq.*
[2]*Department of Biology, College of Science, University of Wasit, Wasit, Iraq.*
*Corresponding author: rhassan@uowasit.edu.iq

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition characterized by persistent synovial inflammation and progressive joint damage. Copeptin, a stable biomarker of arginine vasopressin secretion, has recently been implicated in several inflammatory disorders. This study aimed to evaluate serum copeptin levels in patients with RA and to investigate their association with inflammatory markers and disease activity. A case-control study was conducted on 90 participants, including 45 patients diagnosed with RA and 45 age- and sex-matched healthy controls. Serum copeptin levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique, while erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Disease Activity Score-28 (DAS28) were assessed in RA patients. The findings demonstrated significantly elevated serum copeptin levels in RA patients compared with controls (7.94 ± 2.63 vs. 4.38 ± 1.51 ng/mL; $P < 0.001$). In addition, serum copeptin showed significant positive correlations with ESR ($r = 0.44$, $P = 0.004$), CRP ($r = 0.51$, $P = 0.001$), and DAS28 score ($r = 0.56$, $P < 0.001$). Multiple stepwise linear regression analysis further revealed that DAS28 score and CRP were independent predictors of serum copeptin levels. These findings suggest that serum copeptin is elevated in RA patients and may reflect inflammatory activity and disease severity.

Keywords: Rheumatoid arthritis; Copeptin; DAS28; CRP; Inflammation.

ارتباط مستويات الكوبيبتين في مصل الدم بالحالة الالتهابية ونشاط المرض لدى مرضى التهاب المفاصل الروماتويدي

رحاب عبد الرزاق الهماشي [1] ، علي حيدر الجليباوي [2]

[1]قسم علوم الحياة، كلية التربية للعلوم الصرفة، جامعة واسط، واسط، العراق
[2]قسم علوم الحياة ،كلية العلوم، جامعة واسط ، واسط ، العراق

الخلاصة

يعد التهاب المفاصل الروماتويدي (RA) مرضًا التهابيًا مناعيًا ذاتيًا مزمنًا يتميز بالتهاب مستمر في الغشاء الزليلي وتلف تدريجي في المفاصل. وقد أظهرت الدراسات الحديثة أن الكوبيبتين(Copeptin) ، وهو مؤشر حيوي مستقر لإفراز هرمون الأرجينين فازوبريسين، يرتبط بعدة حالات التهابية مختلفة. هدفت هذه الدراسة إلى تقييم مستويات الكوبيبتين في مصل الدم لدى مرضى التهاب المفاصل الروماتويدي، ودراسة علاقته بالمؤشرات الالتهابية ونشاط المرض. أُجريت دراسة من نوع الحالات والشواهد على 90 مشاركًا، شملت 45 مريضًا مصابًا بالتهاب المفاصل الروماتويدي و45 شخصًا سليمًا متطابقين بالعمر والجنس. تم قياس مستويات الكوبيبتين في المصل باستخدام تقنية المقايسة المناعية المرتبطة بالإنزيم(ELISA) ، في حين تم تقييم معدل ترسيب كريات الدم الحمراء (ESR)، والبروتين المتفاعل(CRP) C ، ودرجة نشاط المرض DAS28 لدى المرضى. أظهرت النتائج ارتفاعًا معنويًا في مستويات الكوبيبتين لدى مرضى التهاب المفاصل الروماتويدي مقارنةً بمجموعة السيطرة (7.94 ± 2.63 مقابل 4.38 ± 1.51 نانوغرام/مل؛ $P < 0.001$). كما وُجدت ارتباطات إيجابية معنوية بين مستويات الكوبيبتين وكل من ESR ($r = 0.44$، $P = 0.004$)، و CRP ($r = 0.51$، $P = 0.001$)، ودرجة DAS28 ($r = 0.56$، $P < 0.001$). كذلك أظهر تحليل الانحدار الخطي المتدرج المتعدد أن درجة DAS28 ومستوى CRP يُعدّان من العوامل المستقلة المتنبئة بمستويات الكوبيبتين في المصل. وتشير هذه النتائج إلى أن ارتفاع مستويات الكوبيبتين في مصل الدم لدى مرضى التهاب المفاصل الروماتويدي قد يعكس شدة النشاط الالتهابي وحدّة المرض.

1. Introduction

Rheumatoid arthritis is an autoimmunity inflammatory disease that is marked by chronic synovitis, cartilage erosion, bone erosion, and extra-articular manifestations [1]. Rheumatoid arthritis is caused by a number of different factors including genetics of an individual, environmental influences, immunological disorders, and inflammation. Acute arthritis is different from rheumatoid arthritis as the latter entails chronic autoimmune synovitis that may cause deformities in joints, and the whole disease process itself. In other words, RA is viewed as a multisystem inflammatory disorder that goes beyond the joints [2].

RA is considered one of the most common forms of autoimmune rheumatic disorders that affect many people around the world. According to recently published estimates of the Global Burden of Disease, more than 17.6 million people were suffering from RA in 2020. At the same time, females were more likely to develop this health condition, and its burden grew during recent decades [3]. While a breakthrough in therapeutic interventions to treat RA occurred, an appropriate cure for this medical condition is not available, and inflammatory processes persist in a significant number of patients [4]. The mechanism of the onset of rheumatoid arthritis involves the stimulation of both innate and adaptive immune responses. Inflammation due to the immune system's reaction against the antigens of its own self, especially citrullinated proteins, causes the activation of T and B lymphocytes, phagocytes, and albumin cells. The activated immune cells generate a lot of inflammatory cytokines and enzymes involved in initiating inflammatory processes within the synovial lining and destruction of joints [5]. The inflammatory cytokines involved in the development of inflammation include TNF-α, IL-1β, IL-6, and IL-17. These cytokines are involved in the process of attracting leucocytes, bone destruction, blood vessel formation, and cartilage degradation. The inflammation leads to an abnormal functioning of blood vessels and oxidative and metabolic functions in individuals with RA [6].

According to the latest studies, autoimmune diseases such as RA, along with many others, are associated with neuroendocrine stress mechanisms such as the HPA axis and vasopressinergic pathway [7].In addition, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are involved in producing AVP because of inflammation caused activation of the signaling pathway triggered by stress [8]. This means that the chronic inflammation of RA is associated with the development of a pathological disorder involving physiological stress and inflammation [7].

Assessment of the disease activity in RA commonly involves the analysis of comprehensive scales, including DAS28, in addition to the inflammatory markers ESR and CRP. Although effective, these indicators cannot always provide comprehensive information about inflammation and physiological processes in RA patients. In other words, it is possible that a particular patient suffers from a clinically active condition even though his or her inflammatory markers remain within normal limits [9]. Hence, the development of other biomarkers to account for inflammation and physiological responses is a current priority in RA studies. In new emerging biomarkers, copeptin has received increasing scientific attention in inflammatory and systemic diseases. Copeptin is a 39 amino acid glycopeptide that comes from the C-terminal part of pro-arginine vasopressin and is released together with AVP in equimolar ratios from the posterior pituitary gland. As AVP is unstable, hard to measure due to its short life cycle and fast clearance from plasma, copeptin is regarded as a stable alternative marker for the secretion of vasopressin [10]. From a physiological point of view, the AVP/copeptin pathway is stimulated by osmotic, hemodynamic, inflammatory and

metabolic stress. Besides its established role in water and blood volume homeostasis, AVP is involved in stress adaptation, endothelial stimulation, and regulation of inflammation. The inflammatory response due to the body's tolerance to its own antigens, especially citrullinated proteins, leads to activation of T lymphocytes, B lymphocytes, macrophages, and synoviocytes. The activated immune cells generate a lot of inflammatory cytokines and enzymes involved in initiating inflammatory processes within the synovial lining and destruction of joints [5]. The inflammatory cytokines involved in the development of inflammation include TNF-α, IL-1β, IL-6, and IL-17. These cytokines lead to leukocyte migration, osteoclastogenesis, angiogenesis, and cartilage degradation. There is a dysfunction in the activity of blood vessels and oxidation/ metabolism in patients suffering from RA [6].

As stated in recent literature, there exists a relation between inflammatory disorders, like RA, and neuroendocrine stress response systems, which include HPA axis and vasopressinergic system [7]. Furthermore, some pro-inflammatory cytokines, like IL-1β, IL-6, and TNF-α, stimulate the production of AVP through stress-related signaling pathways caused due to inflammation [8]. This implies that chronic inflammation in RA results in a pathological condition characterized by physiological stress and synovitis [7]. As an example, for RA, the present studies on biomarkers have focused mostly on the autoantibody, cytokine, acute-phase reactant, adipokine, and other disease activity biomarkers. On the other hand, the neuroendocrine pathway of inflammatory stress biomarkers remains underexplored [11],[12]. In addition, recently conducted researches investigating biomarker serum levels in RA patients reveal that associations between such biomarker levels and disease activity could be influenced by disease activity grade, type of therapy, methods used in analyses, and other methodological issues; therefore, the necessity of further investigation of copeptin as a potential biomarker in RA persists [13].

According to literature available at present, there is scarce information on copeptin levels in RA patients from the Middle East and Iraq. Moreover, there are few published research papers where copeptin levels were assessed simultaneously with the levels of inflammatory biomarkers in relation to DAS28-based disease activity. Hence, the current research could generate new information on the role of copeptin as a biomarker reflecting an inflammation-neuroendocrine relationship in RA. Considering the changes in the inflammatory and neuroendocrine processes characteristic of rheumatoid arthritis, it can be suggested that serum copeptin levels would be high and positively associated with inflammatory load and disease activity in RA.

The current study was conducted to assess serum copeptin levels in patients with rheumatoid arthritis in comparison with normal controls and correlate copeptin with inflammatory markers such as CRP and ESR and DAS28 score indicating inflammation and disease activity, respectively. The purpose was to explore the possible role of copeptin as an inflammatory biomarker in the context of rheumatoid arthritis.

2. Materials and Methods

2.1 Study Design

A case-control study was conducted to determine copeptin levels in the serum of patients with RA and to evaluate the relationship between serum copeptin and inflammatory parameters in these individuals. The study was carried out during the period from July 2025

to February 2026 at Al-Zahraa Teaching Hospital, Al-Karama Teaching Hospital and Wasit investment hospital in Wasit city of Iraq.

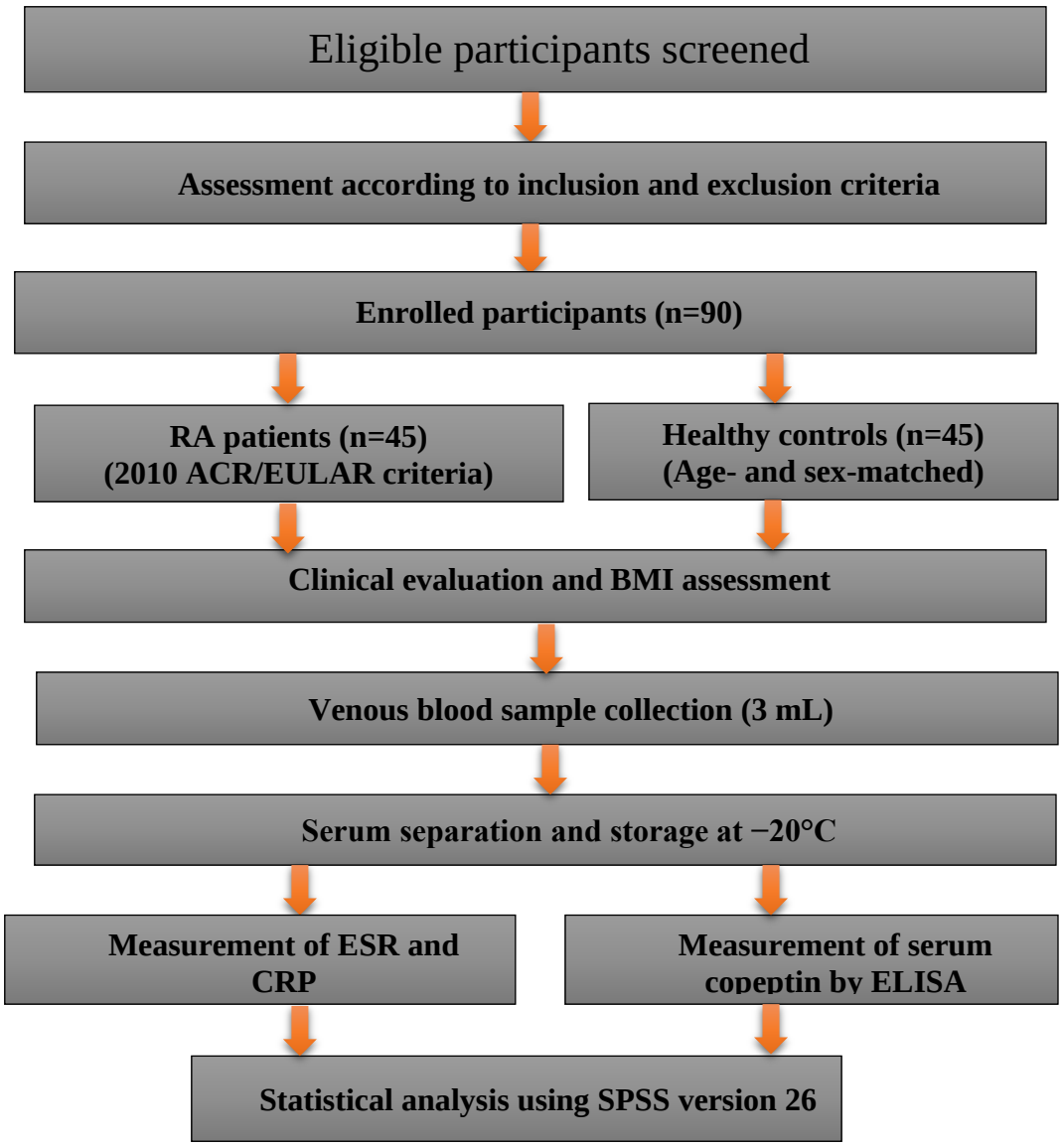

Figure -1 Case control study design

2.2 Study Participants

The sample comprised of 90 subjects, which was randomly allocated into two groups, including 45 subjects who have been diagnosed as having rheumatoid arthritis, and 45 subjects as healthy controls, who were matched according to age and sex. The patients were selected from the Rheumatology Department of Al-Zahraa Teaching Hospital, Al-Karama Teaching Hospital, and Wasit Investment Hospital. The diagnosis of rheumatoid arthritis was made by a rheumatologist using the ACR-EULAR classification criteria 2010.

The healthy controls did not have any signs of autoimmunity, inflammation, renal, liver diseases, cancer, and infections.

2.3 Inclusion Criteria

The patients included if had the following criteria:

1. Adults aged 18 years or more.
2. Rheumatoid arthritis was diagnosed according to the 2010 ACR/EULAR criteria.
3. Willingness to be part of the study.
4. For the control group, we included apparently healthy persons that were matched in terms of age and sex and lack of history of chronic inflammatory or autoimmune conditions.

2.4 Exclusion Criteria

Participants were excluded if they had:

1. Other autoimmune disorders.
2. Acute or chronic infections.
3. Diabetes mellitus.
4. Chronic kidney disorder.
5. Hepatic disorder.
6. Cardiovascular disorder.
7. Cancer.
8. Pregnant participants.
9. Concurrent corticosteroid pulse therapy.

2.5 Clinical Evaluation

Demographic and clinical information such as age, sex, body mass index (BMI) and duration of disease was obtained from all study subjects. Body mass index was determined through dividing weight (in kg) by height (in m^2).

The activity status of the disease in RA patients was evaluated using DAS28 score through the attending rheumatologist on blood collection day.

2.6 Collection of Blood Samples

Venous blood sample of about 3 mL was drawn from all study subjects aseptically. The collected samples were allowed to clot under room temperature, followed by centrifugation for 10 minutes at 3000 rpm. The resulting serum samples were collected in sterilized Eppendorf tubes kept at −20°C prior to further analysis.

2.7 Measurement of Serum Copeptin Concentration

The concentration of serum copeptin was measured using Human Copeptin ELISA Kit purchased from MyBioSource, Inc. (San Diego, CA, USA) on the basis of quantitative sandwich enzyme-linked immunosorbent assay technique as per the manufacturer's protocol.

The sensitivity of the assay is 0.024 ng/mL, and the detection range was 0.05–20 ng/mL. The intra-assay variability was less than 8%, whereas the inter-assay variability was less than 10%. The Human Copeptin ELISA Kit was manufactured under the ISO 9001:2015 certification.

The serum samples along with their respective standards were tested in duplicates, and the optical density was read with ELISA microplate reader at wavelength 450 nm. The concentration of serum copeptin was determined from the standard calibration curve.

2.8 Measurement of Inflammatory Markers

The erythrocyte sedimentation rate (ESR) was determined by the Westergren method. The level of CRP in serum was measured using an immunoturbidimetric test in the hospital laboratory.

2.9 Statistical Analysis

The Statistical Package for the Social Sciences (IBM SPSS Statistics) was utilized to analyze the statistical data. Data were presented as means ± standard deviation (SD) for continuous variables, while percentages were used for categorical variables. For normal distribution and homogeneity of data, we used the Shapiro-Wilk test and Levene's test, respectively. Independent sample t-test and one-way ANOVA coupled with Tukey post hoc test were used to compare between two groups and several groups, respectively. For the evaluation of the relationship between serum copeptin levels and other variables, the Pearson correlation analysis was conducted. In order to find out independent predictors of serum copeptin levels, variables that showed statistically significant results in univariate analysis were included in a multiple stepwise linear regression analysis. A P-value of ≤ 0.05 was taken to be statistically significant.

2.10 Ethical Considerations

The study received ethical approval from Wasit University, Al-Zahraa Teaching Hospital, Al-Karama Teaching Hospital and Wasit investment hospital. Written informed consent was obtained from all participants before their inclusion in the study, in accordance with the ethical principles of medical research conducted on humans.

3. Results

As shown in Table 1, there was no significant difference between RA patients and controls regarding mean ages (47.2 ± 9.6 vs. 45.8 ± 8.9 years; P=0.468). The percentage of females in the RA and control groups were 80.0% and 75.6%, respectively, while that of males were 20.0% and 24.4%, respectively. There was no statistically significant difference in terms of sex distribution between the two groups (P=0.614). In addition, there was no significant difference between RA patients and controls in terms of mean BMI (28.4 ± 4.2 vs. 27.7 ± 3.8 kg/m², P=0.401).

Table 1- Demographic Characteristics of the Study Groups

Variable	RA Patients (n=45)	Controls (n=45)	P-value
Age (years)	47.2 ± 9.6	45.8 ± 8.9	0.468
Sex, n (%)			
Female	36 (80.0%)	34 (75.6%)	0.614
Male	9 (20.0%)	11 (24.4%)	
BMI (kg/m²)	28.4 ± 4.2	27.7 ± 3.8	0.401

The results presented in Table 2 shows that the average serum copeptin concentration was significantly increased in patients suffering from RA compared to controls (7.94 ± 2.63

ng/mL) vs (4.38 ± 1.51 ng/mL), respectively, with a statistically significant difference observed between the two groups (P<0.001).

Table 2- Serum Copeptin Levels in Patients with Rheumatoid Arthritis and Healthy Controls

Biomarker	RA Patients (n=45)	Controls (n=45)	P-value
Serum Copeptin (ng/mL)	7.94 ± 2.63	4.38 ± 1.51	<0.001

Correlation analysis between serum copeptin concentration and clinical and inflammatory parameters in patients with RA is presented in Table 3, where the results showed that a positive significant correlation was revealed between serum copeptin concentrations and ESR (r=0.44, P=0.004), CRP (r=0.51, P=0.001), and DAS28 scores (r=0.56, P<0.001). The strongest correlation between serum copeptin levels and studied parameters was found for DAS28 scores.

Table 3- Pearson Correlation of Serum Copeptin Levels with Clinical and Inflammatory Parameters in RA Patients

Variable	Pearson correlation (r)	P-value
ESR (mm/hr)	0.44	0.004
CRP (mg/L)	0.51	0.001
DAS28 score	0.56	<0.001

Multiple stepwise linear regression analysis of parameters associated with serum copeptin concentrations in patients with RA was presented in Table 4, the results DAS28 score was shown to be a significant independent predictor of serum copeptin concentration (B=0.46, 95% CI: 0.22–0.71, P<0.001). Moreover, a significant relationship was found between CRP concentration and serum copeptin levels (B=0.34, 95% CI: 0.11–0.55, P=0.004). The model showed statistical significance with the adjusted R^2 equaling 0.39 (F=11.21, P<0.001).

Table 4- Multiple Stepwise Linear Regression Analysis of Factors Associated with Serum Copeptin Levels in RA Patients

Variable	Unstandardized B	95% CI	P-value
DAS28 score	0.46	0.22 – 0.71	<0.001
CRP (mg/L)	0.34	0.11 – 0.55	0.004
Dependent variable: serum copeptin level.			
Adjusted R^2 = 0.39, F = 11.21, P < 0.001.			

As shown in Table 5, RA patients were categorized based on their DAS28 disease activity. The high disease activity group comprised the majority, representing 46.7% of the total number of patients, whereas moderate and low disease activity accounted for 33.3% and 20.0% of the studied RA patients, respectively.

Table 5- Distribution of RA Patients According to DAS28 Disease Activity

Disease Activity	Number (%)
Low activity	9 (20.0%)
Moderate activity	15 (33.3%)
High activity	21 (46.7%)

The copeptin serum levels of RA patients according to their DAS28 disease activity categories are displayed in Table 6. The average copeptin serum levels showed an increasing trend as the disease activity increased; in patients with low, moderate, and high disease activity, the levels were 5.74 ± 1.39 ng/mL, 6.88 ± 1.82 ng/mL, and 9.16 ± 2.41 ng/mL, respectively. There was a significant difference between the groups with P-value <0.001.

Table 6- Serum Copeptin Levels According to DAS28 Disease Activity in RA Patients

Disease Activity	Serum copeptin (ng/mL)
Low activity	5.74 ± 1.39
Moderate activity	6.88 ± 1.82
High activity	9.16 ± 2.41

4 . Discussion

The current investigation revealed that there was a marked elevation in serum copeptin concentrations in RA patients, which had a positive correlation with inflammatory markers and disease activity scores. However, even more important, the associations between copeptin concentration and various markers extended beyond the simple difference between the two groups, pointing to the role of copeptin in the integrated inflammatory-neuroendocrine stress reaction accompanying active RA. The biological significance of this finding is due to the emerging recognition of RA as a systemic immunoinflammatory syndrome, where besides synovial inflammation and bone destruction, there are multiple physiological and neuroendocrine changes. [3]

One should acknowledge that the lack of significant differences in age, sex ratio, and BMI among the investigated populations is a critical strength of the current research. The matching of the control group to the patient group reduced the possible influence of demographic and metabolic factors on serum copeptin concentrations. It is especially important since copeptin synthesis might be modified by obesity, metabolic stress, cardiovascular dysfunction, renal insufficiency, and general illness. In this situation, the higher levels of copeptin in RA patients could be explained by some pathophysiological effects rather than demographic disparities. The fact that there is a predominance of females among the RA population also reflects the current scientific data regarding the nature of RA as this condition affects women at the middle stage of their life [2],[3].

High concentrations of copeptin in serum in patients with RA are the core finding in this case study. This substance is considered the C-terminal portion of pre-pro-arginine vasopressin and is always produced in the same amount as AVP. Due to the unstable nature of AVP, co-opeptin has emerged as one of the major markers of vasopressin activity and the stress response [14]. Persistent inflammation activity in rheumatoid arthritis patients may lead to the participation of the hypothalamus-pituitary system and vasopressin activation through

inflammatory neuroimmune signaling pathways. Pro-inflammatory cytokines like IL-1b, IL-6, and TNF-α have proven to be able to exert effects on the stress response in the hypothalamus. Therefore, the secretion process results in increased AVP release under inflammatory conditions, thereby explaining the high colibacillin concentration in rheumatoid arthritis patients.

The explanation above is backed by what is currently known about the pathogenesis of RA. The synovitis observed in patients with RA occurs due to activation of macrophages, fibroblast-like synoviocytes, auto-reactive T lymphocytes, and B cells that constantly release inflammatory cytokines and matrix degrading factors. Such inflammatory phenomena are not isolated to the joints but rather extend to endothelial dysfunction, oxidative stress, autonomic dysfunction, metabolic disturbances, and systemic immune activation [6]. Thus, the activation of the AVP-copeptin system in RA can be considered biologically justified in the context of adaptation to inflammatory stress and neuroendocrine disorders.

One of the most interesting findings of the present study was the existence of a positive correlation between the level of copeptin in the blood and ESR. This parameter characterizes chronic inflammation due to changes in the composition of plasma acute-phase proteins, including fibrinogen and immunoglobulins. The correlation between copeptin and ESR indicates that copeptin concentration increases with the persistent presence of systemic inflammatory load. However, the correlation strength makes it possible to regard copeptin as not just another inflammatory marker but as a unique physiological characteristic.

Consequently, the link between copeptin and CRP adds another piece of evidence concerning the role of copeptin in inflammatory processes in RA. Indeed, CRP production is mainly regulated by IL-6-mediated hepatic acute phase activation and constitutes one of the most precise biomarkers of systemic inflammation in RA. The independence of CRP as a predictor of copeptin elevation in the regression model indicates a direct contribution of inflammatory activation in copeptin elevation. However, despite the strong link between copeptin and CRP, copeptin should not be considered as a surrogate of CRP due to different biological mechanisms underlying their production. Whereas CRP reflects the inflammatory activation in the liver, copeptin reflects activation of stress-related neuroendocrine systems. This fact could account for a significant yet incomplete correlation between copeptin and inflammatory markers.

Finally, the greatest correlation found in this investigation was established between copeptin serum concentration and DAS28 disease activity score. Such a result is especially relevant given the nature of DAS28. As a matter of fact, DAS28 encompasses many aspects of RA pathology, such as the number of affected and swollen joints, inflammatory markers, and general patient assessment. Thus, taking into account the correlation between copeptin and DAS28, it may be concluded that copeptin correlates with the cumulative physiological stress caused by an active process of RA, rather than inflammation.

In relation to the possible mechanism underlying the association between copeptin elevation and RA activity, it is possible to assume that RA activity exacerbates neuroendocrine stress via several potential mechanisms, including pain, cytokine production, endothelial dysfunction, autonomic dysfunction, impaired sleep, fatigue, and immune activation. In other words, active RA can induce the release of AVP from the hypothalamus, thus elevating the serum copeptin level. This hypothesis is consistent with the results obtained in this study serum copeptin increased progressively in accordance with the progression of RA activity. Therefore, it may be stated that the findings of the current

investigation provide more support for the suggested hypothesis than just comparing patient and control groups, as there was a clear dependence on RA activity.

In this regard, the results of multiple linear regression analysis revealed that DAS28 and CRP were independently associated with copeptin, which implies that not only clinical RA activity but also inflammation are involved in the regulation of copeptin production. DAS28 remained the most significant predictor of copeptin. It would make biological sense since DAS28 incorporates multiple facets of RA activity at once, such as joint inflammation, patient symptomatology, and inflammation. Thus, DAS28 might be more representative of the overall inflammatory and physiological stress state leading to vasopressinergic system activation.

The results of the current study largely coincide with the body of literature on copeptin as a marker of systemic inflammatory and stress disorders.Stressed that copeptin was an invaluable biomarker in diagnosing and predicting inflammatory and systemic conditions due to its ability to detect neuroendocrine stress activation rather than organ damage alone[10]. Likewise, [14]. viewed copeptin as a clinically valuable biomarker that reflected vasopressinergic stress responses in various pathological states. Despite the lack of dedicated research into RA and copeptin, the results of the present study appear biologically sound.

One might agree with studies examining copeptin in inflammatory states associated with cytokine stimulation and systemic physiological stress. For example, [15]. identified a strong link between copeptin and inflammatory burden in neonatal sepsis. While sepsis and RA are two very different clinical entities in terms of their course of illness and immunopathogenesis, both conditions share mechanisms of inflammation based on cytokine stress signaling, endothelial dysfunction, and systemic inflammation. This commonality might partly account for the similar inflammatory profile seen with copeptin levels in various inflammatory disease [16].

However, it is important to recognize the discrepancies that have been observed among prior studies regarding the relationship between copeptin levels and disease activity once other factors have been taken into consideration such as cardiovascular risk profile, renal function, metabolic derangements, hydration status, and treatment effects. Discrepancies can arise from variations in study methodology with respect to sample size, ethnicity, disease duration, laboratory techniques used, treatment effect, and disease severity. Furthermore, biologic agents and steroid treatments may independently affect inflammatory and neuroendocrine pathways, regardless of the underlying disease activity.

In the current study, several confounding factors that could impact copeptin levels were avoided such as diabetes mellitus, chronic kidney disease, liver disease, cardiovascular disease, infections, malignancy, and pregnancy. This enhances the biological hypothesis suggesting that the increase in copeptin is mainly associated with the level of inflammation in RA patients. In addition, the simultaneous measurement of ESR, CRP, DAS28, and the severity of disease provides a better analytical approach compared to simply comparing biomarkers [17].

In modern RA research on biomarkers, it has been recognized that none of the currently available biomarkers represents the whole pathophysiology of RA. Established biomarkers such as CRP and ESR have significant clinical value but represent only the acute phase inflammation. On the other hand, the use of copeptin could offer new insights into the neuro-endocrine response to inflammatory diseases. Therefore, the usefulness of copeptin

cannot be seen in its replacement of already known biomarkers but in their integration by assessing inflammatory-physiological relationship [8] .

The innovation introduced by the current research is the evaluation of copeptin from a wider perspective of inflammatory activity and physiological reaction to stress in RA patients from Iraq. Earlier RA biomarker researches had mostly concentrated on cytokine, autoantibody, adipokine, or joint structural biomarker biomarkers, but little work has been done on biomarkers indicative of neuroendocrine stress-inflammatory pathway. Hence, the current research adds further weight to the theory that RA is an extensive process with interplay of systemic inflammation and stress biology [15].

5. Conclusion

In conclusion, this study shows that serum copeptin concentration is higher in RA patients and positively correlates with ESR, CRP, and DAS28 score. The independent role of DAS28 score and CRP as predictors of copeptin concentration suggests that copeptin acts as an integrator reflecting systemic inflammation and disease activity simultaneously. The increasing trend in copeptin concentration along with increasing disease activity further strengthens the hypothesis that copeptin is a marker of inflammation-neuroendocrine stress in RA patients. Taken together, the above results indicate that copeptin might be considered as a physiological biomarker of systemic stress in active RA.

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Conflict of interest

No conflict of interest

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