Evaluation of Serum Antioxidants in Rheumatoid Arthritis of Iraqi Women

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Abstract

Background: Rheumatoid arthritis (RA) , an autoimmune condition affecting joints, affects 1% of Iraqi patients. A study highlights the importance of antioxidant levels in treating RA, emphasizing the role of antioxidant markers in disease treatment and the need for balance in autoimmune conditions.

Objectives: The presented work aimed to investigate the effect of rheumatoid arthritis on antioxidant status such as superoxide dismutase and total antioxidant capacity in sera of Iraqi women.

Materials and Methods: A case-control study involving 130 female subjects with ages ranging between 35-65 years, who were divided into two groups: 70 rheumatoid arthritis patients and 60 apparently healthy individuals as a control. Serum superoxide dismutase activity levels and the total antioxidant capacity (TAC) were measured using an ELISA technique

Results: The study revealed a significant decrease in the levels of superoxide dismutase (SOD) and TAC represented by Ferric Reducing Ability of Plasma (FRAP), in blood capacity, respectively, when comparing patients to a healthy control group. Receiver operating curve (ROC) analysis for SOD and FRAP, respectively, also showed high sensitivity and high specificity .

Conclusion: Antioxidant levels play an important role in the pathophysiology of RA, so SOD and FRAP can be considered biomarkers for the evaluation of RA. Maintaining a balance between oxidative and antioxidant status is essential in the treatment of rheumatoid arthritis and other autoimmune diseases.

تقييم حالة مضادات الأكسدة في أمصال التهاب المفاصل الروماتويدي لدى النساء العراقيات

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خلاصة

الخلفية: تسلط الدراسة الضوء على أهمية مستويات مضادات الأكسدة لدى الإناث العراقيات المصابات بالتهاب المفاصل الروماتويدي، وتسليط الضوء على دور مضادات الأكسدة في علاج الأمراض، والتأكيد على الحاجة إلى التوازن في حالات المناعة الذاتية.

الأهداف: يبحث البحث في تأثير مضادات الأكسدة مثل ديسموتاز فوق أكسيد SOD وقدرة البلازما FRAP على تقليل الحديد على تطور التهاب المفاصل الروماتويدي لدى الإناث العراقيات.

المواد والطرق: دراسة الحالات والشواهد التي شملت 130 أنثى تتراوح أعمارهن بين 35-65 سنة، وتم تقسيمهن إلى مجموعتين: 70 مريضة بالتهاب المفاصل الروماتويدي و60 فرداً سليماً كمجموعة تحكم. تم قياس مستويات SOD و FRAP في الدم باستخدام تقنية ELISA

النتائج: كشفت الدراسة عن انخفاض ملحوظ في مستويات فوق أكسيد ديسموتاز ,SOD,TAC، ممثلاً بإنزيم الحديديك المختزل FRAP، في بلازما الدم، على التوالي، عند مقارنة المرضى بمجموعة مراقبة صحية. أظهر تحليل منحنى تشغيل المستقبِل ROC ـ SOD وFRAP، على التوالي، حساسية عالية وخصوصية عالية..

الاستنتاج: تلعب مستويات مضادات الأكسدة دورا هاما في الفيزيولوجيا المرضية لمرض RA، لذلك يمكن اعتبار SOD و FRAP مؤشرات حيوية لتقييم التهاب المفاصل الروماتويدي. يعد الحفاظ على التوازن بين حالة الأكسدة ومضادات الأكسدة أمرًا ضروريًا في علاج التهاب المفاصل الروماتويدي وأمراض المناعة الذاتية الأخرى

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune condition affecting joints, often causing localized inflammation and eventually progressing to systemic inflammation. Its prevalence is high in the Middle East and North Africa, but its epidemiology is limited due to insufficient data (Hasan et al., 2022). The prevalence of rheumatoid arthritis (RA) is estimated to be around 1% in most highly industrialized nations, with occurrence rates ranging from 0.1-1.9% in different global surveys. In Iraq, the prevalence of RA is reported to be 1% (Al-Ghazaly and Jassim, 2022). Among the population, individuals affected by rheumatoid arthritis range from 0.5% to 1.0%, with an annual occurrence of 3 to 5 new cases per 100,000 individuals. This condition displays a female predominance with a ratio of 3:1, which is consistent with other autoimmune conditions (Chancay et al., 2019). Antioxidants are molecules capable of counteracting and slowing down oxidation reactions of substances that can form free radicals (Parcheta et al., 2021). They neutralize or divert reactive oxygen species (ROS) such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), interrupt free radical reactions, and destroy ROS such as vitamins E and C, flavonoids, glutathione, and uric acid. They also bind/inactivate metal ions (catechins, ferritin, and ceruloplasmin), protecting cells against damage (Hadi et al., 2023).

There are three mechanisms of the body's defense against ROS and reactive nitrogen species (RNS). The first line of defense involves enzymes such as CAT and SOD, which prevent ROS and RNS from reacting with essential cell compounds (Orabi and Abou-Hussein, 2019). The second mechanism, which entails the participation of antioxidants such as glutathione and uric acid, serves to halt free radical chain reactions. The third mechanism is concerned with the restoration and/or elimination of harm induced by the interplay of reactive oxygen species (ROS) and reactive nitrogen species (RNS) with biomolecules. Enzymes exhibiting oxidoreductase functionality, for instance, paraoxonase or thioredoxin, are implicated in facilitating this process (Parcheta et al., 2021)). The primary categories of antioxidants of utmost significance encompass the enzymes known as superoxide dismutase, which play a crucial role in the restoration of oxidative harm. An instance of oxidative stress unfolds when the generation of reactive species surpasses the capacity of antioxidants, resulting in disparities within the physiological system. Various elements such as xenobiotics, reduced levels of antioxidants, or elevated ROS/RNS species have the potential to incite this disproportion, consequently impacting the body's defensive mechanism (Aziz et al., 2019). TAC is a biomarker used to assess the body's antioxidant potential (Tudorachi et al., 2021). The overall antioxidant capacity (TAC) plays a vital role in maintaining cellular redox homeostasis. The intake of antioxidant-rich foods such as fruits and vegetables has the potential to enhance TAC levels in the plasma. Increased TAC levels could potentially mitigate metabolic imbalances and hurt plasma C-reactive protein (CRP), which serves as a biomarker for systemic inflammation (Mohammadi et al., 2022). The decline in antioxidant levels among individuals diagnosed with rheumatoid arthritis is attributed to elevated levels of inflammatory and oxidant markers. In a study conducted by Das *et al* 2021, markedly elevated concentrations of these markers were observed, alongside reduced levels of vitamin C in patients with RA in comparison to individuals in good health. This oxidative stress is a major mechanism in the progression of arthritis, as highlighted in the study by Rao et al (Liu et al., 2022). The decrease in antioxidant levels in patients with rheumatoid arthritis is likely due to the inflammatory nature of the disease and the oxidative stress associated with it (Soltani Bajestani et al., 2023). Antioxidants play a crucial role in rheumatoid arthritis (RA) by reducing oxidative stress, which

is linked to inflammation and disease progression (Ross et al., 2020). The presented work aims to investigate the levels of antioxidants in sera of Iraqi women with rheumatoid arthritis and to evaluate the effects of these effects on oxidative stress and inflammation and then on the pathogenesis of the disease.

2. Materials and Methods

A case-control research approach was used to collect data from 130 females between mid-October 2023 from to March 2024. The females, aged between 35-65 years, were selected from the Rheumatology Unit at Al-Hassan Teaching Hospital, Kerbala Health Directorates in Kerbala, Iraq. They were divided into two groups: the first group contained 70 patients with rheumatoid arthritis (diagnosed by a rheumatologist according to clinical examination and laboratory testing to ensure inclusion in the American College of Rheumatology (ACR). /European League Against Rheumatism (EULAR) 2010 (ACR/EULAR-2010) (Aletaha et al., 2010) and another 60 samples were obtainedned from an apparently healthy control group. The Exclusion criteria included people with any chronic disease such as diabetes, cirrhosis, kidney disease, heart disease, malignancy, and other inflammation, autoimmune conditions. A questionnaire was developed for the study based on the literature review and discussions between the researcher and the supervisory team. The questionnaire included age, type of treatment, and family history of rheumatoid arthritis.

The blood sample was drawn from each participant to measure serum SOD and FRAP levels measured using the Sandwich-ELISA technique (Sino Biological Inc, Beijing, China), Both CRP and RF were measured using a chemical analyzer (DIRIUI CS480/China)(DIRUI/ China kit) In addition, ESR was measured using Fast Detector (skgmes, China). The TAC or FRAP is a method that determines the capacity of a sample to reduce iron (Fe^{3+}) and TPTZ at the acidic condition, pH (3.6) to ferrous ion. An intense blue color was formed when the ferric tripyridyltriazine (TPTZ-Fe^{3+}) complex was reduced to ferrous tripyridyltriazine (TPTZ-Fe^{2+}) and the absorption is measured at 593 nm, the FRAP levels were measured using an ELISA technique and reader which evaluated relative to different Fe^{3+} concentrations and by expressing it as mM of Fe^{2+} equivalents per kg or per L of the specimen, the FRAP values can be determined (Wojtunik-Kulesza, 2020).

2.1.Statistical Analysis

Data analysis was performed utilizing IBM's Statistical Package for Social Sciences, version 22.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics were used to present scale variables for data with a normal distribution in the form of mean ± standard deviation. The distribution of the data was checked for normality using the Box plot test. Statistical comparisons of biomarker mean across different groups were carried out using T-tests and analysis of variance tables. Statistical significance was determined by a p-value lower than 0.05. The identification of the optimal sensitivity and specificity threshold for critical cases was achieved through the implementation of receiver operating characteristic (ROC) analysis.

3. Results

Table 1 demonstrates the mean ± SD levels of serum SOD and FRAP between study groups RA and control. SOD levels were significantly lower in RA patients (4.19 ± 1.49 U/L) as compared with the control group (8.16 ± 0.74 U/L), ($P \leq 0.0001$) respectively. Also, a decrease in the levels of the total capacity of antioxidants was observed by determining FRAP level in the blood when comparing RA patients (341.25 ± 91.24 µmol/L) with the healthy control

group (709.30 ± 141.32 µmol/L), P ≤ 0.0001 respectively. The age distribution among the studied group showed a non-significant difference (P=0.164), so the sample was homogenous in age.

Table 1: Demographic Characteristics of This Study and The Mean Difference of Biomarkers For RA Compared to The Control Group

Parameter	RA Mean ± SD	Control Mean ± SD	P-value
	N = 70	N = 60	
Age	48.62 ± 6.62	46.07 ± 7.99	0.164 [NS]
SOD	4.19 ± 1.49	8.16 ± 0.74	≤ 0.001[S]
FRAP	341.25 ± 91.24	709.30 ± 141.32	≤ 0.001[S]
T-test was significant at p ≤ 0.05; SD: standard deviation; S: significant; NS: non-significant			

Fig.1 shows The percentage of patients with pre-existing medical conditions and those who had no medical history was (66% and 44%), respectively, while these percentages in the control group of healthy individuals were (34% and 66%), respectively.
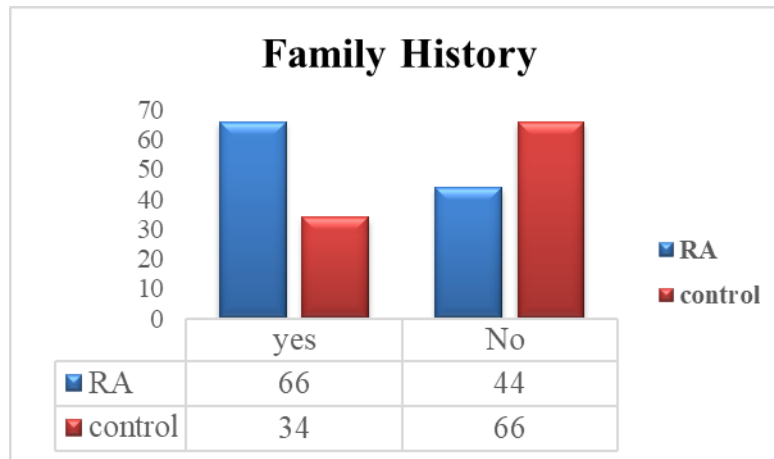

Family History

	yes	No
RA	66	44
control	34	66

Figure 1: Differences in Family History Rates of Patients and Healthy Control Groups.

Table 2 and Fig.2 indicate the analysis of receiver operating curve (ROC) analysis for each of SOD and FRAP respectively showed a (sensitivity of 89% and a specificity of 88%. 95% confidence interval (CI) ranged from 0.75-0.92, and the area under the curve (AUC) was 0.95 The cut point was set at 5.17U/L or higher) (sensitivity of 71% and specificity of 73%. 95% confidence interval (CI) ranged from 0.91-0.99, and the area under the curve (AUC) was 0.84 The cut point was set at 403.5 µmol/L or higher.

Table 2: Receiver Operating Characteristic (ROC) Curve Analysis of SOD and FRAP in RA Patients Groups

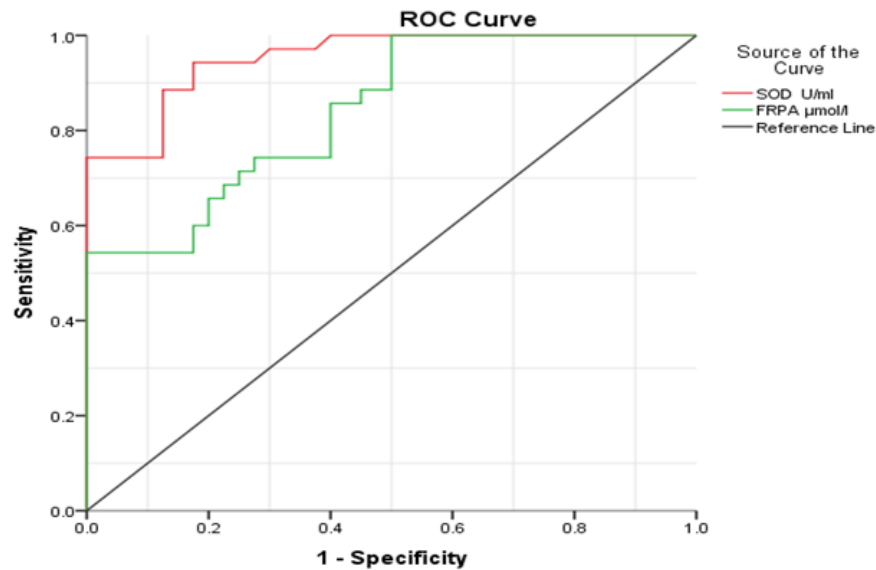| Parameters	Cut-off	Sensitivity	Specificity	AUC	P-value	95% CL	
FRPA, (µmol/l)	403.5	%71	%73	0.841	0.0001	0.912	0.994
SOD, (U/l)	5.17	%89	%88	0.953	0.0001	0.756	0.927
AUC: Area under the curve, **ROC**: Receiver Operating Characteristic							

Figure 2: ROC of SOD and FRAP in The RA Group

4. Discussion

CRP indicates inflammation and is high in rheumatoid arthritis patients and RF aids in diagnosing this condition (Atzeni et al., 2017; Puentes-Osorio et al., 2021). The study measured these signs and obtained results resembling previous studies. Higher RF in early arthritis patients increases arthritis risk. Rheumatoid joints involve T cells stimulating B cell responses and antibody production (Jang et al., 2022). CRP and RF are essential biomarkers for diagnosing and monitoring RA, reflecting inflammatory and autoimmune processes (Cui and Qian, 2023; Mun et al., 2021; Rodríguez-Muguruza et al., 2021).The investigation was conducted exclusively on female subjects. This choice was made based on the greater occurrence of rheumatoid arthritis in women compared to men. The disparity in rheumatoid arthritis prevalence between sexes may be linked to an imbalance in estrogen levels, rendering women more prone to autoimmune conditions than their male counterparts (Sciarra et al., 2023)**.** the current study was similar to most other studies (Osman et al., 2021)**.** Table 1 The lack of statistically significant differences in mean age between individuals with rheumatoid arthritis and control groups is attributable to careful matching of study groups and an unbiased approach toward any specific age group, and the results were consistent with both (Alattabi and Zenki, 2023)**.** Additionally, studies showed that prolonged treatment in RA patients significantly increased oxidative stress and

decreased antioxidant potential. In the current study, evidence indicates that a positive and statistically significant family history of rheumatoid arthritis (RA) suggests a predisposition to RA, offering potential early benefit (Mun et al., 2021). This discovery may aid in the diagnosis of rheumatoid arthritis and in providing necessary care. First-degree relatives of individuals with rheumatoid arthritis demonstrate an increased probability of experiencing arthritis symptoms. These findings are consistent with the consensus in contemporary research (Kronzer et al., 2021; Sparks et al., 2018; Tanner et al., 2019). Research has shown that an imbalance between oxidant and antioxidant processes plays a significant role in rheumatoid arthritis. Studies have demonstrated that patients with rheumatoid arthritis have higher levels of oxidative factors such as malondialdehyde (MDA) and lower levels of antioxidants like superoxide dismutase (SOD). These findings suggest that oxidative stress and inflammation contribute to the development and progression of rheumatoid arthritis, highlighting the importance of studying antioxidant levels to better understand the disease and potentially develop new treatment strategies (Direito et al., 2021; Quinonez-Flores et al., 2016). Lower levels of SOD were found among patients with rheumatoid arthritis compared to the healthy group, which explains the fact that lower levels of antioxidants in the blood are associated with an increased susceptibility to developing rheumatoid arthritis, and this is consistent with what was found by (Zamudio-Cuevas et al., 2022a, 2022b). The depletion of antioxidants in the blood is believed to be due to their utilization in attenuating inflammatory mediators. The SOD activity is thought to modulate the organism's immune response by reducing H_2O_2 concentration, leading to a decrease in lymphocyte proliferation and exerting a mild anti-inflammatory effect. Its possible involvement in the regulation of chronic inflammation of various pathogens is also hypothesized. This is similar to the many studies (Scheffer and Latini, 2020; Zheng et al., 2023).

In the current study, lower levels of FRAP were observed among individuals diagnosed with rheumatoid arthritis, indicating an increase in oxidative stress and generation of reactive oxygen species (ROS) and this was in agreement with another study (Kondo et al., 2023; Mateen et al., 2016). This oxidative stress is implicated in causing damage to the body's tissues and contributing to the chronic nature of the disease. The activity of the antioxidant defense system is diminished in patients with rheumatoid arthritis, which subsequently leads to increased oxidative stress (Fonseca et al., 2019). The study has some potential limitations the relatively small number of patients included in the study; due to the high cost of tests as well as the short time of study. Research findings indicate a significant involvement of oxidative stress in the development of rheumatoid arthritis. It is suggested that reducing oxidative stress levels and enhancing antioxidant capabilities could be beneficial in the treatment of rheumatoid arthritis. The findings underscore the importance of understanding and treating oxidative stress as part of the therapeutic approach to rheumatoid arthritis (Hitchon and El-Gabalawy, 2004; Huang et al., 2022; Zeng et al., 2021).

5. Conclusion

Superoxide Dismutase (SOD) and Ferric Reducing Ability of Plasma (FRAP) serve as crucial diagnostic markers for female patients with rheumatoid arthritis, suggesting a notable association between antioxidant status and the prognosis of RA. It is imperative to effectively address these factors in the management of rheumatoid arthritis in women..

6. Acknowledgment

7. Ethical Approval

Ethical approval for the study was confirmed by the College of Medicine, Kerbala University, and Kerbala Health Directorate (Ethics Board, 23-43 on 12/21/2023).

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