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Relationship between Oxidative Stress and Inflammation in Ankylosing Spondylitis

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disorder in the vertebral spine and sacroiliac joints. The assessment of systemic oxidative stress has been accurately linked to the pathogenesis of various illness processes, including AS. The relationship among oxidant and antioxidant stress biomarkers in AS was investigated, and their possible contribution to its pathogenesis was determined. The research included 80 patients diagnosed with AS, along with 48 healthy volunteers. Serum levels of total antioxidant status (TAS) and total oxidant status (TOS) were measured using Erle's method, and the oxidative stress index (OSI) and other routine tests were calculated. Serum TOS, OSI, CRP, and ESR values were found to be significantly elevated in patients compared to healthy controls (HCs) ($P < 0.01$). Conversely, serum TAS levels were found to be reduced in patients ($P < 0.01$). These variables are considered critical in the pathogenesis of AS, where they contribute to its diagnosis and management.

Keywords: Total Oxidant Status, Ankylosing Spondylitis, Oxidative Stress, Inflammation, Total Antioxidant Status.

العلاقة بين الإجهاد التأكسدي والالتهاب في التهاب الفقار اللاصق

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الخلاصة

التهاب الفقار اللاصق (AS) هو اضطراب التهابي مزمن في العمود الفقري والمفاصل العجزية الحرقفية. تم ربط تقييم الإجهاد التأكسدي الجهازي بدقة بآلية تطور العمليات المرضية المختلفة، بما في ذلك التهاب الفقار اللاصق. بحثت هذه الدراسة في العلاقة بين مؤشرات الإجهاد التأكسدي ومؤشرات الإجهاد المضاد للتأكسد في التهاب الفقار اللاصق (AS) وحددت مساهمتها المحتملة في مسببات المرض. شمل البحث 80 مريضًا تم تشخيصهم بالتهاب الفقار اللاصق (AS) بالإضافة إلى 48 متطوعًا صحيًا. تم قياس مستويات مصل الحالة المضادة للأكسدة الكلية (TAS) والحالة المؤكسدة الكلية (TOS)، باستخدام طريقة إيرل وتم حساب مؤشر الإجهاد التأكسدي (OSI) والاختبارات الروتينية الأخرى. وجدنا أن مستويات TOS و OSI

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و CRP و ESR في المصل كانت مرتفعة بشكل كبير لدى المرضى مقارنةً بالمجموعة الضابطة الصحية ($P < 0.01$)؛ وعلى العكس، كانت مستويات TAS في المصل منخفضة لدى المرضى مقارنةً بالمجموعة الضابطة الصحية ($P < 0.01$). تُعتبر تلك المتغيرات حاسمة في مسببات مرض التهاب الفقرات التصلبي حيث تساهم في تشخيص المرض وإدارته.

1. Introduction

Ankylosing spondylitis (AS) is a primary subclass of spondyloarthropathies, that mainly impacts the sacroiliac articulations and the axial bone structure, potentially resulting in joint structural deformities, abnormal ossification, and impairment [1]. As AS worsens, it may impact several organs and systems, lowering quality of life. These include the eyes, integumentary skin, kidneys, gastrointestinal tract, and cardiovascular system [2]. The aetiology of ankylosing spondylitis is unclear; nonetheless, oxidative stress is believed to have a significant influence on its progression [4].

For the sake of simplicity, we term the process by which very energetic and reactive so-called free radicals carry out their damaging reactions "oxidation.". Cellular constituents, including lipids, proteins, and DNA, may be damaged by this oxidation process [5]. Some of these compounds can be produced due to external factors such as pollutants and radiation as well as internal factors such as cellular metabolism [3]. In most cases, free radicals are scavenged by cellular antioxidants, preventing further oxidative injury. This typically occurs when reactive species are produced in excess within the human body after the body absorbs reactive oxygen species (ROS). ROS encompass free radicals including nitric oxide (NO), molecular oxygen (O₂), and hydroxyl radicals (OH) [6]. Inflammatory illnesses and autoimmune illnesses, including ankylosing spondylitis, cause cellular damage throughout their origin [7]. Cells involved in inflammation release enzymes that generate reactive oxygen species, leading to pathways that activate inflammatory response-intensifying mechanisms, which in turn have role in both resorption of bones and new bone creation [8]. Elevated levels of reactive oxygen species in areas of inflammation trigger signaling pathways that enhance the formation of osteoclasts and the processes of bone resorption. An important component of the intricate interplay among inflammatory processes and bone deterioration in AS is oxidative stress. Moreover, it is reasonable to assume that oxidative stress also contributes to the presence of new bone, a hallmark of AS [9]. Total antioxidant status (TAS) and total oxidant status (TOS) are measures of oxidative stress that have a significant impact on bone remodeling in AS patients. This highlights the need of developing efficient methods for managing bone health [3]. The availability of these biomarkers provides additional information regarding the balance of oxidation and reduction within a cell. Some studies have shown elevated levels of these biomarkers in AS patients, whereas others have failed to detect any change [10]. It is biologically acknowledged that oxidative stress is complex in AS and helps to further the pathogenesis of the condition through destructive cellular processes [11]. Neutrophils, while protective, exhibit dual functionality by generating reactive nitrogen and oxygen species, ultimately leading to tissue damages and inflammation [12].

In autoimmune illnesses such as ankylosing spondylitis, it is common to observe elevated oxidative stress resulting from the overproduction of reactive oxygen species or insufficient synthesis of antioxidant enzymes [13]. Furthermore, oxidative stress and elevated levels of ROS may amplify the immunological response by activating pro-inflammatory pathways, which are mediated by pro-inflammatory cytokines secreted by immune cells. It is critical to emphasize the feed-forward connection among inflammation and oxidative stress, which is crucial for the chronic nature of AS [14]. Additionally, AS has been documented to correlate with extra-articular manifestations, including but not limited to uveitis, gastrointestinal

disorders, and cardiovascular illnesses linked to oxidative stress, as frequently observed in inflammatory disorders, including rheumatoid arthritis and inflammatory bowel illness [15]. Research into the exact ways in which oxidative stress causes AS is still in its early stages. Nevertheless, it has been suggested that reactive oxygen species contribute significantly to tissue damage and inflammation in ankylosing spondylitis [16]. Novel treatment approaches that reestablish a balance among oxidants and antioxidants may be possible if the processes of oxidative stress in AS are better understood, ultimately impeding illness development and enhancing clinical outcomes. The precise roles of oxidative stress in AS, as well as the potential therapeutic benefits of treatments aimed at lowering oxidative damage, need more investigation [17].

The objective of this study was to investigate the relationship among inflammatory biomarkers in AS patients and markers of oxidative stress, such as TOS and TAS, in comparison to healthy control individuals. By delving into this connection, this study hopes to provide light on possible treatment targets, highlighting its significance as a fresh contribution to our understanding of the pathophysiology of AS.

2. Materials and Methods

Subjects

The study was conducted on ankylosing spondylitis patients in Baghdad, Iraq, after obtaining approval from the Ethics Committee of the Department of Biotechnology, College of Science, University of Baghdad, and after acquiring certified permission from all participants. Eighty individuals with an AS diagnosis were included in the research. All participants were over 20 years old and had been attending the Rheumatology unit, at Baghdad Teaching Hospital, Medical City from November 2023 to January 2024. In addition, 48 healthy adults, spanning the ages of 21 to 63, served as HCs. Patients selected based on the Assessment of Spondylarthritis International Society (ASAS) classifying criteria of spondylarthritis [18]. The study did not include patients with other inflammatory overlapping disorders such as Rheumatoid arthritis psoriasis or inflammatory bowel illness. The Bath Ankylosing Spondylitis Illness Activity Index (BASDAI) was employed to evaluate illness activity in patients with AS [19]. Active AS illness: patients exhibiting a BASDAI score of 4 or higher at the time of the study were classified as having active illness. The patients were categorized into two groups based on the BASDAI score values. The first group included 50 active patients (BASDAI >4), while the second group consisted of 30 inactive patients (BASDAI <4). The study protocol was approved by the Ethics Committee at the Iraqi Ministry of Higher Education and Scientific Research (No. CSEC/1124/0103) on November 25, 2024.

Blood samples

Sample collection required 3 mL of venous blood collected in a gel tube at room temperature and then centrifuged for 15 minutes at 3,000 RPM spins per minute. The serum was placed in an Eppendorf tube and preserved in a -20°C freezer for analysis.

Determination of TAS, TOS and OSI

Serum levels of TAS and TOS were evaluated utilizing Erel's procedures [20, 21]. The findings were presented as (micromolar peroxide of hydrogen equivalent per liter; $\mu\text{mol H}_2\text{O}_2 \text{ Eq./L}$) values of TOS and (millimolar vit.C per liter; mmol vit.C/L) values of TAS. The oxidative stress index (OSI) was calculated in serum samples using the following equation [22]: $\text{OSI} = \text{TOS } (\mu\text{mol H}_2\text{O}_2 / \text{L}) / \text{TAS } (\text{mmol vit.C} / \text{L})$.

Determination of inflammatory markers

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured and evaluated as AS inflammatory markers. Serum CRP levels were measured by the latex agglutination test. The ESR was assessed using the Westergren technique, which included adding tri-sodium citrate to the blood and measuring the sedimentation rate of erythrocytes in millimeters, and results were expressed as mm/hour [23].

Statistical Analysis

Statistical analyses were performed using SPSS version 20 (Statistical Package for the Social Sciences). Data distribution was assessed using the Shapiro–Wilk test. Compared using the independent samples t-test, distributed continuous variables (e.g., age, BMI, BASDAI) were expressed as mean $\pm$ standard deviation (SD) and. Non-normally distributed continuous variables (e.g., TAS, TOS, OSI, and ESR) were reported as medians with interquartile ranges (25th–75th percentiles) and analyzed using the Mann–Whitney U test. Categorical variables (e.g., sex, smoking status, and CRP positivity) were expressed as frequencies and percentages, and group comparisons were assessed using Fisher’s exact test. In addition, Pearson correlation analysis was used to evaluate the relationships among oxidative stress markers (TAS and TOS) and inflammatory marker (ESR) among ankylosing spondylitis patients. A p-value less than 0.05 was considered statistically significant, and values less than 0.01 were considered highly significant.

3. Results

Table 1 is a summary of the demographic features of the study groups. The patient group consisted of 16 females (20%) and 64 males (80%), while the HCs had 9 females (18.8%) and 39 males (81.2%). No significant differences in age or Body Mass Index (BMI) were detected among the groups. However, smoking status was significantly different, with 60.4% of HCs being smokers compared to 43.8% of AS patients ($P=0.04$).

Table 1: Demographic distribution of subjects by sex, smoking status, age, and BMI

Demographic characteristic		Group		P-value
		HCs (N=48)	Patients (N=80)	
Sex N (%)	Female	9 (18.8)	16(20.0)	0.1 NS
	Male	39 (81.2)	64 (80.0)	
Smoking status N (%)	Smoking	29 (60.4)	35 (43.8)	0.04*
	Non-Smoking	19 (39.6)	45 (56.2)	
Age (mean $\pm$ S.D.) year		37.12 $\pm$ 9.7	39.58 $\pm$ 10.3	0.1 NS
BMI (mean $\pm$ S. D.) kg/m ²		28.33 $\pm$ 4.63	27.82 $\pm$ 6.34	0.06 NS

N: Frequency; %: percentage; S. D.; standard deviation; kilogram; m²: Square meter; p: probability; BMI: body mass index; *: Significant differences; NS: non-significant.

Compared to the HCs, a significantly greater proportion of AS patients tested positive for CRP, and their ESR levels were also significantly elevated, indicating a heightened inflammatory state. A negative CRP status was found in 79.2% of HCs and 20.0% of patients, whereas 80% had a positive CRP result compared to 20.8% of healthy individuals ($P<0.01$). The significantly higher proportion of CRP-positive results in AS patients underscores the elevated inflammatory condition linked to the illness. The median ESR level in patients was

13.50, whereas in HCs it was 8.00 ($P < 0.01$), indicating an increased inflammatory response in patients. BASDAI scores were measured only in AS patients, with a mean score of 3.3 ± 1.58 , reflecting moderate illness activity. HCs, expectedly, had a BASDAI score of 0.00 as they did not suffer from AS. The P-values for both ESR and BASDAI were < 0.01 , indicating significant differences (Tables 2 and 3).

Table 2: CRP status of AS patients in comparison with HCs

CRP		Group		P-value
		HCs (N=48)	Patients (N=80)	
Negative	N	38	16	<0.01*
	%	79.2%	20.0%	
Positive	N	10	64	
	%	20.8%	80.0%	

N: Frequency; %: percentage; p: probability; CRP: C-reactive protein; *: Significant differences.

Table 3: ESR and BASDAI levels of ankylosing spondylitis patients in comparison with HCs

Group	No. of subjects	ESR (mm/hr) Median (25th–75th)	BASDAI (Mean±S.D.)
HCs	48	8.00(1.00-35.00)	0.00 ±0.00
Patients	80	13.50 (2.00-108.00)	3.3 ±1.58
P-value		<0.01**	<0.01**

No.; Number; ESR: erythrocyte sedimentation rate; BASDAI: bath ankylosing spondylitis illness activity index; S.D: standard deviation; **: Highly significant; (25th–75th): Interquartile Range; p: probability.

The correlation among indicators of oxidative stress in both patients and HCs matched for age and gender was examined, as shown in Table 4. Patients diagnosed with AS demonstrated a statistically significant elevation in mean TOS levels relative to HCs ($P < 0.01$), indicating a heightened level of oxidative stress in those with AS. Conversely, the degree levels of TAS, indicating the body's antioxidant ability, were decreased in AS individuals compared to the HCs ($P < 0.01$). The oxidative stress index value, indicating the percentage of TOS to TAS, was significantly elevated in AS subjects ($P < 0.01$), suggesting that AS patients have a greater tendency for oxidative damage than healthy individuals.

Table 4: Median (25th–75th) of TAS, TOS and OSI

Group		TOS Median (25th–75th) ($\mu\text{mol H}_2\text{O}_2$ /L)	TAS Median (25th–75th) (mmol vit.C /L)	OSI Median (25th–75th)
HCs	48	54.89(33.70-101.09)	16.59(0.70-29.65)	3.3 (1-104)
Patients	80	70.65(36.96-143.48)	14.54(1.00-33.04)	4.6 (1-56)
P-value		<0.01*	<0.01*	<0.01*

OSI: oxidative stress index; TOS: total oxidant status; TAS: total antioxidant status; p: probability; *: Significant differences; *: Significant differences; (25th–75th): Interquartile Range.

Results in Table 5 compare the median, the lowest, and the highest values regarding TAS, TOS and OSI related to illness severity (as assessed by BASDAI) in patients suffering from AS with the control cohort. There is a statistically significant ($p < 0.01$) differentiation among

healthy subjects and patients with AS who are already inflammatory, as indicated by TAS and TOS endpoints. There is also a difference among HCs and patients who are not actively AS in terms of these parameters. However, in comparisons among active and inactive patients, these parameters such as potential indicating activity are not significant with $p = 0.06$ for TOS, $p = 0.4$ for TAS, and $p = 0.057$ for the OSI, which means that not much significance can be placed on oxidative stress and antioxidant levels among these two subgroups of patients. This analysis reveals oxidative stress in individuals with AS, regardless of illness activity as assessed by TOS, TAS, and OSI.

Table 5: Median (25th–75th) of TAS, TOS and OSI according to illness activity (BASDAI)

Group		N	TOS ($\mu\text{mol H}_2\text{O}_2$ /L) Median (25th–75th)	TAS (mmol vit.C /L) Median (25th– 75th)	OSI Median (25th–75th)
HCs		48	54.89(33.70-101.09) A**	16.59(0.70- 29.65) A**	3.3 (1-104) A**
Patients	Active	30	68.47(39.13-114.13) B**	14.52(1.00- 19.39) B**	4.43(2.62-56.52) B**
	Inactive	50	72.82(36.96-143.48) C ^{NS}	14.63(9.87- 33.04) C ^{NS}	4.77(1.88-13.99) C ^{NS}

A: Level of OSI, TOS and TAS to Patients (Active) compared HCs; B: Level of TAS, TOS and OSI to Patients (Inactive) compared HCs; C: Level of OSI, TOS and TAS to Patients (Active) compared Patients (Inactive); TAS: total antioxidant status; TOS: total oxidant status; p: probability; OSI: oxidative stress index; **: Highly significant (<0.01); NS: non-significant (>0.05); (25th–75th): Interquartile Range.

Table 6 presents the Pearson relationships among TAS, TOS, and ESR in individuals with AS. No significant relationships were seen among TAS and TOS ($r = -0.103$, $p = 0.246$) or ESR ($r = 0.246$, $p = 0.246$). TOS had a substantial positive correlation with ESR ($r = 0.448$, $p < 0.01$), indicating that elevated oxidative stress is related to heightened inflammation in AS.

Table 6: Correlation coefficients among TAS, TOS, and ESR in AS patients

Pearson Correlation	TAS	TOS	ESR
TAS	1	-0.103	0.246
p-value		0.246	0.246
TOS	-0.103	1	0.448**
p-value	0.246		0
CRP	-0.16	0.557**	0.557**
p-value	0.07	0	0
ESR	0.246	0.448**	1
p-value	0.246	0	
BASDAI	-0.839**	-0.024	0.336**
p-value	<0.01	0.828	0.002

TOS: total oxidant status; TAS: total antioxidant status; ESR: erythrocyte sedimentation rate; p: probability; **: Highly significant.

ROC curve analysis was used to evaluate the diagnostic efficacy of TAS and TOS as indicators of oxidative stress. The p-value of 0.0001 indicates that the area under the curve (AUC) for TOS was 0.755 (95% CI: 0.667–0.843), demonstrating substantial discriminative ability among the patient and HCss, as seen in Figure 1. TAS had insufficient diagnostic

accuracy, with an AUC of 0.414 (95% CI: 0.298–0.528, $p = 0.101$). These results indicate that, for this research population, TOS serves as a more effective biomarker for distinguishing individuals with oxidative stress-related illness.

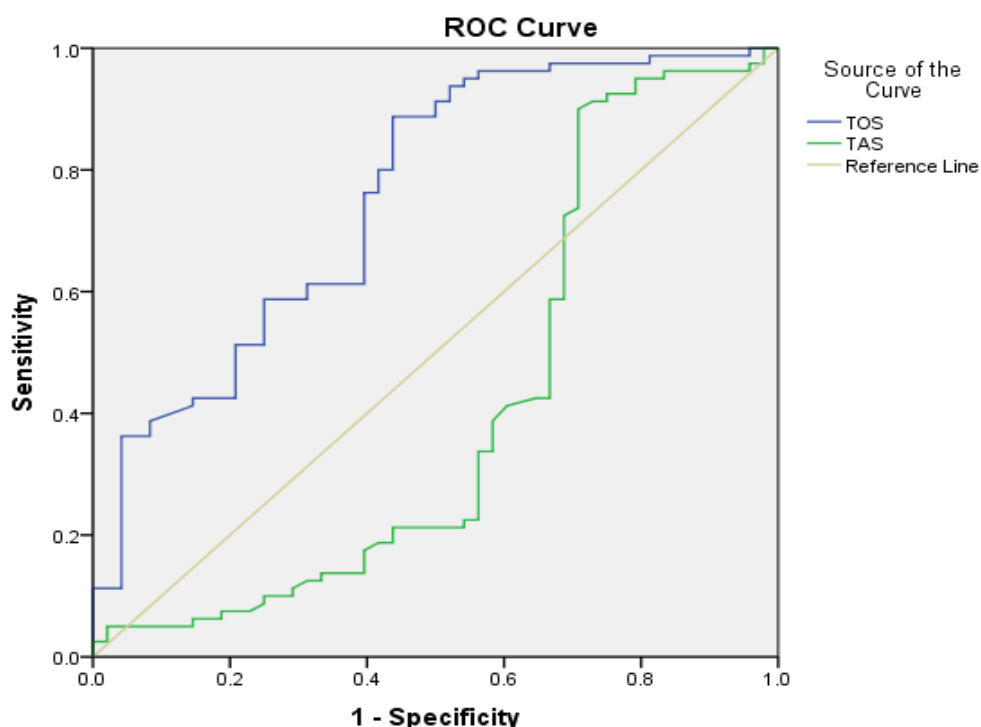


Figure 1: Receiver Operating Characteristic (ROC) curves for TOS and TAS in distinguishing among patients and HCs.

Table 7: Area Under the Curve (AUC) of TOS and TAS for Discriminating Ankylosing Spondylitis Patients from Healthy Controls

Area Under the Curve					
Test Result Variable(s)	Asymptotic Sig. ^b	Std. Error ^a	Area	Asymptotic 95% Confidence Interval	
				Upper Bound	Lower Bound
TOS	0.0001	0.045	0.755	0.843	0.667
TAS	0.101	0.059	0.413	0.528	0.298

In both the positive and negative groups of actual states, there is at least one tie for the test result variables TAS and TOS. Some data might be skewed. a. Assumption of nonparametric data b. Null hypothesis: actual area equals half.

4. Discussion

The findings of this study highlight a significant association among oxidative stress and inflammation in AS. Elevated TOS levels alongside decreased TAS levels suggest an imbalance favoring oxidative stress in AS patients. Research demonstrates a significant association among oxidative stress and the pathogenesis of numerous inflammatory conditions, like Behcet's illness, rheumatoid arthritis, and AS [24]. The TOS level are believed to correlate with activity and inflammation [25]. Elevated oxidative stress markers have been previously proven in AS [26]. Certain research has indicated that oxidative stress is more evident during active illness conditions [12]. Consistent with prior research, the present

study found an elevation in TOS in AS, and subgroup analysis indicated that AS patients with active illness exhibited greater TOS levels compared to HCs. Karakoc *et al.*, [27] reported that the levels of TAS in AS had decreased, as shown in our research. As in the present study, the majority of researchers agreed that illness activity could affect oxidative biomarker levels. A research study categorized patients into inactive (BASDAI ≥ 4) and (BASDAI < 4) cohorts, demonstrating that the total oxidative bio-marker levels were heightened in active patients [3, 16]. Oxidative stress indicators and antioxidant levels have been earlier investigated in rheumatic illnesses. Numerous indicators have been employed for this analysis in various researches; nevertheless, individuals diagnosed with ankylosing spondylitis primarily exhibit reduced antioxidant levels and increased oxidant levels in comparison to healthy individuals [16]. A study employing identical automated methods in the present investigation demonstrated significant differences in OSI, TOS, and TAS, among individuals with ankylosing spondylitis and a healthy control cohort. [27]. The current research showed that the TAS levels in AS patients were much lower, while the TOS and OSI levels were significantly greater compared to healthy control volunteers. The following theories might clarify the higher oxidative variables in serum identified with ankylosing spondylitis patients and the importance of oxidative stress in the etiology of AS. Oxidative stress might damage the extracellular matrix, nucleic acids, lipids, cellular membranes, and amino acids, resulting in elevated levels of oxidative injury products [28]. ROS, typically formed during oxidative stress, are highly reactive molecules characterised by one or several unpaired electrons, hence promoting protein oxidation and lipid peroxidation [29]. At the inflammatory site in ankylosing spondylitis, the concentration of active leukocytes increases, resulting in the secretion of reactive oxygen species and enzymes. Hypochlorous acid induces protein oxidation and tissue damage by interacting with cartilage components [3]. Consequently, T cells may be stimulated to secrete additional interleukins, worsening inflammation and lipid peroxidation, resulting in a vicious cycle [30]. Oxidative stress arises due to a disparity among oxidative and antioxidative states. Consequently, it is essential to examine the complicated interactions among an individual's antioxidants in vivo [27]. Previous research has shown that pro-inflammatory cytokines, especially TNF- α , elevate oxidative stress [31]. While it has been documented that anti-tumor necrosis factor (TNF) medicines suppress the generation of neutrophil chemotaxis and reactive oxygen species (ROS), the variability among studies might be related to the complicated interactions among oxidative and antioxidative molecules [32]. The elevated ROS attack may be attributed to the presence of cytokines and heightened neutrophil activity in the bloodstream of individuals with AS. Studies have demonstrated that patients with chronic inflammatory disorders, including AS, have an imbalance in the release of reactive oxygen species (ROS), including superoxide anion and NO, from activated polymorphonuclear leukocytes in their blood and synovial fluid. Peroxidation of lipid and oxidative stress were heightened in untreated people with active AS, and antioxidant medications may be advantageous in their therapy [33]. Solmaz *et al.*, [34] proposed that inflammation and neutrophil activation resulted in oxidative stress in individuals with AS, shown by decreased thiol levels, increased myeloperoxidase, and accelerated oxidation of protein products. We still don't know what causes the increased oxidative stress in AS [35].

5. Conclusions

The research demonstrates a strong correlation among illness activity, oxidative stress, and inflammation in AS. This discrepancy is shown by lower TAS and higher TOS and OSI. The diagnostic accuracy of TOS for AS was moderate. The findings suggest that oxidative stress indicators, particularly TOS, may aid in illness monitoring and management. More research into antioxidant treatment and its potential to supplement traditional anti-inflammatory drugs is required.

6. Disclosure and conflict of interest

No conflicts of interest were disclosed by the writers.

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