Evaluation of Serum Oxidant and Antioxidant Levels in Axial Spondyloarthritis

Aksiyel Spondiloartritte Serum Oksidan ve Antioksidan Düzeylerinin Değerlendirilmesi

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ABSTRACT

Aim: To evaluate the relationship between serum oxidant-antioxidant levels and the duration of the illness, disease activity and treatment modality in patients with axial spondyloarthritis (axSpA).

Material and Methods: Fourty two patients with axSpA and 20 healthy controls were included in this cross-sectional study. To evaluate the serum oxidant-antioxidant levels of the patients, total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) levels were measured. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), ASQoL (Ankylosing Spondylitis Quality of Life Index) scores, chest expansion, and number of enthesitis were recorded.

Results: No difference was observed in terms of demographic characteristics, laboratory findings, serum TOS and TAS levels between the patient and control groups ($p > 0.05$). The TOS and TAS concentrations did not differ between patients treated with biological agents and those treated with conventional agents; and did not differ between cases of active (BASDAI ≥ 4) and inactive axSpA ($p > 0.05$). Only the TAS levels were found to be higher in patients with axSpA whose disease duration is >1 year than patients with disease duration ≤ 1 year ($p < 0.05$); but there was no significant difference between the TOS and OSI levels in terms of disease duration. No correlation was found between laboratory and clinic parameters.

Conclusion: Serum oxidant and antioxidant levels may not be the guiding parameters in the treatment and follow-up of axSpA disease.

Keywords: Axial spondyloarthritis; Ankylosing spondylitis; Oxidative stress

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ÖZET

Amaç: Bu çalışmanın amacı aksiyel spondiloartritli (axSpA) hastalarda serum oksidan-antioksidan düzeyleri ile hastalık süresi, hastalık aktivitesi ve tedavi modalitesi arasındaki ilişkiyi değerlendirmektir.

Materyal ve Metod: Bu kesitsel çalışmaya axSpA'lı 42 hasta ve 20 sağlıklı kontrol dahil edildi. Hastaların serum oksidan-antioksidan düzeylerini değerlendirmek için toplam antioksidan durumu (TAS), total oksidan seviyesi (TOS) ve oksidatif stres indeksi (OSI) düzeyleri ölçüldü. Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI), Bath Ankilozan Spondilit Fonksiyonel İndeksi (BASFI), Bath Ankilozan Spondilit Metroloji İndeksi (BASMI), ASQoL (Ankilozan Spondilit Yaşam Kalitesi İndeksi) skorları, göğüs ekspansiyonu ve entezit sayısı gibi veriler kaydedildi.

Bulgular: Hasta ve kontrol grupları arasında demografik özellikler, laboratuvar bulguları, serum TOS ve TAS düzeyleri açısından fark izlenmedi ($p> 0.05$). TOS ve TAS konsantrasyonları açısından, biyolojik ajanlarla tedavi edilen hastalar ile geleneksel ajanlarla tedavi edilen hastalar arasında farklılık gözlenmedi; aktif (BASDAI ≥ 4) ve aktif olmayan axSpA ($p> 0.05$) vakaları arasında farklılık gözlemlenmedi. Hastalık süresi >1 yıl olan axSpA'lı hastalarda, hastalık süresi ≤ 1 yıl olan hastalara göre sadece TAS düzeyleri daha yüksek bulundu ($p<0.05$); ancak hastalık süresi açısından TOS ve OSI düzeyleri arasında anlamlı bir fark yoktu. Laboratuvar ve klinik parametreler arasında bir ilişki bulunmadı.

Sonuç: AxSpA hastalığının tedavi ve takibinde serum oksidan ve antioksidan düzeyleri yol gösterici parametreler olmayabilir.

Anahtar Kelimeler: Aksiyel spondiloartrit; Ankilozan spondilit; Oksidatif stres

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by inflammation in the sacroiliac joint and axial skeleton and is divided into two groups: 1) Ankylosing spondylitis (AS): there is significant structural damage in the sacroiliac joints radiographically and is also defined as radiographic axial spondyloarthritis; 2) Non-radiographic AxSpA: it has no definitive evidence of sacroiliitis on conventional radiographs, but with magnetic resonance imaging (MRI) evidence of inflammation in sacroiliac joints can be detected (1). Although axSpA is known to occur through immune mediated mechanisms, its pathophysiology has not been fully clarified (2). Recent studies have revealed the importance of Reactive oxygen species (ROS) produced from polymorphonuclear leukocytes (PMNL) in rheumatic diseases (2-4). ROS are highly reactive chemical products that can harm cell structures such as lipids, proteins and DNA (5). The deterioration of the balance between the oxidant system and the antioxidant system in favor of oxidants is defined as oxidative stress. The increase in ROS production in the body by various physiological or environmental factors causes oxidative stress and subsequently cell damage (3). Reducing oxidative stress, which is involved in the physiopathology of many chronic diseases, may help prevent possible diseases. There are many oxidant-antioxidant molecules in the organism and they can be measured separately. However, it is not practical and applicable to measure all of them one by one in routine. Since oxidant-antioxidant effects are cumulative, it is more practical and meaningful to measure the total oxidant and antioxidant capacity of a sample (6, 7). Activated PMLNs in the bloodstream and synovial fluid of patients with rheumatoid arthritis (RA) have been shown in the literature. ROS and proteolytic enzymes released from these PMLNs are thought to be responsible for joint and other tissue damage (8, 9).

There are few studies examining the relationship between serum oxidant-antioxidant levels, disease activity, and treatment in patients with axial spondyloarthritis (2, 3, 8). In addition, there are contradictions in the results of the studies. In the study conducted by Karakoç et al., in which AS patients who had never received any treatment before were included, AS patients had higher TOS and OSI results

and lower TAS results compared to the control group. (2). In the study of Karkucak et al., AS patients were compared with healthy controls. AS patients were divided into two groups in accordance with the treatment they received: biological therapy group and conventional therapy group. When the patient group and the control group were compared in terms of oxidative parameters, the TOS level was higher in the conventional treatment group, and the authors claimed that biological therapy reduced oxidative stress more (10). However, in a similar study conducted by Solmaz et al., it was concluded that TOS levels in AS patients did not differ according to the treatment given, but changed according to the disease activity measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Researchers divided the patients into two groups with high disease activity and low disease activity using BASDAI. In the group with a BASDAI score of 4 and above, that is, in the group with high disease activity, they detected high TOS levels (6).

Therefore, we planned to examine the results of axSpa patients who were followed up in our hospital in this study. In the present study we aimed to investigate how serum oxidant - antioxidant levels and oxidative stress index are affected in axSpA and also to evaluate the relationship between disease duration, disease activity and treatment received.

METHODS

Study design and patient selection

Forty-two patients with axSpA and 20 healthy controls were included in the study between July 2020 and November 2020 at Kirsehir Training and Research, Hospital Physical Medicine and Rehabilitation outpatientclinic. The patients were diagnosed according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria (11). Individuals who smoked or took alcohol and those with active infection, malignancy, other rheumatic diseases, renal failure, hepatic insufficiency, cardiovascular diseases, and cerebrovascular diseases were not included in the study. Written and informed consent was obtained from all patients. Approval was obtained from Kırsehir Ahi Evran University Clinical Research Ethics Committee (Date: 07/07/2020 Resolution Number: 2020-10 / 84)

Age, gender, height and weight information of all participants were recorded. Disease duration of

patients in AxSpA group, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath

Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology

Index (BASMI), ASQoL (Ankylosing Spondylitis Quality of Life Index) scores, chest expansion

value and number of enthesitis were recorded (12-15). BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) evaluates disease activity in AS. Patients answer 6 questions about the 5 main symptoms of AS: fatigue, spine pain and joint pain / swelling, localized areas of tenderness, morning stiffness duration, and morning stiffness severity. The final score ranges from 0 to 10, the the higher score suggesting the more severe activity of the disease (13). BASFI (Bath Ankylosing Spondylitis Functional Index); It is a 10-item index that evaluates the functional level of patients with AS in performing their daily activities. The average of the results of ten scales is the BASFI score (0-10), higher values indicate worse functional status (12). Bath Ankylosing Spondylitis Metrology Index) which consists of five steps: cervical rotation, tragus to walldistance, lumbar side flexion, modified Schober's and inter-malleolar distance. Each is allocated on a numerical scale from zero to ten and the final score of BASMI is the arithmetic mean of the five values, the end result may vary from 0 to 10 (14). ASQoL comprises 18 disease-specific yes/no questions that evaluate the quality of life of patients with AS. The answer 'yes' is given a

score of 1 point and 0 points are given to 'no' answers; the total score ranges between 0 and 18. Higher scores indicate a worse quality of life (15). The Turkish version of these scales were translated and validated (16-18).

Blood Sample Collection

Blood samples were taken between 8 and 10 am after at least 12 hours of fasting. After waiting for blood to coagulate in gel tubes, it was centrifuged at 2000 rpm for 15 minutes and separated into aliquots. Aliquots were stored at -80 degrees until TAS, TOS measurement. Blood samples taken for measurement of hemogram, C-Reactive Protein (CRP) and Erythrocyte sedimentation rate (ESR) were measured without waiting.

Measuring Inflammation Parameters

Hemogram was measured on automatic analyzer (Sysmex XN-1000, Sysmex Company, Japan); CRP levels were measured on a biochemistry automatic analyzer (Cobas 8000, Roche Diagnostic Corp., Mannheim, Germany). ESR levels were measured on automatic analyzer (Ves-Matic Cube 200, Diesse Diagnostica Senese Spa, Siena, Italy). TAS, TOS levels were measured with brand commercial kits (Rel Assay Kit Diagnostics, Gaziantep, Turkey) on autoanalyzer (Cobas c501, Roche Diagnostic Corp., Mannheim, Germany) (19, 20). We calculated OSI levels using the formula below:

OSI = ((TOS, μmol H 2 O 2 Eq/l)/(TAS, μmol Trolox Eq/l) × 100).

Statistical analysis

All statistical comparisons were conducted using Statistical Package for Social Sciences (SPSS) software program (Chicago, IL, USA) for Windows version 21.0 software. Data were assessed for normality using the Kolmogorov −Smirnov and Shapiro-Wilk tests. Explanatory statistics of the variables are given as Mean ± standard deviation, and frequencies as n (%). Group comparisons of quantitative variables were made using the Independent t test, and comparisons of categorical variables were made using Pearson Chi-Square and Fisher's Exact tests, considering expected values. P value was taken as 0.05 in all statistical analyzes. Relationships between variables were analyzed using Spearman rho correlation analysis.

RESULTS

Sixty-two participants were included in the study. 69.4% (n = 43) of the participants were male and 30.6% (n = 19) were female. The mean age of the participants was 40.09 ± 11.71 (21-67) years. There was no significant difference between the control and axSpA groups with regards to variables in the study (P> 0.05) (Table 1). Of the AxSpa patients included in the study, 22 of them were treated with NSAID (%52,4) and 20 of the patients were treated with anti-TNF (%47,6). Of the patients who received anti-TNF, 4 were using adalimumab, 3 were using etanercept, 8 were using infliximab, 3 were using golimumab, and 2 were using certolizumab. Whether the treatments the patients received (nonsteroidal anti-inflammatory drugs and TNF blocker drugs) had an effect on the variables in the study was examined. A significant difference was found only with regards to BMI between the patients who took non-steroidal anti-inflammatory drugs (NSAID) and TNF blockers (p<0.05). No significant difference was found between NSAID and TNF groups in terms of TAS, TOS, OSI (p> 0.05) (Table 2).

AxSpa patients participating in the study were divided into two groups as active disease and inactive disease using BASDAI and the effect of Basdai value of ≤4 (inactive) or >4 (active) on the variables examined was found to be statistically insignificant (P>0.05) (Table 3).

The AxSpa patient in the study were divided into two groups according to their disease duration.

Table 1. Descriptive statistics and group comparisons of the control and AxSpA groups
Tablo 1. Kontrol ve axSpA gruplarına ait açıklayıcı istatistikler ve grup karşılaştırmaları

Variables	**Control (n=20)**	**axSpA (n=42)**	**P**
	Mean ±SD	Mean ±SD	
Age (years)	42.3±14.3	39.0±10.2	0.311
Sex (male/female)	13 (30.2%)/7 (36.8%)	30 (69.8%)/12 (63.2%)	0.608[1]
BMI (kg/m^2)	25.5±3.2	25.9±4.1	0.684
Hemoglobin (g/L)	14.2±1.37	14.43±1.36	0.646
WBC (x10^9/L)	8075.0±1533.0	8373.3±1482.4	0.467
TAS (mmol TroloxEq/L)	1.94±0.12	1.94±0.13	0.907
TOS (μmol H_2O_2 Eq/L)	7.41±3.01	8.24±2.87	0.301
OSI (AU)	382.9±156.7	423±148.8	0.329

1: Pearson Chi-Square test, SD: Standart deviation, axSpA: Axial Spondyloarthritis, BMI: Body Mass Index, WBC: White Blood Cell, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index

Table 2. Descriptive statistics and group comparisons in accordance with the treatment
Tablo 2. Aldıkları tedaviye göre açıklayıcı istatistikler ve grup karşılaştırmaları

Variables	NSAID **(n=22)**	**TNF blockers (n=20)**	**P**
	Mean ±SD	Mean ±SD	
Age (years)	36.6±11.2	41.6±8.5	0.119
Sex (male/female)	15(50.0%)/7 (58.3%)	15 (50.0%)/5 (41.7%)	0.625[1]
BMI (kg/m^2)	**24.6±3.8**	**27.3±4.2**	**0.036**
Hemoglobin (g/L)	14.2±1.4	14.6±1.2	0.436
WBC (x10^9/L)	8188.1±1392.3	8577.0±1586.2	0.403
TAS (mmol TroloxEq/L)	1.93±0.1	1.96±0.1	0.418
TOS (μmol H_2O_2 Eq/L)	8.55±3.0	7.90±2.7	0.469
OSI (AU)	444.0±164.4	400.0±130.0	0.352

1: Pearson Chi-Square test; SD: Standart deviation; NSAID: non-steroidal anti-inflammatory drugs; TNF: Tumor Necrosis Factor, BMI: Body Mass Index, WBC: White Blood Cell, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index

Table 3. Descriptive statistics and group comparisons of Basdai≤4 and Basdai>4 groups
Tablo 3. Basdai≤4 ve Basdai>4 gruplarına ait açıklayıcı istatistikler ve grup karşılaştırmaları

Variables	**Inactive (n=17)**	**Active (n=25)**	**p**
	Mean ±SD	Mean ±SD	
Age (years)	37.47±7.83	40.12±11.87	0.419
Sex (male/female)	11(12.1%)/6(50.0%)	19(63.3%)/6(50.0)	0.498[1]
BMI (kg/m^2)	26.84±4.22	25.32±4.11	0.253
Hemoglobin (g/L)	14.51±1.48	14.37±1.29	0.738
WBC (x10^9/L)	8222.94±1686.81	8475.60±1352.90	0.594
TAS (mmol TroloxEq/L)	1.93±0.11	1.96±0.13	0.415
TOS (μmol H_2O_2 Eq/L)	8.28±2.65	8.21±3.06	0.939
OSI (AU)	427.06±123.08	420.92±166.58	0.898

1: Fisher Exact test, SD: Standart deviation, BMI: Body Mass Index, WBC: White Blood Cell, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index

The effect of disease duration >1 year on variables studied was examined. It was determined that the TAS value (1.96 ± 0.12) of the group with disease duration >1 year was higher than the TAS value (1.86 ± 0.08) of the group with disease duration ≤1 year. It was determined that this difference between the groups was statistically significant ($p<0.05$) (Table 4). According to the Spearman rho correlation coefficients, no significant relationship was found between TAS, TOS, OSI and Chest Expansion, BASDAI, BASFI, BASMI, ASQOL, BMI, Hemoglobin, white blood cell (WBC), Entheside number, Platelet number, ESR, CRP levels.

DISCUSSION

The pathophysiology of AxSpA is still not clearly established. In a small number of studies on oxidant / antioxidant status in patients with AxSpA, slightly different results were found. In this study, a significant change could not be detected in TAS, TOS or OSI levels in patients with axSpA compared to healthy controls. No significant relationship between the parameters of disease activity and functional status (BASDAI, BASFI, BASMI, ASQOL, Chest expansion, CRP, ESH) and TAS, TOS and OSI levels was found. In this study, patients with a disease duration of more than 1 year were found to have significantly higher TAS levels than patients with a disease duration ≤1 year. Ho et al. investigated superoxide anion radical production in the blood of patients with AS at rest and by stimulation of N-formylmethionyl-leucyl-phenylalanine (fMLP) or phorbol-12-myristate-13-acetate (PMA). They found a significant increase of superoxide anion radical production in patients' blood unlike healty controls. In addition, patients with AS had significantly higher chemiluminescence maximum light intensity after fMLP or PMA stimulation than healthy subjects. As a result, they showed that the phagocytes of patients with AS are partially activated at rest and are more sensitive to fMLP or PMA stimulation. They reported that in the onset of AS, the activation of phagocytes in the bloodstream may be the main factor (8). In the present study we found an association with disease duration in TAS in axSpa.

Antioxidant or oxidant effects are additive. Therefore, measuring TAS and TOS instead of measuring oxidant and antioxidant parameters one by one is both more practical and meaningful. It has been claimed that in axSpa, the oxidative balance shifts to the side of oxidants and therefore the underlying cause of the disease is the deterioration of the oxidative balance.

Table 4. Descriptive statistics of disease duration and group comparisons
Tablo 4. Hastalık süresine ait açıklayıcı istatistikler ve grup karşılaştırmaları

Variables	**Disease Duration =1 Year (n=7)**	**Disease Duration >1 Year (n=35)**	**P**
	Mean±SD	Mean ±SD	
Age (years)	42.42±13.27	38.37±9.64	0.346
Sex (male/female)	4 (13.3%)/3 (25.0%)	26 (86.7%)/9 (75.0%)	0.387[1]
BMI (kg/m^2)	25.15±3.13	26.09±4.39	0.593
Hemoglobin (g/L)	13.64±2.05	14.58±1.15	0.094
WBC ($x10^9/L$)	8272.85±1430.83	8393.42±1512.02	0.847
TAS (mmol TroloxEq/L)	**1.86±0.08**	**1.96±0.12**	**0.043**
TOS ($\mu mol\ H_2O_2$ Eq/L)	9.11±4.31	8.06±2.54	0.384
OSI (AU)	488.29±229.02	410.43±128.18	0.211

1: Fisher's Exact test, SD: Standart deviation, BMI: Body Mass Index, WBC: White Blood Cell, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index

Karakoc et al. showed in their study that AS patients had higher TOS and OSI levels and lower TAS levels than controls. But, they could not find a significant relationship between oxidant / antioxidant parameters and disease activity (2). Similarly, in our study, there was no statistically significant relationship between disease activity and TAS / TOS, OSI levels, and similarly, there was no statistically significant difference in TAS / TOS or OSI levels compared to healthy controls. In the study of Karakoç et al., AS patients consisted of newly diagnosed patients who had never received any treatment. In our study, patients were under treatment.

Karkucak et al. reported that AS patients who received TNF had lower TOS and OSI levels compared to controls, and that patients who received non-steroidal anti-inflammatory drugs had higher TOS and OSI levels than healthy controls (10).

Solmaz et al. indicated that oxidative stress levels were higher in AS patients than controls (6). Additionally, contrary to our study and the abovementioned study of Karakoc et al. (2), they found that patients with an active disease state had significantly higher levels of oxidative stress than patients with an inactive disease state and controls. In addition, unlike the above-mentioned study by Karkucak et al (10), they could not find any effect of treatment status (TNF or other) on TOS (6). In our study, we could not detect the effect of treatment on TAS, TOS and OSI. In our study, no significant difference was found between patients receiving anti-TNF and other patients in terms of TAS, TOS and OSI levels.

Özgöçmen et al. measured superoxide dismutase (SOD) activity, NO (nitric oxide) and malondialdehyde (MDA) levels in patients with AS. They found higher MDA and catalase enzyme activity in the active" patient group (3). They suggested that ROS-mediated lipid peroxidation increased in AS patients who did not receive treatment.

It has been found that MPO (myeloperoxidase) activity and advanced oxidation protein products (AOPP) are high and thiol levels are low in AS patients. The suggested that neutrophil activation and ROS-mediated protein oxidation may be the cause of oxidative stress in AS patients (21).

These contradictory results regarding TAS, TOS, and OSI levels in patients with AxSpA may be due to different study designs and the fact that the participants in the studies have parameters such as variable levels of disease activity and disease duration.

Our study has some limitations. First we studied a small group. In addition, since we did not have enough newly diagnosed patients in the current study, patients who were previously treated and followed up were included instead of newly diagnosed patients. Since the drugs taken by the patients may affect TAS, TOS, OSI levels, it would be more reasonable to evaluate patients who did not receive treatment at the time of diagnosis while investigating the relationship of TAS, TOS, OSI with axSpA. In addition, examining the synovial fluid or biopsy sample from the patients may give a more accurate and precise result.

CONCLUSION

In essence, axSpA patients had similar levels of TAS, TOS, OSI compared to the control group. The difference was not significant. Additionally, we could not find a relationship between these parameters and the disease activity and treatment received. We found higher TAS levels in patients with disease duration >1 year than patients with disease duration ≤1. The results may be effected by the treatment regimes including TNF-alpha blockers. Further studies may be performed in larger series comparing treatment regimes and exercise therapy. There is a need for further studies with a larger population, in which newly diagnosed patients are included in the treatment, the effect of exercise therapy is also examined, and tissue examination is performed.

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