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Value of ischemia-modified albumin in ankylosing spondylitis

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Ethics Committee Approval
The study was approved by the Ethics Committee of Mersin University Mersin University (Approval number: 2023/78, Date: February 1, 2023).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ankylosing spondylitis (AS) is a chronic inflammatory illness with a poorly known pathogenesis. Current biomarkers that are used to estimate inflammation are normal in some patients despite having active disease. Recent studies have revealed that oxidative stress may have a role in AS and that there is a close relationship between oxidative stress and inflammation. Ischemia-modified albumin (IMA) is a promising new biomarker for oxidative stress. Thus, the aim of this study was to assess IMA levels and their relationship with disease activity and other inflammatory markers in patients with AS.
Methods: This prospective case-control study included 48 patients with AS and 25 healthy controls (HCs). The measured serum levels of IMA, interleukin (IL)-17, and IL-23 were compared between patients with AS and the HC group. We also analyzed the correlation between IMA and disease activity, acute phase reactants, and HLA-B27 positivity. The Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used to determine disease activity.
Results: There was no difference in serum IMA levels between the AS and HC groups (25.08 [20.49-46.83] vs. 29.89 [29.89-42.0], *P*=0.146). Only IL-23 was significantly higher in patients with AS (10.81 [7.25-14.06] vs. 7.95 [6.85-10.46], *P*=0.039). Furthermore, there was no correlation between IMA and IL-23, IL-17, CRP, ESR, BASDAI, or ASDAS-CRP (r=-0.079, *P*=0.593; r=-0.043, *P*=0.771; r=-0.018, *P*=0.906; r=0.047, *P*=0.751; r=0.281, *P*=0.053; r=0.162, *P*=0.271). There was no significant difference between IMA, IL-17, and IL-23 levels in patients with low disease activity (BASDAI <4, ASDAS-CRP <2.1) and high disease activity (BASDAI ≥4, ASDAS-CRP ≥2.1) (BASDAI: *P*=0.146, *P*=0.303, *P*=0.071, and ASDAS-CRP: *P*=0.451, *P*=0.410, *P*=0.324, respectively). There was no difference in IMA levels between HLA-B27-positive patients and HLA-B27-negative patients (*P*=0.070).
Conclusion: Although oxidative stress has been suggested to play a role in AS pathogenesis, we did not find an increase in serum levels of IMA, an oxidative stress biomarker, in patients with AS. Our results suggest that IMA may not be a reliable indicator of inflammation. Further research is needed to determine whether IMA may have a role as a biomarker in AS.

Keywords: ankylosing spondylitis, disease activity, ischemia-modified albumin, oxidative stress

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that has a hallmark of low back pain and leads to reduced quality of life. It primarily involves the axial skeleton and may result in structural and functional limitations due to the formation of new bone and ankylosis [1]. Although the pathophysiology of AS has not been fully elucidated, the factors that have been identified include genetic susceptibility and interactions of various immunological and environmental factors. Human leukocyte antigen B27 (HLA-B27) and the interleukin (IL)-23/17 axis have been proposed to have crucial roles in the pathogenesis of AS [2].

Oxidative stress is defined as a perturbation of the balance between pro-oxidant and antioxidant systems that favors oxidation. Free radicals and reactive oxygen species are generated as a consequence of oxidative stress and can cause cellular damage [3]. Recent research has indicated that immunological and oxidative stress factors have an important role in the etiology of AS, which is likely to be mediated by inflammation [4,5]. Oxidative stress is induced by the activation of neutrophils in patients with AS, which generate toxic free radicals such as reactive nitrogen and oxygen species, especially during the active phase of AS [5,6].

Transitional metals such as cobalt, copper, and nickel tend to bind mainly to the amino-terminal ("N-terminal") end of the albumin molecule. Exposure to ischemia alters the N-terminus of albumin, which reduces its ability to bind metals and leads to the production of ischemia-modified albumin (IMA) [7]. Hypoxia, superoxide radical damage, and acidosis have been suggested as factors that cause the conversion of serum albumin to IMA. The production of IMA is closely correlated with a high state of oxidative stress, which could affect various tissues [8].

It has been established that patients with AS have a disturbed balance of antioxidants and oxidants, and various biomarkers of oxidative stress are elevated [9]. However, studies exploring the value of IMA in AS are very limited. The aim of this study was to investigate the levels of serum IMA in patients with AS and the relationship between acute-phase reactants, serum levels of IL-17 and IL-23, and disease activity. As far as we know, this is the first study to investigate the relationship between IMA and interleukin levels.

Materials and methods

Study protocol

The study was approved by the Ethics Committee of Mersin University Mersin University (Approval number: 2023/78, Date: 01/02/2023). All participants were informed about the concept of the study. Informed written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

This prospective case-control study was carried out at Mersin University between March and May 2023. The study comprised a total of 25 healthy controls (HC) and 48 patients with AS who satisfied the modified New York criteria [10]. Patients who were receiving non-steroidal anti-inflammatory treatment were included. Patients were excluded if they had peripheral joint involvement, infections, cardiac disease, severe renal or hepatic insufficiency, malignancies, diabetes, or rheumatic diseases other than AS. The healthy control group consisted of individuals with no rheumatic illness or known comorbidities. AS was excluded from the controls based on history and examination. All patients with AS were assessed radiologically.

Demographic features (age, sex) and clinical data were recorded. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) were used to assess disease activity. ASDAS-CRP ≥2.1 and BASDAI ≥4 were considered as indicating high disease activity, and ASDAS-CRP <2.1 and BASDAI <4 indicated low disease activity.

IMA and IL measurements

Blood samples were centrifuged at 4000 rpm for 10 minutes after being collected in biochemistry tubes. Until the day of analysis, aliquots of serum were stored at -80°C. On the day of testing, samples were reduced to room temperature. An investigator who was blinded to the study groups measured IMA and interleukins using ELISA processing equipment (BT-Lab, Bioassay Technology Laboratory Shanghai, China).

C-reactive protein and erythrocyte sedimentation rate measurements

CRP was analyzed using the immunoturbidimetric method on a Cobas Integra 800 device (Roche Diagnostics Mannheim, GmbH) within 2 hours of obtaining a serum sample on the same day with IMA and ILs. The erythrocyte sedimentation rate (ESR) was measured using an infrared reading technique using serum collected in EDTA tubes.

Statistical analysis

The sample size was determined using a power analysis in the software G*Power 3.1 (Franz Faul, University of Kiel, Germany). A sample size of at least 21 participants per group was required to achieve 80% power with a two-tailed significance threshold of 0.05 and an effect size of 0.92. IBM SPSS software v22.0 for Windows (SPSS Inc., Chicago, USA) was used for analysis.

The Kolmogorov-Smirnov test was used to identify the normality of the data distribution. Categorical data are presented as numbers (n) or percentages (%), and continuous data are given as the mean (standard deviation (SD)) or the median for normally distributed data. Otherwise, they are given as a median and interquartile range (IQR). The Student's t-test was used for normally distributed or the Mann-Whitney U for non-normally distributed data to determine the difference in continuous variables between groups. Pearson's correlation was used for relationships between normally distributed data; otherwise, Spearman's test was used. $P<0.05$ was used as a criterion for statistical significance.

Results

Table 1 shows the demographic and clinical features of the HC group and patients with AS. ESR , CRP, and IL-23 were higher in patients with AS than in HCs ($P<0.001$, $P<0.001$, and $P=0.039$, respectively). However, there was no difference in IMA and IL-17 levels between the patients with AS and HCs (25.08 [20.49-46.83] vs. 29.89 [29.89-42.0], $P=0.146$, 0.22 [0.08-0.78] vs. 0.28 [0.13-0.54], $P=0.843$) (Table 2).

Table 1: Demographic and clinical characteristics of AS patients and healthy controls

	AS patients (n=48)	Healthy control (n=25)	*P*-value
Age (years) (median, IQR)	40 (30.5-52.4)	37 (30.5-42.5)	0.191
Gender (Female/Male, n,%)	23/25 (47.9% F, 52.1% M)	11/14 (44% F, 56% M)	0.626
Disease duration (months) median, (min-max)	60 (24-120)	N/A	
HLA-B27 positivity (n,%)	37 (77.1%)	N/A	
BASDAI, mean (SD)	3.84 (1.53)	N/A	
ASDAS-CRP, mean (SD)	2.80 (0.97)	N/A	

AS: Ankylosing Spondylitis; HLA-B27: Human Leukocyte Antigen-B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein; N/A: not assessed; IQR: Interquartile range; *P* <0.05 considered statistically significant

Table 2: Differences in laboratory variables of AS patients and healthy controls

	AS Patients (n=48) Median (IQR)	Healthy Control (n=25) Median (IQR)	*P*-value
ESR, mm/h	12.0 (8-20)	3.0 (2-4.5)	<0.001 ⁋
CRP, mg/L	5.80 (2-15.25)	1.20 (0.45-2.95)	<0.001 ⁋
IMA, ng/mL	25.08 (20.49-46.83)	29.89 (24.97-42.0)	0.146
IL-17, pg/mL	0.22 (0.08-0.78)	0.28 (0.13-0.54)	0.843
IL-23, pg/mL	10.81 (7.25-14.06)	7.95 (6.85-10.46)	0.039 ⁋

AS: Ankylosing Spondylitis; IQR: Interquartile range; ESR: Erythrocyte sedimentation rate; CRP: C-Reactive protein; IMA: Ischemia-modified albumin; IL-17: Interleukin 17; IL-23: Interleukin 23; *P* <0.05 considered statistically significant; ⁋ Mann Whitney U Test.

There was no significant difference between IMA, IL-17, and IL-23 levels in patients with low disease activity (BASDAI <4, ASDAS-CRP <2.1) and high disease activity (BASDAI ≥4, ASDAS-CRP ≥2.1) (BASDAI: *P*=0.146, *P*=0.303, *P*=0.0.71, and ASDAS-CRP: *P*=0.451, *P*=0.410, *P*=0.324, respectively) (Table 3). No correlation was observed between IMA and IL-23, IL-17, CRP, ESR, ASDAS-CRP, or BASDAI (r=-0.079, *P*=0.593; r=-0.043, *P*=0.771; r=-0.018, *P*=0.906; r=0.047, *P*=0.751; r=0.162, *P*=0.271, r=0.281, *P*=0.053) (Table 4). There was a significant positive correlation between ESR and CRP levels (r=0.595, *P*<0.001). There were no differences in IMA, IL-17, and IL-23 levels, ESR, and CRP between patients with HLA-B27 positivity and HLA-B27 negativity (*P*=0.070, *P*=0.957, *P*=0.714, *P*=0.105, *P*=0.871 respectively).

Table 3: Comparison of IMA, IL-17, and IL-23 levels according to BASDAI and ASDAS-CRP

	BASDAI Scores			ASDAS-CRP Scores		
	Low Activity (n=24)	High Activity (n=24)	*P*-value	Low Activity (n=13)	High Activity (n=35)	*P*-value
IMA (ng/mL)	24.52 (19.92-33.73)	28.13 (21.32-66.81)	0.146⁋	24.95 (20.16-32.27)	25.09 (20.46-65.72)	0.451⁋
IL-17 (ng/mL)	0.21 (0.08-0.54)	0.32 (0.09-1.40)	0.303⁋	0.20 (0.07-0.46)	0.32 (0.08-0.93)	0.410⁋
IL-23 (ng/mL)	9.46 (6.78-13.27)	12.93 (7.68-16.77)	0.071⁋	9.45 (6.93-13.55)	10.95 (7.33-15.18)	0.324⁋
ESR, mm/h	11.0 (7.25-19.75)	14.0 (10.25-23.75)	0.176⁋	8.0 (3.5-16)	13.0 (10-21)	0.029⁋
CRP, mg/L	4.7 (1.75-11.5)	8.9 (2.37-19.75)	0.146⁋	1.9 (1.70-4.7)	11 (2.9-19.0)	0.001⁋

Values are presented as Median (IQR). IQR: Interquartile range; IMA: Ischemia-modified albumin, IL-17: Interleukin 17, IL-23: Interleukin 23, ESR: Erythrocyte sedimentation rate; CRP: C-Reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein ⁋ Mann Whitney U Test, *P* < 0.05 considered statistically significant

Table 4: Correlations between IMA and IL levels, acute phase reactants, disease activity scores of AS patients

	IMA (ng/mL)	
	r	*P*-value
Age	0.057	0.699
IL-17, pg/mL	-0.079	0.593
IL-23, pg/mL	-0.043	0.771
CRP, mg/L	-0.018	0.906
ESR, mm/h	0.047	0.751
BASDAI	0.281	0.053
ASDAS-CRP	0.162	0.271

IMA: Ischemia-modified albumin, IL-17: Interleukin 17, IL-23: Interleukin 23, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score; *r*: Correlation coefficient.

Discussion

In this study, there was no significant difference between the IMA levels of patients with AS and the HC group. IMA was not correlated with IL-17, IL-23, disease activity, ESR, CRP, or HLA-B27 positivity. There is limited research on IMA in patients with AS [11,12], and as far as we know, this is the first study investigating the relationship of IMA with serum IL-17 and IL-23 in patients with AS.

Despite the evidence for autoimmune factors, genetic pathways, and the generation of various cytokines of inflammation, the pathogenesis of AS remains elusive. Inflammation promotes the generation of pro-inflammatory cytokines, which trigger tissue damage by accelerating the generation of free radicals [13]. Reduced antioxidant and enhanced oxidant capacity have been implicated in the pathophysiology of AS. Karakoc et al. [14] demonstrated that total oxidative status and oxidative stress index were higher in patients with AS than HCs, whereas total antioxidant status was decreased. However, no correlation was found between oxidant and antioxidant markers and disease activity in their study.

Reactive oxygen species serve as signaling compounds in the early stages of the inflammatory response and modulate essential processes like phagocytosis, secretion, gene expression, and apoptosis, consequently promoting dysregulation of the inflammatory response [15]. But the redox state of a specific organ or tissue may not be accurately reflected by the systemic redox status by analyzing one or more pro-oxidant and antioxidant indicators [16]. Plasma cysteine and glutathione redox states have been shown in studies to be reliable indicators of oxidative stress, but they are not equilibrated in either cells or plasma [17]. Similarly, without broad alterations in the thiol/disulfide redox couples, excessive oxidation may occur, and redox signaling may take place via particular signaling pathways.

Despite the lack of achieving a state of equilibrium and disruption of redox circuits, oxidative stress might occur in the absence of an overall imbalance between pro-oxidants and antioxidants. Thus, it is suggested that oxidative stress can be better defined as a condition that disrupts redox signaling and control [18]. Despite the fact that oxidative stress is implicated in the pathogenesis of ankylosing spondylitis, plasma levels of oxidative stress biomarkers may not be elevated. This hypothesis may explain why serum IMA levels were not substantially different between patients with AS and the HC group in our study.

Adıgüzel et al. [19] found that patients with AS had lower serum total antioxidant status (TAS) levels and higher oxidative stress index (OSI) scores than healthy individuals. However, there was no significant difference in total oxidant status (TOS) between the two groups. The study also reported a moderate negative correlation between ASDAS and TAS levels, but no correlation was observed between ASDAS, TOS, and OSI. Yazici et al. [20] proposed that inflammation and the activation of neutrophils contribute to oxidative stress in AS. This is supported by elevated levels of myeloperoxidase and advanced oxidation protein products, along with reduced thiol levels, particularly in patients with active disease.

Ozgocmen et al. [21] found no difference in malondialdehyde nitrite (MDA) levels and serum nitric oxide, catalase, or superoxide dismutase activities between untreated patients with AS with inactive disease and HCs. Catalase and MDA enzyme activities were only higher in patients with active

AS than in HCs. None of the oxidant/antioxidant parameters were correlated with disease activity, ESR, or CRP.

Ischemia-modified albumin (IMA), which is generated during ischemia, has been linked to hypoxia, acidosis, and the formation of reactive oxygen species during ischemia and reperfusion. Although initially identified as a promising biomarker for acute myocardial ischemia, recent studies have shown that IMA is elevated in many rheumatic and non-rheumatic diseases in association with inflammation and oxidative stress [22-25]. Sertpoyraz et al. [11] recently evaluated IMA in 63 patients with AS and 48 HCs and reported that IMA was higher in those with AS. In addition, IMA was higher in cases of active AS than inactive AS, and there was a positive relationship between IMA, disease activity (BASDAI), and CRP.

Türkon et al. [12] also found that IMA was higher in patients with AS than in HCs, and there was a positive correlation with ASDAS-CRP, BASDAI, and the Bath AS Metrology and Functional Index. Studies on rheumatoid arthritis and Behcet's syndrome have also revealed higher levels of IMA compared to HCs [26, 27]. While some studies have demonstrated an increase in IMA levels in rheumatic diseases, there are also studies with conflicting results. Ermurat et al. [28] reported no difference in IMA levels between SLE patients and HCs in their study.

Similarly, no statistically significant differences were found between IMA levels in HCs and patients with primary Sjögren's syndrome. No correlation was observed between IMA levels and inflammatory markers, clinical parameters, or carotid intima-media thickness [29]. Furthermore, Ahn et al. [30] reported that IMA levels were higher in healthy controls than in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, which they attributed to differences in the milieu of the affected tissues. In our study, although patients with AS had higher IMA levels than the control group, the difference was not statistically significant.

Th17 T cells and the IL-23/IL-17 axis have been linked to the pathophysiology of AS [31]. IL-17 and IL-23 levels in the sera of patients with AS were shown to be high in numerous studies and to have a correlation with disease activity [32,33]. However, there are contradictory findings where serum levels are similar to those of the healthy group [34]. We examined the oxidative stress marker IMA as well as IL-17 and IL-23, which play a role in pathogenesis. Only IL-23 levels increased among these three parameters in our study. Similarly, Milanez et al. [35] also reported elevated IL-23 levels in patients with active AS, although IL-22 and TNF levels were similar to those of the healthy group.

Proinflammatory cytokines TNF, IL-22, and IL-17 may all be induced in innate immune cells by IL-23. Exposure to IL-23 in vivo is sufficient to trigger extremely targeted entheseal inflammation in the absence of Th17 cells, and it has been shown that IL-23 is elevated locally in affected target organs [36]. This may be due to the increased entheseal inflammation in our sample of patients as a result of the inclusion of patients who had radiographic spondyloarthritis with structural damage.

Limitations

The limitations of our study are the small number of samples and the lack of evaluation of other oxidative stress markers. In addition, patients receiving biologics, which have a significant impact on cytokine balance and inflammation, were excluded from the study to avoid influencing cytokine levels, and the effect of these treatments on IMA levels was not assessed. Although individuals with co-morbidities such as diabetes, a history of cardiovascular disease, and hyperlipidemia were not included in the study, it is difficult to control and eliminate all oxidative stress factors that could influence the results. Additionally, the effect of disease progression on IMA levels was not assessed.

The recruitment of only patients with AS with prominent radiographic damage and the exclusion of patients in earlier phases, such as non-radiographic spondyloarthritis, may have resulted in bias. Furthermore, the presence of metabolic disorders that may impact IMA levels, such as cardiovascular disease hypertension, was excluded based on the patient's history but not by laboratory or imaging. Further studies with a large number of participants and a variety of oxidative stress markers may be useful in better determining the role of IMA in the pathogenesis of AS. Assessing the impact of biologics and other treatments on IMA levels, as well as including tissue-level markers from sites of local inflammation, may offer more comprehensive insight into the relationship between oxidative stress and AS.

Conclusion

In conclusion, our results indicated that IMA levels in patients with AS did not differ from those of healthy individuals. Furthermore, there was no correlation between IMA and other markers such as IL-17, IL-23, CRP, ESR, or indexes of disease activity. While oxidative stress is generally considered a key factor in the disease's pathophysiology, these results suggest that IMA may not be a reliable indicator of inflammation. The lack of higher IMA levels in AS implies a complicated interplay of oxidative stress and inflammation in this disease. Further comprehensive research is needed to further understand the role of IMA and other oxidative stress markers in the diagnosis and pathogenesis of AS.

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