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Original article

The Serum Ischemia-Modified Albumin in Patients with Ankylosing Spondylitis

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ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic, inflammatory disease that primarily affects the axial spine. Involvement of the sacroiliac joint is a hallmark of AS. AS is also associated with an increased risk of CVD (cardiovascular disease) which constitutes one of the main causes of death in these patients. AS is a complex immune-mediated condition whose pathogenesis is not fully understood. It is assumed that Reactive oxygen **species** is a major event in inflamed tissues leading to AS. Albumin acts as an antioxidant by removing oxidative stress products. Ischemia modified albumin (IMA) had gained wide acceptance as a systemic biomarker of oxidative stress. The aim of study to evaluate the serum level of ischemia-modified albumin in patients with ankylosing spondylitis and to correlate the ischemia-modified albumin serum level with disease activity indices, and carotid artery intima media thickness.

Objective: The aim of the study was to evaluate the serum level of IMA in patients with AS and to correlate the IMA serum level with disease activity indices, and Carotid intima media thickness.

Subjects and Methods: This cross-sectional study included 40 AS patients and 40 matched healthy controls. In AS patients, the activity parameters (BASDAI score, ASDAS-ESR, ASDAS-CRP, ESR and serum CRP levels) as well as BASFI score and BASMI score and treatment regimen were assessed. In addition, the cIMT and was measured for AS patients and controls. Ischemia-modified albumin (IMA) was also measured.

Results: Patients with AS had significantly higher serum IMA level than controls. The ROC curve analysis revealed a strong ability of the IMA to discriminate the AS patients from controls. In AS patients, the serum IMA was significantly correlated with the cIMT and was higher in AS patients with plaques than those without plaques.

Conclusion: our study has shown that the serum level of IMA was significantly higher in patients with AS than matched healthy controls. MA serum level was significantly correlated with AS activity and severity. Serum IMA can be used as a marker for subclinical atherosclerosis in AS.

Keywords: Ankylosing Spondylitis, Serum Ischemia-Modified Albumin, sacroiliac joints, and Carotid artery intima media thickness.

Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory disease that primarily affects the axial spine. Involvement of the sacroiliac joints (SIj) is a hallmark of AS [1]. Chronic back pain and progressive spinal stiffness are the most common features of AS. However, AS can manifest with various clinical manifestations including impaired spinal mobility, postural abnormalities, peripheral arthritis, enthesitis, and dactylitis [2].AS is also associated with an increased risk of cardiovascular disease which constitutes one of the main causes of death in these patients [4] .An accurate prediction of cardiovascular risk may lead to the development of preventive strategies to improve the overall outcome [5]. Consequently, the identification of molecules implicated in the development of subclinical atherosclerosis and CVD that may be used as biomarkers of CVR in AS patients is clinically relevant. AS is a complex immune-mediated condition which its pathogenesis is not fully understood. A genetic predisposition and dysregulated inflammatory pathways including elevated levels of interleukin (IL)-23 and IL-17 and reactive oxygen species (ROS) are involved in the development of AS [6].It is assumed that ROS is a major event in inflamed tissues leading to AS [7] ROS is generated by activated polymorphonuclear leukocytes and damaged articular tissues due to ischemia in the inflamed joints. The over production of free radicals induces the generation of ischemia-modified albumin (IMA) via chemical modifications of the amino terminal region of albumin for cobalt binding [8].Albumin acts as an antioxidant by removing oxidative stress products. Damage to albumin, which may occur due to hypoxia, acidosis, and oxidative stress, decreases the albumin capacity to bind and remove ions, such as copper, nickel, and cobalt in the N-terminus. IMA is generated as a result of changes in albumin's capacity to bind heavy transition metals. IMA had gained wide acceptance as a systemic biomarker of oxidative stress [9]. Increased oxidative stress which comes along with systemic inflammation is an important factor in the development and progression of ATS [10]. Numerous studies had focused on the relationship between IMA and atherosclerotic heart disease [11].An issue of major importance is to determine the presence of CVD in subclinical stages before the development of CV events. Several validated noninvasive imaging techniques are currently available to determine subclinical ATS in patients with rheumatic diseases [12]. Carotid artery intima media thickness (cIMT) is a non-invasive technique that can detect early signs of ATS and is found to be good predictor of CVD in the general population [13] In addition, it had been reported that cIMT is a valid marker of subclinical ATS and a strong predictor of CVD in patients with AS [14]. This study was done to evaluate the serum level of ischemia-modified albumin in patients with ankylosing spondylitis and to correlate the ischemia-modified albumin serum level with disease activity indices, and carotid artery intima media thickness.

SUBJECTS AND METHODS

This cross-sectional study included 40 consecutive AS patients who fulfilled the modified New York criteria [15] based on independent central reading of radiographs of the Sacroiliac joints (SIjs). The study was approved by the ethical committee, Faculty of Medicine, Mansoura University; code number: MS.21.15.1504 in 30/06/2021. An informed written consent was obtained from all participants. Patients were recruited from the Rheumatology and Rehabilitation Outpatient Clinics, Mansoura University Hospital, between October 2021 and October 2022. In addition, 40 age- and sex-matched healthy volunteers were randomly collected and invited to participate in the study to serve as controls. We excluded patients with history of overt ischemic CVD e.g., coronary artery disease ischemic cerebrovascular accident, with traditional risk factors for CVD, with diabetes mellitus, with BMI >25 kg/m2, with history of hepatic or renal diseases, with history of malignancy, with other rheumatic autoimmune inflammatory diseases.

Every included subject was evaluated by history taking that included personal history (age, sex, and special habits including smoking), complaint (taken in patient's own words), detailed present history regarding the manifestations of AS with special stress on; duration of AS, onset and disease course, presence of constitutional symptoms as fever, fatigue, weight loss, malaise, presence of low back pain, presence of morning stiffness, peripheral joint affection, other systems involvement as ocular manifestations, cutaneous manifestations or cardiopulmonary manifestations, and any functional disability. We asked about other systems involvement as constitutional manifestations, any dermatological symptoms, any symptoms of vascular system involvement, any ocular manifestations, and any cardiopulmonary symptom. We asked also about past history for relevant conditions e.g., presence of renal or hepatic diseases, endocrinal diseases or other autoimmune diseases and therapeutic history. The

general examination included assessment of general appearance and complexion, measurement of vital signs (temperature, pulse, and blood pressure), measurement of height and body weight with calculation of BMI, and gait.

Sacroiliac joint evaluation was done .The joint tenderness was examined by applying pressure directly over the joint. Tenderness in the joint can also be elicited by several maneuvers [16] as FABER test , Distraction test ,Compression test and Gaenslen's test.

Spinal Mobility was assessed by the several techniques [17]; as Schober test, assessment of the amount of chest expansion, range of Motion or the tragus to wall test is a test to measure cervical mobility. We used several techniques to assess the peripheral joints[18] and entheses [19] in patients with AS by examination of the large joints of the lower limbs for tenderness and/or swelling or examination for enthesitis at insertion sites around the pelvis (the ischial tuberosities, iliac crests, and greater trochanters) and enthesitis at the site of the insertion of the Achilles tendon and plantar fascia onto the calcaneus.The assessment of the disease activity and severity was done by using Bath Ankylosing Spondylitis Disease Activity Index; its score ranged from 0 (no disease activity) to 10 (very active disease) [20]. A cut-off of 4 was frequently used to define active disease[21], Ankylosing Spondylitis Disease Activity Score was a data-driven index that combined questions of patient reported outcomes (about back pain, peripheral pain/swelling, and duration of morning stiffness) as well as the patient global assessment of disease activity, with either the ESR or the CRP in a weighted manner [22], Bath Ankylosing Spondylitis Functional Index was a 10-item self-reported index that was developed to define and monitor physical function in patients with AS using the visual analog scale (VAS) [23] and Bath Ankylosing Spondylitis Metrology Index was developed to quantify the mobility of the axial skeleton in AS patients[24].Blood samples were obtained for measurement of; ESR, CRP, serum total cholesterol, HDL-C, triglycerides.

Ischemia-modified albumin (IMA) was measured [3] Blood samples were collected in simple tubes without preservatives or separation gels, and the samples were then allowed to clot for 30 to 90 minutes and centrifuged 15 min at 3000 rpm before separating the serum.Specimens were frozen at -70°C until the time of the laboratory analysis.The assay procedure included adding 50 mL of cobalt chloride (0.1%; Sigma, CoCl2.6H2O in H2O) to 200 mL of serum, gently blending, and waiting 10 minutes for sufficient cobalt-albumin binding.As a coloring agent, 50 µ-liters of dithiothreitol (Sigma, 1.5 mg/ml H2O) were added. After 2 minutes, 1.0 mL of 0.9% NaCl was added to stop the reaction.Using a spectophetometer at 470nm by (Techan infinite F50, Austria).

A duplex ultrasound system (HP Sonos 5500, 10 MHz linear array transducer) was used to assess the cIMT by a single observer. During examination, the neck of the patient was placed in a slight hyper-extension position and the head rotated away from the probe. Images were performed bilaterally one cm proximal to the carotid bulb in the far wall. The cIMT was defined as the distance between the first and second echogenic lines from the lumen, taking the average of 10 measurements on both sides [25]. Values of cIMT were expressed in mm. Carotid plaque was defined as a focal structure encroaching into the arterial lumen by at least 50% of the surrounding IMT value, or with a thickness >1.2 mm [26].

Statistical Analysis

All statistical analyses were performed using SPSS for windows version 20.0 (SPSS, Chicago, IL). All continuous data were normally distributed and were expressed in mean ±standard deviation (SD). Categorical data were expressed in number and percentage. The comparisons were determined using Student's t test for two variables with continuous data and ANOVA test for more than two variables with continuous data. The Chi-square test was used for comparison of variables with categorical data. The correlation co-efficient test was used to test for correlation between variables containing continuous data. Receiver operating characteristic curve (ROC curve) analysis was used to test the ability of the IMA to discriminate the AS patients from controls. Statistical significance was set at $p<0.05$.

RESULTS

The present study included 40 AS patients, 35 (87.5%) males and 5 (12.5%) females. The study also included 40 control volunteers, 32 (80.0%) males and 8 (20.0%) females. The mean age of the AS patients and the controls was 36.9 ±8.1 years and 35.4 ±10.1 years respectively. The mean BMI of the AS patients was 27.3 ±3.9 kg/m2 and of the control group was 26.3 ±3.6 kg/m2. The waist circumference of the AS patients and the controls was 98.1% ±10.6 cm and 95.5 ±11.8 cm respectively. Current or ex-smoking were reported in 27.5% in the AS patients and 17.5% in the controls. Dyslipidemia, hypertension, and DM were found in 25%, 20% and 15% of the AS

patients respectively, while these co-morbidities were reported in 15%, 12.5% and 10% of the controls respectively. The patients and controls were matched regarding the age, sex distribution, BMI, waist circumference, smoking status, and presence of co-morbidities (Table 1).

The mean duration of the AS was 11.4 ±5.6 years. Regarding the AS-related clinical manifestations, 37.5% of the patients had arthritis and 25% of the patients had enthesitis. As regards the activity scores, the mean BASDAI score was 4.5 ±1.3, the mean ASDAS-ESR score was 1.97 ±0.91 and the ASDAS-CRP score was 1.79 ±0.78. Regarding the severity scores, the mean BASFI score was 3.4 ±1.2 while the mean BASMI score was 2.8 ±1.2 (Table 2).

Based on the BASDAI score cut off point, 45% (n=18) had inactive AS while 55% (n=22) had active AS (Figure 1). On the other hand, based on the ADAS-ESR score, 27.5% (n=11) AS patients were in remission, while 45% (n=18) had low disease activity and 27.5% (n=11) had high disease activity (Figure 2). Similarly, based on the ADAS-CRP score, 32.5% (n=13) AS patients were in remission, 32.5% (n=13) had low disease activity and 35% (n=14) had high disease activity (Figure 3).Table (3) shows that AS patients had significantly higher mean ESR level than controls (57.9 ±23.5 vs 16.7 ±8.1 mm/hour respectively, p<0.001). In addition, the mean serum CRP levels in the AS patients was significantly higher than controls (50.1 ±24.9 vs 11.6 ±5.3 mg/dl respectively, p<0.001). On the other hand, the serum level of the total cholesterol, triglycerides, LDL and HDL did not differ significantly between the AS patients and controls.

Table (4) shows that the serum IMA level in the AS patients was 0.52 ±0.23 absorbance units (ABSU) compared to 0.24 ±0.11 ABSU in the controls. This difference was significant (95% CI, 0.19 to 0.36, p<0.001). Regarding the markers of ATS, the cIMT in the AS patients and controls was 0.78 ±0.18 vs. 0.56 ±0.13 mm respectively. This difference was significant (95% CI, 0.15 to 0.29, p<0.001). Also, the carotid plaques were significantly more frequent in the AS patients compared to the controls (47.5% vs 15% respectively, p=0.002). Figure (4) shows the ROC curve analysis that revealed a strong ability of the IMA to discriminate the AS patients from controls (AUC=0.936), The optimal cutoff point was 0.37 ABSU with a sensitivity of 75% and specificity of 82.5%.Table (5) shows that serum IMA level did not show significant correlation with age, BMI or the waist circumference in the AS patients. Table (6) shows that in AS patients, the serum IMA was significantly correlated with the BASDAI score (p=0.023), ASDAS-ESR (p=0.009), ASDAS-CRP (p=0.036), BASFI score (p=0.041) and BASMI score (p=0.011), while IMA did not show significant correlation with the duration of AS.

As shown in Figure (5), the IMA serum level in AS patients with inactive disease was 0.43 ±0.21 ABSU compared to 0.59 ±0.21 ABSU. This difference was significant (p=0.022). Figure (6) demonstrates the comparison of the IMA serum level among AS patients with remission, low disease activity and high disease activity based on ASDAS-ESR. The serum IMA level in AS patients in remission was 0.34 ±0.17 ABSU while the IMA serum level in AS patients with low disease activity was 0.56 ±0.22 ABSU and in AS patients with high disease activity was 0.63 ±0.16 ABSU. These differences were significant (p=0.004). Figure (7) shows that the IMA serum level was compared among AS patients with remission, low disease activity and high disease activity based on ASDAS-ESR. The serum IMA level in AS patients in remission was 0.38 ±0.18 ABSU while the IMA serum level in AS patients with low disease activity was 0.57 ±0.23 ABSU and in AS patients with high disease activity was 0.60 ±0.17 ABSU. These differences were significant (p=0.012). Table (7) shows that Serum IMA showed no significant correlations with serum total cholesterol, triglycerides, LDL or HDL levels. However, serum IMA level was significantly correlated with the ESR level (p=0.040), serum CRP level (p=0.038) and the cIMT (p=0.002). Figure (8) shows that AS patients with carotid plaques had significantly higher IMA level than AS patients without carotid plaques (0.43 ±0.21 vs 0.61 ±0.21 ABSU respectively, p=0.013).

Table1: Comparison of the age, sex and BMI between patients with AS and controls

	AS patients	Controls	Student's t test	
	Mean ±SD	Mean ±SD	t	P
Age (years)	36.9 ±8.1	35.4 ±6.6	0.892	0.375
Sex (n, %)				
Females	5, 12.5%	8, 20.0%		
Males	35, 87.5%	32, 80.0%	0.827*	0.363
BMI (kg/m^2)	27.3 ±3.9	26.3 ±3.6	1.167	0.247
Waist circumference (cm)	98.1 ±10.6	95.5 ±11.8	1.063	0.291
Current of ex-smoking (n, %)	11, 27.5%	7, 17.5%	1.147*	0.284
	AS patients	Controls	Student's t test	AS patients
	Mean ±SD	Mean ±SD	t	Mean ±SD
Co-morbidities				
Dyslipidemia (n, %)	10, 25.0%	6, 15.0%	1.250*	0.264
Hypertension (n, %)	8, 20.0%	5, 12.5%	0.827*	0.363
Diabetes mellitus (n, %)	6, 15.0%	4, 10.0%	0.457*	0.499
* X^2 value, Chi-square test				

Table 2: Descriptive analysis of the duration, activity, and severity score of AS

	Range	Mean ±SD
Duration of AS (year)	3 – 20	11.4 ±5.6
Arthritis (n, %)	15, 37.5%	
Enthesitis (n, %)	10, 25%	
Activity scores		
BASDAI	2.6 – 6.7	4.5 ±1.3
ASDAS-ESR	0.77 – 3.80	1.97 ±0.91
ASDAS-CRP	0.53 – 3.25	1.79 ±0.78
Functional assessment and severity scores		
BASFI	1.5 – 5.7	3.4 ±1.2
BASMI	0.7 – 4.6	2.8 ±1.2

Table3: Comparison of the laboratory findings between patients with AS and controls

	AS patients	Controls	Student's t test	
	Mean ±SD	Mean ±SD	t	P
Total cholesterol (mg/dl)	200.9 ±29.9	199.2 ±38.6	0.232	0.817
Triglycerides (mg/dl)	102.2 ±38.5	99.1 ±30.1	0.403	0.688
LDL cholesterol (mg/dl)	124.6 ±34.5	123.9 ±31.6	0.094	0.926
HDL cholesterol (mg/dl)	55.8 ±18.9	52.6 ±22.1	0.690	0.492
ESR (mm/h)	57.9 ±23.5	16.7 ±8.1	10.483	<0.001
CRP (mg/dl)	50.1 ±24.9	11.6 ±5.3	9.565	<0.001

Table 4: Comparison of the serum IMA level and cIMT between patients with AS and controls

	AS patients	Controls	Student's t test	
	Mean ±SD	Mean ±SD	t	p
IMA serum level (ABSU)	0.52 ±0.23	0.24 ±0.11	6.946	<0.001
cIMT (mm)	0.78 ±0.18	0.56 ±0.13	6.357	<0.001
Carotid plaques (n, %)	19, 47.5%	6, 15.0%	9.833	0.002

Table5: Correlation of the serum IMA level with age, BMI

	r	p
Age	0.196	0.081
BMI	0.023	0.836
Waist circumference	0.160	0.155

Table 6: Correlation of the serum IMA level with clinical manifestations of the AS

	r	P
Duration of AS (year)	0.202	0.210
BASDAI	0.358	0.023
ASDAS-ESR	0.408	0.009
ASDAS-CRP	0.333	0.036
BASFI	0.325	0.041
BASMI	0.398	0.011

Table7: Correlation of the serum IMA level with laboratory findings and cIMT of the AS

	r	P
Total cholesterol	0.156	0.337
Triglycerides	0.194	0.231
LDL cholesterol	0.238	0.139
HDL cholesterol	-0.250	0.119
ESR	0.326	0.040
CRP	0.330	0.038
cIMT	0.467	0.002

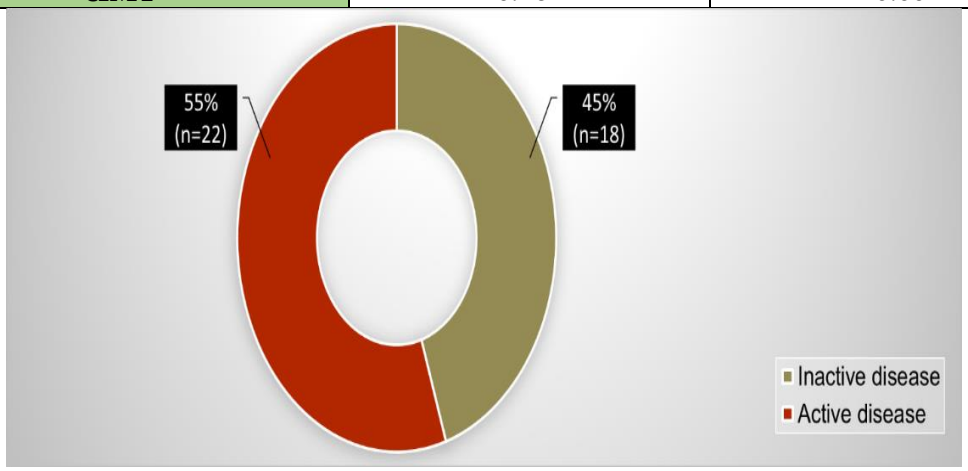

Figure (1): The distribution of the activity status of the AS patients based on the BASDAI score.

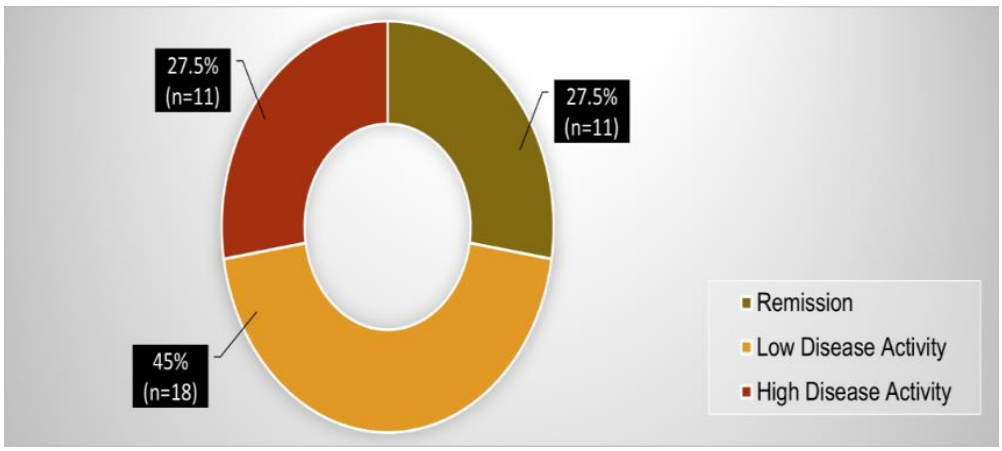

Figure (2): The distribution of the activity status of the AS patients based on the ASDAS-ESR score.

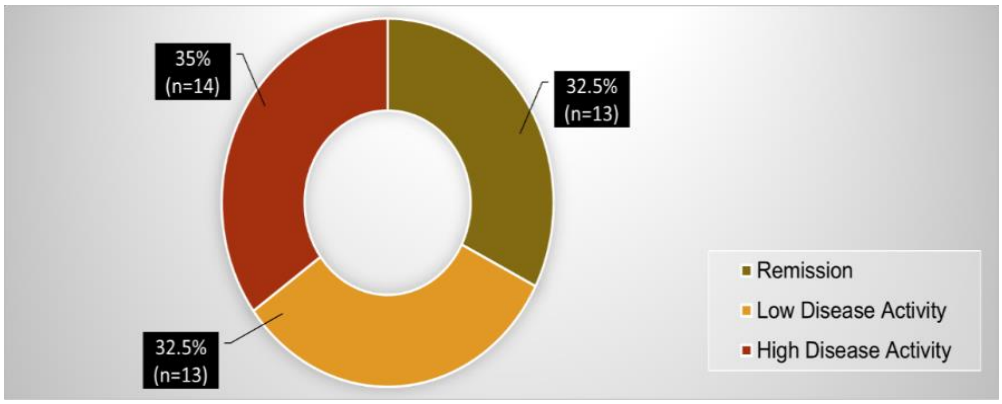

Figure (3): The distribution of the activity status of the AS patients based on the ASDAS-CRP score.

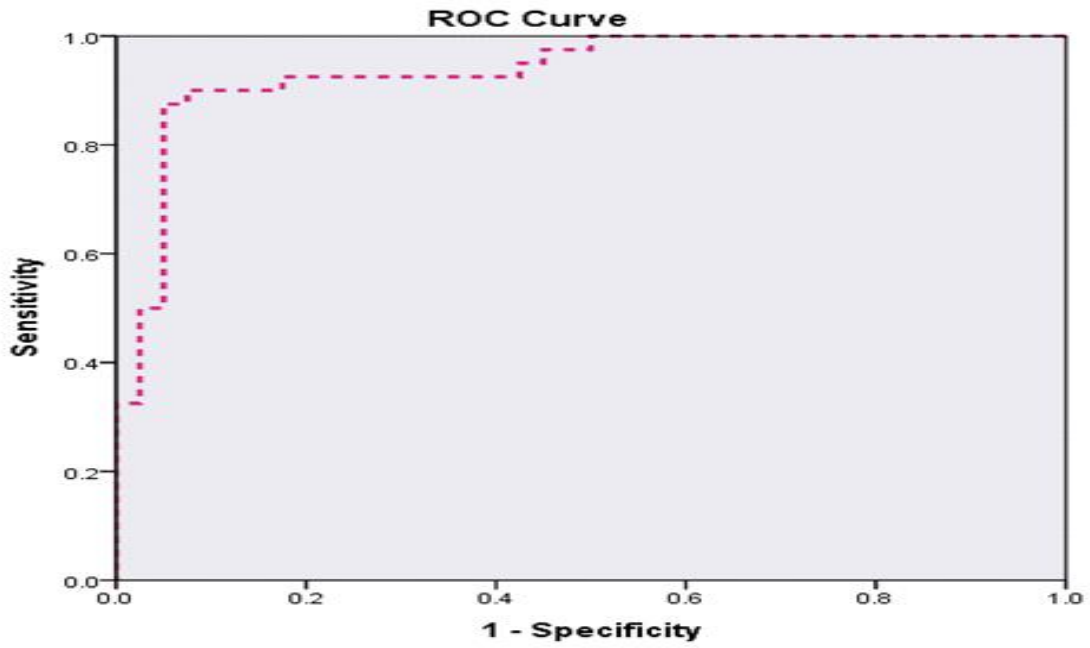

Figure (4): ROC curve analysis of the ability of the IMA to discriminate the AS patients from controls (AUC=0.936).

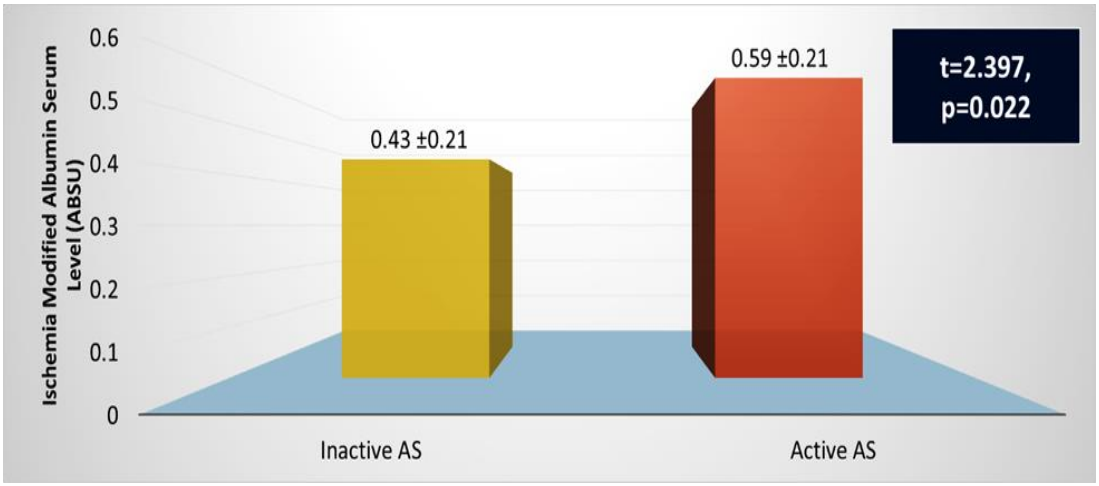

Figure (5): Comparison of the IMA serum level between patients with inactive and active AS based on BADSAI score.

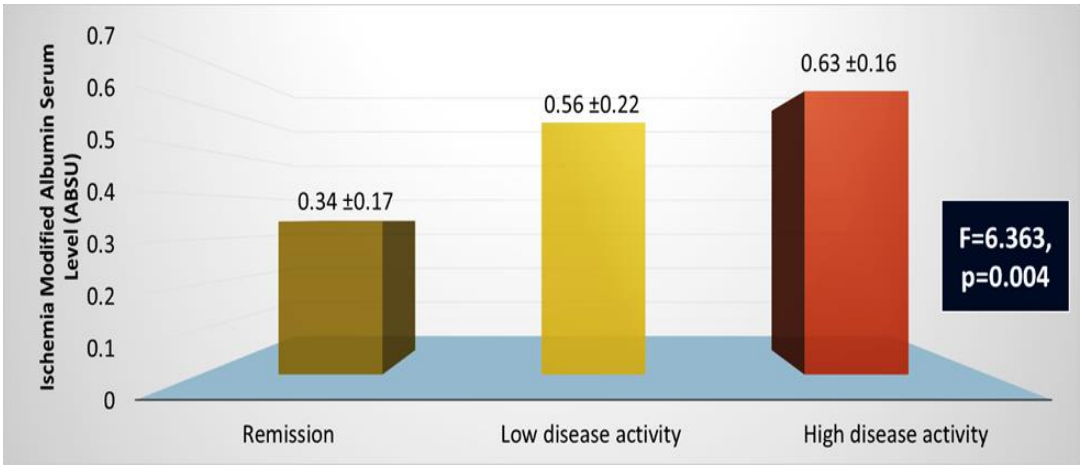

Figure (6): Comparison of the IMA serum level among patients AS patients with remission, low disease activity and high disease activity based on ASDAS-ESR.

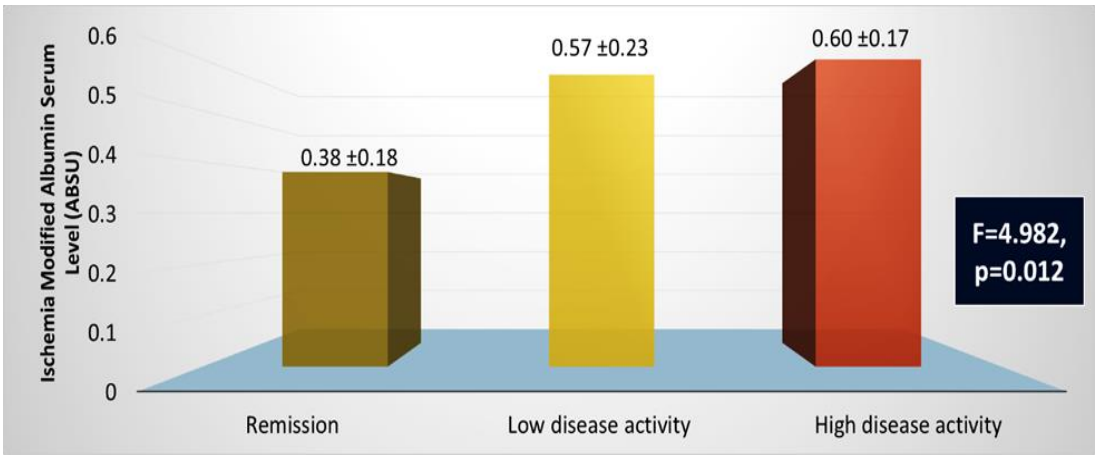

Figure (7): Comparison of the IMA serum level among patients AS patients with remission, low disease activity and high disease activity based on ASDAS-CRP.

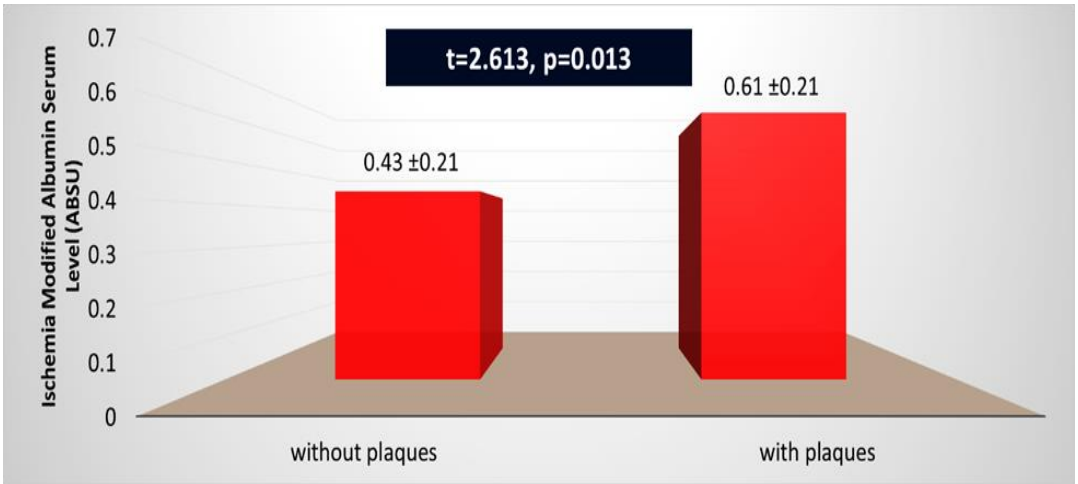

Figure (8): Comparison of the IMA serum level AS patients without and with plaques.

DISCUSSION

AS is associated with an increased risk of CVD which constitutes one of the main causes of death in these patients [4]. An accurate prediction of CVR in the subclinical stage may eventually lead to the development of appropriate and effective prevention management strategies to improve the overall outcome [5]. Numerous studies had focused on the relationship between IMA and atherosclerotic heart disease [11].

This study included 40 AS patients and 40 matched healthy controls. In AS patients, the activity parameters (BASDAI score, ASDAS-ESR, ASDAS-CRP, ESR and serum CRP levels) as well as BASFI score and BASMI score and treatment regimen were assessed. In addition, the cIMT and was measured for AS patients and controls. The major findings of the study were (a) patients with AS had significantly higher serum IMA level than controls; (b) the ROC curve analysis revealed a strong ability of the IMA to discriminate the AS patients from controls; (c) In AS patients, the serum IMA was significantly correlated with the activity parameters (BASDAI score, ASDAS-ESR, ASDAS-CRP, ESR and serum CRP levels) as well as BASFI score and BASMI score and (d) In AS patients, the serum IMA was significantly correlated with the cIMT and was higher in AS patients with plaques than those without plaques.

A major finding of the present study was that patients with AS had significantly higher serum IMA level than controls. This finding is in agreement with the findings of a previous study that compared the serum IMA level between 63 patients with AS and 48 controls and found that the AS patients had significantly higher IMA levels than controls [27].

Also, Türkön et al. compared the serum IMA level between in 40 AS patients and 35 healthy controls and found that the serum IMA levels were significantly higher in patients with AS than healthy controls. The findings of the study of Türkön et al. were consistent with the results of the present study [28].

Inflammation increases the rate of proinflammatory cytokines, such as TNF-α and IL-1β, which leads to tissue damage by increasing the rate of free radical formation [29]. A previous study has found that the oxidant levels were higher, and the antioxidant levels were lower in the AS patients compared to healthy controls [30]. Wang et al. had investigated oxidation status in AS patients and reported an increased inflammatory marker and oxidation products in patients with active disease and suggested that oxidative stress plays an important role in the pathogenesis of AS [31].

It is consistent with these findings, it had been observed that serum level of IMA is increased in patients with diseases involving ischemia and hypoxia, and in patients with chronic inflammatory diseases including the inflammatory rheumatic diseases such as RA[32], IBD [33], Behçet disease[34], and vasculitis [35] On the other hand, a previous study evaluated the IMA levels, and their relationship with ATS in Sjögren syndrome, and found no relationship between the IMA levels and inflammatory parameters or subclinical ATS in this disease [36].

Several previous studies had reported that AS patients had greater ATS burden than matched general population. A Swedish study assessed the CV events in AS, RA and the general population found that the adjusted relative risk (RR) for stroke

was equivalent between AS and RA (RR=1.5) while there was a slight increase for acute coronary syndrome in RA than in AS (1.7 and 1.3, respectively)[37]. Another Swedish study found higher incidence of acute coronary syndrome and stroke in AS patients compared to general population (4.3 and 5.4/1,000 person years compared to 3.2 and 4.7, respectively) [38]. Ischemic heart disease and cerebrovascular disease prevalence in AS were estimated to be 2.7% and 1.3%, respectively [39]. Results from a cross-sectional study in Spain examined the CV burden in patients with r-axSpA and nr-axSpA indicated that the atherosclerotic involvement was similar between these two types of patients [40].On the contrary, another study did not find an increased prevalence of acute myocardial infarction or stroke among patients with AS compared to those without AS [41].

In a meta-analysis, based on 11 studies, there was no significant increase in myocardial infarction or stroke in AS [42]. In the present study, patients with overt CVD were excluded since our study aimed to assess the ability of the IMA to identify patents with subclinical ATS.Regarding the markers of ATS, cIMT is an easy-to-use, cheap, and safe marker used to assess atherosclerosis [43].

In the present study, we aimed to measure the cIMT and presence of carotid plaques in the AS patients and compared the findings of the patients with the matched controls. The results of the present study showed that AS patients had significantly higher cIMT compared to the matched controls. Moreover, the carotid plaques were significantly more frequent in the AS patients compared to the controls.

Consistent to our findings, results from a previous studies indicated cIMT significantly increased in patients with AS compared with healthy controls, which showed AS is associated with subclinical ATS revealed by increased cIMT and more prevalent cplaques [14]. Another study had assessed the cIMT in 30 patients meeting modified New York criteria for AS compared to 25 matched controls. Interestingly, patients with traditional CV risk factors were excluded from the study. The study showed increased CIMT in AS patients without traditional CVR factors compared to healthy controls [44].Another important finding of the present study is that, in AS patients, the serum IMA was significantly correlated with the activity biomarkers (ESR and CRP serum levels) as well as activity indices (BASDAI score, ASDAS-ESR, ASDAS-CRP). In addition, serum IMA was significantly correlated with BASFI score and BASMI score.

The IMA levels in AS patients with active disease were higher than those with inactive disease. In a similar study, Türkön et al. investigated the relationship between serum IMA levels and the oxidant/antioxidant ratio in patients with AS. IMA was positively correlated with BASDAI, ASDAS-CRP, and CRP, which suggested that increased IMA levels are related to the pathogenesis and activity of the disease. Moreover, Türkön et al. found theta the serum IMA levels showed significant correlations with BASFI and BASMI [14].

In the study of Sertpoyraz et al. the CRP and IMA levels were high in patients with active AS, and there was a positive correlation between them [45]. Consistent with these findings, it was previously found that high CRP values were associated with radiological changes and SIj inflammation and correlated with the BASDAI scores [46].

The increased CRP is considered an indicator of inflammation and high IMA an indicator of oxidative stress. Karataş et al. found that the IMA levels were higher in the acute period and correlated with acute phase reactants in patients with rheumatic diseases while the IMA level was similar to healthy controls in the chronic period [47] IMA levels might be associated with acute inflammation. Among patients with Behcet's disease, the IMA levels were found to increase in those with active disease and vascular involvement [48].In agreement with the findings of the present study, Sertpoyraz et al. found that the IMA and CRP levels in the patients with active AS were higher than those with inactive AS. In patients with AS, the IMA levels had a positive correlation with the disease activity criteria, BASDAI and CRP [27].

The results of the present study also showed that, in AS patients, the serum IMA was significantly correlated with the cIMT. In addition, serum IMA was significantly higher in AS patients with plaques than those without plaques. This is the first study that investigated the relationship between IMA serum level and presence of atherosclerosis in patients with AS. However, a previous study had evaluated the association of IMA with ATS in patients with RA, by assessing the relationship between IMA and cIMT [49]. The study enrolled 52 patients with RA and 46 healthy controls. At enrollment, the no significant difference was detected between the patients and controls with respect to age, sex and BMI. The study found that

serum IMA level and cIMT values were significantly higher in the RA patients group than control group. Interestingly, the study observed a positive correlation was found between IMA, cIMT and RA activity. The study concluded that since the values of IMA were higher in the RA patients group compared to controls and because of its positive correlation with cIMT, suggesting the use of IMA as an early marker of ATS in RA patients. The findings of the present study suggest the use of IMA as an early marker of ATS in AS patients.

Although the definite mechanism which AS patients develop ATS is not yet known, the etiological factors can be quite complex. ATS is characterized by the atheromatous plaque formation within the inner layers of the arterial wall leading to narrowing or even obstruction of the arteries, resulting in hypoxia and ischemia. Increased oxidative stress, which comes along with chronic systemic inflammatory conditions, is an important factor in the development and progression of ATS [10].

IMA is a systemic marker of oxidative stress and has recently gained wide acceptance as such [50]. IMA is generated as a result of changes in albumin's capacity to bind heavy transition metals and there have been numerous studies focusing on its relationship with atherosclerotic heart disease [51]. Free oxygen radicals, released by the systemic inflammation process, have an important role in the progression of RA [52]. A systemic inflammation process has direct effects on vascular, peripheral tissue and organs and this leads to endothelial damage, dysfunction and oxidative changes, all of which help the development of ATS [53].

Limitations

Limitations of this study include the cross-sectional designs and the small sample size. A larger multi-center study may be helpful in providing more reliable results that are more generalizable. In addition, a longitudinal study is worthy to establish the temporal relationship between the IMA and ATS, hence, providing a clue of the ability of IMA in prediction of future development of ATS in those patients with high IMA but without subclinical ATS. Another limitation of the present study is the lack of consideration of other markers for oxidant/antioxidant status and its relationship with the IMA and the ATS.

Recommendations: The findings of the current study denote that increased serum concentrations of IMA may be associated with the pathogenesis and activity of AS. More comprehensive future studies with a larger sample size may help understand the relationship in greater detail.

CONCLUSION

The serum level of IMA was significantly higher in patients with AS than matched healthy controls. IMA serum level was significantly correlated with AS activity and severity. Serum IMA can be used as a marker for subclinical atherosclerosis in AS.

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