Atherosclerosis in Egyptian patients with ankylosing spondylitis

Dahlia A. Hussein[a], Hanan M. Farouk[a], Sameh A. Mobasher[a], Noran O. El-Azizi[a], Rasha N. Thabet[a], Remon Z. Elia[b]

[a]Internal Medicine Department, Rheumatology Division [b]Radiology Department, Ain Shams University, Cairo, Egypt

Correspondence to Sameh A. Mobasher, MD, Internal Medicine Department, Rheumatology Division, Ain Shams University, 5th Settlement, 3rd District, Area 6, Villa 66, Cairo, Egypt
Postal code: 11835
E-mail: drsom7@yahoo.com

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Background
Ankylosing spondylitis (AS) is a systemic inflammatory disorder with extra-articular features including cardiovascular diseases.

Objective
The objective of this study was to assess the presence of atherosclerosis in Egyptian patients with AS and its relation to disease activity.

Patients and methods
Thirty patients with AS of at least 18 years of age and 30 age-matched and sex-matched controls were included. Assessment of medical history, clinical examinations, and assessment of AS disease activity using BASDAI, BASMI, and BASFI as well as dobutamine echocardiography were performed only for patients. Complete blood count, ESR, C-reactive protein, lipid profile, serum von Willebrand factor (vWF) Ag level by ELISA, ECG, and carotid duplex were performed for all participants.

Results
In patients, 11 had active disease and 19 were in remission. A hypertensive response (HTNR) appeared in eight patients; six of them had active disease. There was a significant increase in the level of vWF in actively diseased patients than inactive patients and controls. Carotid intima-media thickness (IMT) was significantly increased in AS patients than controls. Levels of low-density lipoprotein were significantly higher in AS patients than the controls and in AS patients receiving biologics than those not receiving biologics. In the inactive group, vWF and IMT were significantly increased in patients receiving biologics. vWF correlated positively with BASDI, BASMI, BASFI scores, ESR, and carotid IMT and negatively with high-density lipoprotein.

Conclusion
Patients with AS are more susceptible to atherosclerosis, which is related to disease activity, and receiving biologics may place them at a higher risk. vWF, as a useful marker of atherosclerosis in AS patients, was correlated positively with disease activity scores and IMT.

Keywords:
ankylosing spondylitis, antitumor necrosis factor blockers, atherosclerosis, von Willebrand factor

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Introduction

Ankylosing spondylitis (AS) is a systemic inflammatory disorder that causes arthritis of the spine, sacroiliac joints, and even the peripheral joints. It involves extra-articular structures including the eyes, lung, heart, vessels, kidneys, and nerves [1]. Studies have shown that patients with AS have several cardiovascular disease risk factors, which are driven in turn by systemic inflammatory mediators [2]. Indeed, there is increased evidence that the underlying inflammatory process in chronic inflammatory disorders contributes toward various stages of atherothrombosis [3].

Among traditional Framingham risk factors, AS has been associated with a high prevalence of metabolic syndrome including dyslipidemia and high ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) [4]. Moreover, inflammatory mechanisms underlying AS may be the key factors that lead to atherosclerosis and vascular disease. Sustained systemic inflammation in AS is accompanied by elevated serum levels of C-reactive protein (CRP) [5], which is an acute-phase protein with documented proatherogenic effects [6].

von Willebrand factor (vWF) plays an important role in platelet adhesion to subendothelial structure; it is considered an indirect measure of endothelial dysfunction [7]. vWF levels are also associated with inflammation. vWF levels are elevated in a number of inflammatory disorders such as rheumatoid arthritis and vasculitis. Several cytokines or other mediators of inflammation induce endothelial vWF secretion [8].

Arterial duplex of the common carotid artery is usually used to evaluate the extent of subclinical atherosclerosis by measuring the intima-media thickness (IMT) [9]. Stress echocardiography is a noninvasive technique to evaluate the patients with suspected coronary

artery disease by visualization of its functional consequences [10]. It is the most frequently used technique to assess systolic wall motion. Both physical exercise and pharmacological stress can be used. Resting wall motion abnormalities mainly represent infarcted myocardium, whereas those induced by stress reflect ischemia [11].

The aim of the present study was to assess the presence of atherosclerosis in Egyptian patients with AS and its relation to disease activity.

Patients and methods

Clinical evaluation

The present cross sectional case–control study was carried out on 60 participants: 30 AS patients diagnosed according to the modified New York criteria 1984 [12] and 30 healthy age-matched and sex-matched volunteers selected randomly as a control group.

The patients were recruited randomly from the Rheumatology Outpatient Clinic and the Rheumatology In-patient Department of Ain shams university hospital. All participants provided written informed consent to participate, which was approved by the Medical Ethics Committee. Patients with diabetes mellitus, obesity, hypertension, heart failure, manifestations of ischemia (angina, TIA, or claudication pain), and smokers were excluded from the study.

Patients were subjected to the following procedures: full assessment of medical history and a thorough clinical examination including general, systemic [Especially (esp.) blood pressure (BP) measurement and BMI calculation], and musculoskeletal examinations. Assessment of AS disease activity was performed using Bath ankylosing spondylitis disease activity index (BASDAI) [13], BASMI [14], and BASFI [15] scores.

Laboratory evaluation

Patients' venous blood samples (8 ml each) were collected by venipuncture; 5 ml was placed in EDTA for a complete blood count and for the determination of the erythrocyte sedimentation rate. A 3 ml aliquot was placed in a clean tube and serum was separated and kept until used.

Complete blood count: [Beckman Coulter counter T660 Automated Hematology Analyzer (Beckman instrument incorporation, California, USA)]. First hour erythrocyte sedimentation rate was estimated using the Westergren method. CRP was determined by ELISA. Blood urea nitrogen, serum creatinine, serum alanine, and aspartate aminotransferase (AST and ALT) were measured using the calorimetric method. Lipid profile [total cholesterol, triglycerides (TG), LDL, HDL] was measured using the enzymatic method. Serum vWF Ag level was assessed by ELISA [16].

Radiological assessment

Plain X ray chest posteroanterior view and common carotid arterial duplex were obtained [17]. A duplex ultrasound system was used to assess the common carotid arteries by a single observer. Longitudinal high-resolution B-mode ultrasound scans were used over both right and left common carotid arteries and were R-synchronized and recorded. The offline measurements were performed 1 cm proximal to the carotid bulb in the far wall. Sites of carotid plaques were avoided. The IMT was defined as the distance between the first and the second echogenic lines from the lumen, taking the average of 10 measurements on both sides. Values of IMT were expressed in mm [17].

Cardiovascular assessment included ECG and dobutamine stress echocardiography [18], which was performed only for patients.

Dobutamine stress echocardiography is a valuable diagnostic tool in patients with suspected or known coronary artery disease for the detection of myocardial ischemia and myocardial viability [10]. Two-dimensional echocardiography evaluates global and regional left ventricular function. Left ventricular regional wall motion is analyzed using the 16-segment model recommended by the American Society of Echocardiography [18]. Dobutamine is a sympathomimetic agent with predominant β-receptor stimulation. Its effect on the β1 receptor is more pronounced than that on the β2 receptor. The effects on β1 receptors are minor. B-receptor stimulation exerts positive inotropic, chronotropic effects on the heart [18]. Oxygen and metabolic supplies to the myocardium depend on coronary blood flow. Reduced coronary blood flow provides myocardial ischemia as a result of oxygen and metabolite deprivation. Under resting conditions, basal coronary artery flow is maintained at normal levels until coronary artery stenosis becomes severe; under conditions of stress, coronary blood flow normally increases, mediated by the increased demand for oxygen and metabolites. The ability of coronary arteries to increase coronary blood flow is reduced in significantly stenosed vessels [19].

The vital parameters of the patient (heart rate, BP, ECG, oxygen saturation) are monitored throughout the procedure. The patient is positioned optimally (usually left lateral decubitus) for proper image acquisition. At baseline, the resting images are acquired (parasternal long axis and short axis, apical

two-chamber and four-chamber views), which are digitized and stored. Dobutamine infusion is then initiated at 5 μg/kg/min and increased every 3 min to 10, 20, 30, 40, and 50 μg/kg/min. At the peak dobutamine dose, 0–25 mg atropine is added as a bolus at intervals of 1 min up to a maximum dose of 1 mg until an end point is reached.

The end points are as follows:

(1) Target heart rate (85% of age – predicted maximal heart rate).
(2) Development of new regional wall motion abnormality.
(3) Ventricular tachycardia or sustained supraventricular tachycardia.
(4) Severe hypertension (systolic BP > 220 mmHg or diastolic BP > 110 mmHg).
(5) Decrease in systolic BP from the previous level.
(6) Intolerable symptoms.

Findings of dobutamine stress echocardiography

In order to interpret stress echocardiography, all 16 left ventricular segments are evaluated using a scoring system. Normokinesia is graded with a score of 1, hypokinesia with 2, akinesia with 3, and dyskinesia with 4. A new wall motion abnormality with an increase in score of more than 1 in more than one segment is considered to be a marker for ischemia [18].

In healthy normotensive adults, increased BP response to exercise may be associated with a higher risk of developing hypertension at rest and increased incidence of hypertensive left ventricular hypertrophy [20].

The data collected were coded, tabulated, and analyzed statistically on an IBM computer using Statistical Package for Social Science version 17.0 (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc). Quantitative variables were described as mean, SD, and range. Qualitative variables were described as number and percentage. The unpaired *t*-test was used to compare two groups for quantitative variables. The χ^2-test was used to compare qualitative variables between groups. The Spearman correlation test was used to rank different variables against each other positively or inversely. *P*-value 0.05 or less was considered statistically significant, *P*-value more than 0.05 was considered statistically insignificant, and *P*-value more than 0.001 or less was considered highly statistically significant.

Results

Thirty AS patients were included in the study (they were all men). Their mean ± SD age was 34.4 ± 9.3 years. Thirty age-matched and sex-matched healthy volunteers (all were also men) were included as the control group. Their mean ± SD age was 27.7 ± 7.1 years. There was no significant difference between the groups in sex, age, or their BMI.

AS patients had significantly higher ESR ($P = 0.0001$), CRP positivity ($P = 0.005$), LDL-C ($P = 0.012$), and levels of vWF (0.0001) than the controls (Table 1).

We then divided the patients according to the BASDAI score into patients with active disease (BASDAI^{3}4), and patients in remission (BASDAI<4). Patients with disease activity were found to have higher ESR ($P = 0.006$), CRP ($P = 0.017$) and vWF ($P = 0.001$) levels than those in remission (Table 2).

There were significant positive correlations between vWF levels and ESR levels ($r = 0.577$, $P = 0.001$), disease activity by BASDAI score ($r = 0.761$, $P = 0.0001$), BASMI score ($r = 0.687$, $P = 0.0001$), BASFI score ($r = 0.790$, $P = 0.0001$) (Table 3), and carotid IMT ($r = 0.355$, $P = 0.005$) (Fig. 1). In addition, there was a significant negative correlation with HDL-C levels ($r = -0.418$, $P = 0.022$).

AS patients receiving antitumor necrosis factor (TNF) therapy were found to have significantly higher levels of LDL ($P = 0.021$) than AS patients not receiving anti-TNF therapy group, but no significant difference

Table 1 Comparison between the ankylosing spondilitis patient group and the control group in the studied parameters

Variables	Mean ± SD		*P*-value
	AS patients group (*n* = 30)	Control group (*n* = 30)	
Age (years)	34.50 ± 9.30	27.70 ± 7.10	0.108
Sex [*n* (%)]			
Male	6 (15)	6 (30)	0.171
Female	34 (85)	14 (70)	
BMI (kg/m^2)	25.23 ± 2.22	25.80 ± 2.06	0.310
Hemoglobin (g/dl)	10.79 ± 1.18	12.23 ± 1.18	0.000
Platelets (× 10^3/mm^3)	292.70 ± 76.02	272.70 ± 44.41	0.282
ESR (mm/1st hour)	37.43 ± 27.15	15.07 ± 4.64	0.0001
CRP [*n* (%)]			
Positive	8 (27.7)	0 (0)	0.005
Negative	22 (73.3)	30 (100)	
vWF (μg/dl)	68.42 ± 25.32	6.46 ± 4.40	0.0001
TC (mg/dl)	158.87 ± 30.68	171.97 ± 25.42	0.077
LDL (mg/dl)	112.37 ± 18.05	100.73 ± 16.46	0.012
HDL (mg/dl)	40.53 ± 10.06	43.73 ± 7.24	0.163
TG (mg/dl)	82.93 ± 38.30	84.13 ± 32.35	0.896
Carotid IMT (mm)	0.71 ± 0.12	0.65 ± 0.10	0.037

AS, ankylosing spondilitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IMT, intimal media thickness; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; vWF, von willebrand factor.

Table 2 Comparison between ankylosing spondilitis patients in the activity group and ankylosing spondilitis patients in the remission group according to the Bath ankylosing spondylitis disease activity index score for the studied parameters

Variables	Mean±SD		*P*-value
	AS patients in the activity group (*n* = 11)	AS patients in the remission group (*n* = 19)	
ESR (mm/1st hour)	58.64 ± 31.34	25.16 ± 14.44	0.006
CRP [*n* (%)]			
Positive	6 (54.5)	2 (10.5)	0.028
Negative	5 (45.5)	17 (89.5)	
vWF (μg/dl)	92.98 ± 15.68	54.21 ± 17.73	0.001
TC (mg/dl)	154.00 ± 25.60	161.60 ± 33.61	0.518
LDL (mg/dl)	106.82 ± 15.59	115.50 ± 18.97	0.205
HDL (mg/dl)	40.82 ± 14.23	40.37 ± 7.10	0.163
TG (mg/dl)	76.27 ± 17.49	86.79 ± 46.38	0.908
Carotid IMT (mm)	0.71 ± 0.15	0.72 ± 0.10	0.885
Dobutamine [*n* (%)]			
Positive	6 (54.5)	2 (10.5)	0.028
Echo negative	5 (45.5)	17 (89.5)	

AS, ankylosing spondylitis; BASDAI score, bath ankylosing spondylitis disease activity index score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IMT, intimal media thickness; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; vWF, von willebrand factor.

Table 3 Correlation between von willebrand factor with different activity scores, erythrocyte sedimentation rate, and lipid profile

Variables	vWF (μg/dl)*r*	*P*-value
BASMI score	0.687	0.0001
BASFI score	0.790	0.0001
BASDAI score	0.761	0.0001
ESR (mm/1st hour)	0.577	0.001
TC (mg/dl)	−0.003	0.989
LDL (mg/dl)	0.190	0.316
HDL (mg/dl)	−0.418	0.022
TG (mg/dl)	0.216	0.251

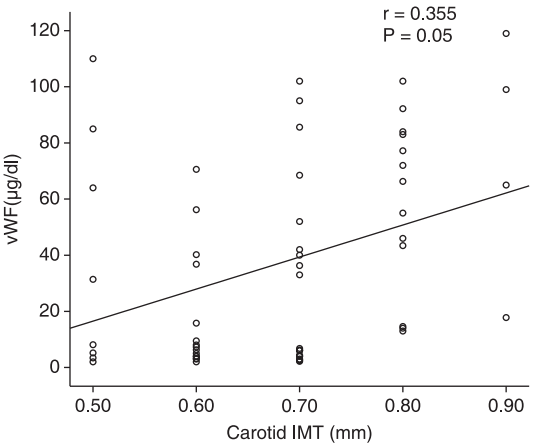
BASDAI, the bath ankylosing spondylitis disease activity index; BASFI, the bath ankylosing spondylitis functional index; BASMI, the bath ankylosing spondylitis metrology index; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IMT, intimal media thickness; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; vWF, von willebrand factor.

was found between both groups in other lipid parameters (total cholesterol, TG, HDL), ESR, CRP, vWF, or carotid IMT (Table 4), although statistically significantly higher levels of vWF (P = 0.045) and greater carotid IMT (P = 0.009) were found in patients who were in remission because they were receiving anti-TNF therapy than those in remission but had not received anti-TNF treatment.

Discussion

Growing evidence suggests the role of inflammation in the pathogenesis of CVD, especially in atherosclerosis [21]. Atherosclerosis has been shown to be increased in chronic inflammatory diseases including AS [22].

Figure 1



Correlation between carotid intima-media thickness (IMT) and von willebrand factor (vWF) levels.

Markers of inflammation (e.g. CRP), rather than traditional coronary heart disease risk parameters, may better predict the risk for vascular events in autoimmune diseases [2].

In the present study, we found significantly higher levels of ESR and CRP in AS patients compared with healthy controls and in active AS patients than those in remission. In addition, ESR correlated significantly with all the activity scores used in our study (BASMI, BASFI, and BASDAI scores). Similarly, it has been reported that ESR and CRP levels are elevated in ~75% of AS patients and correlated with disease activity [23].

Impaired endothelial function, the first step in atherosclerosis, may be reflected by changes in various endothelial biomarkers of hemostasis [22]. Plasma vWf was postulated previously to be a useful marker of endothelial injury in atherosclerosis because it is specific for endothelial cells, is stable, may be relevant to the disease process, and is simple to assay [24].

In our study, we found that vWF levels were significantly higher in the AS patient group compared with the controls; in addition, the levels were significantly higher in the active cases compared with those in remission. Our results are in agreement with those of Taylan *et al.* [22], who found that vWF was higher in the sera of AS patients compared with controls and also with those of a previous Russian study that found that signs of endothelial injury (increased level of circulating endothelial cells and vWF activity) and endothelial dysfunction were found in patients with AS [25].

Table 4 Comparison between ankylosing spondylitis patients receiving antitumor necrosis factor therapy and ankylosing spondylitis patients not receiving antitumor necrosis factor therapy in the studied parameters

Variables	Mean ± SD		*P*-value
	AS patients receiving anti-TNF therapy (*n* = 9)	AS patients not receiving anti-TNF therapy (*n* = 21)	
ESR (mm/1st hour)	31.89 ± 27.12	39.81 ± 27.48	0.476
CRP [*n* (%)]			
Positive	6 (54.5)	2 (10.5)	0.028
Negative	5 (45.5)	17 (89.5)	
vWF (μg/dl)	78.90 ± 24.92	63.93 ± 24.71	0.141
TC (mg/dl)	165.89 ± 37.67	155.80 ± 27.66	0.421
LDL (mg/dl)	123.78 ± 21.42	107.40 ± 14.32	0.021
HDL (mg/dl)	38.11 ± 9.82	41.57 ± 10.22	0.397
TG (mg/dl)	97.89 ± 56.09	76.52 ± 26.92	0.302
Carotid IMT (mm)	0.74 ± 0.15	0.70 ± 0.10	0.360
Dobutamine [*n* (%)]			
Positive	4 (44.4)	4 (19)	0.195
Echo negative	5 (55.6)	17 (81)	

AS, ankylosing spondylitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IMT, intimal media thickness; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; TNF, tumor necrosis factor; vWF, von willebrand factor.

Moreover, AS patients were reported to have a high risk for thrombosis because of elevated levels of prothrombogenic factors (fibrinogen, vWF, platelets) and subnormal fibrinolytic blood activity [26].

vWF levels were significantly correlated with ESR, CRP, and all the activity scores used in our study (BASMI, BASFI, and BASDAI scores). Bernardo *et al.* [8] suggested that inflammatory cytokines may stimulate the vWF release and inhibit its cleavage, resulting in the accumulation of hyper reactive vWF in plasma and on the surface of endothelial cells to induce platelet aggregation and adhesion on the vascular endothelium.

Plasma vWF levels have been proposed as a risk factor for cardiovascular events [27]. In addition, a correlation was found between vWF with IMT of the common carotid artery in the RA patients [28]. Similarly, a positive correlation was found in our study between levels of vWF with carotid IMT, and patients with HTNR of dobutamine echo were found to have significantly higher levels of vWF than those with normal echo findings. These results suggest a potential linkage between inflammation, endothelial damage, and the development of atherosclerosis.

In addition to the direct effect of inflammation on endothelial cells, inflammation can increase CVD through deterioration of the lipid profile, which is supported by the findings of the study carried out by Burger and Dayer [29], in which a decrease in HDL-C and apolipoprotein A1 levels and increase in TGs and apolipoprotein B levels were observed during an acute-phase response. Also, an association was found between the increase in lipids such as LDL-C and proinflammatory cytokines such as CRP, IL-6, and TNFα [30].

In the present study, LDL levels were found to be significantly higher in patients with AS compared with the controls. Also, HDL levels were found to be lower in the patient group, although the difference was not statistically significant. These results are in agreement with those of Malesci *et al.* [4], who found lower levels of HDL and higher levels of LDL in AS patients compared with the controls. Also, lower HDL-C in AS patients was reported by the studies carried out by Divecha *et al.* [2] and van Halm *et al.* [21].

There is considerable debate on the effect of anti-TNF therapy on the plasma lipids in different inflammatory disorders. Our data showed significantly higher LDL-C levels in AS patients receiving anti-TNF than those who are not receiving anti-TNF.

Popa *et al.* [31] found that the plasma concentration of total cholesterol, LDL-C, and the atherogenic index was increased after 1 year of therapy with infliximab in RA patients and concluded that long-term therapy with infliximab may lead to a more proatherogenic pattern of plasma lipids.

In contrast, Vis *et al.* [32] investigated the short-term effect of infliximab on the lipid profile in RA patients and found that it was associated with a significant increase in both total cholesterol and HDL-C levels, but without a significant effect on the atherogenic index. Also, Tam *et al.* [33] found that after 14 weeks of infliximab treatment in patients with RA, total cholesterol, HDL-C, LDL-C, TGs, and apolipoprotein B levels all increased significantly from baseline, although the atherogenic index remained unchanged.

Furthermore, no significant changes in plasma lipids were found either after 14 weeks [34] or after 48 weeks of infliximab therapy [35] in RA patients, and also after 14 weeks of infliximab therapy in AS patients [36].

Graces *et al.* [37] reported that it seems to be a class effect as they found that in patients with RA or AS treated with anti-TNF blockers, infliximab treatment increased the total cholesterol and LDL-C levels, but had no effect on HDL-C and TGs production, whereas etanercept increased HDL-C significantly but had no effect on total cholesterol or LDL-C levels.

In our study, we found that patients with AS showed greater carotid IMT than their matched healthy controls (P = 0.037). Our results are in agreement

with those of Mathieu *et al.* [5], Gonzalez-Juanatey *et al.* [38], and Bodnár *et al.* [17] as they reported significantly increased carotid IMT in AS patients compared with healthy controls. However, these results are not in agreement with those of Choe *et al.* [39] and Sari *et al.* [40], who found no difference in carotid IMT between AS patients and healthy controls, which could be attributed to the younger age group in the former study and the different sex distribution of the study carried out by sari as about half the participants were women and in addition, no difference in lipid profile was found between their patients and controls.

There are conflicting results on the effect of anti-TNF therapy on carotid IMT in patients with different inflammatory disorders. Del Porto *et al.* [41] observed significant carotid IMT reduction in RA patients after 12 months of receiving anti-TNF blockers and attributed this to their role in reducing inflammation. However, Gonzalez-Juanatey *et al.* [38] reported worsening of carotid IMT during 2–3 years of TNFα blocking therapy.

Our study showed no difference in carotid IMT between AS patients receiving anti-TNF and those not receiving anti-TNF. However, we found significantly increased carotid IMT in AS patients who were in remission following anti-TNF therapy in comparison with those in remission but not on anti-TNF therapy. Our study may be underpowered by the small number of patients using anti-TNF and that we do not have baseline data for the patients before the use of anti-TNF.

In our study, dobutamine echo showed a HTNR in eight (27%) of the 30 AS patients included in our study and was found to be significantly higher in patients with active disease than those in remission. Similarly, in a study by Yildirir *et al.* [42], echocardiographic examination of AS patients showed significantly increased incidence of diastolic dysfunction among AS patients, particularly an abnormal relaxation pattern.

Conclusion

We found a higher prevalence of atherosclerosis in AS patients, which was related to disease activity and not disease duration. vWF is a useful marker of atherosclerosis in AS patients and it was also correlated positively with disease activity scores and IMT. Patients with AS receiving anti-TNF blockers may be at a higher risk of developing atherosclerosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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