Assessment of subclinical atherosclerotic cardiovascular disease in patients with ankylosing spondylitis

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ABSTRACT

Objective: The aim of the present study was to compare patients with ankylosing spondylitis (AS) with healthy controls with respect to subclinical atherosclerotic cardiovascular disease (CVD).

Methods: A total of 44 patients with AS with no history of CVD, diabetes mellitus, hypertension, chronic kidney disease, and lipid-lowering drug use were compared with 40 age- and sex-matched healthy controls with respect to carotid intima-media thickness (CIMT) and pulse wave velocity (PWV), which are surrogate markers of subclinical atherosclerosis. Correlation analysis was also performed to examine the association between surrogate markers and disease activity with inflammation [Ankylosing spondylitis disease activity score with C-reactive protein (ASDAS-CRP)].

Results: In addition to age and sex, both groups were comparable with respect to cigarette smoking, body mass index, and high-density lipoprotein cholesterol (p=0.425, p=0.325, and p=0.103, respectively). The level of total cholesterol was significantly lower in patients with AS (p=0.002). Nonsteroidal anti-inflammatory drug and tumor necrosis factor alpha inhibitor use ratios in patients with AS were 79.5% and 65.9%, respectively. There was no significant difference between both groups regarding PWV and CIMT (p=0.788 and p=0.253, respectively). In patients with AS, there was a significant correlation between ASDAS-CRP and CIMT (r=0.315, p=0.038), but the correlation between ASDAS-CRP and PWV was not significant (r=−0.183, p=0.234).

Conclusion: The results of the present study could not provide sufficient evidence whether disease activity with inflammation caused subclinical atherosclerotic CVD in patients with AS without overt CVD. The increased atherosclerotic CVD risk is most probably multifactorial in patients with AS, but the extent of the contribution of disease activity with inflammation to increased atherosclerosis is controversial. *(Anatol J Cardiol 2019; 22: 185-91)*

Keywords: ankylosing spondylitis, carotid intima-media thickness, pulse wave velocity, subclinical cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the leading cause of death in patients with ankylosing spondylitis (AS) (1). The increased prevalence of cardiovascular (CV) morbidity and mortality in patients with AS has been attributed to AS-specific CV manifestations, traditional CVD risk factors, systemic inflammation, and nonsteroidal anti-inflammatory drug (NSAID) use (2, 3).

Although CVD has become the leading cause of death for patients with AS (1), the direct relationship between AS itself (sys-temic inflammation) and increased atherosclerotic CVD risk is not as clear as in rheumatoid arthritis (4). Since it may not be exactly possible to determine the extent of the isolated effects of all risk factors associated with atherosclerosis including inflammation, to examine vascular damage biomarkers that reflect the cumulative effect of all defined and unidentified risk factors can make more sense. Of these biomarkers, carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) have been suggested as independent risk factors for future CVD (5, 6). However, inconsistent results have been reported regarding the value of CIMT and PWV

in the detection of subclinical atherosclerotic CVD in patients with AS (7-15). In a recent meta-analysis, increased risk of subclinical atherosclerosis based on increased values of CIMT and PWV has been reported (16). However, it was also noted that studies included in the meta-analysis were heterogeneous, and some studies did not provide information about atherosclerotic risk factors and disease activity (16). The aim of the present study was to investigate the presence of disease-specific subclinical atherosclerosis using CIMT and PWV in patients with AS without overt CVD by controlling some main traditional risk factors for CVD including age, sex, hypertension, and diabetes mellitus.

Methods

Study design

This was a cross-sectional study conducted between January 2016 and December 2017. The study was approved by the Local Ethics Committee and conducted according to the Declaration of Helsinki. Written consent was obtained from each of the participants of the study.

Patients and controls

Individuals with an age ≥18 years in a hospital cohort of patients with AS, diagnosed according to the 1984 modified New York criteria (17), were included in the study. The patient group was matched to the control group based on age and sex. The control group was examined similar to the patient group. Individuals with psoriatic arthritis, reactive arthritis, spondylarthritis related to inflammatory bowel disease, a known history of CVD (angina pectoris, myocardial infarction, cerebrovascular infarction, transitory ischemic attack, or peripheral arterial disease), diabetes mellitus, hypertension, and chronic renal disease were excluded from the study. Individuals with a family history of premature coronary heart disease and those receiving lipid-lowering drugs were also excluded. Other exclusion criteria included pregnancy, breastfeeding, and the suspicion of having any aforementioned disorder at inclusion.

Demographics and disease characteristics

Patient demographics, including age, sex, body mass index (BMI), and smoking, were recorded. In addition to disease duration (duration since symptom onset), each patient's Ankylosing spondylitis disease activity score with C-reactive protein (AS-DAS-CRP) was calculated (18).

Laboratory measurements

Glucose, creatinine, complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured from venous blood samples after at least 8 h of fasting for all participants.

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Arterial stiffness

Arterial stiffness was measured via PWV by a validated (19) non-operator-dependent portable brachial cuff-based oscillometric device (Mobil_O_Graph PWA; I.E.M., Stolberg, Germany), which was used by an experienced clinician (E.T.). All participants were cautioned not to drink caffeine or smoke for at least 8 h prior to the analysis. All participants were asked to rest for 10 min prior to the measurement. Before starting the measurement, an appropriate cuff was selected based on the subject's upper arm circumference, and this cuff was then placed on the non-dominant arm. Thereafter, the device was set so as to obtain automatic recordings in a sitting position. The signals obtained via the oscillometric device were then transferred to a computer via an infrared wireless communication network. The data processing (pulse wave analysis) was performed independently via special software developed for this device. Then, PWV values were extracted from the pulse wave analysis parameters. PWV is used to measure the speed of the pulse wave through the arteries. It is estimated indirectly via the Mobil-O-Graph PWA device through a mathematical model based on pulse wave analysis and wave separation analysis (20). In addition to PWV, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also extracted.

Carotid intima-media thickness

The carotid intima-media area was described as the area between the leading edges of the lumen-intima and media-adventitia interfaces of the far wall of the common carotid artery (21). CIMT measurement was performed according to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus (21) using a Toshiba Applio 300 device with a high-frequency (5–11 MHz) linear probe, which was operated by a radiologist (L.I.). Longitudinal images of the common carotid arteries were obtained, in which the subjects were in the supine position with a slight hyperextension of the neck. During diastole, intima-media thickness was measured on the far wall of the common carotid arteria at least 5 mm below the carotid bifurcation. In the case of plaque detection during the examination, these patients were considered as having overt CVD and were excluded in the study. Three measurements were performed across the entire 1 cm length of a straight arterial segment; thereafter, these measurements were averaged. Finally, the mean intima-media thickness values from both sides were again averaged, and a single value was selected as the CIMT value.

Sample size

The results of the study by Bodnár et al. (10) were used to calculate the minimum required sample size. A priori minimum required sample size that was calculated based on an alpha of 0.05, a power of 90%, and an effect size of 0.73 for CIMT was 82 (41 participants in each group).

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Statistical analysis

Data were analyzed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium) for statistical analyses. Shapiro–Wilk test was used for the normal distribution of numerical variables. Normally distributed variables were presented as mean values and standard deviations (SDs). Non-normally distributed variables were presented as median values and interquartile ranges (IQRs). Independent samples t-test or Mann–Whitney U test was used to analyze between-group differences according to the normality. Chi-square test was used to analyze categorical variables. Pearson's or Spearman's correlation coefficient was used to analyze the correlation between the numerical variables, as appropriate. Point biserial correlation coefficient was used to analyze the correlation between the numerical variables and binominal categorical variables. A p-value <0.05 was considered statistically significant.

Results

A total of 84 participants, of which 40 were volunteer controls and 44 were patients with AS, were examined. The median (IQR) age of the study population was 43 (37–48) years. Of the 84 participants, 38 (45.2%) were female.

In addition to age and sex, both groups were comparable with regard to smoking status and BMI. CRP and ESR were significantly higher in the AS group than in the control group (p<0.001 and p=0.006, respectively), TC was significantly higher in the control group (p=0.002). Other laboratory measurements, such as PWV and CIMT, were also comparable across the groups. The median (IQR) symptom duration was 210 (120–300) months, and a mean (SD) ASDAS-CRP of 2.5 (0.9) was found in the AS group. The percentages of NSAID, disease-modifying antirheumatic drug (DMARD) (sulfasalazine or methotrexate), and tumor necrosis factor alpha (TNF-α) inhibitor use were 79.5%, 25%, and 65.9%, respectively. The demographic and clinical characteristics of the participants according to groups are presented in Table 1.

In the correlation analyses, PWV was significantly correlated with age, CIMT, and SBP in both groups. PWV was also significantly correlated with TC and LDL-C in the control group. In addition, PWV was significantly correlated with BMI, DBP, and disease duration in the AS group. CIMT was significantly correlated with age in both groups. CIMT was also significantly correlated with ASDAS-CRP, disease duration, and TG in the AS

Table 1. Anthropometric, demographic, and clinical characteristics of the participants across the groups

	Controls (n=40)	AS (n=44)	*P*
Age, years, median (IQR)	44 (37.5-47.5)	42 (37.0-49.0)	0.993
Sex, male, n (%)	20 (50)	26 (59,1)	0.403
Smoking, n (%)	13 (32.5)	18 (40.9)	0.425
BMI, kg/m^2, mean (SD)	25.3 (3.0)	26.1 (4.3)	0.325
Duration of AS, months, median (IQR)		210 (120-300)	-
ASDAS-CRP, mean (SD)		2.5 (0.9)	-
Current use of medication			
NSAID, n (%)		35 (79.5)	-
DMARD, n (%)		11 (25.0)	
TNF-α inhibitor, n (%)		29 (65.9)	
SBP, mm Hg, mean (SD)	118.5 (13.1)	122.0 (12.7)	0.225
DBP, mm Hg, mean (SD)	79.1 (10.0)	81.1 (11.0)	0.400
TC, mg/dL, mean (SD)	216.2 (46.6)	184.9 (44.5)	0.002
HDL-C, mg/dL, median (IQR)	50 (45.0-63.0)	49.5 (41.5-56.5)	0.103
LDL-C, mg/dL, mean (SD)	139.7 (38.3)	125.6 (37.4)	0.092
TG, mg/dL, median (IQR)	117 (87.0-171.5)	111.5 (73.5-173.5)	0.720
ESR, mm/h, median (IQR)	9 (6-19)	22.5 (6.5-35)	0.006
CRP, mg/dL, median (IQR)	1.1 (0.7-2.7)	3.9 (2-12.6)	<0.001
Surrogate markers of subclinical CVD			
CIMT, mm, median (IQR)	0.59 (0.54-0.65)	0.56 (0.52-0.64)	0.253
PWV, m/s, median (IQR)	6.3 (5.6-6.6)	6.0 (5.7-7.2)	0.788

AS - ankylosing spondylitis; IQR - interquartile range; BMI - body mass index; SD - standard deviation; ASDAS-CRP - ankylosing spondylitis disease activity score with C-reactive protein; NSAID - nonsteroidal anti-inflammatory drug; DMARD - disease-modifying antirheumatic drug; TNF-α - tumor necrosis factor alpha; SBP - systolic blood pressure; DBP - diastolic blood pressure; TC - total cholesterol; HDL-C - high-density lipoprotein-cholesterol; LDL - low-density lipoprotein-cholesterol; TG - triglyceride; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; CVD - cardiovascular disease; CIMT - carotid intima-media thickness; PWV - pulse wave velocity

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Table 2. Correlations between surrogate markers of cardiovascular disease, traditional risk factors, and disease activity by the groups

| | Control | | | | AS | | | |
| | PWV, m/s | | CIMT, mm | | PWV, m/s | | CIMT, mm | |
	r	*P*	r	*P*	r	*P*	r	*P*
Age, years	0.766	**<0.001**	0.684	**<0.001**	0.879	**<0.001**	0.385	**0.010**
Sex, male	0.058	0.616	0.078	0.516	0.002	0.962	0.104	0.396
Smoking, yes	0.097	0.675	0.186	0.285	0.248	0.184	0.119	0.197
BMI, kg/m^2	0.255	0.112	0.078	0.633	0.316	**0.037**	0.163	0.290
Disease duration, months	-	-	-	-	0.582	**<0.001**	0.456	**0.002**
ASDAS-CRP	-	-	-	-	-0.183	0.234	0.315	**0.038**
NSAID use, yes	-	-	-	-	0.035	0.838	0.029	0.804
DMARD use, yes	-	-	-	-	0.244	0.054	0.201	0.290
TNF-α inhibitor use, yes	-	-	-	-	0.043	0.259	0.066	0.776
SBP, mm Hg	0.379	**0.016**	0.102	0.533	0.395	**0.008**	0.013	0.932
DBP, mm Hg	-0.063	0.698	-0.147	0.364	0.495	**0.001**	0.163	0.291
TC, mg/dL	0.489	**0.001**	0.243	0.132	0.064	0.681	0.150	0.330
HDL-C, mg/dL	0.038	0.816	0.004	0.982	0.136	0.377	-0.181	0.239
LDL-C, mg/dL	0.470	**0.002**	0.218	0.177	0.045	0.774	0.113	0.467
TG, mg/dL	0.010	0.950	0.032	0.847	-0.033	0.831	0.364	**0.015**

AS - ankylosing spondylitis; BMI- body mass index; ASDAS-CRP - ankylosing spondylitis disease activity score with C-reactive protein; NSAID - nonsteroidal anti-inflammatory drug; DMARD - disease-modifying antirheumatic drug; TNF-α - tumor necrosis factor alpha; SBP - systolic blood pressure; DBP - diastolic blood pressure; TC - total cholesterol; HDL-C - high-density lipoprotein-cholesterol; LDL - low density lipoprotein-cholesterol; TG - triglyceride; ESR - erythrocyte sedimentation rate; CRP - C-reactive protein; CVD - cardiovascular disease; CIMT - carotid intima-media thickness; PWV - pulse wave velocity; CVD - cardiovascular disease

group. Neither PWV nor CIMT was correlated with sex, smoking, NSAID use, DMARD use, and TNF-α inhibitor use in the AS group. PWV and CIMT were not correlated with sex and smoking among the controls (Table 2).

Discussion

The purpose of the current study was to investigate whether two independent predictors of subclinical atherosclerosis and future CV events, such as CIMT and PWV, differed in patients with AS without overt CVD as compared with controls. In general, there were no differences between the controls and patients with AS with respect to PWV and CIMT. The only factor that was significantly associated with CIMT and PWV in both controls and patients with AS was age. There was no association between disease activity and PWV, whereas CIMT was poorly associated with disease activity.

PWV is the gold standard measurement of aortic stiffness and an independent predictor of future CV events (22). Inflammation has been shown to cause vascular stiffness by affecting the structural elements of the vessel wall, including the endothelium and muscular layer (23). Thus, increased arterial stiffness due to increased inflammation, as well as a concomitant increased risk of atherosclerosis, is expected in inflammatory rheumatic dis-

eases. Despite this expectation, inconsistent results have been achieved in clinical trials in patients with AS. Some have reported no difference between patients with AS and controls with respect to aortic stiffness as measured with PWV (13, 14, 24). On the other hand, Avram et al. (25) reported higher PWV in patients with AS than those in controls, as well as an association between arterial stiffness and disease activity. In addition, there was no significant PWV progression reported when inflammation and disease activity were controlled with TNF-α inhibitors (26, 27), with no significant improvement in PWV with such inhibitors (27). Consistent with some of these trials (13, 14), our results also failed to show an association between arterial stiffness and disease activity using CRP. The lack of association between disease activity with inflammation and arterial stiffness in the current study may have resulted from a small sample size, cross-sectional study design, and high percentage (65.9%) of TNF-α inhibitor use.

Another independent risk factor for future CV events is increased CIMT, an independent indicator of subclinical atherosclerosis (5). Similar to PWV, inconsistent results have been reported regarding the relationship between disease activity with inflammation and CIMT in patients with AS, especially in cross-sectional studies (8, 14, 15, 28-30). Choe et al. (8) have reported no difference between patients with AS and controls, as well as those between inactive and active patients with AS with

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respect to CIMT values. Although some authors have reported significantly higher CIMT values in patients with AS than those in controls, they found no significant correlation between CIMT and disease activity (28, 29). On the other hand, Verma et al. (30) have reported a moderately positive correlation between disease activity and CIMT. In a prospective nonrandomized controlled study with a heterogenous group of patients with inflammatory arthropathies, including rheumatoid arthritis, AS, and psoriatic arthritis, who were receiving TNF-α inhibitors, improvements in CIMT progression was reported with long-term (1 year) TNF-α inhibitors (31). As with PWV, controlling inflammation via the TNF-α blockers may prevent the progression in CIMT (26, 32). In the current study, the only result that suggested an association between AS and subclinical atherosclerosis was the weak association between CIMT and disease activity with inflammation. Although the present study could not reveal the acceptable level of association between AS and accelerated atherosclerosis, prospective studies have consistently reported that there was a relationship between change in CIMT over time and AS (26, 31, 32).

The increased cardiovascular risk is thought to be multifactorial (2). In the present study, although there was no or a weak association between disease-specific factors and surrogate markers of atherosclerotic CVD, there was a strong association between age and both PWV and CIMT. Both PWV and CIMT are well-known to be strongly related to age (33, 34). Another traditional risk factor, TC, was lower in patients with AS than in controls, with no association with surrogate markers of CVD. A discrepancy in lipid profile, especially reduced TC and HDL-C in cases of active disease, was reported in patients with AS (35, 36).

In addition to the unmodifiable risk factors (sex and age) controlled in the present study, some modifiable risk factors, including hypertension and diabetes mellitus associated with atherosclerotic CVD, were also controlled across the groups. Even though smoking status was not controlled, groups were comparable with respect to smoking status. There were only significant group differences with respect to TC, which was lower in the AS group than in the control group. HDL-C, another risk factor for CVD, was also comparable. The control of important traditional risk factors was important to be able to demonstrate the direct relationship between the disease itself and surrogate markers of subclinical atherosclerotic CVD. However, in the present study, the association between the disease itself and atherosclerotic CVD was not shown despite the control of traditional risk factors. In addition to cross-sectional study design, another underlying reason for this lack of association may be the high rate of TNF-α blocker use. The use of TNF-α blockers might have prevented the progression of PWW and CIMT in patients with AS. NSAIDs commonly used in the treatment of AS, such as in our AS study population (79.5%), are associated with increased cardiovascular events (37). The use of single-time indomethacin has been reported to increase PWV in old but not young people (38). However, how is PWV affected in young people with continuous cyclooxygenase inhibition as in patients with AS? This question is waiting to be answered. Capkin et al. (39) have not found a difference regarding PWV among patients with AS using NSAIDs or TNF-α inhibitors. Another question waiting to be answered is that how is PWV affected if two drugs are used together? Since the effect of TNF-α blocker and NSAID use on PWW and CIMT was not studied in the present study, we could not comment on these issues. Indeed, the causal relationship between AS itself and increased atherosclerotic CVD risk can be elicited by monitoring patients who will not be treated for years, but this is not ethical.

Study limitations

Our study has limitations. The limitations of the present study include its small sample size and cross-sectional study design. Another limitation was the inability to isolate the effect of TNF-α blocker and NSAID use on PWV and CIMT. Manual measurement, instead of automatic measurement of CIMT, was also a limitation. Another limitation was related to the PWV measurement technique. Although PWV measurement with a brachial cuff-based oscillometric device has been reported to be valid (19), the gold standard method of arterial stiffness assessment is carotid–femoral PWV measurement (40).

Conclusion

In conclusion, the present study could not provide sufficient evidence of whether the disease itself caused atherosclerotic CVD in patients with AS without overt CVD when the main traditional risk factors for CVD were controlled. The inference from the results of the present study is that the increased atherosclerotic CVD risk is most probably multifactorial in patients with AS, but the extent of the contribution of disease activity with inflammation to increased atherosclerosis is controversial. The new longitudinally controlled studies, examining the contribution of disease activity and inflammation to changes in arterial structure and function, will provide more robust evidence.

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