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Concise Report

Impaired endothelial function in patients with ankylosing spondylitis

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Objective. **In recent years, accelerated atherosclerosis and increased risk of cardiovascular events have been described in patients with rheumatic disease, particularly for rheumatoid arthritis and systemic lupus erythematosus. However, the link between inflammation, atherosclerosis and ankylosing spondylitis is controversial. We evaluated the degree of atherosclerosis and endothelial function of ankylosing spondylitis patients ultrasonographically.**

Methods. **Fifty-four patients with ankylosing spondylitis (37 ± 11 yr, 29 males, 25 females) and 31 healthy controls (35 ± 9 yr, 16 males, 15 females) were consecutively enrolled in the study. Serum lipids, creatinine, glucose, and acute-phase proteins were assessed. The Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were also evaluated. Flow-mediated dilatation and endothelium-independent dilatation of the brachial artery and intima–media thickness of the common carotid artery were measured sonographically.**

Results. **Left, right and averaged intima–media thickness of the common carotid artery did not show a statistically significant difference between the ankylosing spondylitis and control groups. However, flow-mediated dilatation was significantly lower in the ankylosing spondylitis patients (14.1 ± 6.7 *vs* $17.6 \pm 8\%$; $P = 0.03$). Likewise, nitroglycerin-induced dilatation was lower in the patient group, but the difference was not significant (16.4 ± 6.8 *vs* $19.8 \pm 10\%$; $P = 0.07$). No correlation was detected between flow-mediated dilatation and age, sex, serum lipids, CRP, ESR, smoking habits and disease activity scores. Intima–media thickness of the common carotid artery was positively correlated with age and BASMI score ($r = 0.55$, $P = 0.00$; $r = 0.22$, $P = 0.04$, respectively).**

Conclusion. **This study demonstrates impairment of endothelial function in ankylosing spondylitis.**

KEY WORDS: Ankylosing spondylitis, Arteriosclerosis, Ultrasonography.

In recent years, research in the inflammatory rheumatic diseases has revealed an increased risk of developing atherosclerosis, which is thought to be (partly) related to inflammation [1]. This association is well described for diseases such as systemic lupus erythematosus, antiphospholipid syndrome and rheumatoid arthritis [2]. On the other hand, patients with ankylosing spondylitis (AS) are known to have an overall mortality of about 1.6–1.9 times that of the general population [3], and excess mortality from circulatory disease has been found to be increased [4]. However, the association between inflammation, atherosclerosis and AS is controversial [5].

Recent progress in ultrasonographic techniques has made possible the early detection of atherosclerotic lesions, with the aim of preventing ischaemic heart diseases [6]. One of the non-invasive methods of evaluating such lesions is measurement of the intima–media thickness (IMT) in the common carotid arteries (CCA) [7]. However, IMT is not useful for early detection of atherosclerotic lesions [8]. Recently, flow-mediated dilatation (FMD) in the brachial artery has been used to detect endothelial function and is widely accepted as a non-invasive technique [9]. The main advantage of FMD is that it can detect endothelial dysfunction, which is frequently an initiator of the atherosclerotic process [10].

The aim of this study was to evaluate the degree of atherosclerosis and endothelial dysfunction in AS patients by using IMT and FMD techniques, respectively.

Patients and methods

This study was conducted between March and June 2004. Fifty-four AS patients (37 ± 11 yr, 29 males, 25 females) and 31 healthy controls (35 ± 9 yr, 16 males, 15 females) were enrolled consecutively in the study. Written informed consent was obtained from all subjects and the research protocols were approved by the Ethical Committee of the Dokuz Eylul University School of Medicine. Patients were selected from the rheumatology out-patient clinic and each patient fulfilled the modified New York criteria for AS [11]. Healthy controls matched for age, sex and body mass index (BMI) were recruited from the staff of the same hospital. Patients and controls were excluded if they reported any of the following in their history: myocardial infarction,

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diabetes mellitus, hypertension, renal failure, family history of premature coronary heart disease (<55 yr in males, <65 yr in females). Subjects on lipid-lowering therapy and patients who had been treated with systemic corticosteroids within 4 weeks before the study were also excluded. The diagnostic criteria of the American Diabetes Association based on the 75-g oral glucose tolerance test was used to define diabetes [12] and the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) criteria were used to define hypertension [13]. Participants who reported smoking at least one cigarette per day during the year before the examination were classified as smokers.

Laboratory evaluation

In the morning after an overnight fast, venous blood was sampled for the measurement of serum concentrations of glucose, creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR). Thereafter, a 75-g oral glucose load was administered to all subjects and repeat venepuncture was performed 2 h later for measurement of serum glucose.

Sonographic study

All of the sonographic examinations (IMT and FMD) were performed by the same examiner, who was unaware of the subject's clinical status throughout the study. Each subject was studied in the morning hours (8:00 a.m. to 10:00 a.m.) after having abstained from alcohol, caffeine, tobacco and food for ≥8 h before the examination. None of the participants was using vasoactive drugs. Studies were performed in a quiet, temperature-controlled room (20–25°C). Images were obtained by high-resolution Doppler ultrasonography (HDI-5000; ATL, Bothell, WA, USA) with a 7.5-MHz linear-array transducer. Sonographic images were recorded on VHS videotapes for subsequent analysis and evaluated by the same investigator to avoid interobserver variations.

Measurement of flow-mediated and nitroglycerin-induced dilatation of the brachial artery

The right brachial artery was studied in all subjects. ECG was monitored throughout the scans and the artery diameter was measured at end-diastole (concurrent with the onset of the QRS complex on the electrocardiogram). Three cardiac cycles were analysed for each scan, and measurements were averaged. Subjects were in the supine position with the arm outstretched, after at least 10 min of rest. The brachial artery was imaged over a longitudinal section approximately 5 cm above the antecubital fossa. At baseline, two-dimensional ultrasound images were obtained. Thereafter, a blood pressure cuff placed around the arm above the scanned part of the artery was inflated to 200 mmHg for 5 min. The blood pressure cuff was then deflated, resulting in a reactive hyperaemia, which causes an increase in shear stress and dilatation of the brachial artery. The ultrasound image was recorded on videotape for 5 min, commencing 1 min after cuff deflation. After another 10 min of rest, a single dose of nitroglycerin 0.4 mg was administered sublingually and brachial artery diameter was recorded after 3 min in order to evaluate endothelium-independent vasodilatation. Endothelium-dependent FMD was expressed as the percentage change in brachial artery diameter from baseline. Likewise, nitroglycerin-induced endothelium-independent peripheral vasodilatation was expressed as the percentage change in brachial artery diameter 3 min after sublingual nitrate administration, relative to baseline values.

Measurement of intima–media thickness of the common carotid artery

Bilateral assessment of wall thickness was made in the CCA. IMT was measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first line represents the lumen–intima interface, and the second line the collagen-containing upper layer of tunica adventitia. Three determinations of IMT were made at the site of greatest thickness and at two other points, 1 cm upstream and 1 cm downstream from the site of greatest thickness in CCA. The average of six readings was recorded.

Other measurements

Height, weight, waist circumference and waist/hip ratio (WHR) were recorded. BMI was calculated according to Quetelet's index as the ratio of weight (kg) to height (m) squared (kg/m^2). Blood pressure was measured with a mercury column sphygmomanometer. Spinal mobility was assessed using the Bath Ankylosing Spondylitis Metrology Index (BASMI) [14]. A clinical index of disease activity (Bath Ankylosing Spondylitis Disease Activity Index; BASDAI) [15] and functional status (Bath Ankylosing Spondylitis Functional Index; BASFI) [16] were also evaluated.

Statistical analysis

Results are presented as mean ± S.D. To compare continuous variables we used Student's *t*-test. Differences between categorical variables were analysed with the χ^2 test. The relationships between the different variables were analysed with the Pearson correlation test. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 11.0 (SPSS, Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

Results

As summarized in Table 1, age, sex, BMI, smoking status and serum lipids were comparable in the two groups. All subjects tolerated the sonographic examination well. Table 2 displays the ultrasonographic study results. Left, right and averaged CCA IMT measurements did not show a statistically significant difference between the AS and control groups. However, FMD was significantly lower in the AS patients (14.1 ± 6.7 *vs* $17.6 \pm 8\%$; $P = 0.03$). Likewise, nitroglycerin-induced dilatation was lower in the patient group, but the difference was not significant (16.4 ± 6.8 *vs* $19.8 \pm 10\%$; $P = 0.07$). On univariate correlation analysis, FMD (%) correlated negatively with the BASMI score ($r = -0.24$, $P = 0.03$). No correlation was detected between FMD (%) and age, sex, triglycerides, total cholesterol, HDL, LDL, CRP, ESR, smoking habits, BMI, BASFI and BASDAI ($r = -0.16$, $P = 0.13$; $r = -0.18$, $P = 0.09$; $r = 0.14$, $P = 0.19$; $r = -0.06$, $P = 0.60$; $r = -0.05$, $P = 0.63$; $r = -0.09$, $P = 0.43$; $r = -0.03$, $P = 0.76$; $r = -0.1$, $P = 0.38$; $r = -0.12$, $P = 0.26$; $r = -0.93$, $P = 0.40$; $r = 0.07$, $P = 0.60$; $r = 0.26$, $P = 0.54$, respectively). On the other hand, averaged IMT of the CCA was correlated positively with age and BASMI score ($r = 0.55$, $P = 0.00$; $r = 0.22$, $P = 0.04$, respectively). However, sex, triglycerides, total cholesterol, HDL, LDL, CRP, ESR, smoking status, BASFI and BASDAI scores did not show any correlation ($r = 0.03$, $P = 0.98$; $r = 0.02$, $P = 0.98$; $r = 0.11$, $P = 0.29$; $r = 0.07$, $P = 0.94$; $r = 0.12$,

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TABLE 1. Clinical and laboratory characteristics of the subjects

	AS patients ($n=54$)	Controls ($n=31$)	P-value
Age (yr)	37 ± 11	35 ± 9	0.32
Male/female (number)	29/25	16/15	0.85
Disease duration (yr)	12.4 ± 9.2		
BASFI	2.4 ± 2.4		
BASDAI	3.3 ± 2.0		
BASMI	2.3 ± 2.2	0.4 ± 0.6	0.000
Height (cm)	164.2 ± 10.1	165.9 ± 9.2	0.44
Body mass index (kg/m^2)	25 ± 5	24.4 ± 3.7	0.61
Waist (cm)	78.5 ± 14.4	79.2 ± 13	0.83
Waist/hip ratio	0.83 ± 0.12	0.83 ± 0.08	0.80
Smoking (%)	37	35	0.88
Creatinine (mg/dl)	0.91 ± 0.12	0.94 ± 0.11	0.31
Total cholesterol (mg/dl)	174 ± 40	178 ± 38	0.61
LDL cholesterol (mg/dl)	102 ± 34	103 ± 37	0.87
HDL cholesterol (mg/dl)	53 ± 13	52 ± 11	0.88
Triglyceride (mg/dl)	96 ± 47	115 ± 53	0.09
ESR (mm/h)	24 ± 17	6 ± 4	0.000
CRP (mg/dl)	14 ± 19	2 ± 1.5	0.001
Fibrinogen (mg/dl)	4 ± 1	3 ± 0.5	0.000

Data are mean ± S.D.

TABLE 2. Ultrasonographic results

	AS patients ($n=54$)	Controls ($n=31$)	95% confidence interval of the difference	P-value
IMT study of the CCA				
Right CCA IMT (mm)	0.56 ± 0.11	0.54 ± 0.15	−0.03 to 0.08	0.38
Left CCA IMT (mm)	0.57 ± 0.12	0.54 ± 0.14	−0.03 to 0.08	0.37
Averaged CCA IMT (mm)	0.57 ± 0.12	0.54 ± 0.14	−0.03 to 0.08	0.37
FMD study of the brachial artery				
Baseline lumen diameter of the brachial artery (mm)	3.5 ± 0.6	3.3 ± 0.6	−0.92 to 4.8	0.18
FMD (%)	14.1 ± 6.7	17.6 ± 8	−6.8 to −0.24	**0.03**
Nitroglycerin-induced dilatation (%)	16.4 ± 6.8	19.8 ± 10	−7.0 to 0.26	0.07

Data are mean ± S.D.

$P=0.25$; $r=0.09$, $P=0.43$; $r=0.10$, $P=0.35$; $r=-0.09$, $P=0.37$; $r=0.03$, $P=0.81$; $r=-0.03$, $P=0.79$, respectively).

Discussion

Endothelial dysfunction is a key early event in atherogenesis, appearing long before the formation of structural atherosclerotic changes [17]. Traditional risk factors, such as higher BMI, smoking and impaired lipid status, are partly responsible for the development of endothelial dysfunction [18]. Current data suggest that inflammation has a role in the development of endothelial impairment [19]. Indeed, chronic inflammation leads to accelerated atherogenesis, particularly in patients with rheumatoid arthritis [20].

AS is a chronic inflammatory rheumatic disease of the spine that affects between 0.2 and 0.9% of the population [21]. There are several characteristic extra-articular manifestations involving organs such as the eye, gastrointestinal system, kidneys, lungs and heart [3]. Although mortality from circulatory disease has been found to be increased [4], there is no evidence that it is due to atherosclerosis [5].

Clinically, it is relatively easy to measure endothelial function by using the capacity of the endothelium to elicit vasodilatation. Most investigations have used FMD in the brachial artery as an index of endothelial function [9]. Alterations in FMD have been documented in almost all of the major cardiovascular risk factors, such as diabetes mellitus, hypertension and high cholesterol [17].

Our study revealed that the endothelial function of AS patients was impaired compared with healthy controls. No significant correlation was found between the FMD measurements and parameters such as sex, age, serum lipids, smoking habits, CRP level and disease activity scores; for some of these variables this may have been because of the small number of subjects included in the study. Thus, lack of correlation between FMD and disease activity scores needs to be confirmed by further studies with larger numbers of subjects. Measurement of IMT of the CCA by ultrasound is a highly reproducible method for the evaluation of early atherosclerosis [7]. Using this method, we were unable to detect a significant difference between the patients and the controls. However, the average age of the patients in this study was 37 ± 11 yr. A study including older patients with a longer duration of disease might have a better chance of showing a difference in IMT between patients with AS and matched controls.

Nitroglycerin is an exogenous source of nitric oxide, which acts as an endothelium-independent, smooth muscle-dependent dilator [22]. Some studies revealed that cardiovascular risk factors might impair the vasodilator response to nitroglycerin [23]. However, information about this subject is limited [22]. In this study, nitroglycerin-induced dilatation showed a trend to be lower in the patient group, just missing statistical significance.

The most significant limitation of this study is the small sample size and limited statistical power. Therefore, a larger study is needed to confirm our findings. Another limitation is that intraobserver variation was not assessed in this study.

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Despite these limitations, this study demonstrates impairment of endothelial function in AS. Further research should clarify the mechanisms involved and the clinical significance of this finding.

Rheumatology	Key messages
	• Endothelial dysfunction may be present in ankylosing spondylitis. • Endothelial damage and dysfunction may be related to the excess mortality from circulatory disease reported in atherosclerosis.

The authors have declared no conflicts of interest.

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