Assessment of Preclinical Atherosclerosis in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** Epidemiological studies recently confirmed the increased risk of vascular morbidity and mortality during ankylosing spondylitis (AS). Increase of intima-media thickness (IMT) of the common carotid artery is a useful and noninvasive marker of preclinical atherosclerosis. The aim of our study was to compare IMT in patients with AS with matched controls and to determine risk factors of atherosclerosis related to AS.

Methods. We performed a prospective study of 60 consecutive patients meeting modified New York criteria for AS, compared to 60 controls matched for age and sex. Disease-specific measures were determined. Measurement of IMT was performed by the same radiologist using the same machine and probe in right and left common carotid arteries, and the average of the 2 measurements was considered.

Results. In total 48 male and 12 female patients were recruited, and 60 corresponding controls; mean age was 36 ± 11 years. We found significantly increased IMT in the AS group (0.51 ± 0.12 mm) compared with controls (0.39 ± 0.09 mm; p = 0.001). After adjustment for confounding factors, increased IMT was still present (p = 0.003). Age at onset of AS (p = 0.001), Bath AS Disease Activity Index (p = 0.002), AS Disease Activity Score (ASDAS) erythrocyte sedimentation rate (ESR; p = 0.047), ASDAS C-reactive protein (CRP; p = 0.012), Bath AS Functional Index (p = 0.008), global spine visual analog scale for pain (p = 0.000), Schober index (p = 0.039), Bath AS Metrology Index (p = 0.028), modified Stoke Ankylosing Spondylitis Spine Score (p = 0.035), and high ESR (p = 0.001) and CRP (p = 0.000) were correlated with high IMT in patients with AS. Otherwise, status of arthritis (p = 0.442), enthesitis (p = 0.482), and HLA-B27 (p = 0.528) seemed to have no effect on IMT.

Conclusion. AS is associated with an increased risk of atherosclerosis independent of traditional risk factors. Disease activity, functional and mobility limitations, structural damage, and inflammation are the most incriminated risk factors. (J Rheumatol First Release Jan 15 2012; doi:10.3899/jrheum.110792)

Key Indexing Terms:
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Several epidemiological studies recently confirmed the high risk of cardiovascular morbidity and mortality in ankylosing spondylitis (AS), a link that cannot be explained by valvular involvement and cardiac conduction disorders[1,2,3,4,5]. Indeed, chronic inflammatory connective tissue disease seems to be an independent risk factor for atherosclerosis[6,7]. Some factors are incriminated in increasing the vascular risk in patients with AS. The most important are the associated metabolic disorders, the spinal and joint ankylosis that limits physical activity, the genotype, the inflammatory context, and the use of nonsteroidal antiinflammatory drugs (NSAID)[5,8]. Nevertheless, the relative participation of each of these factors in increasing vascular risk remains unknown.

Increase of carotid intima-media thickness (IMT), determined by high-resolution ultrasound of the common carotid artery, is a useful and noninvasive marker of preclinical atherosclerosis that has a high predictive value for the development of cardiovascular events[9,10]. Interpretation of this marker may help in detecting asymptomatic carotid alterations in patients with AS in order to determine those with high risk for cerebral and cardiovascular diseases.

The objectives of our study were to compare IMT in patients with AS and in controls matched for age and sex, and to determine risk factors for atherosclerosis related to AS.

MATERIALS AND METHODS

Patients. We performed a prospective study of 60 consecutive patients meeting the modified New York criteria for AS[11] and seen at the Department of Rheumatology of the Kassab Institute. We excluded patients with known history of myocardial infarction, stroke, diabetes mellitus, hypertension, renal failure, or family history of premature coronary heart disease and subjects receiving lipid-lowering drugs.

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Our study was approved by our institutional bioethics committee. Written informed consent was obtained from each patient.

Controls. Sixty controls matched for age and sex were recruited. They were either healthy volunteers or patients consulting for acute noninflammatory diseases (osteoarthritis, back pain). Subjects with known vascular risk factors were also excluded.

Clinical data. Traditional vascular risk factors were assessed in patients and controls. All patients underwent a clinical evaluation that included the following: the Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), Bath AS Functional Index (BASFI), Bath AS Global score, the AS Quality of Life score; and measures of mobility: cervical rotation, chest expansion, C7-wall distance, Schober index, and the Bath AS Metrology Index (BASMI).

Radiographic data. Anteroposterior radiographs of spine and pelvis and lateral radiographs of the spine were obtained. The Bath AS Radiological Index (BASRI) and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) were determined.

Ultrasonographic data. High-resolution Doppler ultrasonography was performed with a Philips HD11TM instrument with a high-frequency (15 MHZ) linear probe. The sonographer was a radiologist who was unaware of subjects' clinical and radiographic data. Measurement of IMT was performed in right and left common carotid arteries and the average of the 2 measurements was considered.

Laboratory data. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose levels were measured from venous blood samples after a 12-hour fast in all patients and controls. HLA typing for B locus was performed by HLA class I polymerase chain reaction hybridization with oligonucleotide probe and sequence-specific primers in patients.

Statistical analysis. We used SPSS software, version 13.0 for Windows (SASS Inc., Chicago, IL, USA) for all analyses. Comparison of IMT in patients and controls was assessed by ANOVA. Correlations among IMT and disease measures were assessed by Pearson's correlation coefficient. Linear regression was performed for potential confusion factors. P values < 0.05 were taken to indicate significant correlations.

RESULTS

Traditional vascular risk factors and lipid profiles in patients and controls are shown in Table 1. A high level of plasma glucose was detected in 7 controls and 2 patients with unknown history of diabetes mellitus, and hypertension was discovered in 2 subjects (1 patient, 1 control). Total cholesterol level was higher in controls than in patients ($p = 0.042$) and the HDL cholesterol level was lower in patients than in controls ($p = 0.001$). Other traditional vascular risk factors were comparable in patients and controls (data not shown).

The intraobserver variability of the IMT assessor calculated by the coefficient of concordance kappa was very good ($k = 0.841$). The mean carotid IMT was 0.51 ± 0.12 mm in patients and 0.39 ± 0.09 mm in controls. According to age and sex distribution of reference values of carotid IMT[12,13], 43.3% of patients and 10% of controls had abnormal values. Thus, IMT in common carotid arteries was significantly greater in patients than in controls ($p = 0.001$). Linear regression for traditional vascular risk factors showed that differences between IMT patients and controls were still significant (adjusted for total cholesterol level: $p = 0.001$; for HDL cholesterol level: $p = 0.003$; for smoking: $p = 0.003$; for obesity defined as body mass index > 25 kg/m^2: $p = 0.001$). Thus obesity, smoking, and differences in cholesterol levels in patients and controls seemed to have no effect on IMT. Otherwise, ultrasound examinations detected no atherosclerotic plaques in vessel walls in patients or controls.

Disease measures of patients with AS are shown in Table 2. The age at onset of AS, BASDAI, ASDAS ESR, ASDAS CRP, BASFI, visual analog scale (VAS) for global spine pain, Schober index, BASMI, and mSASSS as well as high levels of ESR and CRP were correlated with high risk for atherosclerosis in patients with AS. Otherwise, arthritis, enthesitis, HLA-B27 status, and treatment seemed to have no effect on IMT.

DISCUSSION

Previous studies showed that increase of IMT in various inflammatory diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), was associated with clinical expression of atherosclerosis[14,15]. Data were lacking to confirm this relationship in AS. Nevertheless, confirming the increase of vascular risk in patients with AS is interesting. Indeed, patients with AS are younger than those with RA and have less interference of metabolic syndrome and corticosteroid treatment than RA and SLE patients, and thus the effect of inflammation and disease-related variables seems to be more obvious.

Our study shows that IMT was significantly greater in patients with AS than in controls paired for age and sex. These results are confirmed by some investigators[16,17,18], but not by others who found no differences or trends toward increased IMT in AS patients[19,20,21]. Indeed, the higher risk of preclinical atherosclerosis is more difficult to confirm in AS and the small sample sizes constitute a major limitation of the studies that did not confirm this relationship[19,20,21,22].

Traditional vascular risk factors may interfere with IMT independent of AS. In our study, linear regression analyses for smoking, obesity, and high levels of cholesterol found no influence of these variables in differences of IMT between patients and controls. Metabolic syndrome seems to be more frequent in patients with chronic inflammatory diseases than in the general population[23], and reduction of HDL cholesterol is frequently described in patients with AS[24,25]. Some studies suggest that biochemical abnormalities in metabolic syndrome may participate in the onset and the persistence of inflammatory arthritis[26]. Moreover, biologic inflammatory measures and lipid profiles seem to be interrelated in patients with chronic inflammatory diseases[27]. Gonzalez-Juanatey, *et al* showed in 64 patients with AS compared to matched controls that atherosclerotic plaques in the carotid vessel wall were predictors of severe macrovascular disease in patients without clinically evident cardiovascular disease, and that increased frequency of carotid plaque was associated with disease duration and ESR at the time of disease diagnosis[18]. Our study showed no carotid plaque in patients and controls.

Table 1. Demographic characteristics and traditional vascular risk factors in patients with ankylosing spondylitis and controls.

Characteristic	Patients, n = 60	Controls, n = 60	p
Age, yrs	36 ± 11	35.2 ± 11.2	0.701
Men	48	48	0.572
Smoking, yes	16	23	0.335
BMI, kg/m^2	24.9 ± 4.9	26 ± 4.4	0.256
Obesity (BMI > 25 kg/m^2, n (%)	3 (5)	9 (15)	0.020
Total cholesterol			
High level, n (%)	5 (8.3)	6 (10)	0.556
Mean ± SD, mmol/l	3.9 ± 1	4.2 ± 0.8	0.042
LDL cholesterol			
High level, n (%)	2 (3.2)	0	0.228
Mean ± SD, mmol/l	2.3 ± 0.9	2.5 ± 0.7	0.287
HDL cholesterol			
Low level, n (%)	26 (43.3)	13 (21.6)	0.004
Mean ± SD, mmol/l	0.9 ± 0.3	1.1 ± 0.2	0.001
Triglyceride			
High level, n (%)	8 (13.3)	5 (8.3)	0.230
Mean ± SD, mmol/l	1.1 ± 0.6	1.2 ± 1	0.713
Plasma glucose			
High level, n (%)	2 (3.2)	7 (11.6)	0.102
Mean ± SD, mmol/l	4.7 ± 0.7	4.9 ± 1.3	0.398
Blood pressure			
High level, n (%)	1 (1.6)	1 (1.6)	0.732
Systolic, mm Hg	10.5 ± 2.7	10.9 ± 3.3	0.480
Diastolic, mm Hg	6.7 ± 2.1	7.0 ± 1.7	0.392
ESR, mm/h	42.6 ± 29.2	10.4 ± 9.5	0.000
CRP, mg/l	18.9 ± 22.9	5.5 ± 1.9	0.000

BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

These results may be related to the younger ages of our subjects (36 ± 11 yrs vs 52.6 ± 14.6 yrs in previous studies[18]) and to the shorter disease duration in our patients compared to patients in the Gonzalez-Juanatey study (13.1 ± 8.5 yrs vs 19.1 ± 11.2 yrs, respectively)[18].

The age at onset of AS, but not disease duration or juvenile onset of AS, was associated with IMT in our study. Gonzalez-Juanatey, *et al* found that IMT was not correlated with disease duration or to age at onset of AS[18]. Bodnar, *et al* found in 43 patients with AS that IMT was correlated to disease duration[17]. This variation between different studies could be explained by a variability of the demographic characteristics and disease durations of the populations.

Concerning specific disease measures, our study showed that BASDAI, ASDAS ESR, ASDAS CRP, and high levels of ESR and CRP were correlated to IMT. These results are confirmed by others[18,19]. Indeed, disease activity and persistent inflammation are associated with vessel wall inflammation and atherosclerosis risk[24]. Otherwise, BASFI, VAS for global spine pain, Schober index, and BASMI were also correlated with IMT. This finding may be related to functional and mobility limitations that reduce physical activity in patients with AS and may contribute to increasing the risk of vascular events[17].

The contribution of structural damage in vascular risk has not been widely studied. Our study showed that mSASSS but not BASRI was correlated with IMT in patients with AS. Mathieu, *et al* found no correlations between mSASSS and IMT[28]. The mean mSASSS was lower in their patients[28] than in our patients (mean mSASSS 3 vs 15.4, respectively). These results suggest that spine structural damage may contribute to risk for atherosclerosis by reducing the patient's spinal mobility and physical activity.

The synovitis, hip arthritis, enthesitis, and HLA-B27 status seemed to have no effect on IMT in our study and in others concerning AS[17,18,19,29].

Although NSAID are known to be associated with increased risk of serious cardiovascular events[28,30], we found no influence of NSAID treatment on IMT in patients with AS. IMT was not associated with NSAID intake, but the majority of patients were exposed to these drugs, therefore their potential effects on carotid IMT cannot be excluded. Otherwise, NSAID improve mobility, thereby lowering the vascular risk. The role of steroids in the occurrence of vascular events in patients with RA and SLE has been confirmed by several studies[31,32]. Steroid therapy can affect many metabolic factors such as body fat distribution, blood pressure, and glucose metabolism. On the other hand, they also may be of benefit because of their antiinflammatory effects[31,32]. Only a few patients in our study were treated with steroids, which may explain the absence of influence on IMT. The role of disease-modifying antirheumatic drugs (DMARD) in increasing ath-

Table 2. Correlations of AS variables and intima-media thickness.

Variable	Result	r (Pearson)	p
Age at onset of AS, yrs	25.1 ± 11.2	0.423	0.001
Juvenile AS (< 16 yrs), n (%)*	10 (16.7)		0.572
Disease duration, yrs	13.1 ± 8.5	0.097	0.466
BASDAI, 0–10	4.9 ± 2.7	0.412	0.002
ASDAS vs	3.5 ± 1.3	0.264	0.047
ASDAS CRP	3.4 ± 1.4	0.325	0.012
BASFI, 0–10	4.4 ± 3	0.361	0.008
ASQoL, 0–18	7.5 ± 6	0.259	0.075
BASG-s, 0–100	53.2 ± 27.6	–0.028	0.828
Hip arthritis* (+)	55		0.487
Walked distance, km	1.33 ± 1.72	–0.140	0.294
Lequesne index	6.1 ± 6.4	–0.125	0.345
Global spine pain VAS, 0–10	5.2 ± 2.6	0.655	0.000
Peripheral arthritis			
(other than hips)* (+)	22 (36)		0.211
Articular pain VAS, 0–10	27 ± 30	–0.112	0.442
MASES, 0–13	2.1 ± 2.9	0.110	0.482
Cervical rotation, degrees	87° ± 2	–0.048	0.722
Chest wall expansion distance, cm	3.1 ± 1.5	–0.277	0.881
Occiput to wall distance, cm	6.4 ± 6.3	0.021	0.881
Schober index, cm	2.2 ± 1.4	–0.296	0.039
Ground to finger distance, cm	18.6 ± 14.9	0.141	0.303
BASMI, 0–10	4.3 ± 1.9	0.348	0.028
mSASSS, 0–72	15.4 ± 17.1	0.315	0.035
BASRI, 0–16	8.7 ± 3.8	0.230	0.092
HLA-B27* (+), %	48		0.528
ESR, % high level*, %	65		0.001
CRP, % high level*, %	50		0.000
Treatment			
NSAID, n (%)*	57 (95)		0.795
Diclofenac, n (%)*	15 (25)		0.977
Indomethacin, n (%)*	31 (51.6)		0.818
Steroids (yes), n (%)*	5 (8.3)	–0.024	0.573
Cumulative dose, mg	147 ± 71		0.858
DMARD, n (%)*	21 (35)		0.905
SSZ, n (%)*	18 (30)		0.540
MTX, n (%)*	3 (5)		0.136
Anti-TNF*	4 (6.6)		0.368
Infliximab, n (%)*	1 (1.6)		0.869
Etanercept, n (%)*	3 (5)		0.351

* Statistics test: ANOVA. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI:: Bath Ankylosing Spondylitis Metrology Index; BASRI: Bath Ankylosing Spondylitis Radiological Index; BASG-s: Bath Ankylosing Spondylitis global score; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drugs; SSZ: sulfasalazine; MTX: methotrexate; TNF: tumor necrosis factor; VAS: visual analog scale; MASES: Maastricht AS Enthesitis Score; ASQoL: AS Quality of Life index.

erosclerosis risk is diversely interpreted by different studies[33]. Use of methotrexate and sulfasalazine can be harmful by inducing hyperhomocysteinemia[34,35] and can have a positive effect by reducing inflammation[36]. Concomitant use of folic acid treatment significantly reduces hyperhomocysteinemia and then these DMARD seem to have a protective effect on vascular risk. Potential benefits with anti-tumor necrosis factor (anti-TNF) therapy associated with improvements of inflammation and lipid profiles have not been confirmed[29]. The small sample of patients treated with DMARD, particularly with anti-TNF, was a major limitation of our study to detect their potential effects on IMT.

Our study shows that AS is associated with an increase of risk for atherosclerosis independent of traditional risk factors. Disease activity, functional and mobility limitations, structural damage, and inflammation are the most incriminated risk factors. Further studies with larger samples of patients may reveal the potential effects of treatment on the increase of the vascular risk.

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