Subclinical Atherosclerosis Is Not Accelerated in Patients with Ankylosing Spondylitis with Low Disease Activity: New Data and Metaanalysis of Published Studies

Aikaterini Arida, Athanasios D. Protogerou, George Konstantonis, Maria Konsta, Evi M. Delicha, George D. Kitas, and Petros P. Sfikakis

ABSTRACT. ***Objective.*** Chronic inflammatory rheumatic diseases are associated with accelerated atherosclerosis, but data in ankylosing spondylitis (AS) are limited and the relative contribution of inflammation versus classical cardiovascular (CV) risk factors remains a matter of controversy. We addressed this in an original study and a metaanalysis of previous studies.

Methods. Atheromatic plaques in carotid and femoral arteries, carotid hypertrophy [intima-media thickness (IMT), cross-sectional area], and carotid stiffness by ultrasound, as well as aortic stiffness by pulse wave velocity, were examined in consecutive nondiabetic, CV disease (CVD)-free patients with AS. Healthy individuals carefully matched 1:1 with patients for age, sex, smoking habits, hyperlipidemia, and hypertension served as controls. A metaanalysis of original studies that examined subclinical atherosclerosis in patients with AS versus controls with comparable CVD risk factors was also performed.

Results. Carotid and femoral atheromatic plaques were slightly less prevalent compared with controls in a contemporary cohort consisting of 67 patients with AS (82% men), aged 47.5 ± 12.5 years (mean ± SD), with a median disease duration of 12 years and a Bath AS Disease Activity Index (BASDAI) of 1.8 (interquartile range 0.4–3.6), of whom 66% were receiving anti-tumor necrosis factor (TNF) treatment. Carotid hypertrophy and stiffness, as well as aortic stiffness, were similar between patients and their matched controls. Metaanalysis of all published studies revealed a significantly increased carotid IMT, but not plaque burden, in AS versus controls. Notably, however, increased IMT was not evident in studies involving patients with low disease activity (mean BASDAI < 4) or in those studies that included > 50% of patients treated with anti-TNF.

Conclusion. Low AS disease activity is not associated with accelerated atherosclerosis. (J Rheumatol First Release October 1 2015; doi:10.3899/jrheum.150316)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
ATHEROMATOSIS
CARDIOVASCULAR DISEASE
ATHEROSCLEROSIS

The role of chronic systemic inflammation in the pathogenesis of accelerated atherosclerosis in patients with rheumatic diseases has been well described. Underlying mechanisms that promote the atherosclerotic process include increased prevalence of classical cardiovascular (CV) disease (CVD) risk factors and metabolic syndrome, alteration of lipoprotein concentrations, oxidative stress, as well as increased inflammatory cell-mediated direct endothelial

From the Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital; Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School, Athens, Greece.

Supported by Athens University Medical School grand ELKE 097.

A. Arida, MSc, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; A.D. Protogerou, PhD, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; G. Konstantonis, MSc, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; M. Konsta, MD, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; E.M. Delicha, PhD, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; G.D. Kitas, Professor, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School; P.P. Sfikakis, Professor, Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Laikon Hospital, and Joint Academic Rheumatology Programme, National Kapodistrian University of Athens Medical School.

Address correspondence to Dr. Petros P. Sfikakis, First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Agiou Thoma 17, GR-11527 Athens, Greece.
E-mail: psfikakis@med.uoa.gr

Accepted for publication July 15, 2015.

injury and dysfunction[1]. According to the European League Against Rheumatism (EULAR) recommendations[2], patients with rheumatoid arthritis (RA) have a 1.5-fold increased risk of CVD than the general population and require more aggressive CV screening and management. Even though data on ankylosing spondylitis (AS) are more limited, these patients also have increased CVD morbidity and mortality compared with the general population[3,4,5], a finding that cannot be fully attributed to the higher prevalence of classical CVD risk factors and metabolic syndrome[6,7,8,9,10].

Several studies have focused on the effect of AS disease *per se* on endothelial dysfunction and the progress of atherosclerosis[7,10–20,21,22,23,24,25,26,27,28,29]. A metaanalysis performed in such studies published up to 2009 concluded that atherosclerosis was accelerated in patients with AS, as evidenced by significantly greater intima-media thickness (IMT) values compared with controls[9]. However, this metaanalysis[9] included only 4 case-control studies examining carotid IMT, and interestingly, results from 3 of them suggested differently[7,12,15]. Along this line, 6 subsequently published original case-control studies showed that IMT in AS was not increased[20,22,24,26,27,28]. Discrepancies are perhaps because of the synergetic damaging effect of chronic inflammation and the different concomitant CVD risk factors across studies. On the other hand, an important limitation of all published studies so far is that none used a strict 1:1 matching methodology between patients with AS and healthy subjects for every classical CVD risk factor.

Therefore, to safely test the hypothesis that subclinical atherosclerosis (atheromatic plaques, arterial hypertrophy, and stiffness) develops earlier in patients with AS compared with healthy individuals, we conducted a case-control study strictly 1:1 matched for classical CVD risk factors. In a further effort to dissociate the involvement of disease status *per se* from that of classical risk factors, we also performed a metaanalysis of those original studies that examined subclinical atherosclerosis in patients with AS versus controls with comparable CVD risk factors.

MATERIALS AND METHODS

Study population and study design. Consecutive consenting patients attending the Laikon Hospital's rheumatology outpatient clinics between 2011 and 2013, who had been diagnosed with AS according to the New York criteria[30], were candidates for our study. Exclusion criteria included clinical CVD, diabetes mellitus (already diagnosed by a physician or 2 fasting plasma glucose levels on different days > 125 mg/dl or HbA1c > 6.5%), malignancy, chronic renal failure, or other concomitant severe disease [i.e., human immunodeficiency virus (HIV) infection]. Indices of AS disease activity and function, namely the Bath AS Disease Activity Index (BASDAI)[31] and the Bath AS Functional Index (BASFI)[32], as well as the Health Assessment Questionnaire Disability Index (HAQ-DI)[33], were calculated. Erythrocyte sedimentation rate, serum C-reactive protein, glucose, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides measured within 3 months from examination were also recorded.

Eighty-one patients, aged 46.8 ± 13.3 years, 85.2% men, were enrolled; 67 of them could be matched 1:1 with healthy controls for age (± 2 years), sex, smoking habits, hyperlipidemia (defined as diagnosis by a physician or LDL fasting plasma levels > 160 mg/dl), and hypertension (HTN; defined as diagnosis by a physician or blood pressure levels > 130/80 using a 24-h monitoring device). The remaining 14 patients meeting inclusion criteria could not be effectively 1:1 matched to healthy controls. Sixteen other patients had been excluded because of coronary heart disease and/or cerebrovascular insult (n = 5), diabetes mellitus (n = 8), concomitant HIV infection (n = 1), severe heart failure (ejection fraction = 20%, n = 1), and chronic lymphocytic leukemia (n = 1). Our study was approved by our Institutional Scientific Board, and informed consent was obtained from patients and controls according to the Helsinki Declaration.

Assessment of subclinical atherosclerosis. Patients and controls abstained from food, drink, or any medication for 12 hours prior to the comprehensive study of (1) subclinical atheromatosis, (2) carotid hypertrophy, and (3) common carotid artery (CCA) elasticity and aortic stiffness. Subclinical atheromatosis was assessed by the presence of atheromatic plaques in a total of 8 arterial beds (left and right, common and internal, carotid arteries and carotid bulb; and both common femoral arteries) by ultrasound (US). Atheromatic plaques were defined as the local increase of the IMT of > 50% compared with the surrounding vessel wall, an IMT > 1.5 mm, or local thickening > 0.5 mm[34]. Carotid hypertrophy was estimated by IMT (adjacent to plaques when present) and cross-sectional area (CSA) in both the right and left common carotid arteries by US[35]. The common carotid arteries were scanned in both transverse and longitudinal planes, and IMT measurements were performed using automatic IMT measurement software. Carotid elasticity was assessed by US and aortic stiffness by carotid-to-femoral pulse wave velocity (PWV) and pressure wave reflections by augmentation index using the Sphygmocor device (AtCor Medical) and pulse wave analysis methodology[36]. Carotid elasticity was assessed by echocardiogram-gated US B-mode derived images that were used for the measurement of both left and right common carotid internal diameters during systole (CDs) and diastole (CDd). Strain was calculated according to the following formula:

$$[(CDs - CDd) \div CDd] \times 100$$

Young's modulus was calculated as:

$$[(\text{systolic pressure} - \text{diastolic pressure}) \div (\text{carotid systolic diameter} - \text{carotid diastolic diameter})] \times (\text{carotid diastolic diameter} \div \text{common carotid artery far wall thickness at end of diastole})$$[37]

Measurements were performed by a single experienced technician (GK) using high-resolution B-mode US (Vivid 7 Pro, GE Healthcare) with a 12 MHz linear matrix array transducer. All measurements were performed twice and the mean was recorded; all measurements exhibited high test-retest correlation coefficient (> 0.80), suggesting very good intraobserver reproducibility. The coefficients of variation for all the herein reported vascular biomarkers ranged from 0.02 to 0.08.

Statistics. Normality of sample distribution was examined by the Kolmogorov-Smirnov test. Continuous, normally distributed variables are expressed as means and SD, and analyzed using the paired Student t test. Continuous, not normally distributed variables are expressed as median and 25th and 75th percentile values, and analyzed using the Mann-Whitney U test. Categorical variables are shown in percentiles and were analyzed using the chi-square test. SPSS version 21 was used for all analyses and significance was defined as $p < 0.05$ in all cases.

Literature search and study selection for metaanalysis. Two researchers (AK and KM) independently performed a thorough search of Medline/PubMed, Cochrane, and Scopus databases for original cross-sectional controlled studies evaluating subclinical CVD in patients with AS published in English from January 2000 through July 2014. Search terms included: "ankylosing spondylitis," "cardiovascular disease," "atheromatosis," "atherosclerosis," "IMT," "arterial stiffness," and "PWV." Any disagreements between the reviewers were resolved by consensus. For studies that published more than

1 article based upon overlapping groups of participants with the same outcome measure and study design, we included only the study with the largest number of participants. Case-control studies were excluded. These were also excluded: studies including patients with clinical CVD, giving inadequate information on study population, providing inadequate data for statistical analysis [no SD or using median and interquartile range (IQR)], or studies in which patients with AS and controls differed significantly in either age, sex, or any classical CVD risk factor (a flow chart of the selection of included articles is available from the authors on request). Information on the following items was extracted from each study with the use of a standardized form: design, sample size, population characteristics (age, sex, prevalence of CVD risk factors, blood pressure levels, lipid profile), and indices of subclinical atherosclerosis examined (carotid plaques, carotid IMT measurements, indices of carotid and aortic stiffness). For patients with AS, disease duration, BASDAI and BASFI scores, and the use of biological therapy were also recorded. Studies meeting the above criteria were stratified according to the mean level of disease activity (BASDAI < or ≥ 4), and the proportion of patients receiving anti–tumor necrosis factor (anti-TNF) biological therapy (≤ or > 50%).

The metaanalysis was conducted in R software using the "metafor" package as downloaded from Comprehensive R Archive Network repository (cran.r-project.org)[38]. Data were analyzed using random-effects models because of heterogeneity between studies, which was assessed by I^2 and Cochran Q tests. The Egger test was considered to assess the presence of asymmetry in the funnel plots. The outcome variables for the metaanalysis were the overall IMT (average IMT of right and left CCA), right IMT, and carotid plaques. In studies in which the overall IMT was not reported, the average over right and left IMT was considered.

RESULTS

Original study. As shown in Table 1, the mean ± SD ages of the 67 patients and 67 control subjects were 47.54 ± 12.47 years and 47.78 ± 12.69 years, respectively, whereas the median disease duration was 12 years. Thirty-three percent of participants in each group had HTN, 15% had hyperlipidemia, and 55% were smokers. Mean blood pressure levels and body mass index were also similar between the 2 groups. Patients with AS were of low current disease activity and good functional class (BASDAI 1.8, IQR 0.4–3.6; BASFI 2, IQR 0.9–2.8; HAQ-DI 0.13, IQR 0–0.5), and the majority (66%) was receiving anti-TNF treatment.

As shown in Table 2, all studied variables were comparable between patients with AS and controls. Carotid and/or femoral plaques were slightly increased in healthy subjects, albeit not reaching significance (plaques present in 23 patients and 32 controls, p = 0.114; Table 2). IMT, the main variable of arterial hypertrophy, was 0.79 ± 0.22 and 0.80 ± 0.20 in the left CCA versus 0.73 ± 0.16 and 0.75 ± 0.21 in the right CCA for patients and controls, respectively (p = 0.784 for left CCA and 0.421 for right CCA). PWV was 7.64 ± 1.7 m/s in patients versus 8.03 ± 1.92 m/s in controls (p = 0.232), and Augmentation Index was 18.58 ± 13.31% versus 17.52 ± 14.16% (p = 0.656; Table 2). By univariate regression analysis, none of the disease variables, such as duration and activity or anti-TNF treatment, were associated with any of the vascular indices.

Metaanalysis. We retrieved 23 studies evaluating subclinical CVD in AS; 14 of them[11,12,15,18,20-29] fulfilled our inclusion criteria. One study was excluded because of possible duplicated reports[20]. Another study was subsequently excluded because it only examined aortic stiffness (PWV), but not carotid hypertrophy or atheromatosis[11]. Variation of stiffness indices examined throughout the studies did not allow metaregression analysis, because data on each index were too limited. Therefore, 12 studies were included that involved a total of 521 patients and 445 matched controls, providing adequate information on IMT from both or either right CCA and/or presence of plaques for both patients and controls. Patient characteristics and results from each of the included studies are provided in Table 3.

Regarding carotid hypertrophy, we found that patients with AS had significantly increased overall IMT (i.e., average of left and right CCA) compared with matched controls (mean 0.046, 95% CI 0.015–0.077; Figure 1), as well as increased IMT of only the right CCA (0.034, 95% CI 0.004–0.064). On the other hand, analysis of those 5 studies examining the presence of carotid plaques in AS revealed no statistical difference in the relative risk (RR) for the presence of plaques between the 2 study groups (RR_{pooled} = 1.07, 95% CI 0.48–2.37), meaning that the chance of observing plaques in patients with AS is 1.07 times greater as compared with controls (Figure 2). We then performed a sub-metaanalysis of those studies involving patients with well-controlled AS with

Table 1. Demographics and clinical characteristics of patients with AS and healthy controls matched 1:1 for age, sex, and classical CVD risk factors. Data are mean ± SD or median (interquartile range) unless otherwise specified.

Characteristics	AS, n = 67	Controls, n = 67	p
Age, yrs	47.54 ± 12.47	47.78 ± 12.69	0.913
Women, %	18	18	
BMI, kg/m^2	26.45 ± 4.22	26.96 ± 3.62	0.455
Systolic BP, mmHg	126.99 ± 14.94	127.21 ± 15.32	0.932
Diastolic BP, mmHg	78.60 ± 9.11	77.31 ± 10.11	0.441
Median disease duration, yrs	12 (3–25)	—	—
CRP, mg/l	3.62 (2–10)	—	
ESR, mm	21 (8–44)		
BASFI	2 (0.9–2.8)	—	—
BASDAI	1.8 (0.4–3.6)	—	—
HAQ-DI	0.13 (0–0.5)		
Biologic therapy*, n	44	—	—
Smoking, n			
Non-smokers	14	14	
Active smokers	37	37	
Ex-smokers	16	16	
Hypertension, n	22	22	
Antihypertensive drug, n	13	20	0.160
Hyperlipidemia, n	10	10	
Lipid-lowering drug, n	5	6	0.753

*Adalimumab: 19 patients, etanercept: 15 patients, infliximab: 6 patients, golimumab: 4 patients. AS: ankylosing spondylitis; CVD: cardiovascular disease; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath AS Functional Index; BASDAI: Bath AS Disease Activity Index; HAQ-DI: Health Assessment Questionnaire-Disability Index.

Table 2. Vascular indices of patients with AS and healthy controls matched 1:1 for age, sex, and classical CVD risk factors. Data are mean ± SD or n unless otherwise specified.

Variables	AS, n = 67	Controls, n = 67	p
Atheromatosis indices			
Subjects with plaques			0.114
Carotid and/or femoral	23	32	
Carotid and femoral	10	17	
Only carotid	3	3	
Only femoral	10	12	
Plaque localization			0.366
Unilateral carotid	8	13	
Bilateral carotid	5	7	
Only 1 site	10	8	0.104
More than 1 site	13	24	
Arterial hypertrophy indices			
IMT, mm			
LCCA	0.79 ± 0.22	0.80 ± 0.20	0.784
RCCA	0.73 ± 0.16	0.75 ± 0.21	0.421
CSA, mm^2			
LCCA	13.54 ± 4.40	13.438 ± 4.35	0.888
RCCA	12.75 ± 3.83	12.61 ± 4.17	0.849
Arteriosclerosis indices			
Augmentation Index, %	18.58 ± 13.31	17.52 ± 14.16	0.656
Pulse wave velocity, m/s, n = 63	7.64 ± 1.71	8.03 ± 1.92	0.232
Young Module, Pascal, n = 59			
LCCA	784.85 ± 309.34	780.42 ± 407.33	0.947
RCCA	852.89 ± 390.33	938.26 ± 562,11	0.398
Strain, n = 58			
LCCA	8.12 ± 3.08	8.56 ± 2.89	0.417
RCCA	8.13 ± 3.20	8.30 ± 3.42	0.785

AS: ankylosing spondylitis; CVD: cardiovascular disease; IMT: intima-media thickness; LCCA: left common carotid artery; RCCA: right common carotid artery; CSA: cross-sectional area.

a mean BASDAI score < 4 and found that the IMT was not increased compared with controls (0.016, 95% CI –0.05 to 0.037, p = 0.1343). In contrast, metaanalysis of studies with patients with AS of moderate or high disease activity (BASDAI score ≥ 4) continued to show significant difference in IMT between cases and controls (0.097, 95% CI 0.077–0.117, p < 0.001; Table 4). Similar findings were derived from a subgroup metaanalysis of those studies in which > 50% of patients were receiving anti-TNF therapy; the difference in IMT between patients and controls did not reach significance (0.018, 95% CI –0.042 to 0.078, p = 0.5766; Table 4). In contrast, in the group of studies with 0–50% proportion of patients receiving anti-TNF treatment, IMT measurements were significantly increased in AS compared with controls (0.064, 95% CI 0.019–0.108, p = 0.0054).

DISCUSSION

Our original data clearly show that in patients with AS with low disease activity, subclinical atherosclerosis — in terms of atheromatosis, carotid hypertrophy, and arterial stiffness — is not accelerated compared with apparently healthy individuals. To avoid an underestimation of the effect of chronic inflammation, and because atherosclerosis is a chronic long-lasting process, we elected to use the New York criteria for AS diagnosis instead of the Assessment of Spondyloarthritis international Society axial criteria[39], which include more early patients. Our results cannot be directly compared with those of previous studies, because none of them consisted of a strict 1:1 matching for each of the classical CVD risk factors. Notably, our metaanalysis confirmed our original data because the subgroup analysis of studies involving patients with a BASDAI < 4 showed that carotid IMT is similar to controls. As expected, however, overall and subgroup metaanalysis revealed that active AS disease is indeed associated with increased carotid IMT.

Table 3. Characteristics and results of 12 published studies included in the metaanalysis.

Studies	No. Patients with AS	No. Controls	Mean IMT of Right CCA and Left		IMT of Right CCA		Carotid Plaques		Mean BASDAI Score	Patients Treated with Anti-TNF, %
			Patients	Controls	Patients	Controls	Patients	Controls		
Sari, *et al*[12]	54	31	0.57 ± 0.12	0.54 ± 0.14	0.56 ± 0.11	0.54 ± 0.15			3.3 ± 2	ND
Choe, *et al*[15]	28	27	0.58 ± 0.06	0.56 ± 0.05	ND	ND			3.3 ± 1.3	0
Gonzalez-Juanatey, *et al*[18]*	64	64			0.74 ± 0.21	0.67 ± 0.14	19	6	3.04 ± 1.95	33
Bodnar, *et al*[21]	43	40	0.65 ± 0.15	0.54 ± 0.15	ND	ND			5.04 ± 1.91	65
Capkin, *et al*[22]*	67	34			0.49 ± 0.12	0.47 ± 0.09			2.65 ± 0.76	51
Cece, *et al*[23]	45	30	0.59 ± 0.07	0.50 ± 0.07	0.60 ± 0.08	0.50 ± 0.06			4.16 ± 1.8	0
Erre, *et al*[24]	17	17	0.64 ± 0.1	0.67 ± 0.1	ND	ND			2.7 ± 2.8	59
Hamdi, *et al*[25]	60	60	0.51 ± 0.12	0.39 ± 0.09	ND	ND	0	0	4.9 ± 2.7	7
Ceccon, *et al*[26]	14	13	0.57 ± 0.15	0.62 ± 0.38	0.55 ± 0.16	0.55 ± 0.12			5.6 ± 1.2	0
Gecene, *et al*[27]	50	50	0.58 ± 0.14	0.54 ± 0.12	0.56 ± 0.14	0.53 ± 0.12	2	5	2.39 ± 1.66	18
Valente, *et al*[28]	42	42	0.62 ± 0.09	0.61 ± 0.09	ND	ND	8	7	ND	67
Gupta, *et al*[29]	37	37	0.62 ± 0.12	0.54 ± 0.04	ND	ND			4.11 ± 1.99	ND

*Left CCA IMT measurement not performed. AS: ankylosing spondylitis; IMT: intima-media thickness; CCA: common carotid artery; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNF: tumor necrosis factor; ND: not determined.

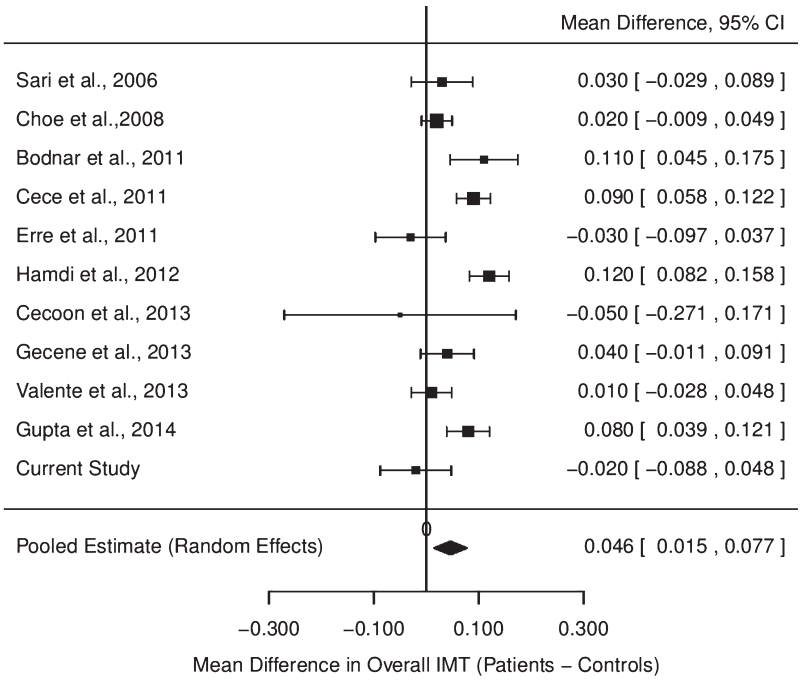

Figure 1. Pooled difference in overall mean IMT (right and left CCA) between patients and controls. IMT: intima-media thickness; CCA: common carotid artery.

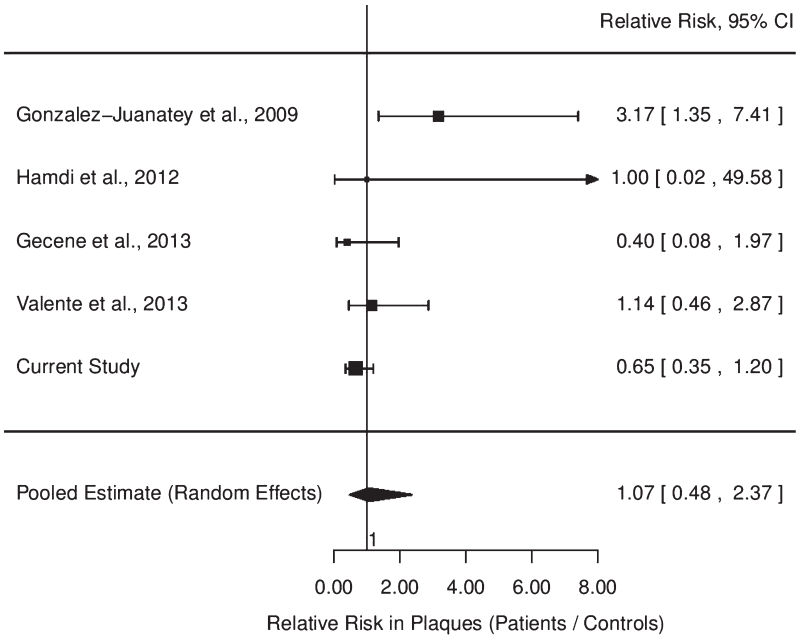

Figure 2. Pooled difference of the relative risk for the presence of carotid atherosclerotic plaques between patients with ankylosing spondylitis and controls.

Chronic systemic inflammation promotes all phases of atherosclerosis and can explain the harmful effect of active AS disease on arterial remodeling. Interestingly, the lack of increased plaque burden in the metaanalysis may be explained by the relatively young age of the patients examined who had AS (mean of 37.7 ± 10.8 yrs); an interaction between age and chronic inflammation has been described[40]. Alternatively, it may be a result of the relatively small number of available studies and cumulative sample size. Plaque formation represents a more advanced stage of atheromatosis

Table 4. Pooled difference in overall IMT (mean of right and left CCA) in subgroups of studies stratified by the level of disease activity as measured by BASDAI or the proportion of patients treated with anti-TNF. Values are mean (95% CI) unless otherwise specified.

Variables	Difference in Overall IMT	p
Anti-TNF ≤ 50%	0.064, 95% CI 0.019–0.108 No. studies: 5 197 patients vs 180 controls	0.0054
Anti-TNF > 50%	0.018, 95% CI –0.042 to 0.078 No. studies: 4 169 patients vs 166 controls	0.5766
BASDAI < 4	0.016, 95% CI –0.05 to 0.037 No. studies: 5 216 patients vs 192 controls	0.1343
BASDAI ≥ 4	0.097, 95% CI 0.077 to 0.117 No. studies: 5 199 patients vs 180 controls	< 0.001

IMT: intima-media thickness; CCA: common carotid artery; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNF: tumor necrosis factor.

than IMT increase, and it is a cumulative result of the effect of many pro-atherogenic factors. Only 1 study involved patients with high disease activity with a mean age of more than 50 years, and in this study, carotid plaques were significantly more prevalent than controls[18]. On the other hand, the presence of increased IMT does not *per se* suggest increased atheromatosis, but it may also be attributed to subclinical vasculitis and/or wall hypertrophy. Such a mechanism of arterial dysfunction has been described in patients with RA, in whom active disease is associated with increased aortic inflammation compared with healthy subjects[41].

The absence of increased carotid IMT in patients with AS with low disease activity could also be attributed to the resolution of vessel wall inflammation. It should be noted that the proportion of our patients receiving anti-TNF therapy is higher than what is commonly seen in clinical practice, but this is because of the fact that patients with severe AS are referred to our Tertiary Academic Hospital. Anti-TNF therapy appears to be involved in ameliorating vascular properties. Anti-TNF therapy in RA succeeded in reducing aortic inflammation along with disease activity, thus decreasing aortic stiffness measured by PWV[41]. Apart from the probable direct effect of TNF inhibitors on vascular inflammation, these agents affect lipid profile[42] and antioxidative capacity of HDL[43], and may even have a specific direct effect on the arterial wall. Nevertheless, reduction of systemic inflammation by anti-TNF agents seems to be the main reason for similar arterial features between patients with systemic inflammatory diseases and healthy individuals, and can explain the lack of increased carotid hypertrophy in patients with AS with low disease activity. A recent review by Tam, *et al*[44] examining the effect of TNF antagonists on the progression of atherosclerosis and in reducing CV risk concluded that anti-TNF agents are probably effective in preventing or even reversing the progression of IMT in patients with systemic rheumatic diseases responding to treatment. Moreover, successful anti-TNF therapy seems to induce a persistent stable vascular function in the long term[45].

Regarding carotid and/or aortic stiffness and vascular function in AS, variation of vascular indices examined did not allow metaanalysis of published data. In patients with AS in particular, published studies, while diverse, suggest that active AS disease causes impaired vascular elasticity and function[14,16,17,19,46]. However, our original data, as well as results from other studies, indicate that effective disease control, particularly by anti-TNF treatment, seems to reverse arterial stiffness and ameliorate functional arterial indices concurrent with reduction in clinical and laboratory inflammatory markers[27,45,46,47,48]. A recent study by Berg, *et al* examining the association between disease activity in AS and markers of vascular pathology concluded that patients with high AS disease activity present with a higher CVD risk[49]. Moreover, another recent 5-year followup study published by the same researchers and evaluating possible factors of CV risk supported that disease activity was related to elevated arterial stiffness and thus future risk of CV disease[50].

To our knowledge, our metaanalysis is the first to examine carotid IMT in patients with AS and apparently healthy controls with comparable classical CVD risk factors. Moreover, this is the first metaanalysis to examine the presence of carotid plaques in AS. Limitations of our metaanalysis include the following: first, differences between patients and controls in some studies regarding age, sex, or CVD risk factors, although not significant, could have affected the final results. Second, concerning IMT calculation, information from published studies regarding methodology is lacking; only a few studies provided detailed information on the method used for IMT calculation and whether sites with plaques were included in IMT measurements. However, mean IMT values and SD from these studies lead us to conclude that this was the case. Finally, we were able to retrieve only 4 studies informing on the presence of plaques in AS, hence overall analysis regarding atheromatosis lacks statistical power.

The original results presented herein and the metaanalysis of previous findings show that subclinical atherosclerosis is not accelerated in patients with AS with low disease activity. However, inadequate control of disease activity results in increased carotid IMT and atheromatosis, especially in older patients. According to the EULAR guidelines for inflammatory arthropathies, the aggressive management of classical CVD risk factors in patients with AS is indicated[2], but the present data clearly show that effective control of disease activity may minimize the CV burden of AS. This should be confirmed in prospective studies that are currently in progress.

REFERENCES

1. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Ann Rheum Dis 2011;70:8-14.
2. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.
3. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 2004;34:585-92.
4. Zochling J, Braun J. Mortality in ankylosing spondylitis. Clin Exp Rheumatol 2008;26 Suppl 51:S80-4.
5. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921-5.
6. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006;33:2167-72.
7. Malesci D, Niglio A, Mennillo GA, Buono R, Valentini G, La Montagna G. High prevalence of metabolic syndrome in patients with ankylosing spondylitis. Clin Rheumatol 2007;26:710-4.
8. Papadakis JA, Sidiropoulos PI, Karvounaris SA, Vrentzos GE, Spanakis EK, Ganotakis ES, et al. High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNFalpha treatment: correlation with disease activity. Clin Exp Rheumatol 2009;27:292-8.
9. Mathieu S, Gossec L, Dougados M, Soubrier M. Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Care Res 2011;63:557-63.
10. Papagoras C, Markatseli TE, Saougou I, Alamanos Y, Zikou AK, Voulgari PV, et al. Cardiovascular risk profile in patients with spondyloarthritis. Joint Bone Spine 2014;81:57-63.
11. Demiralp E, Kardesoglu E, Kiralp MZ, Cebeci BS, Keskin I, Ozmen N, et al. Aortic elasticity in patients with ankylosing spondylitis. Acta Cardiol 2004;59:630-4.
12. Sari I, Okan T, Akar S, Cece H, Altay C, Secil M, et al. Impaired endothelial function in patients with ankylosing spondylitis. Rheumatology 2006;45:283-6.
13. Caliskan M, Erdogan D, Gullu H, Yilmaz S, Gursoy Y, Yildirir A, et al. Impaired coronary microvascular and left ventricular diastolic functions in patients with ankylosing spondylitis. Atherosclerosis 2008;196:306-12.
14. Mathieu S, Joly H, Baron G, Tournadre A, Dubost JJ, Ristori JM, et al. Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. Rheumatology 2008;47:1203-7.
15. Choe JY, Lee MY, Rheem I, Rhee MY, Park SH, Kim SK. No differences of carotid intima-media thickness between young patients with ankylosing spondylitis and healthy controls. Joint Bone Spine 2008;75:548-53.
16. van Eijk IC, Peters MJ, Serné EH, van der Horst-Bruinsma IE, Dijkmans BA, Smulders YM, et al. Microvascular function is impaired in ankylosing spondylitis and improves after tumour necrosis factor alpha blockade. Ann Rheum Dis 2009;68:362-6.
17. Moyssakis I, Gialafos E, Vassiliou VA, Boki K, Votteas V, Sfikakis PP, et al. Myocardial performance and aortic elasticity are impaired in patients with ankylosing spondylitis. Scand J Rheumatol 2009;38:216-21.
18. Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Dierssen T, Vaqueiro I, Blanco R, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. Medicine 2009;88:358-65.
19. Peters MJ, van Eijk IC, Smulders YM, Serne E, Dijkmans BA, van der Horst-Bruinsma IE, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol 2010;37:161-6.
20. Karkucak M, Capkin E, Alver A, Akyuz A, Kiris A, Ak E, et al. The effect of anti-TNF agent on oxidation status in patients with ankylosing spondylitis. Clin Rheumatol 2010;29:303-7.
21. Bodnár N, Kerekes G, Seres I, Paragh G, Kappelmayer J, Némethné ZG, et al. Assessment of subclinical vascular disease associated with ankylosing spondylitis. J Rheumatol 2011;38:723-9.
22. Capkin E, Kiris A, Karkucak M, Durmus I, Gokmen F, Cansu A, et al. Investigation of effects of different treatment modalities on structural and functional vessel wall properties in patients with ankylosing spondylitis. Joint Bone Spine 2011;78:378-82.
23. Cece H, Yazgan P, Karakas E, Karakas O, Demirkol A, Toru I, et al. Carotid intima-media thickness and paraoxonase activity in patients with ankylosing spondylitis. Clin Invest Med 2011;34:E225.
24. Erre GL, Sanna P, Zinellu A, Ponchietti A, Fenu P, Sotgia S, et al. Plasma asymmetric dimethylarginine (ADMA) levels and atherosclerotic disease in ankylosing spondylitis: a cross-sectional study. Clin Rheumatol 2011;30:21-7.
25. Hamdi W, Chelli Bouaziz M, Zouch I, Ghannouchi MM, Haouel M, Ladeb MF, et al. Assessment of preclinical atherosclerosis in patients with ankylosing spondylitis. J Rheumatol 2012;39:322-6.
26. Ceccon FT, Azevedo VF, Engelhorn CA, Abdalla DS, Faulin TE, Guarita-Souza LC, et al. Evaluation of sub-clinical atherosclerosis and plasma levels of minimally modified LDL in patients with ankylosing spondylitis and its correlation with disease activity. Rev Bras Reumatol 2013;53:470-5.
27. Geçene M, Tuncay F, Borman P, Yücel D, Senes M, Yılmaz BK. Atherosclerosis in male patients with ankylosing spondylitis: the relation with methylenetetrahydrofolate reductase (C677T) gene polymorphism and plasma homocysteine levels. Rheumatol Int 2013;33:1519-24.
28. Valente RL, Valente JM, de Castro GR, Zimmermann AF, Fialho SC, Pereira IA. Subclinical atherosclerosis in ankylosing spondylitis: is there a role for inflammation? Rev Bras Reumatol 2013;53:377-81.
29. Gupta N, Saigal R, Goyal L, Agrawal A, Bhargava R, Agrawal A. Carotid intima media thickness as a marker of atherosclerosis in ankylosing spondylitis. Int J Rheumatol 2014;2014:839135.
30. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
31. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
32. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
33. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005;23 Suppl 39:S14-8.
34. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E; American Society of Echocardiography; Society for Vascular Medicine and Biology. American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Vasc Med 2006;11:201-11.
35. Schiffrin EL, Hayoz D. How to assess vascular remodelling in small and medium-sized muscular arteries in humans. J Hypertens

1997;15:571-84.
36. Stamatelopoulos KS, Kitas GD, Papamichael CM, Chryssohoou E, Kyrkou K, Georgiopoulos G, et al. Atherosclerosis in rheumatoid arthritis versus diabetes: a comparative study. Arterioscler Thromb Vasc Biol 2009;29:1702-8.
37. Roman MJ, Devereux RB, Schwartz JE, Lockshin MD, Paget SA, Davis A, et al. Arterial stiffness in chronic inflammatory diseases. Hypertension 2005;46:194-9.
38. Viechtbauer W. Conducting meta-analyses in R with the meta for package. J Stat Softw 2010;36:1-48.
39. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-83.
40. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011;10:319-29.
41. Mäki-Petäjä KM, Elkhawad M, Cheriyan J, Joshi FR, Ostör AJ, Hall FC, et al. Anti-tumor necrosis factor-α therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. Circulation 2012;126:2473-80.
42. Popa C, van den Hoogen FH, Radstake TR, Netea MG, Eijsbouts AE, den Heijer M, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. Ann Rheum Dis 2007;66:1503–7.
43. Spanakis E, Sidiropoulos P, Papadakis J, Ganotakis E, Katsikas G, Karvounaris S, et al. Modest but sustained increase of serum high density lipoprotein cholesterol levels in patients with inflammatory arthritides treated with infliximab. J Rheumatol 2006;33:2440–6.
44. Tam LS, Kitas GD, González-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? Rheumatology 2014;53:1108-19.
45. Angel K, Provan SA, Fagerhol MK, Mowinckel P, Kvien TK, Atar D. Effect of 1-year anti-TNF-α therapy on aortic stiffness, carotid atherosclerosis, and calprotectin in inflammatory arthropathies: a controlled study. Am J Hypertens 2012;25:644-50.
46. Angel K, Provan SA, Gulseth HL, Mowinckel P, Kvien TK, Atar D. Tumor necrosis factor-alpha antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. Hypertension 2010;55:333-8.
47. Syngle A, Vohra K, Sharma A, Kaur L. Endothelial dysfunction in ankylosing spondylitis improves after tumor necrosis factor-alpha blockade. Clin Rheumatol 2010;29:763-70.
48. van Sijl AM, van Eijk IC, Peters MJ, Serné EH, van der Horst-Bruinsma IE, Smulders YM, et al. Tumour necrosis factor blocking agents and progression of subclinical atherosclerosis in patients with ankylosing spondylitis. Ann Rheum Dis 2015; 74:119-23.
49. Berg IJ, van der Heijde D, Dagfinrud H, Seljeflot I, Olsen IC, Kvien TK, et al. Disease activity in ankylosing spondylitis and associations to markers of vascular pathology and traditional cardiovascular disease risk factors: a cross-sectional study. J Rheumatol 2015;42:645-53.
50. Berg IJ, Semb AG, van der Heijde D, Kvien TK, Olsen IC, Dagfinrud H, et al. CRP and ASDAS are associated with future elevated arterial stiffness, a risk marker of cardiovascular disease, in patients with ankylosing spondylitis: results after 5-year follow-up. Ann Rheum Dis 2015;74:1562-6.