## **ORIGINAL ARTICLE**

# Increased prevalence of subclinical coronary atherosclerosis in young patients with ankylosing spondylitis

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### **KEY WORDS**

#### ABSTRACT

ankylosing spondylitis, atherosclerotic plaques, cardiovascular risk factors, coronary computed tomography angiography

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**INTRODUCTION** There is substantial evidence that spondyloarthropathies, such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), may increase cardiovascular risk.

**OBJECTIVES** The study aimed to compare development of atherosclerotic lesions in coronary arteries between patients with AS and individuals without rheumatic diseases.

**PATIENTS AND METHODS** A total of 37 adult patients with AS (mean [SD] age, 40.4 [9.6] years; men, 26 [70.3%]), with disease duration of less than 10 years were enrolled. The control group consisted of 76 participants without rheumatic diseases. Controls were matched for age, sex, history of hypertension, dyslipidemia, and smoking status. Coronary computed tomography angiography was performed in both groups.

**RESULTS** Atherosclerotic lesions in the coronary arteries were present in 18 patients (48.7%) with AS compared with 20 controls (26.3%) (P = 0.02). Univariate analysis performed in the AS group demonstrated an association between the presence of lesions and age (P = 0.02), hypertension (P = 0.003), and dyslipidemia (P = 0.001). The multivariable logistic regression analysis showed a significant association between coronary atherosclerosis and hypertension (P = 0.008) and with dyslipidemia (P = 0.001). The average plaque burden was higher in patients with AS than in controls (mean [SD], 42.2% [4.7%] vs 36.5% [3.1%], P < 0.001).

**CONCLUSIONS** Atherosclerotic plaques in the coronary arteries were significantly more prevalent in patients with AS. A strong association was demonstrated between atherosclerotic lesions and age, hypertension, and dyslipidemia. Our results confirm the need for cardiovascular risk assessment in patients with AS and cardiovascular prevention, if indicated.

**INTRODUCTION** Patients with chronic inflammatory diseases, such as spondyloarthropathies (SpA), are at higher risk of cardiovascular morbidity and mortality.<sup>1-7</sup> The risk of death in patients with ankylosing spondylitis (AS) is higher than in the general population. Cardiovascular disease (CVD) accounts for 40% of deaths among patients with SpA.<sup>8</sup> The risk of myocardial infarction in AS patients is 1.9- to 3.1-fold higher than in the general population.<sup>9</sup> In AS, the risk of developing CVD is increased even in young patients with short disease duration. It could result from a possible interaction between traditional and inflammatory risk factors, genetic predisposition, and therapies of underlying diseases.<sup>10,11</sup> So far, inflammatory and atherosclerotic lesions in AS patients have been detected mainly in the ascending aorta.<sup>12</sup> Moreover, there have been only a few studies evaluating the involvement of coronary arteries in patients with PsA.<sup>13,14</sup> Finally, to our knowledge, there have been no studies evaluating the use of coronary computed tomography angiography (CCTA) for noninvasive assessment of coronary atherosclerotic lesions in patients with AS.<sup>15</sup> Therefore, we conducted a study using CCTA to evaluate the incidence of atherosclerotic lesions in coronary arteries and to identify risk factors associated with the development of coronary atherosclerosis in patients with AS.

**PATIENTS AND METHODS** This was a 2-center case-control study. Between October 2013 and September 2014, 37 consecutive patients with AS (disease duration <10 years), who provided signed informed consent to participate in the study, were recruited. Patients were diagnosed according to the Assessment in SpondyloArthritis international Society criteria and modified New York criteria for AS.<sup>16,17</sup> Patients with known or suspected CVD, diabetes mellitus, or impaired glucose tolerance were excluded from the study. Demographic and clinical data were collected. Lipid levels and inflammatory parameters were measured in each patient. Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP).18

Controls (n = 76) were retrospectively selected from the cohort of patients who had undergone CCTA at the Institute of Cardiology (Warsaw, Poland) and were referred for CCTA due to atypical chest pain. The CCTA was performed with the aim to exclude stable coronary artery disease (CAD), within a lower range of intermediate pretest probability (15%-50%) for stable CAD. The control group was matched for CAD risk factors but not CCTA results. The risk factors included age, sex, history of hypertension, dyslipidemia, and smoking status, after exclusion of rheumatic diseases. Patients with known history of CAD or diabetes mellitus were excluded from the control group. The CCTA was performed with a dual source 2×128-slice CT scanner (Somatom Definition FLASH, Siemens Medical Solutions, Forchheim, Germany). In all patients, sublingual nitrates (0.8 mg) were administered prior to examination. In case of heart rate exceeding 70 bpm, intravenous metoprolol (up to 20 mg) was administered. A 60-ml to 80-ml bolus of iomeprol was injected intravenously (6.0 ml/s). A retrospective, electrocardiogram-gated acquisition protocol was used, with  $128 \times 0.6$ -mm collimation, and 80 to 120 kV tube voltage adjusted manually depending on body mass. Coronary data sets were reconstructed in mid-diastole (60% to 70% of the R-R interval) and mid-systole (40% to 50% of the R-R interval) with 0.6-mm slice thickness and 0.4-mm increment. Image reconstruction was performed using routinely filtered sinogram-affirmed iterative reconstruction I36f, strength 3.

Coronary atherosclerosis was evaluated visually by an experienced observer, using longitudinal and transverse sections and curved multiplanar reformats and was defined as the presence of any visible coronary atherosclerotic plaques. Atherosclerotic plaque volumes and qualitative plaque compositions in the coronary arteries were evaluated using the QCT program (Medis Medical Imaging Systems BV, Leiden, the Netherlands). The adaptive threshold cutoff values of attenuation for the individual components of atherosclerotic plaques were determined. The measurements were made using a semiautomatic method with manual adjustment of wall contours and the lumen of the vessels when necessary. Plague burden was defined as the ratio of the volume (mm<sup>3</sup>) of the vessel wall to the total volume of the vessel in the evaluated segment, expressed as percent (%).

The study was supported by a State Committee for Scientific Research grant and carried out at the Institute of Cardiology, Warsaw, and at the National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, between October 2013 and September 2014 (9.37/III/13). The design and protocol of the study were approved by the institutional review board (IK-NP-0071-1/2013).

Statistical analysis The distribution of continuous variables was assessed with the Shapiro-Wilk test, and the variables with normal distribution were presented as arithmetic mean values with standard deviation (SD) and those with nonnormal distribution, as median with interquartile range (IQR). The significance of differences between normally distributed variables were evaluated by the *t* test. Differences between nonnormally distributed variables were evaluated by the nonparametric Mann-Whitney test as appropriate. The  $\chi^2$  test was used to compare categorical variables between groups, or the Fisher exact test in cases of a minimum expected count of less than 5. These results were reported as frequencies and percentages. The associations of tested variables were assessed with a logistic regression model using univariate and stepwise multivariable analyses. A significance level of 0.05 was reguired for a variable to be included into a multivariable model, while 0.1 was the cutoff value for exclusion. A variable's risk was presented as odds ratio (OR) with the corresponding 95% confidence interval (CI). The area under the receiver operating characteristic curve (AUC) was calculated as a measure of the accuracy of the model.

*P* values of less than 0.05 for 2-sided tests were considered significant. Statistical analysis was performed with the SAS 9.2 software (SAS Institute Inc., Cary, North Carolina, United States, 2008).

**RESULTS** A total of 37 consecutive patients with AS (mean [SD] age, 40.4 [9.6] years; 26 men [70.3%]) were enrolled. The control group consisted of 76 patients (mean [SD] age, 43.1 [7.8] years,

 TABLE 1
 Demographic and clinical characteristics of patients with ankylosing spondylitis and controls

Variable	AS	Controls	P value
	(n = 37)	(n = 76)	
Age, y, mean (SD)	40.4 (9.6)	43.1 (7.8)	0.11
Male sex, n (%)	26 (70.3)	44 (57.9)	0.20
BMI, kg/m², mean (SD)	24.9 (4.3)	26.4 (4.3)	0.08
Duration from diagnosis, mo, median (IQR)	18 (6.0–48.0)	-	_
Duration of symptoms, months, median (IQR)	100 (48.0–168.0)	-	_
BASDAI, points, mean (SD)	5.3 (2.0)	_	_
ASDAS-CRP, points, mean (SD)	3.10 (1.11)	-	-
CRP, mg/l, median (IQR)	12 (5.0 –28.0)	1.8 (1.0 –2.5)	< 0.001
HLA-B27, n (%)	28/34	-	-
	(82.3)		
Hypertension, n (%)	15 (40.5)	36 (47.4)	0.49
Dyslipidemia, n (%)	18 (48.7)	42/70	0.26
		(60.0)	
Smoking, n (%)	16 (43.2)	32 (42.1)	0.91
TC, mg/dl, mean (SD)	189.2 (39.9)	202.3 (41.4)	0.12
LDL-C, mg/dl, mean (SD)	102.9 (31.0)	125.7 (37.1)	0.002
HDL-C, mg/dl, mean (SD)	59.9 (15.4)	57.6 (14.4)	0.44
TG, mg/dl,	112.5 (82 –142)	96.5 (72.6–134.6)	0.24
median (IQR)			
Atherogenic index,	3.31 (1.01)	2.64 (1.24)	0.006
mean (SD)			
NSAID, n (%)	25 (67.6)	_	-
Methotrexate, n (%)	5 (13.5)	_	-
Statins, n (%)	4 (10.8)	-	-
Biologic treatment, n (%)	3 (8.1)	_	-
Glucocorticoids, n (%)	7 (18.9)	-	-

A P value of less than 0.05 is considered significant.

SI conversion factors: to convert C-reactive protein to nmol/l, multiply by 9.524; TC, HDL-C, and LDL-C to mmol/l, by 38.67; TG to mmol/l, by 88.57.

Abbreviations: AS, ankylosing spondylitis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NSAID, nonsteroidal anti-inflammatory drug; TC, total cholesterol; TG, triglycerides

P = 0.11; men, 57.9% P = 0.20). Patients with AS had a mean (SD) BASDAI value of 5.3 (2.0) and higher concentrations of *C*-reactive protein in comparison with controls (median [IQR], 12 [5–28] mg/l vs 1.8 [1.0–2.5] mg/l, P < 0.001), which indicated high inflammatory activity. The clinical and demographic characteristics of the study and control groups are presented in TABLE 1. Patients with AS had lower low-density lipoprotein (LDL) cholesterol levels (P = 0.002), but higher values of atherogenic index (total cholesterol / high-density lipoprotein [HDL] cholesterol; P = 0.006) (TABLE 1).

Coronary atherosclerotic lesions were more common in patients with AS than in controls

(n = 18 [48.7%] and n = 20 [26.3%], respectively, P = 0.02). Most patients had low-grade coronary artery stenosis (less than 40% narrowing of the vessel), which was hemodynamically and clinically insignificant.

In the AS group, patients with atherosclerotic plaques were older (P = 0.02) and had higher concentrations of total cholesterol (P = 0.008), LDL cholesterol (P = 0.02), and triglycerides (P = 0.02) than patients without atherosclerotic plaques. They also more often had hypertension (P = 0.002) and dyslipidemia (P = < 0.001) (TABLE 2). There were no significant differences in clinical variables between patients with AS with atherosclerotic plaques and the control group and patients with atherosclerotic plaques (TABLE 2).

Atherosclerotic plaque volumes and qualitative plaque composition in the coronary arteries were evaluated in 12 patients with AS and in 48 controls. The CCTA results for the other patients were insufficient to perform detailed analysis. The median CRP level was higher in the AS group than in the control group: 8.0 mg/l (IQR, 5.0-15.0 mg/l) vs 2.0 mg/l (IQR, 1.4-3.9 mg/l), P = 0.002. The atherogenic index was also higher in the AS group than in the control group (mean [SD], 3.6 [1.2] vs 2.9 [1.2], *P* = 0.001). The LDL cholesterol level was lower in the AS group than in the control group (mean [SD], 106.2 [29.1] mg/dl vs 124.7 [38.0] mg/dl, *P* = 0.02). The groups did not differ in the prevalence of traditional atherosclerotic risk factors such as age, sex, hypertension, dyslipidemia, and body mass index (BMI). The average plaque burden in patients with AS was significantly higher than in the control group (mean [SD], 42.2% [4.7%] vs 36.5% [3.1%], P < 0.001) (FIGURE 1).

In the AS group, the univariate logistic regression analysis showed associations between the presence of atherosclerotic lesions and older age (P = 0.02), history of hypertension (P = 0.003), dyslipidemia (P = 0.001), and higher concentrations of total cholesterol (P = 0.02), LDL cholesterol (P = 0.03), and triglycerides (P = 0.03). The multivariable logistic regression analysis showed associations between the presence of atherosclerotic lesions and dyslipidemia (OR, 17.5; 95% CI, 3.3–92.5; P = 0.001), arterial hypertension (OR, 10.9; 95% CI, 1.9–63.1; P = 0.008), and higher concentrations of total cholesterol (OR, 1.14; 95% CI, 1.02–1.28; P = 0.02) (FIGURE 2). For this model, the AUC was 0.841.

**DISCUSSION** Our results suggest that atherosclerotic plaques occurred significantly more often in patients with AS than in the control group matched for traditional cardiovascular risk factors of atherosclerosis. In young patients with a relatively short duration of SpA, a higher incidence of arterial atherosclerosis was probably due to the additive effects of traditional ahterosclerotic risk factors, genetic predisposition, and the therapies of underlying diseases.<sup>1-4,10,11</sup> Adverse changes in lipid profile due to activity of inflammatory

TABLE 2	Differences in clinical variables between patients with ankylosing
spondylitis	with and without atherosclerotic plaques and the control group

Parameter		AS		Controls	P value
	AP (+)	AP (–)	P value	AP (+)	AP (+)
	(n = 18)	(n = 19)		(n = 20)	
Age, y, mean (SD)	44.3 (10.9)	36.7 (6.6)	0.02	44.7 (9.0)	0.88
Male sex, n (%)	14 (77.8)	12 (63.2)	0.33	16 (80)	1.00
BMI, kg/m², mean (SD)	26.3 (3.6)	23.6 (4.5)	0.052	28.5 (4.0)	0.09
Duration from diagnosis, mo, median (IQR)	14.5	18	0.84	-	-
	(6–120)	(5–48)			
Duration of	144	96	0.53	-	-
symptoms, mo, median (IQR)	(48–168)	(48–168)			
BASDAI, points,	5.0 (1.8)	5.5 (2.2)	0.43	-	-
mean (SD)					
ASDAS-CRP, points, mean (SD)	3.0 (1.2)	3.2 (1.0)	0.71	_	-
CRP, mg/l, median (IQR)	8.5	15	0.38	2.4	0.35
	(4–35)	(5.0–28.0)		(2.4–15.2)	
HLA-B27, n (%)	12 (75.0)	16 (88.9)	0.39	-	-
Hypertension, n (%)	12 (66.7)	3 (15.8)	0.002	11 (55.0)	0.46
Smoking, n (%)	10 (55.6)	6 (31.6)	0.14	-	-
Dyslipidemia, n (%)	14 (77.8)	4 (21.0)	0.0006	13 (68.4)	0.71
TC, mg/dl, mean (SD)	206 (42)	172 (30)	0.008	198 (40)	0.54
LDL-C, mg/dl, mean (SD)	114 (30)	91 (28)	0.02	126 (34)	0.28
HDL-C, mg/dl, mean (SD)	60 (18)	60 (13)	0.83	53 (17)	0.21
TG, mg/dl,	133	98	0.02	102	0.09
median (IQR)	(93–162)	(77–124)		(81–132)	
Atherogenic index,	3.6 (1.2)	3.0 (0.7)	0.07	3.0 (1.4)	0.17
mean (SD)					
NSAID, n (%)	12 (66.7)	13 (68.4)	0.91	-	-
Methotrexate, n (%)	2 (11.1)	3 (15.8)	1.00		
Statins, n (%)	4 (22.2)	0	0.046	-	-
Biologic treatment, n (%)	2 (11.1)	1 (5.3)	0.60	-	_
Glucocorticoids, n (%)	4 (22.2)	3 (15.8)	0.69	_	_

A P value of less than 0.05 is considered significant.

a Patients with AS vs controls

SI conversion factors: see TABLE 1

Abbreviations: AP, atherosclerotic plaques; AP (+), patients with atherosclerotic plaques; AP (-), patients without atherosclerotic plaques; others, see TABLE 1

processes have been documented in patients with PsA.<sup>19</sup> Despite relatively low total and LDL cholesterol levels, the lipid profile in patients with AS may be more atherogenic, mostly due to disproportionately greater reductions of HDL cholesterol concentrations.<sup>20</sup> In the present study, AS patients with atherosclerotic plaques had higher levels of total cholesterol, LDL cholesterol, and triglycerides than those without atherosclerotic plaques, with no differences in HDL cholesterol concentrations. The composition of the HDL cholesterol particles may be subject to adverse modifications under the influence of inflammatory processes, which is supported by the fact that in patients treated with tumor necrosis factor- $\alpha$  antagonists, favorable changes in HDL cholesterol were observed.<sup>21-23</sup>

Current evidence supports an important role of inflammation at all stages of the atherosclerotic process: initiation, progression, and complications. Initial damage to the endothelium results in an inflammatory response. This damage is done by hyperlipidemia, hyperglycemia, smoking, arterial hypertension, and also by systemic inflammation. When endothelial cells become inflamed, they express adhesion molecules (eg, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin), which bind monocytes. Proinflammatory cytokines provide a chemotactic boost to monocytes, resulting in their penetration into the intima with platelets adhering to the area of insult. Once resident in the arterial wall, monocytes differentiate into macrophages, which absorb modified lipoproteins (mainly LDL) and turn into large cells called "foam cells". Foam cells eventually die, thus favoring inflammation.<sup>24</sup>

In patients with AS, reduced coronary reserve was observed on dipyridamole stress echocardiography, which suggested impaired coronary circulation.<sup>25</sup> Positron emission tomography study showed increased inflammatory activity in the walls of the carotid arteries in patients with AS.<sup>26</sup> Recently published results of the study by Shen et al<sup>13</sup> showed that patients with PsA had increased prevalence, burden, and severity of coronary atherosclerosis on CCTA. Coronary plaques were identified in 60% of patients with PsA and in 35% of controls (P < 0.001). The prevalence of all types of plaques was increased from twofold to threefold. Longer disease duration was independently correlated with the presence of vulnerable mixed/noncalcified plaque in patients with PsA.

To our knowledge, our study is the first to show higher incidence of subclinical atherogenic lesions in patients with AS. On the basis of the present CCTA results, we demonstrated that coronary atherosclerotic lesions in patients with AS were significantly more frequent than in the control group despite the short duration of SpA (median [IQR], 18 [6.0-48.0] months). AS and control groups did not differ in the prevalence of traditional atherosclerotic risk factors. Differences were observed in CRP and LDL cholesterol concentrations and atherogenic index values, so it can be assumed that the atherosclerotic lesions may result from inflammation and resultant pathological lipid changes. There are no substantial data on the effect of the reduction of LDL cholesterol concentrations, one of the main therapeutic goals in the prevention of CVD, on the incidence and extent of coronary atherosclerosis in patients with AS. Importantly, the control subjects in the present study were not healthy individuals, but symptomatic patients







FIGURE 2 Univariate and multivariable regression analysis of associations between atherosclerotic risk factors and the presence of atherosclerotic lesions in patients with ankylosing spondylitis

Abbreviations: OR, odds ratio; others, see TABLE 1

without known CAD who underwent CCTA. Therefore, the risk of coronary atherosclerosis in patients with AS could be even higher when compared with healthy controls. The univariate logistic regression analysis performed in the AS group demonstrated a significant association between the presence of lesions and older age, history of hypertension, and dyslipidemia and with higher concentrations of total cholesterol, LDL cholesterol, and triglycerides. The multivariable logistic regression analysis showed a significant association between the presence of lesions and history of dyslipidemia, arterial hypertension, and higher concentrations of total cholesterol in the AS group. There was no direct association between CRP concentrations, BASDAI, and ASDAS-CRP and the presence of coronary atherosclerosis. This may be due to the fact that the analyzed parameters of inflammation are subject to dynamic changes in the course of the disease and the development of plaque can be a long-term process, which may explain the lack of correlation between the one--time assessment of inflammatory parameters and coronary atherosclerosis.

It seems that the reduction of the inflammatory process activity along with therapeutic modification of traditional cardiovascular risk factors, especially arterial hypertension, dyslipidemia, and smoking habits are essential in the prevention of cardiovascular events in patients with SpA, which is in line with the latest European League Against Rheumatism guidelines.<sup>3</sup>

Unfavorable structural changes in the coronary arteries in patients with a short duration of SpA diagnosed in the 3rd and 4th decades of life result in a long-time exposure to inflammatory processes, so the cardiovascular risk may be particularly high.<sup>27</sup> Our study confirms the need for a periodic assessment of cardiovascular risk in patients with SpA and intensive strategies for the prevention of further cardiovascular events along with a modern SpA treatment recommended by the current guidelines.<sup>28</sup> Because the changes in the cardiovascular system are observed at early stages of SpA, identification and treatment of traditional risk factors along with the implementation of anti-inflammatory treatment should be started at diagnosis of AS. CCTA or stress imaging techniques may be considered at an earlier stage of the diagnostic workup for CAD in patients with AS presenting with angina symptoms.

Our study has several limitations. This was a 2-center case-control study without follow--up. The size of the study groups was relatively small. Controls were retrospectively selected from the cohort of patients who had undergone CCTA due to atypical chest pain. We considered it unethical to refer healthy controls for CCTA owing to the risk of radiation exposure. Therefore, patients without prior CAD who were referred for CCTA were recruited as controls instead.<sup>13</sup> According to the study design, the effect of treatment on atherosclerotic processes was not analyzed. The study was a combined analysis of peripheral and axial forms of AS and SpA. The CCTA scans were not suitable for detailed analysis in any of the patients. Due to the small number of patients in the analyzed subgroups, it was not possible to evaluate the possible influence of treatment on the occurrence of coronary atherosclerotic lesions.

In conclusion, atherosclerotic plaques in the coronary arteries were significantly more prevalent in young patients with AS. Moreover, the presence of atherosclerotic lesions was significantly associated with older age, hypertension, and dyslipidemia. Our results confirm the need for cardiovascular risk assessment in patients with AS and cardiovascular prevention, if indicated.

**ACKNOWLEDGMENTS** We would like to thank Mr. Brian McBride for reviewing this paper and providing valuable feedback. The study was supported by a State Committee for Scientific Research grant (Institute of Cardiology, Warsaw, Poland, No. 9.37/III/13; to PO).

**CONTRIBUTION STATEMENT** PG, HS, RD and PO conceived the concept for the study. PO, RD, HS, KS, and PG contributed to the design of the research. PO, KS, and RR were involved in data collection. MK, CK, and LW performed the CCTA. IK, PO, RD, KS, MK, CK, and LW analyzed and interpreted the data. IK was responsible for statistical analysis. PO, RD, PG, CK, MK, HS, and BK wrote the manuscript. All authors edited and approved the final version of the manuscript.

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