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Original article

Cardiovascular risk profile in patients with spondyloarthritis

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ABSTRACT

Objectives: The spondyloarthritides (SpA) are associated with an increased cardiovascular risk. We studied cardiovascular risk factors in patients with SpA.
Methods: The following risk factors were assessed in SpA patients and healthy controls: smoking, family history of premature ischemic heart disease, obesity, serum lipids, apolipoproteins, urate and carotid intima media thickness (IMT).
Results: Overall 150 patients (73 with ankylosing spondylitis [AS], 71 with psoriatic arthritis [PsA] and six with other SpA types) were included. Generally SpA patients were significantly more often smokers, while PsA patients had greater values of abdominal obesity. AS patients had significantly lower levels of triglyceride, HDL, ApoB, ApoE and Lp(a) and a higher atherogenic index (total cholesterol/HDL). PsA patients had significantly lower levels of HDL, ApoAI and ApoE, an elevated atherogenic index and higher serum urate. In multivariate analysis the atherogenic index was positively associated with SpA across all patient groups independently of smoking and other lipid parameters. Carotid IMT in SpA patients (0.71 mm) was higher than controls (0.63 mm, $P = 0.017$), although after adjusting for smoking this ceased to be significant. Treatment of patients with previously untreated disease resulted in a small but significant decline in ApoB levels at 6 months ($P = 0.045$), which, however, was no longer evident at 12 months.
Conclusion: Spondyloarthritis patients are at a greater cardiovascular risk owing to the higher prevalence of smoking and a higher atherogenic index. PsA patients have more abdominal fat and higher urate levels. Immunosuppressive treatment of SpA produces minor and temporary effects on the lipid profile.

1. Introduction

The spondyloarthritides (SpA) are a group of systemic inflammatory disorders with a shared pattern of musculoskeletal and often extra-skeletal involvement [1]. Recently, an association between premature atherosclerosis and chronic inflammatory arthritis, predominantly rheumatoid arthritis (RA), as well as the two most common types of SpA, AS and psoriatic arthritis (PsA), has been highlighted [2]. Indeed, there is evidence that AS and PsA patients have higher mortality ratios compared to the general population and also higher rates of cardiovascular death [3,4]. Several studies have further shown that cardiovascular disease, such as ischemic heart disease, cerebrovascular disease, peripheral vascular disease and risk factors such as hypertension, the metabolic syndrome and diabetes mellitus are more common in patients with AS or PsA [5–10]. A meta-analysis has concluded that AS patients have a disturbed lipid profile and increased carotid intima-media thickness (IMT) compared to controls [6]. In PsA, lipid profile comparisons between patients and controls have provided conflicting results [11–15], although almost all studies focusing on vascular morphology and function agree to that PsA patients have impaired vascular integrity [12,13,15,16].

Our aim was to study the cardiovascular risk profile of Greek patients with SpA, particularly AS and PsA, and to compare it with age- and sex-matched controls.

2. Methods

This was a cross-sectional study conducted since January 2008 until July 2010. Study subjects were recruited among adult patients diagnosed and/or followed at the outpatient Rheumatology Clinic of the University Hospital of Ioannina, a tertiary hospital covering northwestern Greece. Patients were eligible, if they fulfilled

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the ESSG criteria for SpA [17]; patients diagnosed with AS should fulfill the 1984-modified New York criteria [18] and those with PsA the ClASsification criteria for Psoriatic Arthritis (CASPAR) [19]. Exclusion criteria were diabetes mellitus or other uncontrolled endocrine disease, hereditary dyslipidemia, autoimmune conditions not pertinent to the SpA spectrum, active infection at the time of the assessment, liver or renal disease, malignancy, alcohol abuse, pregnancy and lactation. Control subjects were recruited among patients seen at the same outpatient Rheumatology clinic for degenerative joint disease and among hospital staff. Controls were matched to patients for age and sex and, in addition to the above exclusion criteria, should have no other chronic disease, except for osteoarthritis. Study subjects' informed consent and approval from the institution's ethical committee were obtained.

For patients and controls epidemiological (smoking status, personal history of cardiovascular disease, family history of premature ischemic heart disease) and anthropometric (body mass index [BMI], waist-to-hip ratio [WHR]) cardiovascular risk factors were recorded. Additionally, blood samples were collected after an overnight fast for the measurement of the following parameters: total cholesterol (TC), high density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein (Apo) AI, ApoB, ApoE, lipoprotein (a) [Lp(a)] and urate. Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula, provided that triglyceride levels did not exceed 400 mg/dL. The atherogenic index (TC/HDL) and the ApoB/ApoAI ratio were also calculated. In all patients, systemic inflammation, disease activity and function were evaluated using the following parameters: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and, for patients with PsA, disease activity score-28 joints (DAS28) and Psoriasis Area and Severity Index (PASI).

Further, a subset of patients and controls underwent ultrasound measurement of the common carotid IMT. For this procedure, subjects lay supine with the neck extended and the common, internal and external carotid arteries were scanned by the same examiner (AKZ) in B-mode and in color Doppler with a LOGIQ 7 (GE Healthcare, Milwaukee, WI, USA) ultrasound equipment using a 10 MHz linear probe. The common carotid IMT was measured 2 cm proximal to the common carotid bifurcation on a longitudinal section of the vessel. The average value of left and right common carotid artery IMT was considered the final IMT value for each patient.

Patients who were diagnosed with SpA for the first time during the study recruitment period and had been receiving no anti-rheumatic treatment other than non-steroidal anti-inflammatory drugs (NSAIDs) were further entered into a prospective follow-up study. Disease activity measures, body mass and lipid parameters were assessed at baseline, 6 and 12 months after treatment initiation.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) software, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparisons were performed using two sample *t*-test for parametric values, Wilcoxon Mann-Whitney Test for non-parametric values and χ^2-test for categorical values. Correlation analyses were performed with Pearson's or Spearman's rank order correlation coefficients, where appropriate, while adjustment for confounding factors was made using linear regression analysis. The level of statistical significance was set at 0.05.

3. Results

One hundred and fifty SpA patients were recruited and 150 age- and sex-matched controls. Among the SpA patients, 73 had AS and 71 PsA, one had axial SpA that had begun as enthesitis-related juvenile idiopathic arthritis, three had non-radiographic axial SpA and two had undifferentiated SpA. Patients' characteristics are shown in Table 1. On average, patients had long-standing disease with low to moderate disease activity. Remarkably, the majority of patients had been exposed to cigarette smoke, while 41.3%, 54.8% and 29.6% of SpA, AS and PsA patients respectively still smoked during the previous year. Regarding the prevalence of already diagnosed cardiovascular diseases, overall 39 patients had arterial hypertension, three ischemic heart disease, one had peripheral arterial disease, but none cerebrovascular disease. The patients received treatment with TNFα blockers and/or disease-modifying anti-rheumatic drugs (DMARDs), while a minority was on low-dose glucocorticoids. Finally, 21 patients (12 with AS and nine with PsA) were on statins for dyslipidemia. For the following comparisons of cardiovascular risk factors between patients and controls, those on glucocorticoids and/or statins were excluded.

Table 1
Clinical characteristics of the SpA patients included in the study and separately of the AS and PsA subgroups.

	SpA	AS	PsA
N	150	73	71
Males, %	74.7	90.4	60.6
Age, years	46.3 (12.8)	44.9 (11.2)	48.9 (13.5)
Disease duration, years	12.8 (10.2)	17.8 (10)	8.3 (8.1)
BASDAI	2.9 (2.4)	2.4 (2.2)	3.3 (2.5)
BASFI	3 (2.7)	3.1 (2.7)	2.7 (2.7)
DAS28	NA	NA	3.3 (1.7)
PASI	NA	NA	2.5 (4.5)
ESR, mm/h	23.2 (19.9)	17.8 (14.9)	28.5 (23.2)
CRP, mg/L	12.4 (21.8)	10 (12.7)	14.1 (28.3)
Fibrinogen, mg/dL	424.3 (127.6)	414 (110.6)	433.9 (138.7)
Smoker ever, %	68.7	80.8	59.2
Smoker current, %	41.3	54.8	29.6
Pack-years	27.2 (22.3)	28.7 (20.8)	26.2 (24.4)
Hypertension, %	26	24.7	29.6
IHD, %	2	1.4	2.8
PAD, %	0.7	0	1.4
Treatment			
DMARDs, %	29.3	19.2	42.3
TNFα blockers, %	61.3	75.3	49.3
Glucocorticoids, %	8.7	8.2	9.9
Statin use, %	14	16.4	12.7

SpA: spondyloarthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; NA: not applicable; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DAS28: Disease Activity Score-28 joints; PASI: Psoriasis Area and Severity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IHD: ischemic heart disease; PAD: peripheral arterial disease; DMARDs: disease-modifying anti-rheumatic drugs; TNFα: tumor necrosis factor α. Values are means (standard deviation) unless otherwise indicated.

3.1. Spondyloarthritis group

As a whole, SpA patients were more often smokers than age- and sex-matched controls ($P < 0.001$, Table 2). Furthermore, although SpA patients' mean BMI (26.8 kg/m^2) was in the range of overweight, it was not significantly higher than controls' BMI (27.1 kg/m^2, $P = 0.341$). However, average WHR was higher in SpA subjects compared to controls ($P = 0.002$). As regards the biochemical parameters, SpA patients had statistically lower levels of TC, triglyceride and HDL, a higher TC/HDL ratio and higher urate levels. However, they also had lower ApoB, ApoE and Lp(a) levels and a lower ApoB/ApoAI ratio. Since variations in smoking prevalence may be a confounding factor when comparing lipid profiles, and given the multitude of significant differences between patients and controls in the univariate analysis, adjustment was made using multivariate analysis. A subsequent linear regression model, in which smoking status, triglyceride, TC/HDL, ApoAI, ApoB, ApoE, Lp(a) and the ApoB/ApoAI ratio were entered as independent variables and having SpA as the dependent variable, showed that