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ORIGINAL ARTICLE

High prevalence of metabolic syndrome in patients with ankylosing spondylitis

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Abstract The objective of this work is to investigate the occurrence of atherosclerosis and metabolic syndrome (MetS) in ankylosing spondylitis (AS) patients (pts). Twenty-four consecutive AS pts (men, 87.5%; median age, 50.5 years; median disease duration, 16.5 years), fulfilling the modified 1984 New York criteria for AS criteria, and 19 age- and sex-matched controls were investigated. Clinical atherosclerosis was evaluated by physical examination for cardiovascular (CV) diseases and history or drug use for CV events. Subclinical atherosclerosis was detected by mean intima media thickness (a-IMT) and maximum IMT (max-IMT) of carotid arteries using ultrasonography. Laboratory investigations including fasting plasma glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides were assessed by standard methods, while homocysteine was assessed by chemiluminescence. MetS was assessed using the updated NCEP-ATP III criteria. Disease activity was defined according to the International Ankylosing Spondylitis Assessment Study criteria. The 10-year CV risk (%) profile was evaluated in agreement to the *Progetto Cuore* criteria. No major CV event was detected in the study population. No significant differences were found when AS pts and controls were compared according to the mean a-IMT (0.52±0.26 vs 0.51±0.13 mm), max-IMT (0.92±0.20 vs 0.85±0.39 mm), prevalence of abnormal max-IMT >1 mm (27.2 vs 5.3%), and 10-year CV risk (9.9±9.6 vs 3.6±1.8%). Systolic blood pressure (p=0.04), triglyceride to HDL cholesterol ratio (p=0.002), and LDL cholesterol (p=0.03) were found significantly higher in AS pts than in controls; on the contrary, HDL cholesterol was pointed out as significantly lower (p<0.001). MetS was found in 11/24 (45.8%) AS pts and in 2/19 (10.5%) controls (p=0.019). No significant relationship emerged in MetS prevalence among AS pts regarding the mean value of age, disease duration, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Disease Activity Index, and the Italian version of Health Assessment Questionnaire. This preliminary report points out a higher prevalence of MetS in AS pts than in controls. Further studies are needed to confirm this finding.

Keywords Ankylosing spondylitis · Cardiovascular risk factors · IMT · Metabolic syndrome

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Introduction

Ankylosing spondylitis (AS) is an inflammatory disease characterized by arthritis and enthesitis at the spine and peripheral joints [1]. Some studies have suggested increased mortality and morbidity rates among patients with AS when compared to the general population [2–4]. Duration and severity of disease and typical AS cardiovascular (CV) complications (i.e., aortic insufficiency, conduction disturbances, mitral valve disease, cardiomyopathy, and pericarditis) have been implicated as risk factors [5, 6]. As far as we know, a few controversial studies have investigated the prevalence of atherosclerosis and the CV risk profile in these patients [7, 8].

In the last few years, a clear relationship between CV risk factors, obesity, and insulin-resistance allowed to propose the existence of a unique pathophysiological condition called metabolic syndrome (MetS), which was shown to promote an

increase of CV mortality risk [9]. Moreover, some studies have pointed out a relationship among some CV risk factors or MetS and inflammation [10, 11].

The aim of this study was to investigate the prevalence of MetS in AS patients and their relationship with atherosclerosis.

Materials and methods

Patients

Twenty-four consecutive AS patients (21 men and 3 women; mean age 47.6±11.8 years), attending the Rheumatology Unit of the Second University of Naples between January 2005 and March 2005, were enrolled in the study, all of whom fulfilled the modified 1984 New York criteria for AS [12] and the European Spondyloarthropathy Study Group criteria for classification of spondylarthropathies [13]. The median disease duration was 16.5 years (range 3–45 years). Psoriasis in two patients and inflammatory bowel disease in two other cases were associated. Fifteen patients were taking sulfasalazine (1–2 g/day), five were taking methotrexate (7.5–10 mg/week), four were on NSAIDs, and three patients were using antihypertensive drugs (ACE inhibitors, beta-blockers, or calcium channel blockers).

Control subjects

The control group included 19 age- and sex-matched patients (16 men and 3 women; mean age 49.6±6.0 years) who had been admitted to the outpatient clinic for either osteoarthritis or soft tissue rheumatism. Eight out of 19 (42.1%) used NSAIDs as required and 3/19 (15.8%) used antihypertensive drugs (ACE inhibitors).

Informed written consent was obtained from all subjects before participation. The study design was approved by local ethical committee.

Methods

Cardiovascular events

We evaluated AS patients and controls by a physical examination for CV disease, health habit questionnaire including history of medical advice, and history or drug use for myocardial infarction, stable or unstable angina, stroke, and hypertension.

Carotid duplex ultrasonography

The mean intima media thickness (a-IMT) and maximum IMT value (max-IMT) were measured with a Philips HDI 1500 and a 7.5- to 10-MHz linear array transducer. Three right and three left far wall values, calculated separately at three carotid artery segments (common carotid, carotid bulb, and internal carotid), were recorded according to Bond et al. [14]. All measurements were performed by the same ultrasonographer, who was unaware of the clinical characteristics of the study population. The max-IMT was considered abnormal when the value was >1 mm [15].

Cardiovascular risk

Each patient and control was evaluated for body mass index (kilogram per square meter), waist circumference (centimeter) measured at the umbilical level, and blood pressure (BP) in the sitting position as mean of two consecutive readings. Fasting blood samples (between 08:00 and 10:00 hours) were taken to determine plasma glucose, total cholesterol, HDL cholesterol, and triglycerides using standard methods. LDL cholesterol was calculated by Friedewald's formula [16]. Homocysteine was assayed using chemiluminescence analyzer IMx (Abbott Laboratories, Indianapolis, IN). Limits for normal range were provided by manufacturers.

The 10-year CV risk (in percentage) was calculated following the *Progetto Cuore* criteria (www.cuore.iss.it), i.e., age from 35 to 69 years, sex, smoking history, history of previous CV event, systolic BP, total cholesterol and HDL cholesterol level, occurrence of diabetes mellitus, and use of antihypertensive drugs [17].

Metabolic syndrome

According to the updated Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III) criteria [18], MetS was defined by at least three of the following five features: (1) waist circumference (men ≥102 cm, women ≥88 cm); (2) triglycerides≥150 mg/dl or drug treatment for elevated triglycerides; (3) HDL cholesterol levels (men <40 mg/dl, women <50 mg/dl) or drug treatment for reduced HDL cholesterol; (4) elevated BP (≥130 mmHg systolic BP or ≥85 mmHg diastolic BP or drug treatment for hypertension); and (5) elevated fasting glucose (≥100 mg/dl or drug treatment for hyperglycemia).

Disease activity

According to the International Ankylosing Spondylitis Assessment Study Consensus Statement for the use of antitumor necrosis factor agents in AS, the disease was considered active when the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was ≥40 mm [19].

Disability

Functional activity was evaluated by Bath Ankylosing Spondylitis Functional Index (BASFI) [20]. Disability was detected by Italian version of Health Assessment Questionnaire (HAQ-DI) [21].

Statistical analysis

Comparisons between groups were performed using two-tailed nonparametric methods. Fisher's exact test was used for differences between proportions. Spearman's rho correlation test was used for correlation analysis. The statistical analysis was made by SPSS software, version 10 for PC. Values of $p<0.05$ were considered significant.

Results

No patients or control subjects suffered from myocardial infarction, stable or unstable angina, and stroke. Physical examination was negative for valve abnormalities.

Table 1 shows the main epidemiological and clinical characteristics of the AS patients.

Table 2 shows the behavior of traditional CV risk factors in AS patients and in controls. Significant differences were found in systolic BP ($p=0.04$), HDL cholesterol ($p<0.001$), triglyceride to HDL cholesterol ratio ($p=0.002$), and LDL cholesterol ($p=0.03$). None of the four AS patients using NSAIDs suffered from hypertension. No significant difference emerged in the prevalence of smokers and patients who were overweight/obese (BMI ≥25), such as increased mean diastolic BP, mean values of total cholesterol, triglycerides, and homocysteine.

No significant difference was found neither in the a-IMT and max-IMT between AS patients and controls, or in the frequency of abnormal IMT value (max-IMT>1 mm; AS patients: 6/22 cases, 27.2% versus controls: 1/19 cases, 5.3%).

To analyze the relationship among a-IMT, max-IMT, and the other variables investigated, a univariate analysis was performed. Significant Spearman's rho correlations were only found among max-IMT and age ($r_s=0.525$; $p=0.012$), systolic BP ($r_s=0.518$; $p=0.013$), BASFI ($r_s=0.533$; $p=0.011$), and HAQ-DI ($r_s=0.448$; $p=0.037$). Nevertheless, controlling for potential confounding factors, as both age and systolic BP, a significant correlation among max-IMT, BASFI, and HAQ-DI was not confirmed.

MetS was found in 11 out of 24 (45.8%) AS patients and in 2 out of 19 (10.5%) controls ($p=0.019$). Significant differences between two groups emerged in some MetS features, as increased systolic BP ($p=0.03$), diastolic BP ($p=0.04$), and reduced HDL cholesterol ($p<0.001$; see Table 3).

When AS patients were divided according to the occurrence of MetS, a greater number of cases with abnormal waist circumference emerged in the group with MetS ($p=0.003$), whereas no significant difference was found when an other individual NCEP-ATP III criteria was analyzed.

Concerning the 10-year CV risk (in percentage), a positive trend was calculated in AS patients (9.9±9.6%) than in controls (3.9±1.8%; $p>0.05$). When AS patients were divided in two subgroups (≤10% 10-year CV risk >10%), no significant difference in MetS prevalence (20.8 vs 25.0%) emerged ($p>0.05$).

Table 1 Epidemiological and clinical characteristics of 24 ankylosing spondylitis patients

Characteristics	Median (range)
Age (years)	50.5 (35–68)
Sex (male/female)	21/3
BMI (kg/m^2)	29.2 (21.7–38.7)
Disease duration (years)	16.5 (3–45)
BASDAI (mm)	21.3 (7–74)
BASFI (mm)	40.0 (5–95)
HAQ-DI	0.88 (0–2)

Table 2 Traditional cardiovascular risk factors in ankylosing spondylitis patients and controls

Characteristics	No. of AS patients (total=24)	No. of controls (total=19)	*P**
Smokers	11/24 (46.8%)	13/19 (68.4%)	ns
BMI≥25 (kg/m^2)	20/24 (83.3%)	12/19 (63.1%)	ns
Systolic BP (mmHg)	134.0±16.9	125.8±10.8	0.04
Diastolic BP (mmHg)	83.0±11.5	80.0±5.5	ns
Total cholesterol (mg/dl)	205.0±56.0	189.1±39.9	ns
Triglycerides (mg/dl)	141.0±59.0	138.7±52.5	ns
HDL cholesterol (mg/dl)	33.8±11.6	56.2±20.9	<0.001
Triglycerides/HDL cholesterol	4.2±5.1	2.8±1.3	0.002
LDL cholesterol (mg/dl)	144.0±46.8	107.9±29.9	0.03
Homocysteine (μmol/l)	8.7±2.0	9.1±1.2	ns
a-IMT (mm)	0.52±0.26	0.51±0.13	ns
max-IMT (mm)	0.92±0.20	0.85±0.39	ns

Values are mean±SD. *P* values were obtained using Mann–Withney *U* test.
BP blood pressure

Table 3 Prevalence of individual metabolic syndrome features in ankylosing spondylitis patients and controls

MetS features	AS patients (total=24)	Controls (total=19)	*p*
Waist circumference: men, ≥102 cm; women, ≥88 cm	11 (45.8%)	4 (21.1%)	ns
Triglycerides ≥150 mg/dl	10 (41.7%)	7 (36.8%)	ns
HDL cholesterol: men, <40 mg/dl; women, <50 mg/dl	18 (75.0%)	2 (5.2%)	<0.001
Systolic BP ≥130 mmHg	17 (70.8%)	7 (36.8%)	0.03
Diastolic BP ≥85 mmHg	11 (45.8%)	3 (15.7%)	0.04
Plasma glucose ≥100 mg/dl	1 (4.2%)	2 (10.5%)	ns

p Values were obtained using Fisher's exact test.
BP Blood pressure

When AS patients with and without MetS were evaluated for the value of age (51.6±8.8 vs 49.5±10.9 years, respectively), disease duration (21.1±2.8 vs 18.8±9.6 mm), BASDAI (30.3±21.7 vs 32.3±26.6 mm), BASFI (45.5±26.4 vs 39.5±27.4 mm), and HAQ-DI (0.9±0.6 vs 1.0±0.8), no significant relationship was pointed out.

Discussion

Over the last years many studies have identified subclinical atherosclerosis and metabolic abnormalities (i.e., lower HDL cholesterol, higher triglycerides, insulin resistance) typical of MetS as a major contributor to the morbidity and mortality of patients with rheumatic diseases such as rheumatoid arthritis (RA) [22] and systemic lupus erythematosus [23]. Concerning AS, subclinical atherosclerosis has not been sufficiently investigated.

Our study did not show any significant difference in IMT values between AS patients and controls, according to the ultrasonographic findings recently reported by Sari et al. [8]. Furthermore, the lack of correlation between max-IMT and disease activity or severity scores led us to suggest that AS may not influence the development of atherosclerosis.

When were investigating the main CV risk factors, we found that AS patients had a significantly higher systolic BP, a lower level of HDL cholesterol, a lower triglyceride to HDL cholesterol ratio, and a higher level of LDL cholesterol than the controls. On the contrary, we were unable to demonstrate any significant difference in other traditional CV risk factors or in the CV 10-year risk rates between AS patients and controls. Nevertheless an influence of less favorable smoking habits in the controls may not be excluded (Table 2).

Few studies investigated the prevalence of conventional CV risk factors in AS. An association between smoking habits and disability [24] has been pointed out, such as a higher BMI in AS patients than in controls [25]. Our data confirmed that the reduction of HDL cholesterol is frequently found in AS patients [25, 26], such as an increased prevalence of systolic or diastolic BP [25, 27] independently by NSAIDs use. In addition, we found no alterations of homocysteine levels in AS patients.

Our results showed that MetS was significantly more frequent in AS patients (46%) than in controls (11%). This prevalence was greater than that registered in Italian adults (25%) [28] or in the general European population (15%) [29]. To our knowledge, this is the first study showing an increased prevalence of MetS in AS patients.

When the single NCEP-ATP III criteria was considered, waist circumference was found out to be significantly greater in AS patients with MetS than in those without, even though did not point out relevant spinal changes (particularly kiphosis) that may significantly have an impact on both waist circumference or BMI measurements. Moreover, a lack of significant relationship in AS patients between MetS occurrence and age or clinical characteristics of the disease (i.e., disease duration, BASDAI, BASFI, HAQ-DI) allows us to hypothesize that other factors would be considered as different nutritional habitus or restricted physical activity.

It is known that MetS increases the relative risk (RR) for CV disease (RR: 1.5–3.0) [30] or the risk for progression to type II diabetes (RR: 5.0) [31] and that the biochemical abnormalities in MetS may participate in the onset and persistence of inflammatory arthritis [32].

Considering that our data showed no significant relationship between MetS occurrence and CV 10-year risk rate, we may hypothesize that MetS criteria as observed in RA [33], are not sufficiently sensitive as traditional CV risk algorithms.

Furthermore, as some epidemiological studies could suggest that CV disease risk in MetS is greater than the sum of its measured risk factors [34, 35], we hypothesize that MetS, defined by the NCEP-ATP III criteria, may be used in AS patients as a preventive tool of CV disease or diabetes mellitus for more intensive intervention.

This study has some limitations. We analyzed a relatively small series of AS patients; thus, a type II error in AS patients considering the trends of abnormal IMT or MetS prevalence in the cases with higher CV risk rates may not be excluded. In addition, we did not investigate the relationship between inflammation and MetS.

In conclusion, our findings showed a greater prevalence of MetS in AS patients than in controls. MetS did not seem to be correlated to the disease, but the role of inflammation may not be excluded. The patients enrolled in the present study are undergoing a prospective evaluation devoted to the detection of the appearance of any CV event and subclinical atherosclerosis.

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