High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNFα treatment: correlation with disease activity

J.A. Papadakis[1*], P.I. Sidiropoulos[2*], S.A. Karvounaris[2], G.E. Vrentzos[1], E.K. Spanakis[2], E.S. Ganotakis[1], H.D. Kritikos[2], D.P. Mikhailidis[3], D.T. Boumpas[1,2]

[1]Department of Internal Medicine, and [2]Department of Rheumatology, Clinical Immunology and Allergy, University Hospital, Heraklion, Greece; [3]Department of Clinical Biochemistry (Vascular Disease Prevention Clinic), Royal Free Hospital and Royal Free University College Medical School, London, UK.

Abstract

Objective

Ankylosing spondylitis (AS) may be associated with an increased risk for cardiovascular diseases (CVD). We investigated the prevalence of cardiovascular risk factors and metabolic syndrome (MetS) in men with AS and assessed any correlation with AS-related factors.

Methods

This was a cross-sectional study of 63 men with AS, median age 40 (19-69) years, and 126 age-matched controls. Patients were on anti-TNFα treatment because of considerable disease activity at some time during the course of the disease. MetS was assessed according to the modified National Cholesterol Education Program Adult Treatment Panel III criteria. The risk for CVD event within the next 10 years was estimated using the Framingham equation.

Results

Patients had lower high-density lipoprotein cholesterol (HDL-C) ($p<0.001$), higher systolic ($p=0.001$) and diastolic ($p<0.01$) blood pressure compared with controls. The prevalence of the MetS was higher in patients compared to controls (34.9% vs. 19.0%; $p<0.05$). AS patients with MetS were older ($p<0.01$), with higher Framingham risk score ($p=0.001$), had longer disease duration ($p<0.05$) and higher BASDAI (5.1 vs. 3.7; $p<0.05$) than those without MetS, while both BASFI and CRP had an inverse correlation with HDL-C levels.

Conclusions

Men with AS have a higher prevalence of cardiovascular risk factors and MetS compared with controls. The presence of MetS was associated with increased 10 year CVD risk in these patients. The association of AS disease activity with MetS suggests that CVD in AS patients may, at least in part, be attributed to the inflammatory burden of the disease.

Key words

Ankylosing spondylitis, metabolic syndrome, cardiovascular risk factors, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

John A. Papadakis, MD
Prodromos I. Sidiropoulos, MD
Stelios A. Karvounaris, MD
George E. Vrentzos, MD
Elias K. Spanakis, MD
Emmanouel S. Ganotakis, MD
Heraklis D. Kritikos, MD
Dimitri P. Mikhailidis, MD
Dimitrios T. Boumpas, MD, FACP

**Both authors contributed equally to the project*

Please address correspondence and reprint requests to:
Prof. Dimitrios T. Boumpas MD, FACP,
Department of Internal Medicine,
Division of Rheumatology,
Clinical Immunology and Allergy,
University of Crete, Medical School,
Voutes 71500, Heraklion,
Greece.
E-mail: boumpasd@med.uoc.gr

Received on June 20, 2008; accepted in revised form on November 21, 2008.

Competing interests: none declared.

Introduction

An increased risk for cardiovascular disease (CVD) in patients with inflammatory rheumatic diseases has been reported (1-3). This may be attributed to accelerated atherosclerosis as a result of both systemic inflammation and the high prevalence of traditional CVD risk factors (3-6). Atherogenic dyslipidemia [*e.g.* high triglycerides (TG) and low high density lipoprotein cholesterol (HDL-C)], obesity, elevated blood pressure and raised plasma glucose, describe a cluster of major CVD risk factors that constitute the metabolic syndrome (MetS) (7-8). Subjects with MetS are at increased risk for developing diabetes mellitus and CVD (7-9). In the general population, men with the MetS are 2-3 times more likely to die of any cause, and 3-4 times more likely to die from coronary heart disease (10). The detection, prevention and treatment of underlying risk factors of the MetS are of paramount importance for the reduction of the CVD burden (11).

Insulin resistance, one of the key components of the MetS is recognized as a chronic, low level inflammatory state (12-13). This may promote endothelial dysfunction and atherosclerosis (14).

Several cross-sectional studies have shown that acute-phase reactants such as C-reactive protein (CRP), circulating levels of pro-inflammatory cytokines [interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)] are associated with features of the MetS such as body mass index (BMI)/waist circumference, measures of insulin resistance/plasma insulin concentration, hypertension, dyslipidemia and endothelial dysfunction (15-20). TNF-α is implicated in the development of an adverse lipid profile and the pathogenesis of atherosclerosis in rheumatic diseases (21-23).

Ankylosing spondylitis (AS) may be associated with an increased CVD mortality (2, 24, 25). Information about the association between traditional CVD risk factors, inflammation and atherosclerosis in AS is limited (6, 25). Recent studies suggested high prevalence of MetS in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus, which may be attributed to the inflammatory burden (26, 27). However, data about the overall prevalence of the MetS in patients with AS are limited. Malesci *et al*. recently reported a high prevalence of MetS in a small cohort (n=24) of AS patients (28).

The present study documents the high prevalence of conventional CVD risk factors and MetS in a cohort of men with AS compared with healthy individuals and a higher 10-year CVD risk in those patients with MetS. We also found higher disease activity in patients with MetS and an inverse correlation between HDL-C and CRP.

Patients and methods

Study population

Consecutive outpatients (n=70; 63 men) meeting the modified New York criteria for the classification of AS (29) attending the Rheumatology Department of the University Hospital of Heraklion, Crete were recruited from March 2006 till February 2007. To minimize confounding by sex, we excluded 7 women with AS. All patients had active axial disease at some time-point during the course of the disease [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4] and were at the time of evaluation on treatment with infliximab (30). Twenty-four patients were also on methotrexate (10-15 mg/week).

For each patient with AS, two individuals without AS or other chronic inflammatory disease were matched for age. Control subjects were residents of rural and semi-urban areas (Heraklion) of the island of Crete, Greece. They were recruited following public invitation by primary care physicians of 7 Primary Health Care Centers throughout the district, during the same period as the AS patients. We used a general population - rather than hospital-based - controls in order to minimize the possibility of bias. Exclusion criteria for both patients and controls were a history of myocardial infarction, angina, and stroke or insulin therapy. All participants signed an informed consent form and the local ethics committee approved this study.

MetS definition

MetS was defined according to the modified National Cholesterol Education

Program Adult Treatment Panel III (NCEP ATP III) criteria for men (7) that required the presence ≥3 of the following: waist circumference (>102 cm), TG level (≥150 mg/dl; ≥1.7 mmol/l), HDL-C (<40 mg/dl; <1.0 mmol/l), fasting glucose (≥100 mg/dl; ≥5.6 mmol/l), and systolic or diastolic blood pressure (≥130/85 mmHg) or self-reported use of antihypertensive medication.

Assessment of the MetS and CVD risk factors

All participants completed a health questionnaire concerning smoking habit, current medication and history of hypertension and diabetes. The patients' weight and height was recorded and BMI (body mass index) was calculated. The waist circumference was also measured (31). Blood samples were taken the morning after 12 h overnight fasting. Serum concentrations of total cholesterol (TC), HDL-C, and TG were measured using an automated chemistry analyzer (Olympus AU-600, Tokyo, Japan) using reagents from the same manufacturer. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula except for samples with serum TGs >400 mg/dl (4.5 mmol/L), for which LDL-C could not be determined with the method used. Serum glucose concentration was determined by standard methods in routine use. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were measured [CRP by immune nephelometry (BN II analyzer, Eschborn, Germany); ESR with an automated analyzer (Ves-matic 20, Florence, Italy)] in patients with AS.

Calculation of cardiovascular risk using the Framingham equation

The Framingham equation [www.bhsoc.org] can only be used to calculate cardiovascular risk over the next 10 years in subjects who do not have CVD. The equation can derive coronary heart disease, stroke risk and overall CVD risk. This equation has an age limitation (32 to 74 years). For the purpose of this study men with AS (n=12) and controls (n=21) aged less than 32 years were entered as aged 32. The following variables are considered in the Framingham equation: age, gender, systolic blood pressure and diastolic blood pressure, serum TC and HDL-C levels, smoking status and the presence/absence of diabetes mellitus or left ventricular hypertrophy based on ECG criteria (32).

AS disease characteristics

The BASDAI was used to assess AS disease activity (33). Functional activity was evaluated by the Bath Ankylosing Spondylitis Functional Index (BASFI) (34). Also, disease duration and medication were recorded.

Statistical analysis and presentation of results

Values are expressed as median and range. All *p*-values are two-tailed. Between group results were assessed by Mann-Whitney tests. Frequency analysis was by χ^2 test, with Yate's correction. Correlation was assessed by Spearman's correlation (r_s). To calculate the odds for MetS in patients with AS a binary logistic regression analysis was performed using MetS as dependent variable and disease status (AS/control) and smoking as independent variables.

Results

Demographics

We recruited 63 AS men and 126 age-matched healthy men (Table I). The median disease duration was 16 (range: 1-43) years and the median BASDAI was 4.3 (range: 0.0-7.8). There were more smokers among AS patients than among controls (Table I). A comparable percentage of patients and controls was on antihypertensive medication (p=0.28) and none was on antidiabetic drugs. Patients with AS were more likely to use statins than controls (p<0.001). None of our AS patients was on any NSAIDs in fixed doses. There were only a few patients (n=8) who took NSAIDs on demand.

Prevalence and characteristics of the MetS

Twenty-two out of 63 AS patients (34.9%) met the criteria for MetS compared with 24 out of 126 controls (19.0%) (p<0.05); [OR= 2.28 (95% CI 1.15-4.51); p=0.018]. When we split the patients into two groups according their median age (41 years), the prevalence of MetS in AS patients was significant greater than controls only in older patients [15 out of 30 (50.0%) *vs.* 15 out of 63 (23.8%),

Table I. Population characteristics. All values are expressed as number (%) or median (range). Between group results were compared by Mann-Whitney test or by χ^2 test with Yate's correction, as appropriate.

Variables	Controls (n=126)	AS (n=63)	*p*
Age (years)	41 (18-70)	40 (19-69)	0.967
Smokers	22 (17.5%)	21 (33.3%)	0.04
MetS	24 (19.0%)	22 (34.9%)	0.018
Glucose (mg/dl)	91 (52-164)	91 (56-187)	0.342
TC (mg/dl)	216 (132-304)	197 (110-353)	0.141
TG (mg/dl)	103 (38-400)	114 (34-313)	0.034
LDL-C (mg/dl)	133 (68-223)	129 (63-258)	0.993
HDL-C (mg/dl)	56 (30-89)	42 (25-83)	<0.001
TC/HDL-C	3.7 (2.4-7.9)	4.8 (2.0-7.4)	<0.001
LDL-C/HDL-C	2.3 (1.2-6.3)	3.1 (1.0-5.6)	<0.001
SBP (mmHg)	115 (90-160)	120 (100-170)	0.001
DBP (mmHg)	73 (50-110)	80 (60-100)	0.007
Framingham risk score (%)	3 (0-21)	2 (0-30)	0.212
On Anti-hypertensives	24 (19.0%)	6 (9.5%)	0.138
On statins	3 (2.4%)	10 (15.9%)	<0.001

AS: ankylosing spondylitis; MetS: metabolic syndrome; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table II. Prevalence of metabolic syndrome components in subjects with MetS. All values are expressed as number (%). Frequency analysis was assessed by χ^2 test with Yate's correction.

MetS components	Controls (n=24)	AS (n=22)	*p*
Fasting glucose ≥100 mg/dl	17 (70.8%)	14 (63.6%)	0.755
TG ≥150 mg/dl	13 (54.2%)	15 (68.2%)	0.378
HDL-C <40 mg/dl	3 (12.5%)	16 (72.7%)	<0.001
Waist circumference >102 cm	24 (100%)	20 (90.9%)	0.223
BP ≥ 130/85 mmHg	19 (79.2%)	17 (77.3%)	0.999

BP: blood pressure; for other abbreviations see Table I.

Table III. Characteristics of metabolic syndrome population. All values are expressed as number (%) or median (range). Between group results were compared by Mann-Whitney test or by χ^2 test with Yate's correction, as appropriate.

Variables	Controls (n=24)	AS (n=22)	*p*
Age (years)	46 (19-70)	46 (19-69)	0.502
Smokers	6 (25.0%)	8 (36.4%)	0.525
Glu (mg/dl)	104 (77-164)	105 (74-187)	0.878
TC (mg/dl)	235 (151-269)	200 (134-292)	0.126
TG (mg/dl)	156 (38-400)	177 (73-313)	0.141
LDL-C (mg/dl)	143 (68-185)	132 (78-205)	0.598
HDL-C (mg/dl)	52 (36-80)	38 (25-67)	<0.001
TC/HDL-C	4.1 (2.5-6.8)	5.5 (3.7-7.4)	0.002
LDL-C/HDL-C	2.6 (1.3-4.6)	3.5 (1.9-5.3)	0.005
SBP (mmHg)	130 (110-160)	135 (100-170)	0.323
DBP (mmHg)	80 (65-100)	80 (60-100)	0.557
Framingham risk score (%)	4 (0-21)	10 (0-30)	0.189

For abbreviations see Table I.

p=0.017, respectively], while in younger patients the difference was not significant [7 out of 33 (21.2%) *vs*. 9 out of 63 (14.3%), *p*=0.401].

Concerning confounding factors for MetS, in multivariate analysis after adjusting for smoking the risk for MetS was still higher in AS compared to controls [OR= 2.14 (95% CI 1.08-4.28); *p*=0.031]. Furthermore, in a subgroup analysis where smokers and those on statins were excluded, although differences were not statistically significant – probably due to the smaller number of individuals (n=39 for AS and n=102 for controls) – there was still a trend for higher prevalence of MetS in AS patients (30.8% *vs*. 17.6%, (*p*=0.1); Moreover, even in this smaller group, the prevalence of MetS in older AS patients (>41 years) was significant greater than controls of the same age-group [8 out of 16 (50.0%) *vs*. 12 out of 53 (22.6%), *p*=0.05, respectively].

Comparison of CVD risk factors and 10 year CVD risk

Patients with AS had significantly lower HDL-C (*p*<0.001) and higher TGs (*p*<0.05) serum levels, as well as higher systolic (*p*<0.001) and diastolic (*p*<0.01) blood pressure compared with controls (Table I). No significant differences in concentrations of fasting glucose, TC and LDL-C were observed between the 2 groups; however, the atherogenic indices (TC/HDL-C, LDL-C/HDL-C) were significantly higher in AS patients (*p*<0.001). Nevertheless, there was no significant difference in the Framingham risk between AS patients and healthy individuals.

When smokers and individuals on statins were excluded for the analysis, still AS patients had higher mean systolic and diastolic BP, lower HDL-C levels and higher atherogenic indeces compared to controls. Thus, even after excluding smokers and those on statins, AS patients had an adverse CVD risk profile compared to controls.

MetS-related features in patients and control subjects with MetS

Concerning MetS-related factors, the incidence of low HDL-C serum levels was significantly higher among AS patients than controls (72.7% *vs*. 12.5%; *p*<0.001), while there was no significant difference in the frequency of other MetS components (Table II). Moreover, within the population of MetS, patients had significantly lower HDL-C (*p*<0.001) serum levels compared with controls (Table III). Both atherogenic indices (TC/HDL-C and LDL-C/HDL-C) were significantly higher in AS patients (*p*<0.01) than in healthy subjects. No significant differences were observed between the 2 groups in fasting glucose, TC, TG and LDL-C serum levels, arterial blood pressure, smoking, age, and Framingham risk score.

AS patients with MetS: disease and MetS-related features

AS patients with MetS were significantly older (*p*=0.005), had longer disease duration (*p*=0.032) and had higher Framingham risk score (*p*=0.001) compared to those without MetS (Table IV). In stepwise multivariate regression analysis using disease duration and age as independent variables, disease duration was the only significant – although marginally – predictor for the risk of MetS [OR=1.07 (95% CI 1.01-1.14); *p*=0.047, per 1-year disease duration]. Moreover, MetS patients had higher disease activity (*p*<0.043) as assessed by the BASDAI index; in logistic regression analysis including age, smoke and BASDAI as independent variables, BASDAI correlated significantly with the presence of MetS (*p*=0.05).

The number of MetS components correlated with BASFI (r_s=0.25; *p*=0.05) and disease duration (r_s=0.28; *p*<0.05), while both BASDAI and CRP were inversely correlated with HDL-C levels in AS patients (r_s=-0.29; *p*<0.05 and r_s=-0.31; *p*=0.01, respectively). No significant differences in acute phase reactants (ESR, CRP) were found between patients with MetS compared with those without MetS.

Table IV. Demographics and disease-related features of patients with ankylosing spondylitis divided into 2 groups according to the presence of metabolic syndrome (MetS). All values are expressed as number (%) or median (range). Between group results were compared by Mann-Whitney test or by χ^2 test with Yate's correction, as appropriate.

Variables	Without MetS (n=41)	With MetS (n=22)	*p*
Age (years)	39 (19-56)	46 (19-69)	0.005
Smokers	12 (29.3%)	8 (36.4%)	0.582
CRP (mg/dl)	0.72 (0.02-6.50)	0.96 (0.16-13.20)	0.814
ESR (mm/h)	16 (1-103)	24 (2-127)	0.209
BASDAI	3.7 (0.0-7.5)	5.1 (0.0-7.8)	0.043
BASFI	3.4 (0.0-10.0)	4.8 (0.0-9.9)	0.158
Disease duration (years)	11 (1-29)	20 (1-43)	0.032
Framingham risk score (%)	2 (0-14)	10 (0-30)	0.001

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; for other abbreviations see Table I.

Discussion

AS patients have an increased prevalence ratio of CVD (2) and an increased risk for CVD mortality (25). In our study, AS patients had higher prevalence of MetS than controls and the presence of MetS correlated with AS disease activity. Moreover, patients had lower HDL-C, higher TGs serum levels, as well as higher systolic ($p<0.001$) and diastolic ($p<0.01$) blood pressure than control subjects. Despite the adverse risk factor profile, there were no significant differences in the Framingham score between the 2 groups. This was probably due to the relative young age of our population (median age 41), resulting in a very low risk score.

Most of the studies assessing the lipid profile in AS patients have shown decreased HDL-C levels (6, 28, 35), while Rossner *et al*. found normal HDL-C levels (35), Furthermore, a few studies found significantly lower total cholesterol levels in AS patients than expected (36,37). Our results corroborate data from the literature supporting an adverse lipid profile.

The prevalence of the MetS was 34.9% in AS patients and 19.0% in controls ($p<0.05$), and this difference was more profound in the older group (>41 years) (50.0% *vs*. 23.8%, $p=0.017$, respectively). The prevalence of MetS gradually increased, as expected (38), with age in both groups. Comparable with our results, Malesci *et al*. found an increased prevalence of MetS in a small (n=24) cohort of AS patients compared with controls (46% *vs*. 11%; $p=0.019$) (28). The lower prevalence of MetS in our cohort compared with that reported by Malesci *et al*., may be due to the younger age of our population (50.5 *vs*. 40 years), or treatment differences, since all our patients were on anti-TNFα agents, which is likely to exert a favourable effect on insulin resistance and increase in HDL-C in patients with AS (39-41). AS patients with MetS were significantly older ($p<0.05$) than those without, with higher Framingham risk score ($p=0.001$) and had a longer disease duration ($p<0.05$).

Analyzing the MetS components within the population with MetS, HDL-C was significantly lower in patients compared with controls ($p<0.001$), while both atherogenic indices (TC/HDL-C and LDL-C/HDL-C) were significantly higher in AS patients ($p<0.01$, Table III). Similarly, in our previous study only HDL-C was significantly lower in female RA patients with MetS compared with controls ($p<0.001$) (27). These data point-out HDL-C as a significant component of the adverse metabolic profile of patients with chronic inflammatory diseases, and although indirectly, underscores the correlation of chronic inflammation with suppressed HDL-C. Data from animal studies support a link between inflammatory cytokines, like TNF-α, and key components of HDL-C homeostasis. Several nuclear hormone receptors, such as Peroxisome Proliferator Activator Receptors (PPAR)-alpha, gamma and beta/delta, liver X Receptors (LXR)- alpha/beta that control certain steps in lipid homeostasis, are down regulated by lipopolysaccharide (LPS) and TNF-α (42). LXR's has been shown to activate the ABC superfamily of membrane transporters, which may increase levels of HDL-C and apo A-I (43-45). Inflammatory molecules, like TNF-α down regulate LXR expression in kidney and this is associated by a concomitant decrease in ABCA1 and ABCG5 expression (46). However, inflammation is not the only explanation for low HDL-C levels in AS patients. Decreased physical activity in this population could contribute to this (47). No matter the pathophysiologic basis of suppressed HDL-C levels, it is of clinical importance since in the Framingham cohort a 10 mg/dl (0.25 mmol/l) lower level of HDL-C was associated with a 50% higher risk for vascular events (48).

Interestingly, both MetS and HDL-C correlated with AS disease activity. Thus, patients with MetS had longer disease duration ($p<0.05$) and this was independent of age as shown in stepwise multivariate regression analysis. Moreover, MetS patients had higher BASDAI index ($p<0.043$), while both BASDAI and CRP correlated inversely with HDL-C levels ($p<0.05$ and $p=0.01$, respectively). These results should be interpreted within the limitation of the cross-sectional design of the study. Indices of the cumulative inflammatory burden of the disease, like structural damage or functional impairment, are more appropriate to assess the correlation between chronic inflammation and MetS. Interestingly, a correlation between the number of MetS components present correlated with BASFI ($p=0.05$), supporting further this correlation between inflammation and MetS. Our results suggest the need for larger prospective studies in order to confirm this relationship in AS patients. It has been proposed that insulin resistance, a basic metabolic disturbance of MetS, is associated with the abundance of pro-inflammatory cytokines (49). The present data corroborate recent data

supporting an association of inflammatory burden in AS patients with altered lipid profile (50), as well as data supporting a correlation of RA disease activity with the presence of MetS in RA patients (27). These data, although indirectly, adds to the growing body of evidence that chronic inflammation is associated with an adverse lipid profile (3, 50, 51), with the development MetS and ultimately an increased risk of CVD (52). To this end and recognizing the importance of chronic inflammation as a risk factor for atherosclerosis, the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials (ESCISIT) has organized a Task Force to develop recommendations for cardiovascular risk management in patients with inflammatory arthritis (53).

The results of our study must be interpreted within limitations, the major one being that all patients were on anti-TNF-α treatment. However, we have already shown that anti-TNF-α increases serum HDL-C levels (40), so we can speculate that the prevalence of MetS in AS patients who are not receiving anti-TNF-α is higher than in our population. Therefore, we may have underestimated the prevalence of MetS. It would be interesting to compare CRP values between patients and controls. Unfortunately, CRP data from controls were not available. Nevertheless, within patients mean CRP values were comparable between those with MetS and without the syndrome and were higher than normal levels. Finally, we cannot exclude the possibility of patient selection bias, since our unit is a tertiary referral center.

In summary, men with AS had a higher prevalence of CVD risk factors and MetS compared with control subjects. The presence of MetS was associated with an increased CVD-10 year risk in these patients. Additionally, the correlation of AS disease activity with MetS suggests that CVD in AS patients may -at least in part- be attributed to the inflammatory burden of the disease. Effective treatment of disease activity and CVD risk factors (especially lipid abnormalities) might lower the CVD risk in these high-risk patients.

References

1. HASKARD DO: Accelerated atherosclerosis in inflammatory rheumatic diseases. *Scand J Rheumatol* 2004; 33: 281-92.
2. HAN C, ROBINSON DW, 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.
3. GAZI IF, BOUMPAS DT, MIKHAILIDIS DP, GANOTAKIS ES: Clustering of cardiovascular risk factors in rheumatoid arthritis: the rationale for using statins. *Clin Exp Rheumatol* 2007; 25: 102-11.
4. DESSEIN PH, STANWIX AE, JOFFE BI: Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. *Arthritis Res* 2002; 4: R5.
5. DESSEIN PH, STANWIX AE, MOOMAL Z: Rheumatoid arthritis and cardiovascular disease may share similar risk factors. *Rheumatology* 2001; 40: 703-4.
6. DIVECHA H, SATTAR N, RUMLEY A, CHERRY L, LOWE GD, STURROCK R: Cardiovascular risk parameters in men with ankylosing spondylitis in comparison to non-inflammatory control subjects: relevance of systemic inflammation. *Clin Sci* (Lond) 2005; 109: 171-6.
7. GRUNDY SM, CLEEMAN JI, DANIELS SR *et al*.: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112: 2735-52.
8. DASKALOPOULOU SS, MIKHAILIDIS DP, ELISAF M: Prevention and treatment of the metabolic syndrome. *Angiology* 2004; 55: 589-612.
9. LAAKSONEN DE, LAKKA HM, NISKANEN LK, KAPLAN GA, SALONEN JT, LAKKA TA: Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 2002; 156: 1070-7.
10. LAKKA HM, LAAKSONEN DE, LAKKA TA *et al*.: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288:2709-16.
11. GALASSI A, REYNOLDS K, HE J: Metabolic syndrome and risk of cardiovascular disease: a meta-analysis *Am J Med* 2006; 119: 812-9.
12. REAVEN GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; 37: 1595-607.
13. HANLEY AJ, KARTER AJ, FESTA A *et al*.: Factor analysis of metabolic syndrome using directly measured insulin sensitivity: The Insulin Resistance Atherosclerosis Study. *Diabetes* 2002; 51: 2642-7.
14. FERNANDEZ-REAL MJ, RICART W: Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocrine Rev* 2003; 24: 278-301.
15. YUDKIN JS, STEHOUWER CDA, EMEIS JJ, COPPACK SW: C-Reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: A potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; 19: 972-8.
16. VISSER M, BOUTER LM, MCQUILLAN GM, WENER MH, HARRIS TB: Elevated C-reactive protein levels in overweight and obese adults. *J Am Med Assoc* 1999; 282: 2131-5.
17. FROHLICH M, IMHOF A, BERG G *et al*.: Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 2000; 23: 1835-9.
18. FESTA A, D'AGOSTINO R JR, HOWARD G, MYKKANEN L, TRACY RP, HAFFNER SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000; 102: 42-7.
19. SAKKINEN PA, WAHL P, CUSHMAN M, LEWIS MR, TRACY RP: Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. *Am J Epidemiol* 2000; 152: 897-907.
20. HAK AE, POLS HA, STEHOUWER CD *et al*.: Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: the Rotterdam study. *J Clin Endocrinol Metabol* 2001; 86: 4398-405.
21. SERIOLO B, PAOLINO S, SULLI A, FASCIOLO D, CUTOLO M: Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. *Ann NY Acad Sci* 2006; 1069: 414-9.
22. KELLER C, WEBB A, DAVIS J: Cytokines in the seronegative spondyloarthropathies and their modification by TNF blockade: a brief report and literature review. *Ann Rheum Dis* 2003; 62: 1128-32.
23. ANDREAKOS ET, FOXWELL BM, BRENNAN FM, MAINI RN, FELDMANN M: Cytokines and anti-cytokine biologicals in autoimmunity: present and future. *Cytokine Growth Factor Rev* 2002; 13: 299-313.
24. LEHTINEN K: Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. *Ann Rheum Dis* 1993; 52: 174-6.
25. 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.
26. CHUNG CP, AVALOS I, OESER A *et al*.: High frequency of the metabolic syndrome in patients with systemic lupus erythematosus: Association with disease characteristics and cardiovascular risk factors. *Ann Rheum Dis* 2007; 66: 208-14.
27. KARVOUNARIS SA, SIDIROPOULOS PI, PAPADAKIS JA *et al*.: Metabolic syndrome is common among middle - to older - age Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross- sectional, controlled, study. *Ann Rheum Dis* 2007; 66: 28-33.
28. 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.
29. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al*.: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
30. FURST DE, BREEDVELD FC, KALDEN JR *et al*.: Updated consensus statement on biological agents, specifically tumor necrosis factor-alpha (TNF-α) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic diseases. *Ann Rheum Dis* 2005; 64 (Suppl.) 4: 2-14.
31. WHO EXPERT COMMITTEE, PHYSICAL STATUS: the use and interpretation of anthropometry. *WHO Tech Rep Ser* 1995; 854: 424-38.
32. ANDERSON KM, WILSON PW, ODELL PM, KANNEL WB: An updated coronary risk profile. A statement for health professionals. *Circulation* 1991; 83: 356-62.
33. BRAUN J, PHAM T, SIEPER J *et al*.: International ASAS consensus statement for the use of anti-tumor necrosis agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003; 62: 817-24.
34. CALIN A, GARRETT S, WHITELOCK H *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.
35. ROSSNER S: Further studies on serum lipoproteins in connective tissue diseases. *Atherosclerosis* 1978; 31: 93-9.
36. JOVEN J, RUBIES-PRAT J, RAS MR, DE LA FIGUERA M, LIENCE E, MASDEU S: High density lipoproteins cholesterol subfractions and apoprotein A-I in patients with rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum* 1984; 27: 1199-2000.
37. MASI AT, ALDAG JC, MOHAN PC: Determinants of significantly lower serum total cholesterol levels in ankylosing spondylitis patients than age-, gender-, and medical service-matched controls patients: results of multivariate analysis. *Arthritis Rheum* 1999; 42 (Suppl.): S300.
38. ATHYROS VG, BOULOUKOS VI, PEHLIVANIDIS AN *et al*.: Mets-Greece Collaboration Group. The prevalence of the metabolic syndrome in Greece: the Mets-Greece Multicentre Study. *Diabetes Obes Metab* 2005; 7: 397-405.
39. KIORTSIS DN, MAVRIDIS AK, VASAKOS S, NIKAS SN, DROSOS AA: Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 765-6.
40. SPANAKIS E, SIDIROPOULOS P, PAPADAKIS J *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.
41. POPA C, NETEA MG, RADSTAKE T *et al*.: Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 303-5.
42. DUFFY D, RADER DJ: Emerging therapies targeting high-density lipoprotein metabolism and reverse cholesterol transport. *Circulation* 2006; 113: 1140-50.
43. KENNEDY MA, VENKATESWARAN A, TARR PT *et al*.: Characterization of the human ABCG1 gene: liver X receptor activates an internal J. promoter that produces a novel transcript encoding an alternative form of the protein. *Biol Chem* 2001; 276: 39438-47.
44. REPA JJ, BERGE KE, POMAJZL C, RICHARDSON JA, HOBBS H, MANGELSDORF DJ: Regulation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 by the liver X receptors alpha and beta. *J Biol Chem* 2002; 277: 18793-800.
45. VAISMAN BL, LAMBERT G, AMAR M *et al*.: ABCA1 over expression leads to hyperalphalipoproteinemia and increased biliary cholesterol excretion in transgenic mice. *J Clin Invest* 2001; 108: 303-9.
46. WANG Y, MOSER AH, SHIGENAGA JK, GRUNFELD C, FEINGOLD KR: Down regulation of liver X receptor-alpha in mouse kidney and HK-2 proximal tubular cells by LPS and cytokines. *J Lipid Res* 2005; 46: 2377-87.
47. KODAMA S, TANAKA S, SAITO K *et al*.: Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med* 2007 May 28; 167: 999-1008.
48. SPRECHER DL, WATKINS TR, BEHAR S, BROWN WV, RUBINS HB, SCHAEFER EJ: Importance of high-density lipoprotein cholesterol and triglyceride levels in coronary heart disease. *Am J Cardiol* 2003; 91: 575-80.
49. ECKEL RH, GRUNDY SM, ZIMMET PZ: The metabolic syndrome. *Lancet* 2005; 365: 1415-28.
50. VAN HALM VP, VAN DENDEREN JC, PETERS MJ *et al*.: Increased disease activity is associated with a deteriorated lipid profile in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 1473-7.
51. HULTHE J, FAGERBERG B: Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR study). *Atherioscler Thromb Vasc Biol* 2002; 22: 1162-7.
52. ROSS R: Atherosclerosis-an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.
53. PETERS M, SYMMONS D, MCCAREY D, NURMOHAMED M: Cardiovascular risk management in patients with rheumatoid arthritis and other types of inflammatory arthritis - A EULAR TASK FORCE. *Arthritis Rheum* 2008; 58: Suppl.