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Original Investigation

Prevalence of the metabolic syndrome in rheumatoid arthritis

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Abstract

Objective: Patients with rheumatoid arthritis (RA) experience a markedly increased prevalence of cardiovascular disease (CVD), but the causal factors have yet to be completely elucidated. Metabolic syndrome (MetS) is a cluster of risk factors of CVD and identifies additional cardiovascular risk beyond the sum of its individual components. In this study, we investigated the prevalence of MetS and its possible relationship with disease-related factors in patients with RA.

Matherial and Methods: Fifty-two patients with RA and 30 age- and sex-matched healthy controls were studied. Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III) and modified World Health Organization (WHO) criteria were used to define MetS. RA disease activity is assessed by the disease activity score of 28 joints (DAS28), and the functional status of patients was evaluated by Health Assessment Questionnaire (HAQ).

Results: Although there was no difference between groups regarding the frequency of MetS according to NCEP-ATP III criteria (17.3% and 6.5% in RA and control groups, respectively (p=0.158)) if modified WHO criteria were used, the prevalence of MetS was significantly higher in patients with RA (28.8%) than in controls (9.7%) (p=0.04). Central obesity and hypertension were found to be more frequent in patients with RA by both NCEP-ATP III and WHO criteria. RA patients with MetS had higher systolic and diastolic blood pressure, BMI and frequency of smoking than patients without MetS. Disease-related factors were similar in RA patients with or without MetS.

Conclusion: The evaluation of patients with RA for MetS, which is a multidimensional risk factor of CVD, may be beneficial.

Key words: Rheumatoid arthritis, rheumatic disease, metabolic syndrome

Introduction

Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease (CVD) compared with the general population (1) and CVD accounts for about half of all deaths in these patients (2). This increase cannot be explained fully with traditional risk factors (3).

Metabolic syndrome (MetS) is a combination of cardiovascular risk factors that identifies additional cardiovascular risk beyond the sum of its individual components. The main components of MetS are abdominal obesity, insulin resistance, increased blood pressure and dyslipidaemia. Insulin resistance is thought to play a key role (4). There are different definitions of MetS; two of the most commonly used are Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III) (5) and modified World Health Organization (WHO) criteria (6). These criteria are quite similar, except that the WHO definition requires direct evidence of insulin resistance. The common goal of different definitions is to predict individuals at high risk of developing CVD and to take preventive measures against it (7). In fact, according to a review of prospective studies, it was demonstrated that both WHO and NCEP defined that MetS are associated with adverse cardiovascular outcomes (8). However, individuals with NCEP-defined MetS have a 65% increased risk of CVD, which increases to 93% when the WHO definition is used compared to those people without MetS (9).

Although several studies have been reported about increased cardiovascular risk and insulin resistance in RA, there are few studies about the prevalence of MetS, a multidimensional risk factor of CVD (9-11). The aims of this study were to assess the prevalence of MetS according to both NCEP-ATP III and modified WHO criteria, and the possible relationships of MetS with disease-related factors.

Material and Methods

Patients and Controls

Fifty-two consecutive RA patients fulfilling the 1987 revised American College of Rheumatology criteria were included in the study. Thirty age- and sex-matched hospital staff members without any inflammatory

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rheumatic disease were enrolled as the control group. None of the patients were taking anti-TNF agents. Those individuals with hypothyroidism or using lipid-lowering agents were excluded.

This study was approved by the regional ethics committee. All participants gave written informed consent.

Patient Assessment

Disease duration, medications, history of traditional risk factors of CVD were noted during a structured interview. Height, weight and waist circumference were measured and body Mass Index (BMI) was calculated as "weight (kg)/ height (m)^2". Obesity was defined as BMI >30 kg/m^2. The waist circumference was measured midway between the lower rib margin and the iliac crest. All of the anthropometric measures were performed by the same investigators (OK and SO). RA disease activity is assessed by disease activity score based on evaluation of 28 joints (DAS28) and functional status by the Health Assessment Questionnaire (HAQ).

Laboratory Tests

Fasting glucose, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, rheumatoid factor, leucocytes, thyroid stimulating hormone (TSH), insulin, C-peptide, and erythrocyte sedimentation rate (ESR) were measured. Insulin resistance was assessed with the Homeostasis Model Assessment (HOMA) Index. HOMA index = (insulin (μU/mL) x glucose (mmol/L))/22.5. If the HOMA index was >2.114, it was defined as insulin resistance (6).

Metabolic Syndrome Definitions

Both NCEP-ATP III and modified WHO criteria were used to define MetS. NCEPATP III definition of MetS requires the presence of three or more of the following conditions (5): central obesity (>88 cm in women and >102 cm in men), increased triglyceride level (≥150 mg/dL), low level of HDL-C (50 mg/dL in women and 40 mg/dL in men), increased fasting glucose (≥110 mg/dL), and increased systolic or diastolic blood pressure (≥130/85 mmHg) or self-reported use of medication for high blood pressure.

The modified WHO definition of MetS requires insulin resistance, defined as having a HOMA index of >2.114, impaired fasting glucose (≥110 mg/dL) or diabetes. In addition, patients need to meet at least two of the following three criteria (6): 1) central obesity (>94 cm in men and >88 cm in women); 2) increased triglyceride level (≥150 mg/dL) and/or low level of HDL-C (<35 mg/dL in men and <40 mg/dL in women); 3) increased systolic blood pressure (≥140 mmHg) and/or increased diastolic blood pressure (≥90 mmHg), or use of antihypertensive drug.

Statistical Analysis

Continuous variables are reported as mean± standard deviation (SD). Variables were compared by using either the Student's t-test or χ^2 test as appropriate. Correlation analyses were assessed using either Pearson's correlation test or Spearman's correlation test as appropriate. p values <0.05 (two tailed) were considered significant. SPSS (Statistical Package for Social Sciences) for Windows version 15.0 (IBM; Chicago, IL, USA) was used for all statistical analysis.

Results

The characteristics of RA patients (n=52, with a mean disease duration of 54 months) and control subjects (n=30) are shown in Table 1. The groups were similar except for LDL-C and systolic blood pressure. Levels of LDL-C and systolic blood pressure were higher in patients with RA than in controls (p=0.032 and p=0.014, respectively).

Nine RA patients (17.3%) and 2 control subjects (6.5%) had MetS according to NCEPATP III definition. Although there was no significant difference between groups (p=0.158), using this definition, central obesity, hypertension and low HDL-C were more frequent in patients with RA (p values are 0.044, 0.03 and 0.004, respectively). However, by using the WHO definition, the frequency of MetS was significantly higher (p=0.04) in patients with RA (15 patients; 28.8%) than in controls (3; 107%) (Table 2). Also, significant differences were found in the prevalence of central obesity and hypertension between groups (p=0.002 and p=0.04, respectively).

RA patients with MetS had higher systolic blood pressure, diastolic blood pressure, BMI and smoking than patients without MetS according to both NCEP-ATP III and modified WHO definitions (Table 3).

Disease-related factors (disease duration, DAS28, prednisolone using, HAQ, and ESR) were similar in RA patients with or without MetS according to both NCEP-ATP III and modified WHO criteria. Additionally, there was no correlation between DAS28 and either insulin or HOMA index.

The prevalence of modified WHO criteria-defined MetS was compared among obese (BMI ≤30 kg/m^2) and non-obese (BMI >30 kg/m^2) patients and controls; it was still higher in patients with RA.

Discussion

The present study showed an increased prevalence of MetS according to modified WHO criteria in RA patients. This result may be important since RA is associated with an increased risk of CVD (12). The aetiology of accelerated

Table 1. The characteristics of RA patients and controls

	RA (n=52)	Control (n=30)	p value
Age (years)	51±10	48±14	0.328
Male sex	15 (29%)	9 (30%)	0.986
Diabetes mellitus	4 (8%)	1 (3%)	0.646
Hypertension	14 (26.9%)	5 (16.7%)	0.258
Myocardial infarction	2 (4%)	1 (3%)	1.000
Family history of CHD	13 (25%)	4 (13%)	0.187
Smoking (pack-year)	5.81±11.1	8.39±14.2	0.440
BMI (kg/m^2)	29±6	28±6	0.478
Waist circumference (cm)	97±13	93±14	0.149
Systolic blood pressure (mmHg)	132±26	120±18	0.014
Diastolic blood pressure (mmHg)	83±17	78±8	0.205
Fasting Glucose (mg/dL)	97±21	92±9	0.209
Triglyceride (mg/dL)	122±55	127±64	0.670
LDL-C (mg/dL)	128±30	113±32	0.032
HDL-C (mg/dL)	55±12	48±10	0.05
TSH (mg/dL)	5.51±2.03	1.58±1.04	0.324
ESR (mm/hour)	28±20	22±12	0.160
DAS-28 score	4.1±1.3	NA	NA

Data are mean±SD unless otherwise stated.

CHD: coronary heart disease; BMI: body mass index; RA: rheumatoid arthritis; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TSH: thyroid stimulating hormone; ESR: erythrocyte sedimentation rate; DAS-28: disease activity score-28 joint

Table 2. Prevalence of metabolic syndrome and its components in patient and control groups

	RA (n=52)	Control (n=30)	p value
NCEP-ATP III criteria			
Central obesity (%)	61	39	0.044
Hypertension (%)	50	26	0.030
Hypertriglyceridaemia (%)	29	32	0.743
Low HDL-C (%)	32	14	0.040
Hyperglycaemia (%)	0	8	0.292
Total meeting definition (%)	17.3	6.5	0.158
Modified WHO criteria			
Insulin resistance (%)	48	36	0.263
Dyslipidaemia (%)	35	42	0.505
Hypertension (%)	46	13	0.002
Central obesity (%)	73	52	0.047
Total meeting definition (%)	28.8	9.7	0.040

RA: rheumatoid arthritis; HDL-C: high-density lipoprotein cholesterol

Table 3. The comparison of cardiovascular risk factors in patients with RA in terms of presence of NCEPATP III criteria-defined MetS

	Metabolic Syndrome (+) (n=9)	Metabolic Syndrome (-) (n=43)	p value
Age (years)	50±10	51±11	0.83
Systolic blood pressure (mmHg)	151±10	129±27	<0.001
Diastolic blood pressure (mmHg)	99±6	80±16	<0.001
BMI (kg/m^2)	34±6	28±5	<0.001
Smoking (pack-year)	6.8±11.9	1.1±3.3	0.01
LDL-C (mg/dL)	137±23	126±31	0.35
HDL-C (mg/dL)	54±12	55±12	0.76
Triglyceride (mg/dL)	139±47	118±56	0.31
HOMA index	3.1±4.7	2.5±1.8	0.70
ESR (mm/h)	29±24	27±19	0.40
DAS 28	4.3±1.3	3.7±1.3	0.22
HAQ	0.9±0.9	0.72±0.6	0.68

Data are mean±SD unless otherwise stated.
NCEP-ATPIII: Adult Treatment Panel III of the National Cholesterol Education Program; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HOMA: Homeostasis Model Assessment; ESR: erythrocyte sedimentation rate; DAS 28: disease activity score of 28 Joints; HAQ: health assessment questionnaire

atherosclerosis in those patients is unknown. Some of the traditional cardiovascular risk factors like age, sex and smoking were found to be associated with carotid and coronary artery atherosclerosis; however, it was also shown that markers of inflammation predicts CVD as well (2, 3).

Although MetS has a predictive value for CVD, there are differences among definitions. Direct evidence of insulin resistance, one of the fundamental factors in increased cardiovascular risk related to MetS according to many authors, is required for modified WHO criteria (13). However, insulin resistance is not included in the NCEP-ATP III definition and this criteria describes MetS as a complication of obesity. However, obesity was not found to be related with CVD in RA (2) and this definition determined insulin resistance by the rate of 20-50% in non-diabetic patients (14). In addition, Dessein et al. (15) found the sensitivity of NCEP ATP III definition in establishing insulin resistance in 100 patients with RA as 23%. Therefore, one can hypothesise that using modified WHO criteria may be more beneficial to define MetS than NCEP-ATP III in patients with RA. In our study, MetS prevalence was higher in patients with RA according to modified WHO criteria, but there was no difference according to NCEP-ATP III criteria; also, we observed a fair agreement between WHO and NCEP-ATP III definitions of MetS (p=0.38). In the present work, the percentages of patients fulfilling the definition of MetS was lower than reported by Chung et al. (9), but was quite similar in other studies (10, 11). Since age, sex, BMI, and smoking status were similar between groups in the present study, the contribution of these possible confounding factors to the observed difference is highly unlikely.

Previously, Chung et al. (9) studied 154 patients with RA and found a higher MetS prevalence than in controls according to both NCEP-ATP III and modified WHO criteria. However, they found an association only between modified WHO criteria and the presence of coronary atherosclerosis. Dessein et al. (10) found similar results when compared with NCEP-ATP III; atherosclerosis was associated with modified WHO criteria. Therefore, modified WHO criteria are not only more useful to determine MetS, but also correlate better with CVD in patients with RA.

Inflammation gives rise to the presence of MetS through many mechanisms. Several cytokines are released from synovial tissue into systemic circulation in RA. High plasma levels of TNF-α, IL-1β and IL-6 are found in these patients. These circulating cytokines affect adipose, skeletal muscle, liver and vascular endothelium and causes a spectrum of pro-atherogenic changes that includes insulin resistance, dyslipidaemia, prothrombotic effects, pro-oxidative stress, and endothelial dysfunction (16). Cytokines, especially TNF-α, can directly inhibit insulin-mediated glucose uptake in skeletal muscle (17). Moreover, TNF-α and IL-6 can stimulate adipocyte lipolysis, leading to the increased release of free fatty acids from peripheral tissues and an enhanced cycle of fatty acids between liver and adipose tissue (18). Increased free fatty acid fluxes play an important role in the pathogenesis of insulin resistance. Previously, it was reported that the prevalence of insulin resistance was markedly increased in patients with RA (9). In this study, insulin resistance was noted in 48% of RA patients and in 36% of controls, but the difference did not reach statistical significance, possibly because our patients were on anti-inflammatory treatment that might improve insulin resistance.

Some of the individual components of both NCEP-ATP III and WHO definitions of MetS were more markedly different between our RA patients and control subjects, as seen in the other study (10). Since the cross-sectional nature and subclinical atherosclerosis was not evaluated in the present study, it may not be possible to reach a sound conclusion as to whether this difference will better identify those patients at risk.

In the present study, we could not demonstrate a relationship between disease-related factors such as DAS-28 scores, HAQ, ESR, disease duration, and the presence of metabolic syndrome. The association of disease status and the presence of Mets have been reported to be controversial in RA. Although in a previous study (9), the prevalence of this syndrome

was shown to be higher among the patients with RA for a longer time than among those in the early phase (42% vs. 31%), some of the previous studies found no association of MetS and disease status (19, 20) ESR (11, 20), DAS-28 scores (20). Additionally, another study showed that there was no relationship between disease duration and the risk of CVD in RA. Therefore, it has been proposed that the increased risk of CVD may precede the clinical onset of RA (2), and that there is a preclinical phase of RA during which inflammatory activity and serological disturbance occur (21).

There are some limitations of this study; first, the number of participants may be insufficient to confidentially eliminate the type II error in comparing the frequency of MetS according to NCEP-ATPIII criteria. The post hoc power calculation showed that 110 participants in each group may be required to demonstrate the difference in rates of NCEP-ATP III defined MetS between RA patients (17.3%) and controls (6.5%). Second, it is a cross-sectional study and longitudinal studies evaluating the effects of MetS on the risk of cardiovascular events in RA patients will be of interest. Third, most of our patients were on steroid treatment, which might improve insulin sensitivity. In fact, previous studies suggest that corticosteroids may have beneficial effects on glucose metabolism and MetS via the control of inflammation.

In conclusion, patients with RA have an increased prevalence of MetS, which is a multidimensional marker of cardiovascular risk. Modified WHO criteria, which need direct proof of insulin resistance, may be more suitable to evaluate cardiovascular risk in patients with RA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Atatürk Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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