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ORIGINAL ARTICLE

The frequency of metabolic syndrome in women with rheumatoid arthritis and in controls

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Abstract

Aim: To compare the frequency of the metabolic syndrome and its components in a sample of patients with rheumatoid arthritis (RA) and controls.

Methods: This case control study was performed on 188 women over 18 years old: 92 RA patients and 96 healthy controls, from 2006 to 2008. Blood pressure, height, weight and waist circumference were measured. Blood was collected for the measurement of fasting glucose, lipid profile and insulin. The frequency of the metabolic syndrome was determined in case and control groups, using both WHO and National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria.

Results: According to the NCEP criteria, the frequency of metabolic syndrome in RA patients and controls were 27.2% and 35.4%, respectively ($P = 0.22$). Based on WHO criteria, 19.6% of RA patients and 21.9% of the control group were subject to metabolic syndrome ($P = 0.70$). The proportion with hypertension was greater in RA patients than the control group. The duration of RA was significantly higher in patients with metabolic syndrome compared to those without metabolic syndrome using both the WHO and NCEP criteria.

Conclusions: There was no evidence of a greater prevalence of metabolic syndrome in RA patients compared with controls in this study. The duration of RA was associated with metabolic syndrome, implicating the role of inflammation in metabolic syndrome development.

Key words: cardiovascular risk factors, duration, metabolic syndrome, rheumatoid arthritis.

INTRODUCTION

Patients with rheumatoid arthritis (RA) are at an increased risk of morbidity and mortality due to cardiovascular risk factors compared with the general population.[1,2] Many factors may contribute to increased cardiovascular risk, including classic risk factors such as smoking, diabetes, hypertension and obesity, and novel risk factors such as systemic inflammation, a prothrombotic state and hyperhomocystinemia.[3]

Metabolic syndrome is a cluster of classic cardiovascular risk factors: hypertension, obesity, glucose intolerance and dyslipidemia. The prevalence of metabolic syndrome varies between 20% and 30% in the adult populations of developed countries.[4,5] There are several definitions for metabolic syndrome, but two of the most commonly used are the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III),[6] and the modified World Health Organization (WHO) definitions.[7,8] The criteria for

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both are the same, except that the WHO definition requires evidence of insulin resistance.

A study has shown that patients with RA have a higher prevalence of metabolic syndrome than controls;[9] however, another study has demonstrated an equally high prevalence between Mediterranean RA patients and local general population controls.[10] The aim of this study was to compare the frequency of metabolic syndrome and its components in a sample of patients with RA and their controls.

METHODS

Patients and controls

In the current case-control study, 188 women older than 18 years of age were enrolled, 92 of which were suffering from RA according to the American College of Rheumatology (ACR) criteria, and the remaining 96 were controls that showed none of the criteria of inflammatory diseases. The patients were consecutive eligible RA cases with at least a minimum disease duration of 1 year from the Rheumatology Centre at Zanjan Valiasr Hospital between 2006 and 2008. The control group was selected from individuals referred to the Dermatology or Gynecology Clinic of the same hospital as well as the hospital staff. Moreover, the control group had no history of using any medication that affects insulin resistance, such as oral contraceptive pills and glucocorticoids. Smokers were not included in either of these groups. The study was approved by the Ethical Committee of the Zanjan University of Medical Sciences and informed consent has been obtained for all subjects.

Evaluation

Participants were evaluated using an interview, physical examination and laboratory tests. Medication use was recorded by asking subjects and checking their medical history. Their height and weight were measured and their body mass index (BMI) was calculated. Blood pressure was determined as the mean of two measurements taken with an interval of 5 min. Patients that took anti-hypertensive drugs or those with a blood pressure of equal or >140/90 mmHg in the sitting position were considered as hypertensive.

Fasting blood samples were taken from all subjects for determination of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood sugar (FBS) and triglyceride (TG). The concentration of insulin in the serum was measured using the enzyme-linked immunosorbent assay (ELISA) method.

Definition of metabolic syndrome

The NCEP-ACT III and the modified WHO definitions were both used to identify subjects with metabolic syndrome. According to the NCEP criteria, metabolic syndrome is defined as the presence of at least three of the following five criteria: waist circumferences > 102 cm in men and > 88 cm in women, hypertriglyceridemia (TG ≥ 150 mg/dL), low HDL < 40 mg/dL in men and < 50 mg/dL in women, high blood pressure (≥ 130/85 mmHg or use of medication for high blood pressure), and FBS ≥ 110 mg/dL.[6]

The modified WHO definition requires the presence of insulin resistance which is determined by one of the three following criteria:

1 Homeostasis Model Assessment (HOMA) Index (fasting glucose [mmol/L] × fasting insulin (μm/mL)/22.5) in the upper quartile of the non-diabetic population;
2 impaired in the fasting glucose (≥ 110 mg/dL);
3 diabetes.

Also two criteria from the three mentioned below are required: waist circumferences > 94 cm in men and > 88 cm in women; triglycerides (≥ 150 mg/dL) or HDL < 40 mg/dL in women or 35 mg/dL in men; and high blood pressure ≥ 140/90 mmHg or use of antihypertensive medications.[8] A HOMA index > 2.11 was considered as representing the top quartile of a non-diabetic population.[9]

Rheumatoid arthritis disease activity was assessed by the Disease Activity Score (DAS28) index. High disease activity was considered as DAS28 > 5.1, moderate as DAS28 > 3.2–5.1, and low disease activity in the range 2.6–3.2.[11]

Statistical methods

The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Values were expressed as mean ± standard deviation, and number (percentage), as appropriate. Comparisons were performed by independent *t*-test for normally distributed variable, Mann–Whitney test for non-normally distributed variables, and chi-square test for categorical variables. Logistic regression models were used to evaluate the association between RA and metabolic syndrome after controlling for age and weight. Analysis of the data was carried out using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic, clinical and laboratory characteristics of RA patients and controls are demonstrated in Table 1. Patients with RA were older, had higher diastolic blood pressure and had higher HDL levels than the control group. The weight, the levels of TG and LDL were higher in the controls compared to patients. No significant differences were observed between the two groups for waist, systolic blood pressure and total cholesterol.

Frequency of metabolic syndrome in RA patients and controls

Based on NCEP criteria, 25 (27.2%) patients and 34 (35.4%) controls were subjected to metabolic syndrome ($P = 0.22$) (Table 2). RA patients and control group were different in hypertriglyceridemia ($P = 0.03$) and low HDL ($P < 0.0001$). The association between RA and NCEP-defined metabolic syndrome did not alter after adjusting for age and weight (OR = 0.56, 95% CI: 0.27–1.17, $P = 0.12$).

Based on WHO criteria, 18 (19.6%) patients and 21 (21.9%) controls had metabolic syndrome ($P = 0.70$). The proportion of hypertension was greater in RA patients than control group (28.3% *vs.* 15.6%, $P = 0.04$); however, dyslipidemia was more prevalent in controls than cases (63.5% *vs.* 35.9%, $P < 0.0001$). The association between RA and the WHO-defined metabolic syndrome remained non-significant after adjusting for age and weight (OR = 0.7, 95% CI: 0.31–1.58, $P = 0.39$).

Characteristics of RA patients on the basis of the presence or the absence of metabolic syndrome

In RA patients, using both the WHO and NCEP criteria, metabolic syndrome was associated with a higher age, waist circumference, systolic and diastolic blood pressure, total cholesterol, triglyceride and fasting glucose. The NCEP-defined metabolic syndrome was also associated with higher LDL and a lower HDL cholesterol levels (Table 3). The HOMA index was significantly greater in RA patients with metabolic syndrome than those without, according to the WHO definition (medians: 3.1 *vs.* 1.7, $P < 0.0001$) (Table 4).

The association between metabolic syndrome and RA disease activity (DAS28 index) was next assessed. The proportions of metabolic syndrome in patients with low, moderate and high disease activity were 21.4%, 25.5% and 10.0%, respectively ($P = 0.36$). No significant difference was also found in DAS28 between patients with and without metabolic syndrome according to either the WHO or NCEP criteria (Tables 3 and 4).

Table 2 Frequency of metabolic syndrome and its criteria in RA patients and controls

	RA ($n = 92$)	Controls ($n = 96$)	*P*-value
NCEP criteria			
Waist circumference	50 (54.3)	39 (40.6)	0.06
Hypertension	36 (39.1)	26 (27.1)	0.08
Hyperglycemia	12 (13.0)	16 (16.7)	0.49
Hypertriglyceridemia	27 (29.3)	43 (44.8)	0.03
Low HDL	41 (44.6)	76 (79.2)	< 0.0001
Metabolic syndrome	25 (27.2)	34 (35.4)	0.22
WHO criteria			
Hypertension	26 (28.3)	15 (15.6)	0.04
Dyslipidemia	33 (35.9)	61 (63.5)	< 0.0001
Insulin resistance	38 (41.3)	41 (42.7)	0.85
Metabolic syndrome	18 (19.6)	21 (21.9)	0.70

Results expressed as number (percentage). NCEP, National Cholesterol Education Program; WHO, World Health Organization.

Table 1 Demographics, clinical and laboratory characteristics of patient and control groups

	RA ($n = 92$)	Controls ($n = 96$)	*P*-value
Age	48.3 ± 14.6	42.2 ± 9.9	0.001
Systolic blood pressure (mmHg)	120 (110–130)	118 (110–129)	0.14
Diastolic blood pressure (mmHg)	80 (75–85)	70 (65–80)	< 0.0001
Weight (kg)	64.8 ± 11.2	68.7 ± 9.4	0.009
Waist (cm)	89.6 ± 11.5	86.9 ± 10.1	0.09
Total cholesterol (mg/dL)	178.6 ± 39.8	187.0 ± 39.7	0.147
High-density lipoprotein (mg/dL)	52.4 ± 12.4	42.8 ± 9.0	< 0.0001
Low-density lipoprotein (mg/dL)	100.5 ± 37.7	111.4 ± 34.9	0.04
Triglycerides (mg/dL)	114 (71.3–163.3)	133 (88.3–225.0)	0.006

Results expressed as mean ± standard deviation, and median (25–75th percentile), as appropriate.

Table 3 Characteristics of RA patients according to the presence or absence of metabolic syndrome

	NCEP		
	With metabolic syndrome (n = 25)	Without metabolic syndrome (n = 67)	P-value
Age	55.6 ± 10.8	45.6 ± 14.9	0.001
Weight (kg)	68.7 ± 10.6	63.3 ± 11.1	0.037
Waist (cm)	98.5 ± 10.1	86.2 ± 10.2	< 0.0001
Systolic blood pressure (mmHg)	130 (120–150)	119 (110–120)	< 0.0001
Diastolic blood pressure (mmHg)	90 (80–100)	80 (70–80)	< 0.0001
Total cholesterol (mg/dL)	192.1 ± 31.2	173.5 ± 41.7	0.046
High-density lipoprotein (mg/dL)	47.6 ± 13.7	54.2 ± 11.5	0.021
Low-density lipoprotein (mg/dL)	114.5 ± 39.6	95.5 ± 36.0	0.036
Triglycerides (mg/dL)	175 (114–201)	93 (70–136)	< 0.0001
Fasting Glucose (mg/dL)	101.1 ± 38.5	81.2 ± 11.0	0.017
HOMA	2.1 (1.4–3.7)	1.8 (1.2–2.4)	0.076
Disease duration (years)	10.5 (8.5–20.0)	6.5 (5–12.8)	0.008
DAS28	4.5 (3.7–4.7)	4.2 (3.4–5.0)	0.80
ESR	26.0 (12.0–34.5)	24.5 (12.3–37.0)	0.78
CRP	9.5 (2.8–17.8)	6.0 (3.0–13.0)	0.39

Results expressed as mean ± standard deviation, and median (25–75th percentile), as appropriate. NCEP, National Cholesterol Education Program; HOMA, Homeostasis Model Assessment; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 4 Characteristics of RA patients according to the presence or absence of metabolic syndrome

	WHO		
	With metabolic syndrome (n = 18)	Without metabolic syndrome (n = 74)	P-value
Age	59.3 ± 8.5	45.6 ± 14.5	< 0.0001
Weight (kg)	67.8 ± 9.5	64.0 ± 11.5	0.197
Waist (cm)	98.8 ± 10.2	87.3 ± 10.7	< 0.0001
Systolic blood pressure (mmHg)	140 (120–150)	120 (110–121)	0.001
Diastolic blood pressure (mmHg)	90 (80–100)	80 (74–80)	< 0.0001
Total cholesterol (mg/dL)	201.3 ± 35.4	173.0 ± 39.1	0.006
High-density lipoprotein (mg/dL)	54.3 ± 15.6	51.9 ± 11.5	0.465
Low-density lipoprotein (mg/dL)	113.4 ± 43.5	97.4 ± 35.7	0.107
Triglycerides (mg/dL)	200.3 ± 154.2	114.9 ± 64.1	< 0.0001
Fasting glucose (mg/dL)	108.2 ± 43.0	81.4 ± 11.0	0.017
HOMA	3.1 (2.4–4.0)	1.7 (1.1–2.1)	< 0.0001
Disease duration (years)	10.0 (7.8–20.0)	7.0 (4.8–13.0)	0.030
DAS28	4.0 (3.5–4.7)	4.3 (3.6–5.0)	0.62
ESR	23.5 (10–29.8)	25.0 (14–37.5)	0.43
CRP	7.3 (2.9–15.2)	6.1 (3.0–13.5)	0.87

WHO; World Health Organization; HOMA, Homeostasis Model Assessment; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

The median RA duration at the time of study was 8 years (IQR: 5–14). Patients with metabolic syndrome based on NCEP criteria had a median duration of 10.5, compared to 6.5 in patients without metabolic syndrome (P = 0.008) (Table 3). RA duration was also significantly different between patients with and without metabolic syndrome according to the WHO criteria (Table 4). No significant differences were observed for patient characteristics such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and metabolic syndrome (Tables 3 and 4). All patients were treated with a similar dose of prednisolone

(2.5–10 mg/day) and methotrexate (7.5–15 mg/day) and more than 90% were taking chloroquine.

Characteristics of the control group on the basis of the presence or the absence of the metabolic syndrome

In controls, using both the WHO and NCEP criteria, metabolic syndrome was associated with a higher age, weight, waist circumference, systolic and diastolic blood pressure, total cholesterol, triglyceride, fasting glucose and HOMA index. The NCEP-defined metabolic syndrome was associated with a lower HDL concentration (Table 5), whereas, the WHO-defined metabolic syndrome was associated with a higher LDL cholesterol level (Table 6).

DISCUSSION

In the present study, the prevalence of the metabolic syndrome in RA patients was 27.2% and 19.6% according to the NCEP and WHO criteria, respectively. No significant differences in the prevalence of metabolic syndrome between patients and controls were found, using both the NCEP and WHO definition. In one study, the prevalence of metabolic syndrome among patients with RA (n = 74, mean age 55.8 years, 86% women) were 14% and 19% according to WHO and NCEP-ATP III criteria, respectively.[12] Karvounaris *et al.*[10] found that the prevalence of metabolic syndrome was high in 200 RA patients (mean age: 63 years) but comparable to that of the 400 age and

Table 5 Characteristics of control subjects according to the presence or absence of metabolic syndrome

	NCEP		
	With metabolic syndrome (n = 34)	Without metabolic syndrome (n = 62)	P-value
Age	47.1 ± 10.0	39.5 ± 8.9	< 0.0001
Weight (kg)	74.6 ± 8.6	65.5 ± 8.2	< 0.0001
Waist (cm)	94.1 ± 10.1	82.9 ± 7.5	< 0.0001
Systolic blood pressure (mmHg)	130 (110–140)	110 (105–120)	< 0.0001
Diastolic blood pressure (mmHg)	80 (70–86.3)	70 (60–75)	< 0.0001
Total cholesterol (mg/dL)	206.1 ± 36.4	176.6 ± 37.8	< 0.0001
High-density lipoprotein (mg/dL)	39.5 ± 8.1	44.6 ± 9.1	0.008
Low-density lipoprotein (mg/dL)	119.4 ± 38.1	107.0 ± 32.4	0.098
Triglycerides (mg/dL)	227 (159–273)	97 (75–146)	< 0.0001
Fasting glucose (mg/dL)	93.5 (85.8–103.3)	88 (83–92)	0.003
HOMA	2.6 (1.8–3.5)	1.4 (0.8–2.0)	< 0.0001

NCEP, National Cholesterol Education Program; HOMA, Homeostasis Model Assessment.

Table 6 Characteristics of control subjects according to the presence or absence of metabolic syndrome

	WHO		
	With metabolic syndrome (n = 18)	Without metabolic syndrome (n = 74)	P-value
Age	59.3 ± 8.5	45.6 ± 14.5	< 0.0001
Weight (kg)	75.0 ± 9.0	67.0 ± 8.7	< 0.0001
Waist (cm)	96.2 ± 11.1	84.3 ± 8.1	< 0.0001
Systolic blood pressure (mmHg)	130.4 ± 19.4	116.0 ± 14.9	0.004
Diastolic blood pressure (mmHg)	78.1 ± 9.9	70.5 ± 11.0	0.005
Total cholesterol (mg/dL)	212.5 ± 34.8	179.9 ± 38.2	0.001
High-density lipoprotein (mg/dL)	40.3 ± 8.6	43.5 ± 9.1	0.162
Low-density lipoprotein (mg/dL)	125.5 ± 30.2	107.5 ± 35.2	0.036
Triglycerides (mg/dL)	200.3 ± 154.2	114.9 ± 64.1	< 0.0001
Fasting glucose (mg/dL)	108.2 ± 43.0	81.4 ± 11.0	0.017
HOMA	3.7 ± 1.5	1.6 ± 1.1	< 0.0001

WHO; World Health Organization; HOMA, Homeostasis Model Assessment.

sex-matched controls (44% *vs*. 41%, 74% women). Chung *et al.* studied the prevalence of metabolic syndrome according to both WHO and NCEP criteria in a group of RA patients (n = 154, mean age 51 years for early RA and 59 years for established disease, 68% women) and compared them with controls. They found that the prevalence of this syndrome was higher in patients with longstanding RA than in those with early disease (42% *vs*. 31%).[9] The low prevalence of metabolic syndrome in our study may be attributed to differences in the characteristics of the study population: participants in this study were all women, with a lower mean age than previous studies.

In this study, the duration of RA was significantly different in patients with metabolic syndrome compared to those without, using both the WHO or NCEP criteria. Accordingly, in the study by Chung *et al.* [9] there was a significant relationship between disease duration and NCEP-defined metabolic syndrome. No significant differences were found regarding DAS28 index or other disease-related factors and the presence of metabolic syndrome. The correlation between disease duration and metabolic syndrome in our study supports the role of chronic inflammation in metabolic syndrome development as stated by previous studies.[9,10,13,14]

At study entry, all patients were on treatment with prednisolone (2.5–10 mg/day) and methotrexate (7.5–15 mg/day) and more than 90% were taking chloroquine. A previous study suggests that the use of corticosteroids may improve insulin sensitivity in patients with RA.[15] Other studies have shown that a high disease activity was correlated with adverse lipid profile[16,17] and insulin resistance.[18] It was also reported that chloroquine could modulate insulin resistance and decrease vascular disease.[19] Therefore, the use of these drugs by patients with RA may decrease the prevalence of metabolic syndrome.

The most common form of dyslipidemia in RA patients is the reduction of total, HDL and LDL cholesterol, and triglycerides.[20] The definition of metabolic syndrome only includes two components of the lipid profile: triglycerides and HDL cholesterol. The use of corticosteroids, independent of dose, increases HDL levels.[21–23] Endogenous glucocorticoid hormones regulate HDL concentration in plasma by increasing synthesis and secretion of HDL by the liver.[24] Therefore, high doses of exogenous glucocorticoid hormone, similar to those used in RA patients, probably accelerate this pathway. Thus in RA, the levels of HDL which were previously reduced by disease activity will increase, and as a result a less atherogenic profile is induced.[25] An increase in HDL levels was observed in patients using glucocorticoids for a long period of time ($P < 0.0001$) in our study. On the other hand, increase in HDL may be due to the indirect effects of glucocorticoids. RA patients with GC use, due to reduction in joint stiffness and damage, may have a more active lifestyle with a further positive effect on their HDL levels.[25]

In conclusion, there was no evidence of a greater prevalence of metabolic syndrome in RA patients compared with controls in this study. The duration of RA was associated with metabolic syndrome, implicating the role of chronic inflammation in metabolic syndrome development.

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