

Original Article

Prevalence of metabolic syndrome in women with rheumatoid arthritis and effective factors

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Abstract: Purpose: Metabolic syndrome (MS), which is framed by cardiovascular risk factors such as hypertension, obesity, glucose intolerance and dyslipidemia, is thought to be associated with the rheumatic diseases. The aim of this study is to examine the frequency of metabolic syndrome (MS) and insulin resistance in patients with rheumatoid arthritis (RA) and to examine the effect of the inflammation symptoms, disease activity and drugs used in treating RA on insulin resistance and presence MS. Method: One hundred women patients diagnosed with RA according to the American College of Rheumatology (ACR) diagnosis criteria and 100 healthy women were included in the study as controls. Insulin resistance were evaluated using the homeostasis model assessment for insulin resistance (HOMA-IR) method and MS was diagnosed according to two Metabolic Syndrome definitions (National Cholesterol Education Programme 2004, International Diabetes Federation). The disease activity of RA was evaluated by the disease activity score including 28 joints (DAS28). Results: In total, 27% and 33% of the RA patients and 28% and 44% of the control group patients according to the diagnostic criteria used were also MS patients. There was no significant difference between the RA and control groups in MS frequency and insulin resistance according to two diagnostic criteria used. The DAS28, erythrocyte sedimentation speed (ESS) and serum uric acid levels in the RA patients with MS were significantly higher than those of the RA patients without MS. The prevalence of MS in patients with RA using methotrexate (MTX) was significantly lower than without RA. Other drugs used in treatment of RA had no effect on the prevalence of MS in patients with RA. Conclusion: Controlling inflammation and disease activity can reduce the MS frequency of RA patients and MTX treatment also may be a protective factor against MS.

Keywords: Metabolic syndrome, rheumatoid arthritis, insulin resistance, HOMA-IR, MTX

Introduction

Metabolic syndrome (MS), which is also called insulin resistance syndrome, syndrome X, poly-metabolic syndrome, mortal quartiles and civilisation syndrome, is a multi factorial endocrinopathy and it is framed by classical cardiovascular risk factors, including insulin resistance, hyperglycaemia, abdominal obesity, essential hypertension and dyslipidemia [1]. The frequency of MS continues to increase worldwide, and it has become the most important reason for the mortality and morbidity caused by cardiovascular diseases [2]. There are five different definitions for the diagnosis of MS, but the National Cholesterol Education Program (NCEP-ATPIII) and International Diabetes Federation (IDF) definitions is most often used two definitions [3].

Rheumatoid arthritis (RA) is a rheumatic diseases characterised by chronic inflammation of the synovial joints, progressive joint damage and deformities [4]. Its most apparent feature is the chronic inflammatory synovitis symmetrically covering the peripheral joints [5]. However, RA may also cause extra-articular involvements such as involvements of the cardiovascular system, haematological system, liver, respiratory system, eyes, muscles, kidneys and the neurological system [5]. RA assumed to be an independent risk factor for cardiovascular disease (CVD) and this increased risk of CVD in RA patients may be due to the presence of MS, because MS is also a syndrome generated by cardiovascular risk factors [3, 6, 7].

In the literature, previous studies suggest an association between the RA and MS. Most of

Table 1. The demographic, anthropometric and biological characteristics of women with RA and healthy controls

	RA group (n=100) Median (min-max)	Control group (n=100) Median (min-max)	P value
Age (year)	52 (24-65)	51 (27-65)	0.351
BMI (kg/m ²)	29.00 (17.60-51.30)	27.55 (18.80-50.40)	0.131
Waist contour (cm)	87.0 (61-138)	86.5 (63-115)	0.472
FBG (mg/dl)	93.0 (60.0-192.0)	92.0 (63.0-165.0)	0.293
HDL (mg/dl)	51 (13-577)	48 (7-92)	0.451
TG (mg/dl)	121 (45-270)	129 (51-560)	0.632
Uric acid (mg/dl)*	4.09±1.13	4.08±0.97	0.936
Insulin (mU/l)	9.06 (3.34-112.30)	8.20 (1.17-129.70)	0.103
Fibrinogen (mg/dl)	314.4 (11.9-5039.2)	352.4 (77.4-3009.0)	0.010
Hs CRP (mg/dl)	0.67 (0.02-12.90)	0.23 (0.02-7.26)	0.000
CRP (mg/dl)	0.44 (0.01-11.50)	0.15 (0.01-6.60)	0.000
ESS (mm/s)	33 (2-120)	20 (2-92)	0.000
HOMA-IR	2.11 (0.60-39.60)	1.74 (0.23-35.50)	0.132
MS presence (IDF 5)	33 (33%)	44 (44%)	0.110
MS presence (NCEPT)	27 (27%)	28 (28%)	0.874

BMI: Body mass index, FBG: fasting blood glucose, HDL: high density lipoprotein, TG: triglyceride, CRP: C-reactive protein, Hs CRP: High-sensitivity CRP, ESS: Erythrocyte sedimentation speed. *=mean±SD.

this studies have claimed that MS frequency in patients with RA varies according to the different definitions and is significantly higher in patients with RA than in healthy controls. However, this relationship is still controversial [3, 8].

In this study we investigated the MS frequency and insulin resistance in RA patients and the relation between insulin resistance and presence MS with inflammation symptoms, disease activity and drugs used in treating RA.

Patients and methods

Study design and subjects

Consecutive one hundred women patients who have diagnosed as RA according to the 1987 American College of Rheumatology (ACR) [9] criteria for RA, after applying to the Policlinics of Department of Physical Medicine and Rehabilitation of Faculty of Medicine, were included in the study. A control group was formed consisting of 100 women of the same age, who had applied to the same policlinics, and who lacked any inflammatory rheumatic disease. Patients with liver and kidney diseases, thyroid functional disorders, chronic lung and cardiovascular system disorders, hernias

that affected the waist contour, a history of chronic alcoholism and who were pregnant were excluded from the study. This study was approved by the Ethical Committee of the Medicine Faculty of University of Mediterranean, and all the patients were informed verbally and with a written form about the research. The approval of all patients was subsequently obtained.

Assessments

The age, height, weight, habits, accompanying diseases and medicines used by the patients within the study and control group were determined and recorded. The waist contours

(in the standing position and at the end of expiration, middle of the line between the edge of last rib and the middle of the anterior superior iliac spine) were measured. The drugs used (systemic corticosteroids, DMARD, biological agents) and the disease activation according to The Disease Activity Score including 28 joints (DAS28) with RA patients were recorded. The presence of MS was evaluated using the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) [10] and the International Diabetes Federation 2005 diagnosis criteria (IDF) [11] and Insulin resistance (IR) was estimated by the homeostasis model assessment for insulin resistance (HOMA-IR) in the RA and control groups.

Biochemical measurements

The fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein (HDL), uric acid, fibrinogen, C-reactive protein (CRP), high-sensitive CRP test (hs-CRP) and erythrocyte sedimentation rate levels of all the patients included in the study were determined at the Central Laboratory of Akdeniz University. For the analysis, 5 cc of venous blood was sampled from all the patients, and the blood samples were placed into tubes with gel separation and cen-

Metabolic syndrome in women with rheumatoid arthritis

Table 2. Characteristics of women with RA according to the presence or absence of MS according to the IDF 2005 criteria and NCEPT criteria

	According to the NCEPT criteria			According to the IDF criteria		
	MS (+) Median (min-max)	MS (-) Median (min-max)	P value	MS (+) Median (min-max)	MS (-) Median (min-max)	p value
Fibrinogen	311 (183-618)	316 (117-5039)	0.975	311 (183-618)	316 (117-5039)	0.959
Ürik asit*	5.02±0.91*	3.74±1.00*	0.000	4.88±0.96	3.70±1.00	0.000
ESS	37 (10-120)	31 (2-120)	0.635	37 (10-120)	31 (2-120)	0.041
CRP	0.47 (0.05-11.5)	0.44 (0.01-7.70)	0.695	0.45 (0.05-11.5)	0.5 (0.01-7.70)	0.898
HsCRP	0.68 (0.02-12.90)	0.65 (0.02-6.46)	0.614	0.50 (0.02-12.90)	0.68 (0.02-6.46)	0.869
DAS28*	4.22±1.31*	3.61±1.21*	0.034	4.18±1.28*	3.57±1.20*	0.022
HOMA-IR*	3.29 (1.15-39.60)	1.69 (0.6-18.40)	0.000	2.93 (1.15-39.60)	1.69 (0.6-18.40)	0.000
Patient number (100)	27	73		33	67	

*=mean±SD.

Table 3. The distribution of the presence of MS based on the IDF 2005 criteria and the NCEPT criteria according to the treatment agents used by RA patients

	Total drug users/ no drug users	According to the NCEPT criteria			According to the IDF criteria		
		MS incidence in drug users (%)	MS incidence in no drug users (%)	P value	MS incidence in drug users (%)	MS incidence in no drug users (%)	P value
Systemic corticosteroids	35/65	7 (20 %)	20 (30.8%)	0.247	8 (22.9%)	25 (38.5%)	0.113
MTX	46/54	8 (17.4%)	19 (35.2%)	0.046	11 (23.9%)	22 (40.7%)	0.074
Sulphasalazine	43/57	14 (32.6%)	13 (22.8%)	0.277	15 (34.9%)	18 (31.6%)	0.728
Hydroxy-chloroquine	26/74	9 (33.3%)	18 (24.7%)	0.449	23 (31.5%)	10 (37.0%)	0.602
Leflunomide	11/89	0 (0%)	27 (27.8%)	0.075*	32 (33.0%)	1 (33.3%)	1.000*
Anti-TNF	17/83	5 (29.4%)	22 (26.5%)	0.772*	6 (35.3%)	27 (32.5%)	0.825

*: The Fisher exact test was used. Anti-TNF (Infliximab 8 patients, etanercept 6 patients, adalimumab 3 patients).

Table 4. HOMA-IR values according to the treatment agents used by the RA patients

	Drug use Median (min-max)	No drug use Median (min-max)	P value
Systemic corticosteroids	2.30 (0.60-9.14)	2.05 (0.65-39.60)	0.940
MTX	2.21 (0.60-21.70)	1.94 (0.70-39.60)	0.871
Sulfasalazine	2.21 (1.10-4.07)	2.07 (0.60-39.60)	0.948
Hydroxychloroquine	2.40 (0.60-8.80)	1.98 (0.70-39.60)	0.704
Leflunomide	4.10 (3.20-8.80)	2.05 (0.60-39.60)	0.036
Anti-TNF	1.98 (0.70-39.60)	2.13 (0.60-22.0)	0.731

trifuged at 4000 rpm for 5 minutes. The serum layer remained on the top of the tubes, which were stored until analysis day at -80°C for the analyses. The routine biochemical measurements were done by using original commercially kits in the Cobas 8000 auto analyser (Roche Diagnostics, Mannheim, Germany). The serum insulin levels were measured using by electrochemiluminescence immunoassay (ECLIA) method in Elecsys 2010 immunoassay analyser (Roche Diagnostics, Mannheim, Germany). The results were expressed as $\mu\text{U/mL}$. The serum high-sensitive CRP analysis was performed using the nephelometric method in a BN II Nephelometer (Siemens Healthcare Diagnostics Inc., USA). The results were expressed as mg/dL . The plasma fibrinogen levels were determined using a coagulometric method in BC-XP coagulation analyser (Siemens Healthcare Diagnostics Inc. USA). The insulin resistance are defined with HOMA IR using [fasting glucose (mg/dL) x fasting insulin ($\mu\text{U/mL}$)/405] [12].

Statistical analyses

The statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, USA).

RA group and control group were compared in terms of demographic, clinical and laboratory parameters. The frequency of the patients with MS according to the IDF criteria and NCEP criteria was calculated in RA group and control group. The patients with drug use and without in RA group were compared in terms of HOMA-IR values and presence of MS according to the IDF criteria and NCEP criteria. Nominal variables were compared by Chi-Square tests. Numeric values were compared using Mann-Whitney test or Student t test. The Kolmogorov-Smirnov test and Shapiro-Wilk test was used to test the normal distribution of the data. As they

were normally distributed, the RA and control (healthy normal) groups were compared with Students t-test. Mann-Whitney U-test was used because the data was not compatible with normal distribution. A P value < 0.05 was considered statistically significant.

Results

Descriptive characteristics of

subjects

The demographic features, anthropometric features and laboratory parameters of the RA group and control group is given in **Table 1**.

There was no significant difference between the RA patients and the control group patients for age, body mass index (BMI), waist contour (**Table 1**).

Biological characteristics of subjects

The inflammation symptoms (fibrinogen, C-reactive protein (CRP), High-sensitivity CRP(Hs CRP), Erythrocyte sedimentation speed (ESS) were determined to be significantly greater in the RA patients than in the control group (**Table 1**).

There was no significant difference between the RA patients and the control group patients for fasting blood glucose (FBG), uric acid, high density lipoprotein (HDL), triglyceride (TG), serum insulin levels (**Table 1**). The serum insulin levels and the insulin resistance as calculated by HOMA-IR of the RA patients were higher than for the control group values, however the difference was not significant ($P=0.103$, $P=0.132$).

Fibrinogen, Hs CRP, CRP and ESS which are indicators of inflammation values were higher in the RA group than in the control group, as expected ($P=0.000$).

Prevalence of the metabolic syndrome according to definition used

It was determined that MS was present at 27 (27%) and 33 (33%) of the group with RA and at 28 (28%) and 44 (44%) of control group according to NCEP-ATPIII and IDF 5 criteria ($P=0.874$,

$P=0.110$). There was no significant difference between the RA group and the control group for the presence of MS, according to the both definitions (**Table 1**).

Associations of the metabolic syndrome in women with RA

The patients with RA with MS and those without were compared among themselves. Disease activity as evaluated using DAS-28, ESS, HOMA-IR and serum uric acid levels were significantly higher than patients without MS (**Table 2**). When the patients with and without MS in RA group were compared for the treatment agents used, it was determined that 11 patients using MTX and 35 patients not using the drug had MS. These differences were significant ($P=0.046$). A significant relation was not identified for the usage of other treatments.

MS and HOMA-IR's relationship with agents used in treating RA

RA patients using and not using drugs were compared among themselves to examine the effect of the agents used in treating RA on MS incidence (**Table 3**). There was no significant difference between drug users and nonusers for the presence of MS in terms of all therapeutic agents.

When the patients with RA were compared according to drugs used in terms of the HOMA-IR value, there was no significant difference between HOMA-IR values (**Table 4**).

Discussion

In this study where we aim to examine the frequency of metabolic syndrome (MS) and the effect of the inflammation symptoms and used treatment medications on presence MS in patients with rheumatoid arthritis (RA), MS frequency and insulin resistance of patients with RA were similar to the control group.

In the literature, there is different results on the prevalence of the MS in RA patients, which range between 18% and 44% [13, 14]. While some authors argue that the MS incidence in patients with RA is similar to the control group, the majority argue that it increases.

Karvounaris et al [15] found that the MS frequency (40%) defined according to the NCEP ATP III criteria in RA patients was similar to that

of the control group. In a study conducted in South Asia, Dodani et al [16] found that the frequency of metabolic syndrome was 13.3% according to WHO and 40% according to NCEP ATP III criteria. In the study conducted by Dao et al [17], they found that prevalence of MS in women with RA varied from 16.2% to 40.9% according to the definitions used for the diagnosis of MS and was higher than in healthy controls.

According to the result of meta-analysis carried out by Zhang et al [8], the prevalence of MS in patients with RA is higher than subjects without RA and of the population. The authors claimed that this result is due to the different geographic regions and different criteria used for MS diagnosis.

In our study, the frequency of MS in RA 27% and 33% were found according to the definitions criteria used. In accordance with the literature. However, In contrast to the literature, we found similar to the frequency of MS in RA group with the control group. Likewise, we found that the HOMA-IR values and the insulin levels of RA patients compared with the control group were higher but that the difference was not significant.

We believe that this different results may be caused from the deficiency of accepted criteria for the definition of metabolic syndrome, geographical differences, eating habits and genetic structures of societies and we are of the opinion that more studies cases covering more cases should be performed to obtain a better understanding of the subject.

In the last decade, most of the studies have investigated the relationship between MS with chronic inflammation and it has been proven that chronic inflammation plays a role in insulin resistance and is connected with MS pathogenesis [18, 19].

In some studies, there is a relation between insulin levels and CRP and that the CRP is alone a predictive value in the occurrence of the insulin resistance as much as the other factors in MS have been reported [20-22]. Laaksonen et al [23] reported, in a study examining the relation between MS and CRP levels, that when CRP levels were above 3 mg/l, there was a risk of MS. In contrast, we did not find an associa-

tion between CRP levels with MS. Rostom et al [24] also reported in their study that there was a positive relation between MS and ESS. We also determined that the ESS in RA group was higher than control group. This high ESR and CRP levels may be because MS an inflammatory disease.

In the literature, It has been reported that there is a positive relation between serum uric acid (UA) levels with insulin resistance and with MS due to insulin resistance and this relation is stronger in women than men [25-27]. In a study, the authors have suggested that serum UA levels may be a biomarker for the glucose metabolism because the serum uric acid levels increase as correlated with the increase of insulin levels [28].

In our study, we also determined that the uric acid levels in RA patients with MS were significantly higher than in patients without MS. Therefore, our evidence supports the view that there is a relation between serum uric acid levels and inflammatory circulation indicators.

Few articles in the literature have reported that the DAS-28 value of RA patients with MS was significantly higher than that of patients without MS [17, 29]. In our study, also, DAS-28 values of the RA patients with MS were significantly higher with without MS. The high disease activity may be increase MS incidence in patients with RA.

The discussions related to the effects of the drugs used by RA patients on the development of MS development maintain their validity. Some authors claim that there is a negative relation between MTX usage and MS and MTX usage could produce a decrease in the MS frequency in RA patients [30, 17].

We compared the treatment agents taken by RA patients according to the presence of MS. We determined that the frequency of MS was only significantly lower for the patients treated with MTX. In addition to the utilization rate of MTX in RA patients with ms found lower than without MS.

Our results also support the view that MTX has an anti-MS protective effect, though the effect mechanism remains to be elucidated.

However, there are also studies that do not support the relation between MTX and a reduction

in MS frequency [31]. The prospective studies with more number patients are needed in this regard.

In the literature, It has been reported also that there is a relationship between the prevalence of MS with tumour necrosis factor-alpha (TNF- α) and glucocorticoids use in RA [32-34].

In our study, no relation was found between the MS frequency or insulin resistance and the use of anti-TNF agents and corticosteroid. We believe that the differences between studies might result from patient selection and differences in the exclusion criteria, in addition to the doses and combinations of the drugs used.

The results of this study indicate that the MS frequency could potentially be decreased in RA patients through the MTX treatment and the control of the inflammation and illness activity.

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Disclosure of conflict of interest

None.

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