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Original Article

Internal Medicine Section

Metabolic Syndrome and its Components in Patients with Rheumatoid Arthritis, and their Association with Disease Activity and Duration

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is the most common inflammatory rheumatic disease and there are some concerns about the association of Metabolic Syndrome (MetS) with this disorder.

Aim: To evaluate the association between MetS and its components with RA disease activity and chronicity.

Materials and Methods: The present investigation was a cross-sectional study on 200 consecutive RA patients (30-60-year-old, all of them female) according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010. MetS was diagnosed according to the definition of 2005 National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP) III and International Diabetes Federation (IDF). Disease activity was measured by the 28 joint count of Disease Activity Score (DAS 28), and functional status was evaluated by Health Assessment Questionnaire (HAQ). Disease chronicity was defined as early or established RA, based on disease duration of less or more than six months. Statistical analysis was performed in SPSS version 19 by Student's t-test and chi-square test and ANOVA tests and results were considered significant at $p<0.05$.

Results: The mean age of RA patients was 50.29±6.2 years, and all were female. MetS according to NCEP/ATP III and IDF criteria was present in 109 (54.5%) and 112 (56%) patients. Hyperglycaemia was significantly higher in patients with established active RA ($p=0.003$), but other MetS components were not different between groups. MetS had more related active disease as assessed by DAS28 and greater disability as assessed by the HAQ ($p<0.001$).

Conclusion: The frequency of MetS was not significantly different in subgroups of RA according to disease activity or duration, but it was found in more than half of RA patients. Comparison of MetS components showed more frequency of hyperglycaemia in patients with active disease.

Keywords: Epidemiology, Frequency, Inflammatory arthritis, Obesity

INTRODUCTION

The RA is the most common inflammatory rheumatic disease with a prevalence of 0.5%-2% worldwide [1]. The prevalence of RA in Iran was estimated as 0.37% [2]. Patients with RA have a reduced life expectancy with a standardised mortality ratio of 2.0 [3]. Patients with rheumatoid arthritis die 1.5 to 1.6 times more than general population. The causes of overall death are similar to those in the general population, with an earlier incidence of cardiovascular disease [4]. Cardiovascular disease is responsible for up to 40%-50% of deaths in RA patients and it was shown that patients with RA have 1.63-fold {OR=1.63; CI 95% = (1.34-2)} higher risk of myocardial ischemia and the incidence of fatal myocardial infarction for 1000 patients with RA/year was 13.3 {CI 95%=(13-13.6)} [5,6]. Due to improved therapies and preventive measures, patients among autoimmune rheumatic diseases live longer, mortality and morbidity from atherosclerosis, particularly myocardial infarcts, are increasing.

There are several factors that predispose RA patients to cardiovascular risk, including prolonged exposure to chronic inflammation, decrease in serum levels of HDL-C, treatment-related factors such as chronic treatment with glucocorticoids, calcineurin inhibitors, and nonsteroidal anti-inflammatory drugs except Methotrexate (MTX) and perhaps higher prevalence of MetS in RA patients [7].

MetS is a cluster of traditional risk factors that include abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance [8]. The presence of MetS is a strong predictor for type-2 diabetes mellitus, stroke, and cardiovascular diseases [9,10]. Although there is some controversy on whether the MetS is a distinct entity and whether the predictive value of the MetS for cardiovascular risk is higher than that expected from individual risk factors alone [11]. The prevalence of the MetS, as defined by the NCEP/ATP III [12], has been reported to be significantly higher in patients with RA [13], as compared with the general population, being from 12.1% to 45.3%, according to the definition used [14].

Few studies were conducted on the prevalence of MeS among RA patients. These considered disease activity, duration and treatment aspects also [15-18].

It is important to do studies on MeS among RA, since the population across the globe show variation in the genetic make up [19,20]. Due to paucity of such information, this research was designed to study the frequency of MetS in RA patients by comparing subgroups with consideration of disease duration and activity.

MATERIALS AND METHODS

The present study was a cross-sectional study conducted from January 2016 to May 2017 involving 200 consecutive RA patients (30-60 years old), according to the ACR/EULAR 2010 [21], who attended the two referral centers, where the study was done. Protocol was approved by the Ethical and Research Committee of University of Medical Sciences IR.MAZUMS.IMAM.HOSPITAL.REC.95.2331.

In order to evaluate the role of disease activity (according to DAS28) [22] and chronicity (less or more than six months) [23], all of the patients were divided in a process of three steps: first based on RA disease activity in two groups with 100 patients in each group (active or inactive) according to DAS 28 score ≥3.2, second disease duration (early or established) in two groups also with 100 patients in each group; and third based on consideration of both activity and chronicity in four groups with 50 patients in each group: group 1, patients with early active RA; group 2, patients with early inactive

RA; group 3, patients with established active RA; group 4, patients with established inactive RA.

Patients with other rheumatologic disorders, including overlap syndrome, and patients using glucocorticoids for other diseases were excluded. The sample size was calculated according to the study of Grundy SM et al., 95% confidence level and power of 90%, 192 patients totally, considering the probability of loss of specimens, 200 patients were considered [12].

After obtaining consent, the patients were assessed to define their MetS profiles: type 2 diabetes with or without treatment; arterial blood pressure; lipid profile (HDL-c and TG); fasting blood glucose; and waist circumference.

Characteristics of RA patients including demographic and clinical features, disease duration, DAS 28, HAQ score [24] and RA treatment modalities were recorded. Current therapies including nonbiologic and biologic DMARDs (Disease Modifying Anti Rheumatic Drugs). Smoking status was categorised as current smoker or non-smoker.

MetS was assessed and recorded consecutively by rheumatologists according to the NCEP ATP III [25] IDF criteria [26]. MetS was considered to be present according to the NCEP criteria if patients met three or more of the following conditions: 1) waist circumference ≥88 cm in women; 2) currently using an antihypertensive drug or systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 3) HDL cholesterol <50 mg/dL in women; 4) TGs ≥150 mg/dL; and 5) fasting blood sugar level ≥100 mg/dL or past history of diabetes mellitus.

The IDF criteria were waist circumference ≥80 cm for women, in addition to two other defining criteria of MetS, including: 1) currently using an antihypertensive agent or systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 2) HDL cholesterol <50 mg/dL for women; 3) TGs ≥150 mg/dL; and 4) fasting blood glucose level ≥100 mg/dL or past history of diabetes mellitus.

Measurements

Waist circumference was measured at the end of a normal expiration, in a horizontal line around the abdomen at the surface of the iliac crest, parallel to the floor. Blood Pressure (BP) was measured twice at rest and the lowest measure was used for systolic and diastolic blood pressure. Blood was drawn from participants after an overnight fasting period, and glucose and lipid profiles (total cholesterol, HDL cholesterol, Low-Density Lipoprotein cholesterol (LDL-c) and Triglyceride (TGs) were measured enzymatically.

STATISTICAL ANALYSIS

The prevalence of MetS and its components, demographic and clinical features of patients were obtained. Then, the differences in clinical and demographic features between RA patients according to activity and duration of RA were analysed. Statistical analysis was performed by Student's t-test and chi square test to compare quantitative and qualitative variables, respectively, between the two groups, and analysis of variance (ANOVA) was used for comparing the four groups using SPSS version 19 (Chicago, USA). Results were considered significant at $p<0.05$.

RESULTS

Two hundred RA patients (all females) were included in the study. The means of age and disease duration were 50.29±6.2 years and 58.98±84.3, months, respectively. One hundred and forty-one patients (70.5%) were urban and family history of Myocardial Infarction (MI) or Cerebero-Vascular Accident (CVA) in first-degree relatives was positive in 74 patients (37%). History of primary hypothyroidism was detected in 8% of the patients. The means of ESR, VAS, and DAS 28 were 29.07±20.0 mm/h, 4.28±2.6, and 3.3±1.31, respectively. RF and Anti CCP were positive in 65.5% and 45.5% of patients, respectively. Patient treatment was as follows: prednisolone in 89%; hydrochloroquine in 57%; methotrexate in 61.5%; and sulfasalazine in 13%. None of the patients received biologic agents. One hundred and nine (54.5%) and 112 (56%) of all patients completed NCEP and IDF criteria for MetS. None of patients were smokers.

Differences Between Patients with RA According to Disease Activity or Chronicity

First, the patients were divided in two groups (each group, N=100) according to disease activity. The frequency of diabetes mellitus was higher in the patients with active disease (p=0.001). MetS (NCEP) was more frequent in patients with active disease (61% vs. 48%) too, although this did not make a significant difference.

Then in second stage, the patients were divided into two groups in considering disease duration. Patients with early disease had higher DAS 28 scores, but patients with established RA were older (p=0.008), more disabled (p=0.025), and consumed higher doses of prednisolone and methotrexate (p<0.05). There was no significant difference in MetS or its component with consideration of chronicity. Demographic and clinical data, and MetS and its components according to RA disease activity or chronicity are demonstrated in [Table/Fig-1].

	RA Activity			RA chronicity		
Characteristic	Active RA (n=100)	Inactive RA (N=100)	p-value	Early RA (N=100)	Established RA (N=100)	p-value
Age: Years±SD	50.63±6.2	49.94±6.3	0.434	49.12±5.8	51.45±6.4	0.008
Disease duration: Month±SD	62.14±91.8	55.81±76.4	0.597	3.47±1.7	114.48±89.7	0.000
BMI: Kg/m^2	31.07±5.6	30.09±6.0	0.236	30.56±6.2	30.60±5.4	0.963
RF: %	72%	59%	0.053	62%	69%	0.298
Anti CCP: %	50%	41%	0.201	43%	48%	0.478
ESR: Mean±SD	37.22±20.8	20.92±15.4	<0.001	31.68±18.7	26.46±21.0	0.065
VAS: Mean±SD	5.60±2.4	2.95±2.1	<0.001	4.11±2.5	4.44±2.7	0.379
DAS 28: Mean±SD	4.27±1.1	2.33±0.6	<0.001	3.54±1.5	3.06±1.1	0.010
HAQ: Mean±SD	1.04±0.7	0.41±0.45	<0.001	0.624±0.5	0.883±0.7	0.025
Dose of prednisolone: Mean±SD	6.31±3.8	5.57±3.1	0.131	5.27±3.5	6.61±3.2	0.006
Dose of hydroxychloroquine: Mean±SD	231.00±146.1	260.00±147.0	0.163	244.00±142.4	247.00±152.1	0.886
Dose of methotrexate: Mean±SD	6.52±5.54	5.70±5.3	0.285	4.62±5.1	7.60±5.3	0.000
FBS	103.46±14.6	99.85±15.4	0.005	98.41±26.9	97.91±26.0	0.894
LDL	104.46±31.2	108.47±27.4	0.335	182.20±44.0	203.60±83.2	0.051
HDL	50.80±15.6	53.25±14.2	0.247	49.98±14.7	54.07±14.9	0.053

Triglyceride	152.22±69.5	137.98±60.3	0.123	143.81±62.6	146.39±68.2	0.781
Glucose≥100 mg/dL or treatment N (%)	37 (37%)	17 (17%)	0.001	30 (30%)	24 (24%)	0.339
Hypertension: N (%)	62 (62%)	63 (63%)	0.884	63 (63%)	62 (62%)	0.884
Hyperlipidemia: N (%)	71 (71%)	60 (60%)	0.102	69 (69%)	62 (62%)	0.298
High waist circumference: (NCEP):N (%)	87 (87%)	80 (80%)	0.820	88 (88%)	79 (79%)	0.086
High waist circumference: (IDF): N (%)	92 (92%)	94 (94%)	0.579	95 (95%)	91 (91%)	0.268
Metabolic syndrome: (NCEP): N (%)	61 (61%)	48 (48%)	0.065	57 (57%)	52 (52%)	0.478
Metabolic syndrome: (IDF): N (%)	60 (60%)	52 (52%)	0.254	57 (57%)	55 (55%)	0.776

[Table/Fig-1]: Clinical and laboratory characteristics in RA patients with considering of disease activity or chronicity.
BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; FBS: Fasting blood sugar; NCEP: National cholesterol educational program; IDF: International diabetes federation. Dose of prednisolone: The mean of current dose of prednisolone in patients

Differences Between Patients with RA According to Both Disease Activity and Duration

In the third stage, the patients were divided according to diseases activity and duration into four groups: 50 patients with early active RA (group 1); 50 patients with early inactive RA (group 2); 50 patients with established active RA (group 3); and 50 patients with established inactive RA (group 4). Patients in established inactive RA were significantly older (p=0.003). Seropositivity for RF or Anti CCP was similar in the four groups. Higher doses of prednisolone and MTX were consumed in patients with established active RA (p<0.001). There were not any significant differences in frequency of hypertension or hyperlipidemia, but diabetes mellitus was more frequent in patients with established active RA (p<0.009). MetS and its components according to both RA disease activity and chronicity is demonstrated in [Table/Fig-2].

		Active RA		Inactive RA		
Characteristic		Duration <6 months (N=50)	Duration >6 months (N=50)	Duration <6 months (N=50)	Duration >6 months (N=50)	p-value
Metabolic syndrome	According to NCEP N (%)	32 (64%)	29 (58%)	20 (40%)	28 (56%)	0.096
	According to IDF N (%)	32 (64%)	28 (56%)	23 (46%)	29 (58%)	0.333
High waist circumference	According to NCEP N (%)	43 (86%)	44 (88%)	36 (72%)	44 (88%)	0.090
	According to IDF N (%)	46 (92%)	46 (92%)	45 (90%)	49 (98%)	0.429
Low HDL or treatment N (%)		30 (60%)	26 (52%)	24 (48%)	21 (42%)	0.331
Triglyceride >150 mg/dL or hyperTG treatment N (%)		24 (48%)	24 (48%)	21 (42%)	22 (44%)	0.909
Glucose ≥100 mg/dL or under Diabetes treatment N (%)		18 (36%)	19 (38%)	6 (12%)	11 (22%)	0.009
Hypertension or under Anti-hypertensive treatment N (%)		32 (64%)	30 (60%)	31 (62%)	32 (64%)	0.972

[Table/Fig-2]: Metabolic syndrome components according to NCEP or IDF definition in 4 groups.
LDL: Low density lipoprotein; HDL: High density lipoprotein; NCEP: National Cholesterol Education Program; IDF:International Diabetes Federation

Differences Between Patients with RA According to Metabolic Syndrome

The patients were compared according to existence of MetS for their characteristics. The mean of age in patients with MetS was 52.06±5.9 in comparison to 48.15±5.9 in patients without MetS (p<0.001). ESR, HAQ score and DAS28 were significantly different in patients with MetS (p<0.05) [Table/Fig-3].

Characteristic	Metabolic syndrome according to NCEP		
	Yes (n=109)	No (n=91)	p-value
Age, mean±SD (years)	52.06±5.9	48.15±5.9	<0.001
Disease duration, mean±SD (months)	63.41±86.6	53.66±81.6	0.416
Prednisone, current daily dose, mean±SD (mg/d)	5.78±3.5	6.12±3.3	0.491
Hydroxychloroquine, current daily dose, mean±SD (mg/d)	248.62±146.3	241.76±148.4	0.743
Methotrexate, current weekly dose, mean±SD (mg/d)	6.10±5.5	6.12±5.4	0.974
ESR (mm/h)	34.16±22.2	22.98±15.0	<0.001
HAQ score, mean±SD	0.890±0.75	0.535±0.475	<0.001
DAS28	3.53±1.4	3.04±1.1	0.007
VAS	4.47±2.7	4.04±2.6	0.260

[Table/Fig-3]: Differences between patients with RA according metabolic syndrome.
ESR: Erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; DAS 28: Disease activity score 28; VAS: Visual analogue scale

DISCUSSION

This study investigated the frequency of MetS in RA female patients and compared this with controls, while considering its relationship to disease activity and chronicity.

The frequency of MetS in the RA patients was approximately 55%, which was not significantly different in separate groups of RA according to disease activity or chronicity, but higher glucose levels (or history of diabetes mellitus) were more frequent in patients with active disease. Older age, more disability and higher doses of prednisolone and methotrexate were more frequent in patients with established disease.

The higher frequencies of MetS in patients with RA (14% to 56%) [27-29] may be due to the differences in the definition of MetS, along with differences in ethnicity, geographic area, study design, and study population. The prevalence of MetS in South Asia and Iran, according to ATPII, were estimated at 26.1% and 29%, respectively [20,30]. MetS in RA patients in Iran was estimated at 45.2%, according to NCEP-ATP III criteria [31]. In the present study, it was detected higher frequency of MetS in patients; this may due to selection of different populations.

As mentioned in [Table/Fig-4], the NCEP and IDF criteria were chosen, because these criteria were used in many previous studies on MetS in RA patients, they are more careful in their definition of parameters such as hyperglycaemia, and they are made with consideration of treatment of hypertension, hyperlipidemia and hyperglycaemia in their classification [13,16-19, 27].

NCEP-ATP III and IDF criteria were similar in detection of MetS in our patients, as was found in previous studies [17,19,32].

There are some studies on the association between RA disease activity and frequency of MetS [13,19,33] but, to the best of our knowledge, there exists no study about RA disease chronicity and MetS. In the present study, we tried to evaluate frequency of MetS and its components in RA patients with consideration of both features.

Fasting blood glucose ≥100 mg/dL was significant in RA patients with active disease, with no significant difference in doses of steroids or other treatments. It may be due to an important role of disease activity in metabolic disturbances. These associations were also

Author	RA patients (n) female (%)	The mean of age (years)	MetS in RA	Diagnostic criteria	Clinical points
Slimani S et al., [16]	249, 85.5%	50.1±14.5	13.9%	NCEP	ESR levels correlate with the presence of MetS.
Abourazzak FE et al., [17]	179, 88%	49±11.5	29%	NCEP, IDF	Methotrexate therapy was identified as an independent factor associated with a reduced risk of having MetS.
Lee S-G et al., [27]	84, 100%	50.6±11.3	19%	NCEP	RA patients with MetS had higher blood pressure and HDL.
Gomes KWP et al., [18]	338	-	51.3%	NCEP	RA in patients was found to be associated with MetS and disease activity.
Chung CP et al., [13]	154, (64-73%)*	51-59**	42% (long-standing RA) vs 30% (early RA)	NCEP, WHO	Patients with the WHO-defined MetS had an increased risk of having higher coronary-artery calcification Scores.
Sahebari M et al., [19]	120, 88.3%	45.5±13	45.2%	NCEP, IDF	RA was not found to increase the risk of MetS and disease activity was not influenced by the presence of MetS.
Present study	200, 100%	50.29±6.2	54.5%	NCEP, IDF	Higher disease activity and disability were seen in patients with MetS.

[Table/Fig-4]: Studies on the frequency of metabolic syndrome in patients with rheumatoid arthritis [13,16-19,27].
MetS: Metabolic syndrome; NCEP: National cholesterol education program; HDL: High density lipoprotein; IDF: International diabetes federation.
*% of female in each group
**The mean of age in each group

previously reported [14,33-35]. The results of this study suggest an important role of the inflammatory burden in the evolution of metabolic disturbances in patients with RA.

Patients with established disease were older, more disabled, with higher doses of prednisolone and methotrexate. Higher levels of LDL and lower levels of HDL were more prevalent in established and early RA, although it was not significantly different. Pro-inflammatory cytokines like TNF alpha attenuate action of insulin and cause insulin resistance, are associated with obesity and endothelial dysfunction. This may be how chronic inflammation contribute to MeS [13,17,36,37].

On the other hand, higher ESR, HAQ score and DAS 28 were more prevalent in patients with MetS. This may be due to a higher age of patients with Mets. A higher HAQ score is likely to be associated with MetS in RA. More the disability less active would be the lifestyle, contributing to obesity and alterations in the lipid profile [14,38,39]. There is some controversy regarding RA treatment and MetS evolution. It is suggested that methotrexate use, is associated with significantly reduced chance of having MetS in RA [14]. The results of the present study do not show these relationships, which may be due to the kind of patient selection or to sample size. But it should be considered that it may be due to the role of other factors such as age, genetic and lifestyle and inflammatory factors.

Limitation(s)

Given the varying length of illness and the potential effect of medication on the components of MetS, it may be considered as a confounding factor.

CONCLUSION(S)

The frequency of MetS and especially high blood glucose in RA patients is high overall and is related more to disease activity than chronicity. Higher disease activity and disability are more frequent in patients with MetS. These may work like a vicious cycle. So, it is suggested that RA patients should be evaluated for MetS.

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