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Original Research Article

Prevalence and predictors of metabolic syndrome in rheumatoid arthritis

Muzafar Naik*, Tariq Bhat, Ummer Jalalie, Mohd Tahir Ganayie, Mir Waseem, Arif Bhat

Department of of Medicine, SKIMS Medical College and Hospital, Srinagar, J&K, India

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***Correspondence:**
Dr. Muzafar Naik,
E-mail: muzafarnaik@gmail.com

ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity and mortality secondary to accelerated atherosclerosis. There is a strong association of metabolic syndrome (MS) with atherosclerosis. The objective of this study was to assess the prevalence of MS in RA and to identify the predictors of MS in RA.
Methods: The study included 100 patients of RA (83 females,17 males; median age 42.5 (17) years diagnosed according to 2010 American College of Rheumatology-European League Against Rheumatism classification criteria who were on treatment and 110 age and sex-matched apparently healthy controls (26 males, 84 females; median age 45 (20) years). The frequency of MS was assessed using joint consensus 2009 criteria. Patients were also assessed in terms of disease activity, using disease activity score 28 CRP. Logistic regression was used to identify predictors of MS in RA.
Results: Metabolic syndrome was found in 45% of RA group and 22.7% of control group according to joint consensus 2009 criteria ($p<0.005$). RA group was significantly more likely to have low high-density lipoprotein (65%), elevated blood pressure (60%) levels and abnormal sugar (28%). In RA group, CRP (odds ratio: 1.101, confidence interval: 1.032-1.174 ($p=0.004$) {adjusted for age, DAS 28 score and Anti-CCP} remained independent predictor for presence of MS in RA.
Conclusions: The frequency of MS was higher in RA group compared to control group. High CRP remained independent predictor associated with presence of MS. There was no association of high disease activity with MS in our RA patients. These findings suggest that the treating physician should screen RA patients early for presence of MS.

Keywords: Metabolic syndrome, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown etiology. RA needs to be diagnosed early and early treatment is of paramount importance or else it will lead to increased disability, morbidity and mortality.[1,2] RA patients have almost a four-fold increase in cardiovascular events and most importantly this increased risk ratio is independent of traditional risk factors for cardiovascular diseases (CVDs). CVDs are the most common cause of death, with approximately 40% of deaths in RA patients attributed to CVD.[3] The reason for increased risk of CVDs in RA is due to the fact that the patients of RA are prone to accelerated atherosclerosis and its complications. The reasons for the increased prevalence

of atherosclerotic risk factors and MS in patients with rheumatic diseases are not totally clear. One of the explanation for such association is that MS and chronic inflammatory states are closely linked. There is increased prevalence of MS in patients of chronic inflammatory diseases and conversely the inflammatory biomarkers are elevated in patients of MS.[4] The European League Against Rheumatism (EULAR) guidelines recommend that cardiovascular risk screening and management to be urgently done in patients with RA.[5]

MS describes a constellation of cardiovascular risk factors such as atherogenic dyslipidemia (increased free fatty acids, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol levels, and increased low-density lipoprotein (LDL) and apolipoprotein B levels), central obesity, insulin resistance, disturbed glucose metabolism (T2DM, impaired glucose tolerance, and impaired fasting hyperglycemia), and hypertension.[6] There are many criteria for defining MS but three most widely used definitions are those from the World Health Organization (WHO), the National Cholesterol Education Program (NCEP), and the International Diabetes Federation (IDF) (Table 1).[7-9] The disturbance of glucose/insulin metabolism must be present in WHO criteria and thus MS and diabetes are considered to be intersecting diagnostic categories. However, in the NCEP criteria, MS is a precursor to, but does not include, T2 diabetes mellitus. The WHO definition is better suited as a research tool, whereas the NCEP definition is simpler and therefore more useful for clinical practice. The most recently proposed criteria released by the IDF and Joint consensus 2009 (JC) include gender- and ethnic group-specific increased waist circumference as a major criterion, underlining the crucial importance of central obesity in MS.

METHODS

This study was conducted in the department of General Medicine, Sher-i-Kashmir Institute of Medical Sciences Medical college and hospital Srinagar, prospectively over a period of two years from April 2014 to March 2016.

Inclusion criteria

One hundred rheumatoid arthritis patients already diagnosed by American college of rheumatology (ACR) and/ newly diagnosed cases of rheumatoid arthritis according to the EULAR (European league against rheumatism) 2010 criteria served as cases.

One hundred and ten age-, sex-, and race-matched apparently healthy volunteers' women and men from urban and rural residences of the Kashmir valley served as the control group in the present study. The healthy subjects were represented by the family members of patients, or families of medical or paramedical staff of the hospital.

Exclusion criteria

Patients with other inflammatory diseases, malignancies, diseases of the central nervous system, chronic kidney disease, chronic liver disease besides RA, were excluded from the study.

Informed consent was obtained from all subjects. The study was approved by the Institutional ethical committee of SKIMS MCH Srinagar.

Clinical assessment

Patients diagnosed as having RA as per the EULAR 2010 criteria were recorded for demographic characteristics (like age, sex and residence), disease specific variables (Duration of RA, number of tender joints, number of swollen joints, duration of treatment, nature and dose of treatment i.e. disease modifying anti rheumatic drugs [DMARDs], steroids, non-steroidal anti-inflammatory drugs [NSAIDs]), co-morbid conditions.

Disease activity score

The disease activity score was assessed by disease activity score 28 (DAS 28 CRP) by counting number of swollen joints and tender joints in 28 joint sites, the patients' global assessment of health measured on a visual analogic scale (VAS, range 0-100 mm), and C reactive protein (CRP). A score of DAS28 CRP between 2. 6-3.2 indicates low disease activity, > 3.2- ≤ 5.1 moderate and > 5.1 high disease activity.[10]

Body mass index

Body mass index (BMI) was calculated from weight/ height 2 (kg/m^2). BMI values < 18.5 kg/m^2 are considered underweight, between 18.5-24.9 as normal, 25-29.9 as overweight and values greater than 30 indicate obesity.[11] Waist circumference (WC) was measured to the nearest 0.5 cm midway between the iliac crest and the lower rib margin. The cut off value for waist circumference was taken as 90 centimeters (cms) and 80 cms for ethnic specific south Asian men and women according to the Joint Consensus criteria 2009 and consensus statement on metabolic syndrome from India.[12,13]

Biochemical measures

Biological tests were performed from venous blood samples obtained the morning after an overnight fast. Plasma fasting glucose (FG) levels were measured using the glucose oxidase method. Plasma sugar values of ≥ 100 mg/dl were considered as criteria for metabolic syndrome according to the JC 2009 criteria. C-reactive protein (CRP) estimation was done by utilizing particle enhanced turbidimetric assay and levels greater than 5 mg/L were considered positive. ESR, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were determined by standard

laboratory methods. Concentrations of serum triglycerides ≥ 150 mg/dl in both men and women, HDL ≤ 40 mg/dl in men and HDL ≤ 50 mg/dl in women were considered as lipid criteria for Metabolic syndrome.

Blood pressure measurement

Blood pressure (BP) measurement were done by trained personnel using a mercury sphygmomanometer and a stethoscope. Measurements were taken from the left upper arm after subjects have been sitting for a period of more than five minutes in accordance with the recommendation of American heart association. Another measurement was taken in a similar way after a rest interval of five minutes. The mean value of the two readings were recorded to the nearest 2.00 mm Hg. BP of ≥ 130/85 were taken as criteria for metabolic syndrome according to the Joint consensus criteria 2009.[12]

Metabolic syndrome criteria

There are many criteria's that have attempted to define metabolic syndrome but as such no consensus has been reached in giving a universal criterion for diagnosis of metabolic syndrome. In this study, we used the JC 2009 criteria (Table 1) for studying the prevalence of metabolic syndrome and analysis of components of metabolic syndrome in RA patients as it is almost same as the NCEP 2004 criteria which is the most widely used criteria of metabolic syndrome.

Statistical analysis

Statistical data analysis was done utilizing SPSS 20. Normality of test was done by Shapiro Wilk test. Mean with standard deviation was calculated for waist circumference as it was normally distributed. Median with Interquartile range (IQR) was calculated for age, duration of disease, duration of treatment, type of treatment, EULAR, DAS 28, ESR, CRP, RF, Anti CCP, waist circumference, systolic and diastolic BP, sugar fasting, HDL and TG as they were not normally distributed. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. Continuous categorical data between the groups were compared using sample t-test.

P<0.05 was considered statistically significant. Multivariate logistic regression models were constructed and odds ratio and 95% confidence interval were calculated to investigate the independent predictors of individual RA-related characteristics and Metabolic syndrome in patients with RA.

RESULTS

A total of one hundred patients diagnosed as having Rheumatoid arthritis were included in this study. One hundred and ten age, sex and race matched healthy relatives of RA patients served as controls. Baseline characteristics of both RA and control groups are shown in (Table 2). Most of the patients in the both the group were females, 83 out of 100 (83%) in the RA group and 84 out of 110 (87.5%) in the control group and the difference was statistically insignificant (p=0.234). Systolic and diastolic blood pressure and were significantly higher and HDL was lower in RA group than in control group, a difference that was statistically significant (<0.005). There was no difference noted between the two groups with respect to age, sex distribution, weight, BMI, waist circumference, sugar and triglycerides level.

Table 1: Joint consensus criteria for metabolic syndrome.

	JC 2009
Number of criteria	**Three or more of**
Obesity	Population- and country-specific definitions. Waist circumference ≥90 cms in men, ≥ 80 cms in women
Blood pressure mm hg	≥ 130/85 or treatment
Dyslipidemia: HDL	HDL-C ≤ 40 mg/dL in men, ≤ 50 mg/dL in women, or treatment
Triglycerides	≥150 mg/dL or treatment
Glucose intolerance or fasting plasma glucose	≥100 mg/dL or type 2 diabetes mellitus

HDL: High density lipoprotein, JC: Joint consensus

Forty-five patients out of 100 (45%) in the RA group and 25 patients out of 110 (22.7%) in the control group were found to have metabolic syndrome utilizing JC 2009 criteria and the difference was statistically significant (p<.000). The most common abnormality noted in the RA group was elevated waist circumference (66%), low HDL (65%), elevated blood pressure (60%), elevated triglycerides (41%) and abnormal sugars (28%). However low HDL, elevated blood pressure and abnormal sugars were the most significant difference between the RA and the control group (p<0.05) (Table 3).

The demographic and biochemical parameters of RA patients with MS and without MS is shown in Table 4. The median(IQR) for disease duration of RA was 5 (8) years. Thirty-three patients were in remission (2 with metabolic syndrome and 31 without metabolic syndrome). Twenty-six had mild disease (17 with MS and 9 without MS). Thirty-four had moderate disease activity (21 with MS and 13 without MS) and 7 had severe disease (5 with MS and 2 without MS). The post hoc analysis of a 2 x 4 contingency table showed prevalence of metabolic syndrome was significantly less in patients who were in remission and mild disease activity (p<0.00).

Sixty patients were on DMARD`s (27 had MS and 33 without MS), 32 were on DMARD plus steroids (16 had MS and 16 without MS), 7 patients were on DMARD plus NSAID (1 had MS and 6 without MS) and one patient was not on any treatment (Had MS). Post hoc analysis of a 2 x 4 contingency table showed no significant correlation between nature of treatment in RA and MS (p=0.239).

Table 2: Demographic and biochemical parameters of rheumatoid arthritis patients and controls.

	RA group		Control group		P value
	Median	IQR	Median	IQR	
Age	42.5	17	45	20	0.598
WC (centimeters)	86	(14)	88	(8)	0.829
SBP (mm Hg)	130	(10)	120	(20)	0.000
DBP (mm Hg)	84	(10)	80	(10)	0.000
HDL (mg/dL)	43	(12)	48	(14)	0.000
TG (mg/dL)	138	(58)	138	(64)	0.521
BSF (mg/dL)	92	(17)	90	(14)	0.191

RA: Rheumatoid arthritis, IQR: Interquartile range, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: High density lipoprotein, TG: triglycerides, BSF: Blood sugar fasting.

Table 3: Components of metabolic syndrome in rheumatoid arthritis and controls.

	RA group		Control group		P value
	(Count)	(Percentage)	(Count)	(Percentage)	
Elevated WC (cms)	66	66	76	69.1%	0.633
Elevated BP (mm Hg)	60	60	20	18.2	0.000
Low HDL (mg/dL)	65	65	45	40.9	0.000
Elevated TG (mg/dL)	41	41	39	35.5	0.409
Abnormal sugar (mg/dL)	28	28	14	12.7	0.006

RA: Rheumatoid arthritis, WC: Weight circumference, BP: Blood pressure, HDL: high density lipoprotein, TG: triglycerides

Table 4: Correlation of demographic and biochemical parameters of rheumatoid arthritis with metabolic syndrome.

	RA with MS	RA without MS	P Value
Age [years] (median (IQR)	48 (15)	38 (20)	0.001
Disease duration [years] (Median (IQR))	5 (8)	3 (7)	0.214
Treatment duration [years] (median (IQR))	4 (7)	2 (5)	0.438
DAS 28 CRP score (median (IQR))	3 (1)	2 (1)	0.001
ESR [mm Hg] (median (IQR))	28 (11)	23 (18)	0.077
CRP [mg/dL] (median (IQR))	17 (12)	5 (8)	0.000
RF IU/mL (median (IQR))	26 (22)	26 (20)	0.988
Anti CCP [U/mL] (median (IQR))	72 (88)	30 (186)	0.067
WC [cms] (mean±SD)	90.36±7.94	82.95±9.91	0.000
SBP [mm Hg] (median (IQR))	140 (10)	130 (8)	0.000
DBP [mm Hg] (median (IQR))	90 (10)	80 (8)	0.000
BSF [mg/dL] (median (IQR))	100 (15)	88 (13)	0.000
HDL [mg/dL] (median (IQR))	40 (11)	46 (11)	0.006
TG [mg/dL] (median (IQR))	164 (56)	121 (41)	0.000
Metabolic score (median (IQR))	3 (1)	1 (1)	0.000

RA: Rheumatoid arthritis, MS: Metabolic syndrome, IQE: interquartile range, DAS: disease activity score, CRP: C-reactive protein, RF: Rheumatoid factor, Anti CCP: Anti citrullinated cyclic polypeptide, WC: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BSF: Blood sugar fasting, HDL: High density lipoprotein, TG: Triglycerides

In univariate analysis, females with RA having MS were older, had higher CRP, and higher DAS28 score (p<0.05) (Table 4). In multivariate analysis, there was a significant association with CRP (odds ratio: 1.101, confidence

interval: 1.032-1.174 (p=0.004) {adjusted for age and DAS 28 CRP score} with prevalence of MS in RA (Table 5).

Table 5: Predictors of metabolic syndrome by multivariate analysis.

	Multivariate analysis		
	OR	**CI 95%**	**P**
Age	1.040	0.998-1.085	0.064
DAS 28 CRP	1.517	0.902-2.550	0.116
CRP [mg/dL]	1.101	1.032-1.174	0.004

OR: Odds ratio, CI: Confidence interval, DAS 28 CRP: Disease activity score 28, CRP: C reactive protein

DISCUSSION

Premature atherosclerosis which leads to adverse cardiovascular events in rheumatoid arthritis has a strong association with metabolic syndrome which has made the researchers to explore the prevalence of MS in RA patients in the last decade.[14] Interestingly the prevalence of MS in RA has varied in different studies from higher than controls to comparable to controls.[15-19] The reason may be the different criteria used to define MS in different studies, however the results have still varied in different studies using the same criteria, which can be explained by the diversity of the study population characteristics, disease presentation and treatment regimen.

The prevalence of MS in RA patients in present study was 45% and 22.7% in controls utilizing the JC 2009 criteria which is in accordance to most of studies that showed increased prevalence of MS in RA ranging from 17% in Mexican, 19% in South African, 19.9% in Dutch, 38.3% in English, to 41.5% in Swedish, 42% in American, and 44% in Greek patients. In India, also higher prevalence of MS has been reported from Silchar (39.28% in RA and 20 % in controls) and Chandigarh (31.57%in RA and 14.9%).[19,21-27]

When exploring the clinical and biochemical parameters in present study, RA patients had lower HDL, higher systolic BP and higher diastolic BP compared with healthy controls, a difference that was statistically significant. These results are in accordance with observations made by Rostom et al and Pandey et al.[16,26] We did not find any significant correlation of body mass index (BMI), waist circumference and sugar between two groups. Similar observations with regards to BMI with MS has been reported by others.[16] However, in these studies increased waist circumference was significantly higher in the RA group.[16.26] The reason behind study patients of RA having lower waist circumference and are lower BMI may be due to the cultural characteristics restricting high caloric diet in RA, however this needs to be substantiated in further studies.

Study also observed that among the five components of metabolic syndrome between RA and controls the most significant were low HDL, elevated BP and impaired fasting sugars. These are in accordance with previous studies but we didn`t find any correlation of remaining two components of metabolic syndrome (abnormal waist circumference and elevated TG`s) with increased prevalence of MS in RA as in these studies.[16,25] The negative correlation of abnormal waist circumference with MS in our RA patients as discussed earlier can be linked to proposed hypothesis of poor nutrition. However, TG`s not having significant correlation with MS in RA patients in present study can be better explained by the fact that the lipid profile of RA patients has been evaluated in several studies that have reported dyslipidemia as well as normal pattern in RA patients when compared to controls.[28-30]

In this study, we found that CRP was the only single factor that was associated independently with MS in RA patients. This association has been previously reported.[26] We didn`t find any significant association between age, duration of disease, disease activity score with MS in RA as has been reported by previous studies.[15,19,26] However, disease activity score has not been associated with MS in RA in many studies.[16,27] This can be explained by the fact that DAS, CRP is a single point measure of disease activity and it can vary with time depending upon the dose of quick relief medications like NSAID`s and steroids.[28]

Contrary to other studies, we did not find any association between ESR and MS in present study.[30] Rheumatoid factor seropositivity was also not associated with prevalence of MS in RA in present study. The same has been reported earlier by Rostom et al and Karvounaris et al.[16,19] Also, we didn`t find any association of nature of treatment with MS in RA as has been reported by earlier studies.[16] This study had a limitation which included the assessment of disease severity by DAS 28 CRP as minor addition of quick relief medications to the stable regimen can alter DAS 28 CRP erroneously. And lastly present study was devoid of any cause effect inferences on relationship of changes in CRP with MS in RA over a period of time.

CONCLUSION

The prevalence of MS in RA is quite high as compared to general population. CRP remains the independent predictor of MS in RA. We suggest that treating physicians in addition to targeting DAS 28 score should be aware of screening the cornerstone of cardiovascular morbidity and mortality i.e. Metabolic syndrome in RA patients. Study also recommend that further studies are needed to conduct any cause-effect inferences of CRP association between MS and RA.

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