

Frequency of metabolic syndrome in Pakistani cohort of patients with rheumatoid arthritis

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Abstract

Objective: To determine the frequency of metabolic syndrome in rheumatoid arthritis patients and its association with different factors i.e., age, gender, disease duration and treatment.

Method: The cross-sectional study was conducted at Shaikh Zayed Hospital, Lahore, from July 2014 to June 2015, and comprised consecutive rheumatoid arthritis of either gender between the ages of 20 and 60 years. Frequency of metabolic syndrome was assessed by the National Education Cholesterol Programme 2004. SPSS 22 was used to compare the frequency of the syndrome among different treatment, age and gender groups.

Results: Of the 384 patients, 287(74.7%) were females, and 97(25.3%) were males with an overall mean age of 43.8 ± 10.6 years (range: 20-60 years). Overall, 173(45.0%) patients were in >45 years of age, and metabolic syndrome was found in 120 (31.3%). A negative association with metabolic syndrome was found when compared with treatment group of methotrexate alone and methotrexate in combination ($p > 0.05$).

Conclusion: Metabolic syndrome, an important risk factor for cardiovascular diseases, was more prevalent in rheumatoid arthritis patients.

Keywords: Rheumatoid arthritis, Metabolic syndrome, Cardiovascular, Disease modifying anti-rheumatic drugs, Methotrexate. (JPMA 66: 671; 2016)

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown aetiology, characterised by systemic symptoms that particularly involve the joints and may lead to joint deformities during the course of the disease.¹ It is affecting from 0.5% to 1% of the general population worldwide. Although primarily considered as disease of joints, it can cause variety of extra-articular manifestations, like ischaemic heart diseases, congestive heart failure, renal failure, respiratory failure, stroke, and occupational disability.²

Epidemiologic data suggests that RA is an independent risk factor for cardiovascular disease (CVD).³ The development of accelerated atherosclerosis and increased risk of CVD in patients with RA may be influenced by the occurrence of metabolic syndrome (MetS).⁴

Chronic inflammation seen in patients with RA is one of the important factors which link it to both MetS and atherosclerosis. Pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF α), interleukin-6 (IL6) seen in patients with RA contribute to insulin resistance which is the basic metabolic disorder seen in MetS. Insulin

resistance leads to other metabolic disturbances like hyperglycaemia, and dyslipidaemia which independently contribute to atherosclerosis and cardiovascular risk. Pro-inflammatory cytokines are also independently involved in the pathogenesis of atherosclerosis through the production of acute-phase reactant C-reactive protein (CRP). Thus, multiple mechanisms, inflammation, insulin resistance and dyslipidaemia increase the burden of cardiovascular risk in these patients.⁵

Therefore, the European League Against Rheumatism (EULAR) guidelines recommend that cardiovascular risk screening and management to be urgently done in patients with RA.⁶

The MetS consists of a constellation of abnormalities that leads to increased risk of CVD and diabetes mellitus (DM). The major features of the MetS include central obesity, hypertriglyceridaemia, low high-density lipoprotein cholesterol (HDL-C), hyperglycaemia, and hypertension (HTN). Most commonly, five definitions for the MetS are used worldwide, but the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF) definitions are commonly used.⁷ These definitions are having many similarities, but they differ in some of their components and cut-offs.

The interest in identifying MetS in patients with RA has emerged recently, justified by the need to better

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understand the determinant factors of CVD in these patients. In 2002, a study assessing the hypothesis that the increased prevalence of interrelated CV risk factors determines the presence of MetS in RA had patients with osteoarthritis (OA) as the control group. The authors reported that more patients with RA had insulin resistance (IR) and low HDL levels compared to patients with OA.⁸

Frequency of MetS in RA varies according to the criteria used for the assessment. In this regard, using the World Health Organisation (WHO) criteria in 154 patients with RA and 85 controls, Chung et al.⁹ observed the presence of MetS in 42% RA patients with long-standing disease, in 31% RA patients with early arthritis, and in 11% controls. In the same study, when NCEP criteria were used, the prevalence of MetS was 30% in RA patients with longstanding disease, 22% in patients with RA with early arthritis and 10% in controls, respectively. Previously, different studies showed varying frequencies of MetS in RA patients, from 14% to 56%.¹⁰ This variation can be explained by the differences in the definition of MetS, ethnicity, geographic area, study design, and study population. However, a lot of studies done by different researchers showed higher prevalence of MetS in RA patients compared to general population,^{11,12} but still others have not.^{13,14} One study¹⁵ showed that the prevalence of MetS according to the IDF and modified ATP III criteria was 34.8% and 49%, respectively. Higher prevalence of MetS was identified in Pakistani cohorts irrespective of the definition used.¹⁵ When effect of management of RA was assessed on MetS, A study¹⁶ reported that methotrexate (MTX) is independently associated with reduced risk of MetS compared to other disease-modifying anti-rheumatic drugs (DMARDs) or gluco-corticoids, making MTX a good firstline DMARD in RA patients at high risk of developing MetS.

The current study was planned to assess the frequency of MetS in RA patients and to assess any possible effect between anti-rheumatic drugs and MetS, and any effect of age or disease duration on MetS.

Patient and Methods

The cross sectional study was carried out at the Rheumatology Division of Shaikh Zayed Medical Complex, Lahore, from July 2014 to June 2015, and comprised consecutive adult patients with baseline RA fulfilling the 2010 criteria of American College of Rheumatology¹⁷ who were selected using non-probability convenient sampling after getting approval from the institutional review board.

Patients included were aged between 20 and 60 years of

either gender who were diagnosed RA cases. Patients with seronegative arthritis, spondylo-arthritis or diagnosed cases of OA by rheumatologists, were excluded and so were those with other autoimmune diseases like systemic lupus erythematosus, systemic sclerosis, and diagnosed cases of infective or metabolic causes of arthritis.

The sample size was calculated by using 95% confidence level, 5% margin of error, with expected frequency of MetS 50% (conservative approach) among RA patients. Informed consent was obtained from all the subjects. Demographic data and history including age, gender, hospital registration number, and disease duration and treatment history was noted. Waist circumference (WC) was measured with an inelastic tape, placed directly on the skin, perpendicularly to the long axis of the body while the subject stood balanced on both feet, with both arms hanging freely. The measurement was taken at the end of expiration, midway between the lower rib margin and the highest point of iliac crest on the mid axillary line and was measured in centimetres (cm). WC of more than 102cm for men and more than 88cm for female was taken as abnormal.

Blood pressure (BP) was measured with mercury sphygmomanometer in the sitting position after five minutes of rest. HTN was defined as BP ≥ 130 mmHg for systolic or ≥ 85 mmHg diastolic or on the basis of HTN treatment.

Biological tests were performed after 12 hours' overnight fasting. With aseptic technique 10ml venous blood samples were obtained in the morning. Samples were collected in BD (Becton, Dickinson and Company) vacutainer serum bottles (red-topped). All samples were analysed on Cobas C III (Roche) through photo spectrometry method. Serum Triglycerides (TG) 150 mg/dl or more, serum HDL-C less than 40 mg/dl for males and less 50 mg/dl for females, or any treatment history on this count was considered abnormal. Plasma fasting glucose (FG) levels were checked through glucometer, and 100mg/dl or more of FG or any treatment history on this count was considered abnormal. MetS was assessed according to the existing definition NCEP ATP III 2004.¹⁸

Data was analysed using SPSS 22. Normality of data was assessed by Shapiro Wilk Test. All numeric variables were not normally distributed, therefore median with inter-quartile range (IQR) for age, disease duration, WC, systolic and diastolic BP, FG, TG and HDL-C levels were calculated. Data for gender, obesity, high BP, high FG, TG levels, and low HDL-C levels were expressed as frequencies and percentages. MetS was described in terms of frequency

and percentage as per the given criteria. Chi square test was used to compare the frequency of MetS among different treatment, age and gender groups. $P \leq 0.05$ was considered statistically significant.

Results

Of the 384 patients studied, 287(74.7%) were females, and 97(25.3%) were males, with an overall mean age of 43.8 ± 10.6 years (range: 20-60 years).

Table-1: Descriptive statistics for age, disease duration, BMI, waist circumference, systolic and diastolic blood pressure, fasting blood glucose level, triglycerides and HDL level.

	Median (IQR)	Minimum	Maximum
Age	45 (35.2 - 52)	20	60
Disease Duration	3 (2 - 7)	0.5	30
Waist Circumference	90 (80 - 99)	69	137
Systolic blood pressure	120 (110 - 120)	100	160
Diastolic blood pressure	80 (70 - 80)	60	110
Fasting Blood Glucose Level	90(85 - 98.75)	66	190
Triglycerides	145 (130 - 186)	63	468
HDL Level	52 (40 - 58)	20	120

BMI: Body mass index

HDL: High-density lipoprotein

IQR: Inter-quartile range.

Table-2: Distribution of rheumatoid arthritis (RA) patients according to age, disease duration and treatments.

Variable	Group	Frequency	Percentage*
Age	≤ 30 years	56	14.6
	30 - 45 years	155	40.4
	> 45 years	173	45.0
Disease duration	≤ 3 years	194	50.5
	> 3 years	190	49.5
Treatments	No treatment	40	10.4
	HCQ	39	10.2
	MTX	68	17.7
	MTX, HCQ, SSZ	136	35.4
	Other groups	101	26.3

*n=384

HCQ: Hydroxychloroquine

MTX: Methotrexate

SSZ: Sulfasalazine.

Median disease duration was 3 (IQR: 2-7) years. WC was 90(IQR: 80-99) cm, systolic BP 120 (IQR: 110-120) mmhg, diastolic BP 80(IQR: 70 - 80) mmhg, FG 90(IQR: 85 - 98.75) mg/dl, fasting TG 145(IQR: 130-186) mg/dl, and HDL-C was 52(IQR: 40 - 58) mg/dl (Table-1).

In terms of age, 173(45.0%) patients were >45 years, while 155(40.4%) in the 30-45 years age group, and only 56(14.6%) females were <30 years (Table-2).

Further, 120 (31.3%) RA patients had MetS, and the most common abnormalities in RA patients were related to WC and increased TG levels followed by low HDL-C level, high BP and abnormal FG (Figure). Overall, 344(89.6%) patients were treated with DMARDs. Among them 39(10.2%) were treated with hydroxychloroquine (HCQ), 68(17.7%) were treated with MTX alone, 136(35.4%) were treated with MTX and combination drugs i.e. HCQ and sulfasalazine (SSZ), while 101(26.3%) were on other groups, like leflunomide alone or in combination with HCQ or

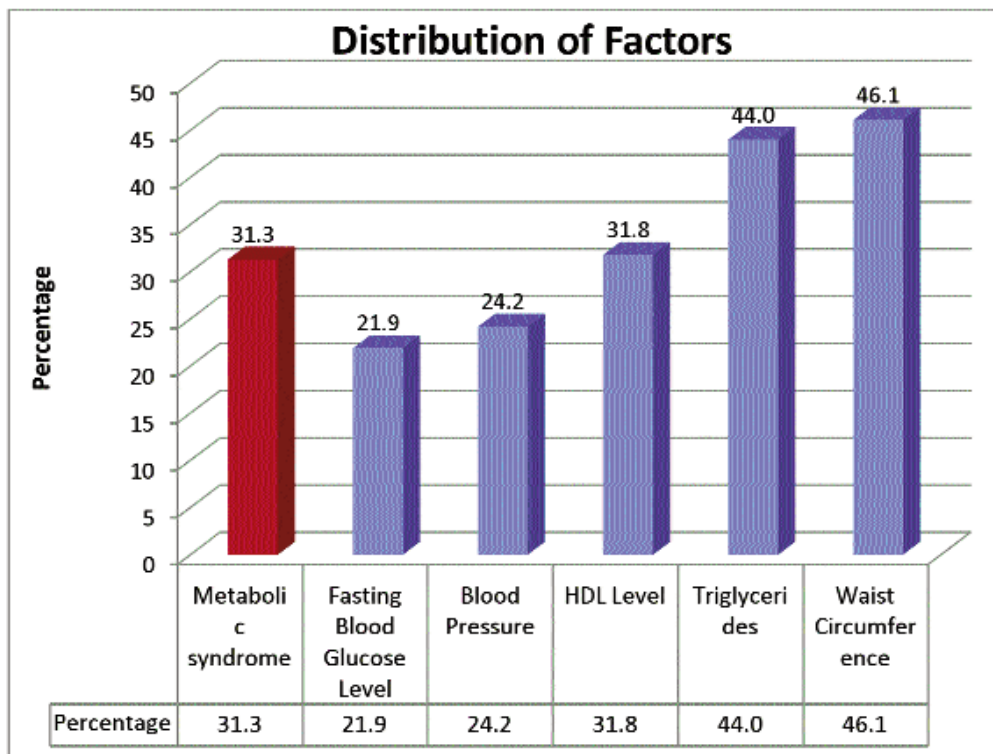


Figure: Pattern of abnormalities in rheumatoid arthritis (RA) patients.

Table-3: Group comparisons for Metabolic Syndrome.

Variable	Group	Metabolic Syndrome		p-value
		Yes	No	
Gender	Male	18	79	0.002
	Female	102	185	
Age	≤ 30 years	9	47	< 0.001
	30 - 45 years	37	118	
	> 45 years	74	99	
Disease duration	≤ 3 years	57	137	0.425
	> 3 years	63	127	
Treatments	No treatment	28	12	< 0.001
	HCQ	21	18	
	MTX	12	56	
	MTX, HCQ, SSZ	19	117	
	Other groups	40	61	

HCQ: Hydroxychloroquine

MTX: Methotrexate

SSZ: Sulfasalazine.

SSZ, and cyclosporine-A.

MetS was associated with the age, gender and treatments whereas there was no significant difference in MetS among disease's duration. MetS was common in female gender and age group of > 45years. It was also found that the Proportion of MetS was less in MTX and MTX +HCQ+SSZ compared to other treatment groups (Table-3).

Discussion

Currently it is evident that both MetS and RA are associated with increased CV morbidity and mortality, which has made the researchers evaluate the prevalence of MetS in RA patients in the last decade.¹⁰ Atherosclerosis, which is a major adverse CV event that often results in death, has strong association with MetS, and it usually occurs prematurely in RA.¹⁹ In literature, it is shown that different studies have demonstrated higher prevalence of MetS in RA patients,^{11,12} whereas other studies showed that MetS prevalence is comparable to the controls.^{13,14,20}

Our results showed that the frequency of MetS was about 31.3%, which is comparable to most studies that showed higher prevalence of MetS in RA. In 2008, study⁹ first demonstrated the increased prevalence of MetS in patients with RA compared to matched controls, with higher prevalence in longstanding disease. Another study¹¹ showed that the prevalence of MetS was about 40.9% in RA females according to NCEP ATP III criteria which was significantly higher compared to the controls. Another²¹ found that the frequency of MetS was 13.3% according to WHO criteria and 40%, according to NCEP ATP III criteria. Yet another study²² showed that the

prevalence of MetS in patients with RA was higher compared to those without RA. It claimed that the result was due to the different geographical regions and different criteria used for MetS diagnosis.

Another study showed that MetS was significantly more prevalent in American patients with longstanding RA (42% - WHO and NCEP/ATPIII criteria) as well as in early RA patients (31% and 30% - WHO and NCEPIII criteria respectively) than in controls (11% and 22% - WHO and NCEP/ATPIII criteria, respectively).⁹ While comparing frequency of MetS in RA with other studies mentioned earlier, it showed that such diversity was because of differences in baseline characteristics and disease characteristics.¹²

A study²⁰ found that the frequency of MetS was 40% when defined according to the NCEP ATP III criteria in RA patients, but it was similar to that of the control group, which showed no significant difference between cases and controls regarding presence of MetS in RA patients. Another study²³ also found no significant difference of frequency of MetS in RA patients when compared with controls according to the definitions of WHO and NCEP ATP III. Similarly, a group²⁴ studied the presence of MetS and CVD risk factors in RA patients in 2010 and found no significant prevalence of MetS between the cases and the controls.

When we assessed the individual components of MetS, obesity was found 46.1%, high TG level 44%, abnormal HDL-C level in 31.8%, abnormal BP in 24.2%, and impaired FG in 21.9%. One study²⁵ found increased prevalence of WC, elevated BP, and increased FG in a series of patients. Another study¹¹ stressed that hypertension ($p < 0.001$), HDL-C ($p < 0.001$) and abdominal obesity ($p = 0.019$) were more common in RA patients. Both dyslipidaemia and IR are considered due to inflammatory process in RA, so patients having active disease have low HDL-C, and high TG levels, which are components of MetS and important risk factors of CVD.²⁶ Obesity is the most important component of the MetS and is generally a prerequisite risk factor of MetS. It has been shown²⁴ that in RA patients, development of MetS is due to specific altered fat content. In our study, WC was more prevalent compared to other components of MetS.

Using MTX alone or in combination with other DMARDs had significantly less prevalence of MetS ($p < 0.001$) compared to other DMARDs like HCQ alone or SSZ or leflunomide, either alone or in combination. MTX and concurrent use of folic acid have their effects through its anti-inflammatory properties which enhances glucose metabolism through insulin and modification of lipid

metabolism.²⁷ One study²³ also showed that there is negative relation with MTX use and MetS, which supported the view that MTX has anti-MetS protective effect in RA patients, although the exact mechanism was not elucidated. Another study¹⁶ showed that unlike other DMARDs or gluco-corticoids, MTX therapy was independently associated with a less risk of MetS. In our study, most of the patients were using cortico-steroids either as rescue pulsed steroid therapy during acute flare of RA or as adjunct therapy with other DMARDs at some part of treatment, so it was difficult to assess cortico-steroid association with MetS, but some other studies proved that there is no significant association of cortico-steroids with MetS.¹⁶ In our study disease duration had no significant association ($p=0.42$) with MetS when the cases were evaluated on the basis of disease duration of more than 3 years and 3 years or less, but one study¹¹ showed that MetS had significant association with RA of disease duration less than 3 years.

In terms of limitations, the cross sectional design of the study limited its ability to describe comparison with controls. Similarly, results cannot be generalised because of its small sample size. Also, logistic regression analyses were not performed to distinguish covariates associated with the determinant - MetS. Doses of gluco-corticoids were not ascertained in the study because gluco-corticoids were not a primary variable of our study, and the patients were not using gluco-corticoids on a regular basis as primary DMARD so anti-inflammatory effect and doses were not ascertained.

Besides, comparison with other inflammatory and non-inflammatory (OA) rheumatic disorders was not performed. Finally, this is the first study in Pakistan to have assessed frequency of MetS in RA, so it was not possible to compare our results to the local population.

Conclusion

The frequency of MetS in RA in Pakistan was comparable to the rest of the world. A lot of factors like ethnicity, socioeconomic status, and study population characteristics have affected the frequency of MetS in RA patients in different studies. More precise work is needed to define the exact relationship between MetS and RA. However, after a brief review, one can conclude that CV risks are higher in RA patients which are due to MetS. So assessing MetS in RA patients and appropriate treatment where necessary, could lead to better control of overall inflammatory process and the CVD.

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