

# Metabolic syndrome and atherogenic indices in rheumatoid arthritis and their relationship with disease activity: A hospital-based study from northeast India

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## ABSTRACT

**Background and Objective:** Metabolic syndrome (MetS), a constellation of metabolic abnormalities including hypertension, obesity, glucose intolerance, and dyslipidemia, is highly prevalent in patients with rheumatoid arthritis (RA). Our aim was to assess the magnitude of MetS and its determinants in RA patients and to evaluate different atherogenic indices that are reflective of the risk for future cardiovascular disease. **Patients and Methods:** The study was conducted on 104 RA patients and 103 age- and sex-matched healthy controls. The frequency of MetS was assessed using the guidelines recommended for Asian Indians. **Results:** A total of 104 RA patients participated with majority being females (85.6%), with a mean age of  $43.82 \pm 13.32$  years. The frequency of MetS in patients with RA (36.5%) was significantly higher than in controls (15.5%). The atherogenic indices were found to be significantly higher in RA patients than controls ( $P < 0.01$ ). On logistic regression, disease activity score (DAS28) scale for 28 joints and disease duration remained significant independent predictors of the presence of MetS in RA patients ( $P < 0.01$  and  $0.05$ , respectively). **Conclusions:** RA is a kind of chronic disease of long course, and MetS and atherogenic indices are often concomitant in these patients. The study showed that the frequency of MetS was higher in patients with RA than in controls, and that DAS28 and disease duration remained significant independent predictors of the presence of MetS in RA patients.

**Key words:** atherogenic indices, cardiovascular disease, disease activity, metabolic syndrome, rheumatoid arthritis

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease that primarily affects small and medium-sized joints with widespread systemic inflammation. The worldwide prevalence of RA is around 0.5–1% with considerable regional variation.<sup>[1]</sup> Despite treatment advances, RA patients continue to have comparatively higher mortality and morbidity rates than the general population, most of which are related to adverse cardiovascular (CV) events.<sup>[2–4]</sup> The widespread systemic inflammation that is

characteristic of RA accelerates atherogenic changes and probably plays the pivotal role in predisposing RA patients to increased risk of CV events.<sup>[5,6]</sup>

Epidemiological studies have indicated that RA may be an independent risk factor for CV events and this risk is influenced by the presence of metabolic syndrome (MetS).<sup>[7,8]</sup> MetS refers to a cluster of conditions, namely hypertension, central obesity, glucose intolerance, and dyslipidemia, which augment the risk of CV diseases (CVDs) and type 2 diabetes mellitus (T2DM).<sup>[9]</sup> MetS

is known to be associated with twofold increase in the risk of CVD and 1.5-fold increase in the risk of all-cause mortality.<sup>[10]</sup> Previous reports have suggested that MetS may be quite prevalent in RA patients, particularly the ones with long-standing disease.<sup>[11]</sup> The European League Against Rheumatism (EULAR) guidelines also recommend screening for CV risk and urgent needful management in patients with RA.

Northeast India has a sizeable prevalence of rheumatic diseases. Previous studies have documented distinct genetic susceptibility loci and suggest the presence of a considerable burden of clinical sequelae such as renal dysfunction and osteoporosis in RA patients from northeast India.<sup>[12–14]</sup> However, there is a paucity of studies investigating CVD risk or the magnitude of MetS and its determinants in RA patients from the region. With this background, the current study aimed to study the magnitude of MetS and its determinants in RA patients from northeast India. In addition, atherogenic indices that are reflective of the risk for future CVD were investigated.

## PATIENTS AND METHODS

### Ethics

The study complied with the tenets of the Helsinki Declaration and it was approved by the Institutional Ethics Committee (P2/17/02). Voluntary informed written consent was procured from all the participants of the study.

### Patients

The present hospital-based study included 104 RA patients (case group) diagnosed according to the 2010 revised American College of Rheumatology criteria and recruited consecutively between October 2017 and September 2018 in the General Medicine out-patient department.<sup>[15]</sup> The exclusion criteria were patients aged below 18 years, concurrent presence of other autoimmune disorders, malignancy, chronic kidney disease, HIV infection, and chronic liver disease. Demographic profile of the patients, including disease-specific variables (disease duration, tender joint count, swollen joint count, drug history, and compliance), comorbidities, family history of RA and CVDs, was recorded. The disease severity was evaluated using the disease activity score (DAS28) scale for 28 joints.<sup>[16]</sup>

### Methods

Assuming the prevalence of MetS in RA in India to be 30%, with 95% confidence limits and an absolute precision of 10%, at least 81 patients with RA would be needed to estimate the prevalence of MetS (using the formula of sample size =  $4pq/d^2$ , where  $p$  = prevalence,  $q$  =  $(1 - p)$ , and  $d$  = allowable error). On this basis, 104 RA

patients were enrolled. Further, 103 age- and sex-matched apparently healthy volunteers from the northeastern region (represented by attendants of patients or families of medical or paramedical staff of the hospital) were also enrolled (control group) for comparison.

Body mass index (BMI) and waist circumference (WC) were measured following the standard protocol as specified by the World Health Organization (WHO). Blood pressure (BP) was measured by a mercury sphygmomanometer in the sitting position after 5 minutes of rest. Sera separated from fasting venous blood specimens were used for the estimation of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting blood sugar (FBS), and uric acid using commercially available photometric kits (Beckman Coulter, USA) in AU2700 plus biochemistry autoanalyzer (Beckman Coulter). The quality of the test results was verified by validating the assays using commercially available third-party control materials (Randox, UK and Christian Medical College, Vellore, India). Seropositivity for rheumatoid factor (RF) was assessed by latex agglutination method. In addition, atherogenic indices of the participants were determined as follows: atherogenic coefficient =  $(TC - HDL-c)/HDL-c$ , atherogenic index of plasma (AIP) =  $\log_{10}(TG/HDL-c)$ , Castelli's Risk Index-I (CRI-I) =  $TC/HDL-c$ , Castelli's Risk Index-II (CRI-II) =  $LDL-c/HDL-c$ , and non-HDL-c =  $TC - HDL-c$ .

Identification of MetS in cases and controls was carried out using the guidelines recommended for Asian Indians, namely the presence of three or more of the following five components: low serum HDL-c levels ( $<50$  mg/dL in females,  $<40$  mg/dL in males) or drug treatment for low HDL-c; increased TG ( $\geq 150$  mg/dL) or drug treatment for increased TG; increased WC ( $\geq 80$  cm for women,  $\geq 90$  cm for men); raised BP (systolic  $\geq 130$  mmHg and/or diastolic  $\geq 85$  mmHg) or antihypertensive treatment in a patient with hypertension (HTN); and increased FBS ( $\geq 100$  mg/dL) or drug treatment for hyperglycemia.<sup>[17]</sup>

DAS28 was used for evaluating the number of swollen joints, number of tender joints, the patient's global assessment of health measured on a visual analog scale (VAS; range 0–100 mm), and erythrocyte sedimentation rate (ESR). A DAS28 of 2.6–3.2 indicates low disease activity,  $>3.2$ – $\leq 5.1$  moderate disease activity, and  $>5.1$  indicates high disease activity.<sup>[16]</sup>

### Statistical analysis

Statistical analyses were performed at a 2-sided alpha set at 0.05 using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and OpenEpi v3.0.1 (<http://www.OpenEpi.com>). The continuous variables were summarized as mean with

standard deviation, while the categorical variables were expressed as count and percentage with 95% confidence intervals (CIs). Comparison of characteristics between the case group and the control group were performed by unpaired *t*-test and Fisher's exact test, as applicable. Besides, subgroup analysis was carried out between the cases with MetS and cases without MetS to identify the variables that could possibly determine the occurrence of MetS in RA. The variables found to differ significantly were taken up for further analysis by binary logistic regression and the resultant odds ratio (OR) and 95% CI were tabulated.

## RESULTS

The present study included 104 RA patients with age- and sex-matched controls. A summary of the sociodemographic and clinical characteristics of the patients is presented in Table 1. The mean age was  $43.82 \pm 13.32$  years. Most of the patients were female (89 [85.6%]), with a male to female ratio of 1:6. The mean duration of disease was  $3.33 \pm 1.99$  years, and the mean DAS28 was  $4.49 \pm 1.44$ . One-fourth of RA patients in the study were treatment naïve, while the rest were on treatment. As compared to age- and sex-matched control group, patients with RA had significantly higher diastolic BP ( $77.8 \pm 8.3$  *vs.*  $75.1 \pm 7.3$  mmHg,  $P < 0.05$ ), BMI ( $22.4 \pm 3.1$  *vs.*  $21.5 \pm 1.4$ ,  $P < 0.01$ ), and WC ( $82.1 \pm 9.2$  *vs.*  $79.2 \pm 6.9$  cm,  $P < 0.05$ ). Regarding laboratory parameters, as compared to controls, RA cases had significantly higher levels of TG ( $144.7 \pm 51.3$  *vs.*  $129.3 \pm 42.4$  mg/dL,  $P < 0.05$ ) and lower HDL-c levels ( $40.7 \pm 10.4$  *vs.*  $50.8 \pm 8.1$  mg/dL,  $P < 0.01$ ). The lipid profiles of all patients showed that, as compared to controls, cases had higher atherogenic risk, as measured by indirect indices (CRI-I:  $4.22 \pm 1.18$  *vs.*  $3.42 \pm 0.76$ ,  $P < 0.01$ ; CRI-II:  $2.84 \pm 2.77$  *vs.*  $2.11 \pm 0.49$ ,  $P < 0.01$ ; AIP:  $0.54 \pm 0.21$  *vs.*  $0.39 \pm 0.18$ ,  $P < 0.01$ ; atherogenic coefficient:  $3.22 \pm 1.18$  *vs.*  $2.43 \pm 0.76$ ,  $P < 0.01$ ) (Table 1). The prevalence of MetS was significantly higher in cases than in controls ([36.5%, 95% CI: 27.9–46.1] *vs.* [15.5%, 95% CI: 9.8–23.8],  $P < 0.05$ ) (Table 2).

Among the cases of RA, 38 (36.53%) patients had MetS. Within cases, as compared to those without MetS, patients of RA with MetS had significantly higher disease duration ( $4.15 \pm 1.89$  *vs.*  $2.86 \pm 1.9$  years,  $P < 0.01$ ) and DAS28 ( $5.29 \pm 1.33$  *vs.*  $4.03 \pm 1.30$ ,  $P < 0.01$ ). There were no significant differences in other parameters like ESR, RA factor positivity, uric acid, and treatment status between those with MetS and RA compared to those with RA without MetS (Table 3). Following from the above, on regression analysis, disease duration (OR = 1.30, 95% CI: 1.01–1.69,  $P < 0.05$ ) and DAS28 (OR = 1.94, 95% CI: 1.35–2.79,  $P < 0.01$ ) were significant predictors of MetS in patients with RA (Table 4).

## DISCUSSION

MetS describes a cluster of major risk factors for CVDs, such as atherogenic dyslipidemia, obesity, HTN, and T2DM. These associated risk factors have been previously called syndrome X or the insulin resistance syndrome. The present study showed that RA was associated with increased frequency of MetS compared to healthy controls. Higher DAS28 and longer disease duration were independent predictors of MetS in patients with RA. However, the risk of developing MetS in RA patients did not appear to be influenced by RF positivity or the type of medication used for RA.

The reported frequency of MetS in RA patients varies markedly (14%–63%) among different studies.<sup>[18–25]</sup> This may be due to use of dissimilar criteria for diagnosing MetS and differences in the baseline parameters and genetic susceptibility among the studied populations. Nonetheless, the association between RA and MetS has been substantiated by systematic reviews and meta-analysis.<sup>[11]</sup> The strength of the association also appears to be influenced by the duration of RA (early *vs.* long-standing) in the study subjects. da Cunha *et al.* reported that the overall risk of developing MetS was significantly higher in patients with long-standing RA than in healthy controls (OR = 1.87).<sup>[26]</sup>

Since the individual traditional lipid parameters analyzed in the present study did not show significant differences between the patient and control groups except for low HDL and elevated TG levels, we further evaluated the lipid pattern using different atherogenic indices. Atherogenic indices are an indicator of serum lipids and lipoproteins to induce atherosclerotic changes. Unlike the traditional serum lipid measures, their use is not limited to predicting the risk for those at lower and higher end of the CVD risk spectrum. Since they are composite measures that take into account different lipid fractions in the serum/plasma, they reflect the two-way cholesterol traffic (inward and outward) through the arterial intima and are robust in predicting CVD risk.<sup>[27]</sup> The present study found that atherogenic indices differed significantly between the RA patients and healthy controls, with the former displaying a remarkably higher propensity for developing atherosclerotic changes, and hence, future CVD events.

On analyzing the specific components of MetS, low HDL was observed to be markedly reduced in RA patients as compared to that in healthy controls. Low HDL is a consistent finding of active RA. The probable theoretical explanations are: reduced synthesis as the amino acids required for the manufacture of enzymes important for lipid metabolism are pre-oriented by the liver for the

**Table 1: Comparison of baseline characteristics between cases and controls**

Variables	Case group (n = 104)	Control group (n = 103)	P-value
Age (years)	43.8 ± 13.3	40.8 ± 12.4	0.09
Sex			
Female	89 (85.6)	86 (83.5)	0.71
Disease duration (years)	3.33 ± 1.99	-	-
DAS	4.49 ± 1.44	-	-
Systolic BP (mmHg)	120.3 ± 13.2	119.3 ± 10.9	0.54
Diastolic BP (mmHg)	77.8 ± 8.3	75.1 ± 7.3	<0.05
BMI (kg/m <sup>2</sup> )	22.4 ± 3.1	21.5 ± 1.4	<0.01
WC (cm)	82.1 ± 9.2	79.2 ± 6.9	<0.05
Laboratory findings			
FBS (mg/dL)	92.9 ± 14.6	91.3 ± 8.9	0.35
Total cholesterol (mg/dL)	163.8 ± 35.3	171.1 ± 33.1	0.13
TG (mg/dL)	144.7 ± 51.3	129.3 ± 42.4	<0.05
HDL-c (mg/dL)	40.7 ± 10.4	50.8 ± 8.1	<0.01
LDL-c (mg/dL)	108.7 ± 82.5	105.2 ± 21.4	0.68
Non-HDL-c (mg/dL)	123.1 ± 33.1	120.4 ± 31.8	0.54
Castelli's Risk Index-I	4.22 ± 1.18	3.42 ± 0.76	<0.01
Castelli's Risk Index-II	2.84 ± 2.77	2.11 ± 0.49	<0.01
Atherogenic index of plasma	0.54 ± 0.21	0.39 ± 0.18	<0.01
Atherogenic coefficient	3.22 ± 1.18	2.43 ± 0.76	<0.01
TG:HDL-c ratio	3.83 ± 1.75	2.64 ± 1.06	<0.01
Uric acid (mg/dL)	4.91 ± 1.69	-	-
ESR (mm after 1 h)	58.3 ± 26.8	-	-
RF positivity	87 (83.7)	-	-
Treatment status			
Regular treatment	30 (28.8)	-	-
Irregular treatment	48 (46.2)	-	-
Treatment naïve	26 (25)	-	-
Drugs received at the time of study			
Methotrexate	63 (60.6)	-	-
Hydroxychloroquine	53 (51)	-	-
Sulfasalazine	43 (41.3)	-	-
Steroids	64 (61.5)	-	-
NSAIDs	21 (20.2)	-	-
Anti-TNF $\alpha$	1 (0.9)	-	-
Leflunomide	2 (1.9)	-	-

Values expressed as mean  $\pm$  SD or n (%).

Anti-TNF $\alpha$ : anti-tumor necrosis factor alpha; BMI: body mass index; BP: blood pressure; DAS: disease activity score; ESR: erythrocyte sedimentation rate; FBS: fasting blood sugar; HDL-c: high density lipoprotein-cholesterol; LDL-c: low density lipoprotein-cholesterol; NSAID: nonsteroidal anti-inflammatory drug; RF: rheumatoid factor; TG: triglycerides WC: waist circumference.

**Table 2: Distribution of metabolic syndrome and its components in the case group and the control group**

Metabolic abnormalities	Case group (N = 104)		Control group (N = 103)	
	n	% (95% CI)	n	% (95% CI)
Type of metabolic abnormalities				
Increased WC	39	37.5 (28.8–47.1)	21	20.4 (13.7–29.2)
Elevated triglycerides	47	45.2 (36.0–54.8)	31	30.1 (22.1–39.5)
Reduced HDL-c	79	75.9 (66.9–83.2)	46	44.7 (35.4–54.3)
Raised blood pressure	29	27.9 (20.2–37.2)	19	18.5 (12.1–27.0)
Elevated fasting blood sugar	19	18.3 (12.0–26.8)	17	16.5 (10.6–24.9)
Number of metabolic abnormalities				
None	10	9.6 (5.3–16.8)	31	30.1 (22.1–39.5)
One	37	35.6 (27.0–45.1)	39	37.9 (29.1–47.5)
Two	19	18.3 (12.0–26.8)	17	16.5 (10.6–24.9)
Three	19	18.3 (12.0–26.8)	5	4.9 (2.1–10.9)
Four	14	13.5 (8.2–21.3)	9	8.7 (4.7–15.8)
Five	5	4.8 (2.1–10.8)	2	1.9 (0.05–6.8)
At least one abnormality	94	90.4 (83.2–94.7)	72	69.9 (60.5–77.9)
Metabolic syndrome ( $\geq 3$ abnormalities)	38	36.5 (27.9–46.1)	16	15.5 (9.8–23.8)

CI: confidence interval; HDL-c: high density lipoprotein-cholesterol; WC: waist circumference.

**Table 3: Comparison of characteristics between RA patients with and without metabolic syndrome**

Variables	RA patients with metabolic syndrome (n = 38)	RA patients without metabolic syndrome (n = 66)	P-value
Age (years)	48.1 $\pm$ 10.8	41.36 $\pm$ 14.1	<0.05
Sex, female	34 (89.5)	55 (83.3)	0.56
Disease duration (years)	4.15 $\pm$ 1.89	2.86 $\pm$ 1.9	<0.01
DAS	5.29 $\pm$ 1.33	4.03 $\pm$ 1.30	<0.01
Newly diagnosed RA cases	29 (76.3)	49 (74.2)	1.0
Treatment status			
Regular treatment	7 (18.4)	23 (34.8)	0.11
Irregular treatment	22 (57.9)	26 (39.4)	0.10
Treatment naïve	9 (23.7)	17 (25.8)	1.0
ESR (mm after 1 h)	61.4 $\pm$ 22.1	56.5 $\pm$ 29.1	0.37
Uric acid (mg/dL)	5.06 $\pm$ 1.93	4.82 $\pm$ 1.55	0.49
RF seropositivity	29 (76.3)	58 (87.9)	0.17
Current medication at the time of study			
Methotrexate	23 (60.5)	40 (60.6)	1.0
Hydroxychloroquine	22 (57.9)	31 (46.9)	0.31
Sulfasalazine	13 (34.2)	30 (45.5)	0.3
Steroids	26 (68.4)	38 (57.6)	0.3
NSAIDs	8 (21.1)	13 (19.7)	1.0

Comparison of continuous variables, expressed as mean  $\pm$  SD, and categorical variables, expressed as n (%), between RA patients with and without metabolic syndrome, performed by unpaired *t*-test and Fisher's exact test.

DAS: disease activity score; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal anti-inflammatory drug; RA: rheumatoid arthritis; RF: rheumatoid factor.

**Table 4: Predictors of metabolic syndrome in RA patients identified by binary logistic regression**

Variables	Odds ratio (with 95% CI)	P-value	Model variance	Model predictions
Age (years)	1.01 (0.97–1.06)	0.52	Nagelkerke R2 = 0.316	Correct classification by model = 67.3%
Disease duration (years)	1.30 (1.01–1.69)	<0.05		
DAS	1.94 (1.35–2.79)	<0.01		

CI: confidence interval; DAS: disease activity score; RA: rheumatoid arthritis.

production of inflammatory mediators in active disease, prolonged immobilization, increased clearance via scavenger receptor pathway, and increased oxidation triggered by the inflammatory environment.<sup>[28]</sup> High WC, elevated TG, and high DBP were among the other metabolic parameters observed in RA patients in comparison to healthy controls. However, the other components of MetS, *viz.* BMI, systolic BP, and FBS, were comparable between the two groups. Similar observations with regards to BMI with MetS have been reported by others.<sup>[23]</sup>

The study also shows that the mean DAS28 is significantly higher in RA patients with MetS as compared to RA patients without MetS. This is in accordance with the study by Lee *et al.* which showed that disease activity is a risk factor for insulin resistance and MetS.<sup>[24]</sup> The correlation between RA disease activity and MetS is an indirect evidence of the role of chronic inflammation in MetS and atherosclerosis development. However, there are previous studies which have not shown any association between DAS28 in RA with MetS.<sup>[22,25]</sup>

## CONCLUSION

MetS is highly prevalent in RA patients of our region. Further, the dismal values of atherogenic indices in our RA patients as opposed to healthy controls is indicative of the higher risk for developing future CV events that these patients are exposed to. Thus, this study reiterates the importance and need of screening for MetS in RA. The presence of MetS in our RA patients was influenced by disease activity and disease duration, but independent of the use of disease-modifying drugs or steroids. The association of RA disease activity with MetS suggests that the increased prevalence of CVD in patients with RA may be attributed to the increase inflammatory burden of the disease.

## Conflict of Interest

None declared.

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