

## Research Article

### Association of Severe Disease Activity with Metabolic Syndrome in Patients with Early Rheumatoid Arthritis: A Cohort Study from Tertiary Care Hospital of Pakistan

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#### Abstract

**Background:** The peripheral joints are particularly vulnerable to the autoimmune disease rheumatoid arthritis. Patients with rheumatoid arthritis often exhibit symptoms of metabolic syndrome. Metabolic syndrome in rheumatoid arthritis is connected with increased morbidity and death. .

**Objective:** This study aimed to examine whether or not rheumatoid arthritis patients who had high levels of disease activity also developed metabolic syndrome.

**Methods:** The cohort study was conducted on 64 patients (32 in each group), included via Non-probability convenient sampling. Disease activity score of 28 joints (DAS-28 score) was used to assess the severity of disease activity in patients of rheumatoid arthritis and two groups were developed i.e. group I with score  $\geq 3.2$  and group II with score  $< 3.2$ . Patients were then assessed for metabolic syndrome. All data was analyzed in SPSS version 21.0. The association between severe disease activity and metabolic syndrome was calculated as relative risk.

**Results:** The mean age of patients in group I & II was  $31.26 \pm 5.07$  years & was  $33.57 \pm 3.73$  years respectively. The mean DAS-28 score of patients in group I was  $4.93 \pm 0.79$  while in group II was  $2.32 \pm 0.40$  and the difference between both groups for DAS-28 score was highly significant ( $p < 0.001$ ). Metabolic syndrome was diagnosed in 13 (40.6%) patients in group I while in 3 (9.4%) patients in group II. The difference was significant, association observed between metabolic syndrome and severity of disease i.e. Relative risk = 2.053 (95% confidence interval: 1.347, 3.128, p-value = 0.0094).

**Conclusion:** Rheumatoid arthritis patients who also have metabolic syndrome tend to have more severe illness.

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**Keywords** | severe disease activity, metabolic syndrome, rheumatoid arthritis, Disease activity score of 28 joints, DAS-28

#### Introduction

Rheumatoid arthritis is an autoimmune condition that has a long course and mostly affects the joints near the body's periphery.<sup>1,2</sup> Systemic inflammation occurs, affecting not only the joints but also the heart, lungs, and kidneys.<sup>1,3</sup> There is a high mortality and mor-



#### Production and Hosting by KEMU

DOI: <https://doi.org/10.21649/akemu.v29i2.5486>  
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idity rate connected with it.<sup>1-3</sup> The prevalence is estimated to be between 0.5% and 1.0%.<sup>3</sup> Some 30% to 60% of people with rheumatoid arthritis will go on to develop cardiovascular disease.<sup>2</sup> This high risk of development of cardiovascular disease is associated with dysfunction in the endothelium and enhanced atherosclerosis as a result of long standing inflammation and associated other risk factors for cardiovascular disorders.<sup>4,5</sup>

The phrase "metabolic syndrome" is used to characterise a cluster of risk factors for cardiovascular disease, cerebrovascular illness, and type 2 diabetes. Rheumatoid arthritis patients often have one or more of the metabolic syndrome risk factors: high blood pressure, diabetes mellitus, abdominal obesity, and abnormal cholesterol or triglyceride levels.<sup>1-5</sup> A study conducted by Silamani et al (2017) it was found that in Algerian adults with rheumatoid arthritis, 19.1% had metabolic syndrome.<sup>1</sup> Other studies reported that metabolic syndrome prevalence varies from 14% to 63% in patients with rheumatoid arthritis.<sup>2,5</sup> The etiology of metabolic syndrome remains unclear, however, it has been postulated that insulin resistance is the main aetiopathological cause of metabolic syndrome.<sup>6-9</sup>

In patients with metabolic syndrome, treatment objective is the reduction in the risk of development of atherosclerosis and other conditions associated with it that can lead to increase morbidity and increased rates of mortality in rheumatoid arthritis patients.<sup>8</sup> Therefore, it is necessary to identify such conditions earlier. In addition to it, the association of disease activity and metabolic syndrome needs clarification so that the concept of sustained remission is made clear that can effect further the mortality related to cardiovascular events.<sup>9,10</sup> Da Cunha et al. (2012) found that patients with rheumatoid arthritis were more likely to have metabolic syndrome (Metabolic syndrome was 39.2% rheumatoid arthritis patients vs. 19.5% in control group,  $p < 0.001$ , OR: 1.87) due to its association with high disease activity.<sup>11</sup>

Various researches have been carried out internationally on the presence of metabolic syndrome with the high disease activity in rheumatoid arthritis patients. According to best of researcher's knowledge, no such study has been conducted so far in Pakistan. Therefore, the purpose of this research is to examine whether or not rheumatoid arthritis cases with metabolic syndrome also have high levels of disease activity. This study will

help in creating awareness among treating physicians regarding the need to control disease activity earlier so that further complications like metabolic syndrome can be avoided thus helping in decreasing the disability and mortality associated with rheumatoid arthritis.

## Methods

This prospective cohort research was place between February 2020 and July 2020 at the Rheumatology Outpatient and Inpatient Department at Mayo Hospital Lahore. Using a 95% confidence interval, a 10% absolute precision, and an anticipated proportion of 19% for rheumatoid arthritis, a sample size of 64 patients was calculated. The sample was selected using a non-random method.

Patients between the ages of 20 and 50 who tested positive for the rheumatoid factor were included. These patients had been diagnosed with early rheumatoid arthritis (with duration of disease for  $\geq 6$  months; "duration" refers to the length of time the patient has had symptoms / disease, not the time since the RA diagnosis; ACR 2015 rheumatoid arthritis guidelines). Patients who had rheumatoid arthritis with severe disease activity according to the Disease activity score of 28 joints (DAS-28) and a score of  $\geq 3.2$  was labeled as moderate-to-severe disease activity (group I). The scores  $< 3.2$  indicated mild disease activity (group II).

Rheumatoid Arthritis patients with joint deformities, other diseases like Systemic lupus erythematosus or mixed connective tissue diseases and osteoarthritis were excluded.

After approval of institutional review board (ERC# 62 dated 16-01-2020), who fulfilled the inclusion criteria were selected from rheumatology OPD, Mayo Hospital, Lahore. Informed consent was taken from patients. Demographic information like age, gender, duration of rheumatoid arthritis, etc. was also obtained. DAS-28 score was estimated and two groups were developed i.e. group I with score  $\geq 3.2$  and group II with score  $< 3.2$ . Patients were called in OPD after 1 week of initial presentation with 8-12 hours fasting. After one week, the following metabolic syndrome measures were recorded on a standard form: waist circumference, fasting blood glucose, blood pressure, fasting triglyceride level, and fasting HDL level. The existence or absence of metabolic syndrome was next evaluated in the patients. To

have metabolic syndrome, as defined by the United States National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), three out of the five following symptoms must be present:

1. Over 40 inches around the waist (men) or 35 inches around the waist (women).
2. Higher than 150 mg/dl in the fasting state.
3. HDL levels below 40 mg/dl (in males) or 50 mg/dl (in women) in the fasting state.
4. If your BP is above 130/85 mm Hg or you're on medication, you may need to see a doctor.
5. Over 100 mg/dl of glucose in the fasting state or using insulin.

All data was analyzed using SPSS 21.0 version. 2×2 contingency table was generated to calculate the association between severe disease activity and metabolic syndrome and was presented by relative risk with value of >1 was considered as significant risk of association.

## Results

Out of 64 patients, 32 were group I with DAS score  $\geq 3.2$  and 32 were group II with DAS-28 score  $<3.2$ . The mean age of patients in group I was  $31.28 \pm 4.97$  years while in group II was  $33.81 \pm 3.56$  years. In group I, there were 2 (6.3%) males and 30 (93.8%) females. In group II, there were no (0%) males while all were females (100%). The mean DAS-28 score of patients in group I was  $4.93 \pm 0.79$  while in group II was  $2.32 \pm 0.40$  and the difference between both groups for DAS-28 score was highly significant ( $p < 0.001$ ). (Table 1)

Patients were examined for parameter of metabolic syndrome. Waist circumference was high in 13(40.6%) patients in group I while in 8 (25.0%) patients in group II. HDL was low in 9 (28.1%) patients in group I while in 3 (9.4%) patients in group II. Triglycerides level was high in 10 (31.3%) patients in group I while in 5 (15.6%) patients in group II. Hypertension was present in 14 (43.8%) patients in group I while in 4(12.5%) patients in group II. Diabetes mellitus was present in 8 (25.0%) patients in group I while in 4 (12.5%) patients in group II. The difference was insignificant for all parameters, except hypertension. (Table 2)

In group I metabolic syndrome was present in 13 (40.6%) patients while in 3 (9.4%) patients in group II. The diffe-

**Table 1:** Demographics of patients

	Group	
	Group I	Group II
<b>n</b>	32	32
<b>Age (years)</b>	$31.28 \pm 4.97$	$33.81 \pm 3.56$
<b>Gender</b>		
<b>Male</b>	2 (6.3%)	0 (0.0%)
<b>Female</b>	30 (93.8%)	32 (100%)
<b>DAS 28 score</b>	$4.93 \pm 0.79$	$2.32 \pm 0.40$

**Table 2:** Assessment of features of metabolic syndrome

	Group		p-value
	Group I	Group II	
<b>N</b>	32	32	
<b>Waist circumference</b>			0.1834
High	13 (40.6%)	8 (25.0%)	
Normal	19 (59.4%)	24 (75.0%)	
<b>HDL</b>			0.1093
Low	9 (28.1%)	3 (9.4%)	
Normal	23 (71.9%)	29 (90.6%)	
<b>Triglycerides</b>			0.2385
High	10 (31.3%)	5 (15.6%)	
Normal	22 (68.8%)	27 (84.4%)	
<b>Hypertension</b>			0.0123
Present	14 (43.8%)	4 (12.5%)	
Absent	18 (56.3%)	28 (87.5%)	
<b>Diabetes</b>			0.3367
Present	8 (25.0%)	4 (12.5%)	
Absent	24 (75.0%)	28 (87.5%)	

**Table 3:** Association of metabolic syndrome with severity of rheumatoid arthritis

		Group	
		Group I	Group II
<b>MetS</b>	Present	13 (40.6%)	3 (9.4%)
	Absent	19 (59.4%)	29 (90.6%)
<b>Total</b>		32 (100%)	32 (100%)

Relative risk = 2.053 (95% confidence interval: 1.347, 3.128, p-value = 0.0094)

rence was significant association observed between metabolic syndrome and severity of disease i.e. Relative risk = 2.053 (95% confidence interval: 1.347, 3.128, p-value = 0.0094). (Table 3)

## Discussion

Individuals having rheumatoid arthritis have seen a three to ten years reduction in their life expectancy than life expectancy of general population during the last two decades. Rheumatoid arthritis is most likely to occur

due to infection caused by some virus or bacteria, or due to the combination of genetics and lifestyle habits, especially smoking. The endocrine pathway has been implicated in several studies. Atherosclerosis and its complications are more common in patients having systemic inflammatory arthritis, such as rheumatoid arthritis. The increased frequency of metabolic syndrome in people with rheumatic diseases is not completely understood.<sup>12</sup>

Three definitions of Metabolic syndrome are usually applied i.e. "National Cholesterol Education Program /Adult Treatment Panel III 2005", "International Diabetes Federation 2005," and "American Association of Clinical Endocrinologists 2003".<sup>13</sup>

The prevalence of metabolic syndrome in rheumatoid arthritis varies depending on the term used, but it is consistently higher in rheumatoid arthritis than in controls (p-value < 0.05 for all the definitions). Increase use of glucocorticoids along with high systemic inflammatory markers were considered to be the important risk factors of metabolic syndrome in rheumatoid arthritis patients.<sup>14</sup>

In our study, we observed metabolic syndrome was two times higher in patients with rheumatoid arthritis having moderate to severe disease activity (40.6%) than patients with mild disease activity (9.4%) and this association was observed as significant i.e. Relative risk = 2.053 (95% confidence interval: 1.347, 3.128, p-value = 0.0094).

In a case-control research, 39.2% cases of rheumatoid arthritis satisfied the criteria for metabolic syndrome, compared to 19.5% of patients in the control group (p < 0.001). After controlling for factors such as age, gender, and years of education, "multiple logistic regression analysis" found that rheumatoid arthritis patients with considerably high risk of having metabolic syndrome than individuals, who did not have RA (odds ratio = 1.87, 95% confidence interval; 1.17 - 3.00, p-value = 0.009). The average DAS-28 was also significantly more in patients of rheumatoid arthritis having metabolic syndrome as compared to those patients of rheumatoid arthritis who were not having metabolic syndrome ( $3.59 \pm 1.27$  vs.  $3.14 \pm 1.53$ ; p-value = 0.01).<sup>15</sup> These findings were slightly dissimilar from that of our study. In our study, the mean DAS-28 score of patients in group I was  $4.93 \pm 0.79$  while in group II was  $2.32 \pm 0.40$  and the difference between both groups for DAS-28 score

was significant (p < 0.0001).

Another study by Pandey et al. found that the prevalence of metabolic syndrome according to the criteria established by the "National Cholesterol Education Programme -Adult Treatment Panel III 2004" was 39.28% in patients with rheumatoid arthritis and 20% in patients without the disease (significance < 0.0001). Higher level of systemic inflammatory marker, disease length, and DAS-28 were considered to be the independent predictors of metabolic syndrome. These studies mean that patients with rheumatoid arthritis should be screened for metabolic syndrome early on to detect and reduce the risk of atherosclerotic artery disease.<sup>16</sup>

Similarly to our findings, Karvounaris et al. found that 40% of rheumatoid arthritis patients, when than age & sex-matched control individuals, who had metabolic syndrome.<sup>17</sup> When looking at the prevalence of metabolic syndrome in rheumatoid arthritis patients, the "National Cholesterol Education Programme 2001" shows a wide range: from about 17% in Mexico, to 19% in South Africa, to 19.9% in the Netherlands, to 42% in the United States, and to 44% in Greece.<sup>17-21</sup> This variation may be explained by distinguishing baseline and illness characteristics. Metabolic syndrome is more common in those with rheumatoid arthritis (31.57%) than in those without the disease (14.9%), according to a research conducted in India by Aman et al.<sup>22</sup>

But one study found that frequency of metabolic syndrome was observed in 61% patients who had active rheumatoid arthritis while in 48% patients who had inactive rheumatoid arthritis. The difference was reported to be insignificant (p > 0.05).<sup>23</sup>

In our study, the sample size was very small, although we have obtained a significant association of metabolic syndrome. Further studies with larger sample size and multi-centric study should be done. But our study is the first of its kind in our country.

## Conclusion

This is concluded that there is significant association of metabolic syndrome with rheumatoid arthritis having moderate to severe disease activity. Now through this study we have got the evidence for local population. It is clear from the statistics that this association is significant and presence of metabolic

syndrome can lead to the cardiovascular diseases in patients of rheumatoid arthritis. Now findings of this study will help in creating an awareness among physicians who are treating the rheumatoid arthritis patients for better control on disease activity earlier so that further complications like metabolic syndrome can be avoided thus helping in decreasing the disability and mortality associated with rheumatoid arthritis.

**Ethical Approval:** Given

**Conflict of Interest:** The authors declare no conflict of interest.

**Funding Source:** None

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