The metabolic syndrome in Rheumatoid Arthritis - A Observational study.

Abstract: Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects mainly the small joints of the hands and feet, it has both articular manifestations and extra articular manifestations. The joints commonly involved in Rheumatoid arthritis are the wrists, small joints of the hands and feet, i.e the metacarpophalangeal (MCP) joints, interphalangeal joints of the thumbs, proximal interphalangeal (PIP) joints of the fingers and metatarsal phalangeal (MTP) joints. Distinctively the distal interphalangeal (DIP) joints are spared. Extra Articular manifestations of Rheumatoid Arthritis are seen in up to fifty percent of patients. Extra articular manifestations are in the form of episcleritis, skin ulcers, scleritis, rheumatoid nodules, neuropathy, pleural involvement, interstitial lung disease, pericarditis, myocarditis, coronary artery disease (CAD), glomerulonephritis, sicca symptoms, vasculitis and atherosclerotic disease. Aim: To Study The Metabolic Syndrome In Rheumatoid Arthritis Patients. Objectives: To Study Metabolic Syndrome in Patients with Rheumatoid Arthritis. To Study the Relationship between Metabolic Syndrome and Disease Activity. Hence it can be concluded that the prevalence of Met S was high in patients of Rheumatoid arthritis. The levels of triglycerides, fasting blood sugar, blood pressure, waist circumference was higher in study subjects having Met S while the HDL level was lower than patients not having metabolic syndrome. This difference was found to be significant statistically. Therefore, it is essential to manage Met S for prevention of CVD in patients of rheumatoid arthritis.

Keywords: Coronary Artery Disease, Confidence Interval CRP C-Reactive Protein, Computed Tomography, Metabolic Syndrome, Proximal Interphalangeal.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects mainly the small joints of the hands and feet, it has both articular manifestations and extra articular manifestations. The joints commonly involved in Rheumatoid arthritis are the wrists, small joints of the hands and feet, i.e the metacarpophalangeal (MCP) joints, interphalangeal joints of the thumbs, proximal interphalangeal (PIP) joints of the fingers and metatarsal phalangeal (MTP) joints. Distinctively the distal interphalangeal (DIP) joints are spared. Extra Articular manifestations of Rheumatoid Arthritis are seen in up to fifty percent of patients. Extra articular manifestations are in the form of episcleritis, skin ulcers, scleritis, rheumatoid nodules, neuropathy, pleural involvement, interstitial lung disease, pericarditis, myocarditis, coronary artery disease (CAD), glomerulonephritis, sicca symptoms, vasculitis and atherosclerotic disease.[1]

RA is one of the commonest inflammatory joint disorders and can cause disability or premature mortality along with compromised quality of life. The incidence of RA raises between 25-55 years of age after which it gets plateaus until the age of 75 years.[2] The overall worldwide prevalence is 0.8% and steadily increases to 5% in females above the age of 70. RA is two to three times more common in females compared to men.3 In India the prevalence has been estimated to be 0.7%.[1] RA patients have a higher mortality rate than normal population. Mortality rates in persons with Rheumatoid arthritis are usually 1.5 times greater than in the overall population, with similar patterns over the

past 50 years.4 The various causes of death that are increased in comparison with the overall population are CVD, infections and respiratory diseases. The higher mortality rate is especially due to CVD. The additional risk depends on systemic inflammation, other increased causes of death are respiratory diseases and infections, most often due to respiratory infection/pneumonia.[4] Cardiovascular disease (CVD) is a leading cause of death among RA patients, accounting for around half of all deaths. Aside from established CVD risk factors, systemic inflammation and metabolic syndrome (Met S) play a role in CVD risk and mortality in RA patients.[5] In the 20th century, CVD contributed as the major cause of mortality and morbidity in the developed countries. Towards of the end of the 20th century, the clustering of CVD risk factors was first described as simultaneous presence of type 2 diabetes, hyperlipidemia, presence of obesity and hypertension. This was put into a unifying term of Met S. The concept of metabolic syndrome has evolved extensively in the past two decade. The study aims to find newer prospects in the spectrum of RA and Met S, as previous research over these topics have been unable to fill the knowledge gap. We aim to determine the actual prevalence of Met S in patients with RA in central India. Currently studies are available from the north and south India, but few studies are available from the central India, thus we wish to evaluate the central Indian population which have a different demography.

MATERIAL AND METHODS

The study was conducted in the Department of General Medicine, Sri Aurobindo Medical College and Post Graduate Institute, Indore (Madhya Pradesh) for a period of 18 Months from 1st January 2020 to 30 th June 2021. The present study assessed to study the metabolic syndrome in Rheumatoid arthritis patients having age more than 18 years under the Department of General Medicine, Sri Aurobindo Medical College and Post Graduate Institute, Indore (Madhya Pradesh).

The present study was an observational study focusing on the assessment of the metabolic syndrome in Rheumatoid arthritis patients having age more than 18 years age group. In the outpatient department (OPD) under the Department of General Medicine, Sri Aurobindo Medical College and Post Graduate Institute, Indore (Madhya Pradesh). 18 Month (From January 2020 to June 2021). Simple Random Sampling Sample Size Estimation: Data of 100 patients of Rheumatoid arthritis patients collected for a period of one and half year. Also, SAIMS OPD had a yearly input of 100 newly diagnosed and old RA cases thereby making our sample size of 100 RA patients as feasible. Patients (male and female) seeking medical attention at Sri Aurobindo medical college and Post Graduate Institute, Hospital, during the period of study, who have been diagnosed with Rheumatoid Arthritis. Patients who attend the Emergency/OPD/IPD were asked to participate in the study. Informed written consent was taken from all the patients. A prestructured proforma was used to collect the baseline data. Detailed clinical examination and biochemical tests was done on all the patients. 1.Patient‟s old documents were reviewed/ Clinical examination for the diagnosis of rheumatoid arthritis.

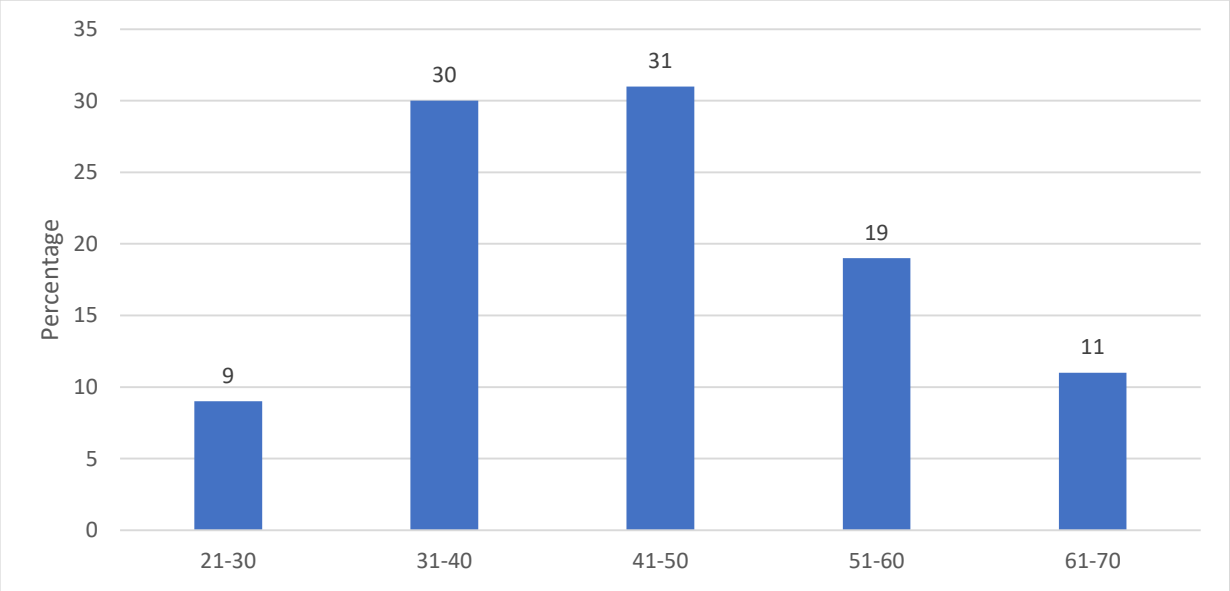
STATISTICAL ANALYSIS PLAN

A descriptive analysis of the population has been carried. The categorical or dichotomous variables is expressed as absolute values and percentages, and are compared with Pearson test. The correlation between two quantitative variables was carried out by using coefficient of correlation. A P value less than 0.05 will considered statistically significant whereas a p value > 0.05 will be taken as non-significant difference.

STUDY METHODOLOGY: Patients (male and female) seeking medical attention at Sri Aurobindo medical college and Post Graduate Institute, Hospital, during the period of study, who have been diagnosed with Rheumatoid Arthritis. Patients who attend the Emergency/OPD/IPD were asked to participate in the study. Informed written consent was taken from all the patients. A prestructured proforma was used to collect the baseline data. Detailed clinical examination and biochemical tests was done on all the patients. Patient's old documents were reviewed/ Clinical examination for the diagnosis of rheumatoid arthritis. They were evaluated for physical parameters like body weight, waist circumference, and height, B.P. Blood samples were drawn and sent for lipid profile, FBS, RA Factor, CBC with ESR, CRP. Then the results were evaluated.

OBSERVATIONS AND RESULT

Fig1: Graphical representation of participants according to Age



Majority (80%) of the study subjects were in the age group of 31 – 60 years. Nearly 30% of study subjects were in fourth and fifth decade of life.

Out of 52 study subjects who had metabolic syndrome, the HDL levels were lower in 98.1% whereas in 48 subjects in which metabolic syndrome was absent only 72.95 lower levels of HDL. This difference was found to be statistically significant ($p<0.001$).

Table 1: Distribution of study participants according to Characteristics of Metabolic Syndrome

NCEP / ATP III Criteria	Metabolic Syndrome						p value
	Absent		Present		Total		
	Mean	SD	Mean	SD	Mean	SD	
HDL (mg/dL)	42.17	7.25	38.62	6.06	40.32	6.86	0.009
Triglycerides (mg/dL)	110.13	30.71	173.88	77.48	143.28	67.57	< 0.001
Fasting Blood Sugar (mg/dL)	95.58	12.44	109.23	12.47	102.68	14.16	< 0.001
Waist circumference (cm)	88.67	3.52	90.96	4.16	89.86	4.02	0.004
Systolic BP (mm of Hg)	126.42	18.22	131.42	14.98	129.02	16.72	0.135
Diastolic BP (mm of Hg)	78.92	9.23	84.54	8.24	81.84	9.14	0.002

As shown in above table the mean value of triglyceride, fasting blood sugar, blood pressure, waist circumference was higher in study subjects having metabolic syndrome while the mean HDL value was lower than subjects not having metabolic syndrome. This difference was found to be statistically significant ($p < 0.05$).

Table 2: Distribution of haematological parameters in study participants

Blood Parameters	Metabolic Syndrome						p value
	Absent		Present		Total		
	Mean	SD	Mean	SD	Mean	SD	
Hb (gm)	10.96	1.97	11.54	1.63	11.26	1.81	0.1160
RBC (lakh)	4.50	0.56	4.50	0.58	4.50	0.57	0.9990
PCV (%)	33.97	5.33	34.80	6.46	34.40	5.93	0.488
MCV	74.17	7.31	79.36	8.91	76.87	8.55	0.002
WBC (in thousand)	10139.58	9588.68	8798.08	2751.51	9442.00	6928.45	0.336
Platelet (in lakh)	3.40	1.07	3.30	1.22	3.35	1.15	0.646
ESR (mm)	21.08	4.63	21.25	5.71	21.17	5.20	0.874
IgM RF	126.54	87.77	136.19	185.57	131.56	146.35	0.744
Total Cholesterol (mg/dL)	144.44	29.49	191.77	44.78	169.05	44.84	< 0.001

The above table shows the various hematological parameters in both the groups. However, the difference in total cholesterol levels and mean corpuscular volume levels were found to be statistically significant.

The mean ACR/ EULAR score was 6.50 in subjects with metabolic syndrome and was 7.04 in subjects without metabolic syndrome. This difference was found to be statistically significant ($p<0.001$).

Table 3: Distribution of study participants according to Body mass index with Metabolic Syndrome

Metabolic Syndrome	Mean	Std. Deviation	p value
Absent	27.69	3.22	0.004
Present	29.39	2.52	

The mean BMI was 29.39 in subjects with metabolic syndrome and was 27.69 in subjects without metabolic syndrome. This difference was found to be statistically significant ($p<0.001$).

DISCUSSION

RA is a systemic, inflammatory, chronic, disorder of unknown aetiology. Epidemiologic data suggests that RA is a one of the independent factors for associated CV disease risk. The presence of Met S influences the development of accelerated atherosclerosis and increased risk of cardiovascular disease in patients with RA. An association between metabolic syndrome and inflammatory activity of rheumatoid arthritis has also been suggested. Out of 52 study subjects who had metabolic syndrome, the HDL levels were lower in 98.1% whereas in 48 subjects in which metabolic syndrome was absent only 72.95 lower levels of HDL (p 150 mg/dl in participants who had Met S whereas only 14.6% of study subjects had higher levels of triglyceride in subjects who did not have Met S (p levels higher than > 110 mg/dl in participants who had metabolic syndrome whereas only 8.3% of study subjects had higher levels of FBS in participants who did not have Met S (p 102 cm in men and 102 cm in men and 130/85 mm Hg in subjects who had Met S whereas only 22.9% of study subjects had greater levels of Blood Pressure in whom Met S was absent (p< 0.05). Similar to our results, increased incidence of Met S has been observed in RA patients by many authors. Da Cunha et al.[18] in 283 RA patients and 226 matched controls, reported that 39% of Rheumatoid arthritis patients had Met Sas compared to 19% in controls (P = 0.001). The authors also found increased prevalence of increased fasting glucose, elevated blood pressure, and waist circumference in RA patients as compared to controls. The authors reported that the risk of participants suffering from Met S was significantly greater (OR= 1.87) in RA patients than controls (p=0.01); and it was significantly greater (3.59 ± 1.27 vs 3.14 ± 1.53) in patients with RA and Met S than in those do not have Met S (P = 0.01). Extra-articular manifestations, the presence of rheumatoid factor and disease duration were similar in cases with and without MS in RA subjects. Observed 42% cases of Met S in long-standing RA disease patients, while 31% with early arthritis, and in 11% controls (154 patients with RA and 85 controls). When NCEP criteria was used in the same study, the Met S prevalence was 30% in long-standing RA disease patients, 22% in patients with early arthritis RA patients and 10% in controls. In this paper, coronary-artery atherosclerosis was studied by CT scan, and rheumatoid arthritis patients with Met S were found to have a higher coronary-artery calcification score (OR = 2.02 (95% CI 1.03–3.97), P = 0.04). The association of rheumatoid arthritis and Met S was confirmed in patients with short disease duration. Dao et al[28] who assessed for the Met S prevalence in 105 women who had rheumatoid arthritis and the total duration of the disease was < 3 years and 105 matched controls of same gender. In this study different definitions for Met S were tested (National Cholesterol Education Program 2004 and 2001, World Health Organization, European Group for Study of Insulin Resistance, International Diabetes Federation and Joint Consensus). Crows on et al.[19] showed that rheumatoid arthritis patients had increased chance to have increased elevated blood pressure and waist circumference than non-rheumatoid arthritis patients without CVD in 232 patients with rheumatoid arthritis with no overt cardiovascular disease and 1241 non-rheumatoid arthritis cases without cardiovascular disease. The authors concluded that rheumatoid arthritis patients were more frequently classified as having Met S, and that Met S was related with large-joint swelling, uric acid levels, and Health Assessment Questionnaire Disability Index, but not with CRPor rheumatoid arthritis therapies. Similarly, Toms et al.[29] reported the 40.1% Met S prevalence in 398 RA patients. However, Met S prevalence did not vary significantly between the different groups. The Met S prevalence in RA patients. For this purpose, 699 RA patients were

studied in which 70% were women with mean age of 51.1 ± 12.7 years. In this study, the Met S prevalence was significantly greater in RA (38%). Similar, to our study the RA patients had a significantly greater prevalence of high blood pressure (56%; P = 0.045), low HDL cholesterol (33%; P < 0.001), impaired fasting glucose (30%; P < 0.001), central obesity (65%; P < 0.001) and high triglycerides level (21%; P = 0.008). In their series, Met S was significantly associated with smoking older age, lower income and lower education levels. Desse in et al.[30] concluded in 74 RA patients that Met S was associated with increased carotid artery intima-media thickness (P = 0.04) but not with carotid plaques in the artery (P > 0.1). With respect to the association between RA and Met S,few exceptions are cited in the current literature using NCEP and WHO criteria.Karimi et al. [13]in a case-control study that included 92 RA patients and 96 healthy controls did not find any difference between the two RA groups with and without Met S. However, higher proportion of hypertension subjects were seen in RA than controls and significantly associated longer duration of the RA disease as compared to with Met Sthan those without Met S. Karvounaris et al. 6 in 200 OPD RA patients and 400 controls found higher prevalence of Met S in middle-to-older aged RA casesal though comparable to controls. However, the risk of having high score (DAS28 > 3.2) was significantly greater in cases with Met S than those without Met S with OR 9.24 (P=0.02) in a multivariate logistic regression analysis after adjusting for demographic variables and rheumatoid arthritis treatment. A study of 120 RA subjects and 431 controls observed that prevalence of IDF or ATPIII Met S was significantly greater in controls and the presence of rheumatoid arthritis was not found to be associated with an increased risk of Met S Moreover a study in 499 RA subjects RA showed that deficiency of Vitamin D was associated with higher levels of hyperlipidemia (OR 1.72) and increased prevalence of Met S (OR 3.45). Whereas, other study reported that in RA patients Vitamin D may play a protective role against Met S. Hence, we can conclude that Met S is not unusual in RA patients. Although, central obesity and insulin resistance play important role in the development of Met S, underlying cause for Met S is still unanswered question. Central obesity which is generally a prerequisite risk factor for Met S, is independently associated with other Met S components. Adipose tissue appears to be a metabolically active and dynamic organ which can mediate widespread effects on vascular homeostasis, immune function and metabolism. Molecular mechanisms of metabolic inflammation and diabetes, potential pathogenic roles in insulin resistance, and CVD are of particular interest. Inflammation associated with obesity is linked to an accumulation of macrophages in adipose tissue. In conclusion, obesity has also been shown to play a role in the development of Met S, as does insulin resistance. Patients with RA have altered body composition, with a reduction of fat-free mass and an increase of fat mass, so that they gain little or no weight or maintain their body mass index. This condition known as “rheumatoid cachexia” and has been linked to increased morbidity and mortality in rheumatoid arthritis and Met S. Rheumatoid arthritis has been linked to an increase in abdominal obesity. The author found that both rheumatoid arthritis patients and controls had identical BMIs and waist circumferences in research that included 131 RA patients and 121 controls. However, in males with RA patients, the adjusted abdominal visceral fat area was 45 cm2 larger (indicating a 51 percent difference) than in men in the control group (P = 0.005), but not substantially different in women. The corrected mean abdomen subcutaneous fat area was 119 cm2 higher in women with RA (indicating a 68 percent difference) than in women without RA (P 0.001) in the same study, although not substantially different. When comparing the RA group to controls, the presence of increased visceral fat area was related with a significantly higher adjusted risk of having an elevated fasting glucose, hypertension, or the composite diagnosis of Met S. Rheumatoid

factor positive and higher cumulative prednisone exposure were both linked to a higher mean adjusted visceral fat area in the RA group. Both visceral and subcutaneous fat regions were related with higher C-reactive protein levels and lower sharp radiography scores. Patients with a body mass index over the 50th percentile and those with rheumatoid cachexia had the highest rates of hypertension and Met S in that study. The average dose of glucocorticoids provided did not differ between individuals who were cachectic and those who were not. As a result, these investigations confirmed that RA patients have aberrant body composition, and that these abnormalities are linked to factors that raise CV risk. The majority of overweight persons are also overfat, yet the two are not synonymous. Patients with RA are frequently overweight. However, discovered that the presence of a certain changed pattern of fat content causes Met S to develop in RA patients. In this regard, the presence of greater visceral fat was related with a considerably higher adjusted probability of fulfilling the composite definition of Met S in individuals with RA than in controls for a same body mass index in patients and controls. This suggests that the development of Met S is the result of a specific pattern of fat deposition, not just the existence of fat. Obesity, rather than MS, was once thought to be a significant risk factor for the development of RA. In conclusion, adiposity and obesity are common in people with RA and are linked to an elevated risk of MS in these patients.

SUMMARY AND CONCLUSION

Hence it can be concluded that the prevalence of Met S was high in patients of Rheumatoid arthritis. The levels of triglycerides, fasting blood sugar, blood pressure, waist circumference was higher in study subjects having Met S while the HDL level was lower than patients not having metabolic syndrome. This difference was found to be significant statistically. Therefore, it is essential to manage Met S for prevention of CVD in patients of rheumatoid arthritis.

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