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PREVALENCE OF METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS AND MOST COMMON PARAMETER CONTRIBUTING TO METABOLIC SYNDROME IN THESE PATIENTS.

Endocrinology

Dr Mir Waseem Senior Resident Dept of Medicine SKIMS Medical College.

Dr Mir Nadeem* Postgraduate Scholar Dept of Medicine GMC Srinagar *Corresponding Author

Dr Jaspreet Singh Postgraduate Scholar Dept of Medicine GMC Srinagar

Dr Shahood Kakroo Postgraduate Scholar Dept of Medicine GMC Srinagar

Dr Saba Maqbool Junior Resident SKIMS Medical College.

KEYWORDS

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by a symmetrical inflammation of the synovium, resulting in tenderness and destruction of bone and cartilage in various joints, particularly the smaller joints of the hands and feet. Although the cause of RA is unknown, autoimmunity plays a pivotal role in its chronicity and progression. RA affects approximately 1.0% of the general population, women more often than men, and the inflammatory burden of the disease results in functional disability.[1] Several contributors to RA pathogenesis have been identified in recent years: genetic factors (shared epitope on locus HLA-DRB1, but also PTPN22, STAT4, 6q23 and TRAF1/C5), cigarette smoking, autoantibodies (rheumatoid factor (RF), anti-cyclic citrullinated protein antibodies (ACPA)), infectious agents, as well as nutritional and hormonal factors. [2] Ultimately, an interplay between these endogenous and exogenous factors has been postulated to break immunological tolerance and trigger the immunological response that manifests itself as RA. [3]The immunological activation of RA leads to infiltration of the synovium by an orchestra of immune cells like T and B cells, macrophages, dendritic cells and fibroblast-like synoviocytes, contributing to the proliferation of cell tissue (i.e. pannus formation) and neovascularization.[4] These immunological processes perpetuate systemic inflammatory responses, leading to a chronic, disabling disease which results in the inability to work and an impaired quality of life. [5]

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)[6]. CVDs are the most common cause of death, with approximately 40% of deaths in RA patients attributed to CVD .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[7]The European League Against Rheumatism (EULAR) guidelines recommend that cardiovascular risk screening and management to be urgently done in patients with RA[8]

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[9]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). NCEP: ATP III 2001 criteria for the metabolic syndrome modified for asian population.

Three or more of the following :

Central obesity: waist circumference >90 (males), >80cm (females).

Hypertriglyceridemia: triglyceride level ≥150mg/dl or specific medication.

Low HDL cholesterol: <40mg/dl for men and <50 mg/dl for women or specific medication.

Hypertension: blood pressure >130mmHg systolic or > 85mmHg diastolic or specific medication.

Fasting plasma glucose level: ≥100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

Metabolic syndrome increases the risk factor of developing diabetes and/or CVD by 30%-40% within 20 years, depending upon the number of risk factors present[10].Various studies have shown high prevalence of Metabolic syndrome in South Asians including India, probably due to high level of insulin resistance among them[11]

Aims and Objectives:

To study Prevalence of metabolic syndrome in rheumatoid arthritis and most common parameter contributing to metabolic syndrome in these patients

Material and Methods:

The present study was conducted in Postgraduate Department of Medicine, Government Medical College Srinagar and Associated Hospitals, Jammu and Kashmir, India over a period of 18 months in patients attending OPD clinic.The study was of prospective nature , and analytical cross sectional study. Ethical clearance was taken from the institution.

Inclusion criteria:

Two 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 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.

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.

Methodology

A total of 200 patients of rheumatoid arthritis who were willing to take part in the study and who had given informed written consent were randomly selected and recruited. Information about subject's age, sex, monthly income, life style, family history of diabetes and other diseases/disorders were recorded. Height, weight and waist

circumferences were measured with the subject barefooted and lightly dressed. The abdominal circumference (waist) was measured at the end of expiration. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured with special precaution individuals were requested to take 10 min rest at sitting position before measuring the BP. Blood pressure was measured by standardized protocols, and hypertension was defined based on the criteria of the Seventh Report of the Joint National Committee guidelines. According to this protocol, systolic and/or diastolic blood pressure ≥130/85 mmHg and/or the current use of antihypertensive medication in diabetes diagnosed as hypertension. Before registering for the study written consent was obtained from each participant

Blood sample (5ml) was collected from each subject. Plasma was separated by centrifuging blood and analyzed for fasting blood glucose,total cholesterol triglycerides and HDL cholesterol were estimated by CHOD-PAP **(12)**, triglycerides **(13)** and HDL-Cholesterol **(14)** was estimated by spectrophotometric assays employing commercially available kits. LDL and VLDL were calculated from Freidewald's formula.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as percentages. Frequency distribution tables, bar and pie charts were used for data presentation. Chi-square test or Fisher's exact test, whichever appropriate, was used to determine association between various categorical variables. P-value less than 0.05 was considered statistically significant. All P-values were two tailed.

Results:

The general characteristics of the 200 patients studied are shown in table1 .The mean age of patients was 48.2+12.1. Most common age group was 35-49 years with 38.4% patients belonging to this group and next 30.1% belonging to 50-64 years age group. Out of a total of 200 patients, 174 (86.8%) were females and 26 (13.2%) were males.ESR was elevated in 58 (29.8%) patients while as it was normal in 142(69%) patients. CRP was positive in 103(51.7%) patients while as it was negative in 97 (48.3%) patients.RF was more than 3 times elevated in 123(61.8%) patients, <3 times raised in 67(34%) patients and negative in only 8 (4%) patients. Anti CCP was more than 3 times elevated in 156 (77.9%) patients, <3 times raised in 13(6.5%) patients and negative in 31 (15.6%) patients. Duration of disease ranged from 1-10 years with a mean of 2.55 ± 2.09 years. The mean total cholesterol was 198.6 ± 43.6 mg/dl with a range of 109-320 mg/dl, whereas the mean HDL-C was 41 ± 8.2 mg/dl with a range of 26-60 mg/dl and a mean LDL-C of 109 ± 28 mg/dl with a range of 50-189 mg/dl. The mean triglycerides were 224.8 ± 89 mg/dl with a range of 69-470 mg/dl, were found to be increased as would be expected in inactive disease. The meanVLDL was 44.82 ±19 with a range of 13-120 mg/dl. The mean TC/HDL ratio was 4.98 ± 1.33 with a range of 2.4-10.

Table 1 – Characteristics of patients with rheumatoid arthritis included in study(n =200)

Parameter	Value (mean) and/or (%)
Female Gender (%)	*86.8%*
Age (mean ± SD)	*48±12.1*
Disease duration, years (mean ± SD)	2.55±2.09
Rheumatoid factor, positive (%)	95.5%
Anti-CCP (%)	*84.4%*
Current use of oral prednisone (%)	30.3%
Disease-modifying drugs used (%)	
Chloroquine	87.8%
Methotrexate	95.5%
Sulfasalazine	15.5%
Leflunomide	5.5%
Anti-TNF (infliximab, adalimumab and/or etanercept)	*0.5%*
Disease Activity Score 28 (DAS28) (mean ± SD)	*3.88±1.42*
Menopause (%)	*62%*
Metabolic syndrome prevalence (%)	*48.6%*
Hypertension (%)	*61.2%*
Triglycerides >150 mg/dL (%)	*38.6%*
Low HDL (<50 mg/dL in men and <40 mg/dL in women)	*60.1%*
Diabetes mellitus (%)	*27.6%*
Central obesity	*71.3%*
Sedentary lifestyles	*81.2%*

Ninety seven patients out of 200(48.6%) in the RA group and 24patients out of 100 (24%) in the control group were found to have metabolic syndrome utilizing NCEP: ATP III 2001 criteria for the metabolic syndrome modified for asian population and the difference was statistically significant (p<.0001). The most common abnormality noted in the RA group was elevated waist circumference (71.3%), elevated blood pressure (61.2%),low HDL (60.1%),elevated triglycerides (38.6%) and abnormal sugars (27.6%). However, elevated blood pressure ,low HDL, and abnormal sugars were the most significant difference between the RA and the control group (p<0.05) illustrated in table(2).

Table 2:comparison of parameters metabolic syndrome in rheumatoid arthritis (n=97)and controls(n=24).

Parameter	RA group	Control group	P value
Wc (centimeters)	69(71.3%)	17(70%)	0.745
Elevated bp (mmhg)	59(61.2%)	5(19%)	<0.0001
Low HDL (mg/dl)	58(60.1%)	10(40.9%)	<0.0001
Elevated TGs (mg/dl)	37(38.6%)	9(37%)	0.467
Abnormal sugars (mg/dl)	27(27.6%)	3(11%)	<0.0001

DISCUSSION

With an increase in prevalence of metabolic syndrome and increased morbidity and morality related to disease various studies have been done and still are being done to diagnose early and decrease the DALY related to condition, several studies on prevalence of MS in RA have already been performed worldwide, the frequency found varies from 14 to 63% among the various populations studied, not always the values found are higher than in controls, and the association of factors related to rheumatoid arthritis (disease activity, inflammatory markers, severity of the disease, treatment) with MS varies greatly in the literature as mentioned by **Karvounaris SA, Sidiropoulos et al** and **La Montagna G, Cacciapuoti F et al**[15,16,17].A frequent explanation for these discrepancies is the use of different criteria for MS classification. Patients of rheumatoid arthritis has increased Premature atherosclerosis which leads to adverse cardiovascular events and has a strong association with metabolic syndrome[18]. In our study mean age of patients was 48.2+12.1. Most common age group was 35-49 years with 38.4% patients belonging to this group and next 30.1% belonging to 50-64 years age group as was seen in study done by **Dr Mir Nadeem et al**[19]. In our study most of the patients where females 174 (86.8%) as was also seen by study conducted by **Naik M et al** [20]. The prevalence of metabolic syndrome in RA patients in present study was 46.8% and 24% in controls utilizing NCEP: ATP III 2001 criteria for the metabolic syndrome modified for asian population the results being in accordance to studies done by **Pandey PK et al** [21](39.28% in RA and 20 % in controls) and **Sharma A, Bhilave N et al**[22] (31.57%in RA and 14.9%). While evaluating the clinical and biochemical parameters of metabolic syndrome in study as well as control population The most common abnormality noted in the RA group was elevated waist circumference (71.3%), elevated blood pressure (61.2%),low HDL (60.1%),elevated triglycerides (38.6%) and abnormal sugars (27.6%). However, elevated blood pressure ,low HDL, and abnormal sugars were the most significant difference between the RA and the control group (p<0.0001) .These results are in accordance with observations made by **Rostom et al and Pandey et al**[21,23].

CONCLUSION:

- The prevalence of MS in RA is quite high as compared to general population.
- Most common parameter contributing to metabolic syndrome in study population as well as controls was waist circumference and least common being abnormal sugars but once comparison was made the statistically significant difference was seen in elevated blood pressure ,low HDL, and abnormal sugars.

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