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PREVALENCE OF METABOLIC SYNDROME IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ITS CORRELATION WITH DISEASE ACTIVITY-A CASE CONTROL STUDY

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ABSTRACT

Background: Accelerated atherosclerosis due to chronic inflammation is the proposed reason for the increased cardiovascular disease related events in rheumatoid arthritis patients. An increased prevalence of metabolic syndrome is also studied worldwide. **Objectives:** To study the prevalence of metabolic syndrome in patients with rheumatoid arthritis and its correlation with disease activity. **Methodology:** A case controlled study was conducted in 80 patients with rheumatoid arthritis and 100 controls without rheumatoid arthritis were studied. Details were obtained in structured format. Prevalence of metabolic syndrome defined by NCEP ATP III criteria among cases and control group was estimated. Disease activity was measured using DAS 28 score based on ESR. **Results:** Statistically significant increased prevalence of diabetes mellitus was noticed in RA group (58.8%) when compared to the control group (33%). Among RA group 50% were overweight and 16.3% were obese. Among control group 32% were overweight and 11% were obese. An abnormal BMI was observed in 66.3% of cases and 43% controls which was statistically significant. {Odds ratio 2.602. 95% CI for OR= 1.415-4.787}. Metabolic syndrome was observed in 42.5% of patients in RA group when compared to 18% in the control group. {Odds ratio 3.367. 95% CI for OR= 1.713-

6.619. The mean DAS score in RA patients with and without metabolic syndrome was 5.4656 and 4.6598 respectively. **Conclusion:** The prevalence of abnormal body mass index, type 2 diabetes mellitus and metabolic syndrome are significantly high patients with rheumatoid arthritis. Disease activity is high in patients with rheumatoid arthritis and metabolic syndrome when compared to patients with rheumatoid arthritis without metabolic syndrome.

KEYWORDS: Rheumatoid arthritis, metabolic syndrome, Disease activity, DAS-28 score, body mass index, tender joint count, swollen joint count.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis of autoimmune etiology, with a prevalence of 0.5%–1%, seen predominantly in females. The hallmark of this disease is disfiguring joint deformities and several other extra articular manifestations. The incidence of this disease is highest in the age group between 25 and 55 years.[1] The classical clinical manifestation includes symmetrical polyarthritis, predominantly of small joints of hands and feet and large joints such as shoulder, elbow and knee joints. The extra articular manifestations include neurological and hematological abnormalities, pulmonary manifestations, subcutaneous nodules and vasculitis. Patients can develop joint destruction, severe physical disability and multiple co-morbidities, but some may have only a self limited illness.[2] Diagnosis of rheumatoid arthritis is based on clinical symptoms and signs and serological markers. The 1987 American College of Rheumatology (ACR) criteria and the revised version published in 2015 are well accepted classification criteria, but they are primarily meant for the purpose of differentiating established cases of rheumatoid arthritis from related rheumatological conditions. As they are not useful for the early detection of RA, a joint working group of both the ACR and European League Against Rheumatism (EULAR) was formed, and a new classification criteria for RA was developed, the "2010 ACR/ EULAR" Classification criteria for RA. Disease Activity Score with 28-joint counts [DAS28] for measuring disease activity is widely used in various clinical trials. This scoring system makes use of information regarding the number of swollen and tender joints, a measure of general health, and the acute phase response of either ESR or CRP to assess the severity of the disease and to check whether the disease is in remission. A score of 3.2 is defined as the threshold for low disease activity and 2.6 as the threshold for remission.[3]

Metabolic syndromes (MetS) include central obesity as a measure of visceral adiposity, systemic hypertension, an elevated triglyceride level, hyperglycemia, and low high-density

lipoprotein cholesterol.[4] There are various criteria to diagnose MetS. The most commonly used are the World Health Organization (WHO), American Association of Clinical Endocrinologists (AACE), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), the European Group for the Study of Insulin Resistance (EGIR) and the International Diabetes Federation (IDF).[5] Of these, the first three are mainly focused on insulin resistance, and the last two (NCEP ATP III and IDF) are mainly used for clinical and epidemiological purposes.[2] The most commonly used criteria for definition at present are from the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF).

The prevalence of MetS in RA is 35.5%, and 8.6% in controls, according to the NCEP III criteria 2001. According to IDF criteria, MetS was prevalent in 46% of patients and in 17.9% of controls.[6] Other studies using NCEP III 2001 criteria showed a prevalence of 21.6%, with a 7.7%. prevalence among men and 33.6% among women.[7] A 30% prevalence of MetS turned out to be 24.8% after adjusting for age in a study in a rural district.[8] Salaroli et al. reported a 29.8% prevalence of MetS in the city of Vitoria.[9] All these studies used the NCEP/ ATPIII 2001 criteria for metabolic syndrome. The result of studies regarding prevalence of MetS in RA revealed an increased prevalence of insulin resistance and low HDL in the RA group. A 2008 study found that the prevalence of MetS in RA patients with long-standing disease is 42%, compared to 11% for controls.[10] Elkan et al. studied the prevalence of rheumatoid cachexia and MS in patients with rheumatoid arthritis, finding a high prevalence of central obesity of 57% for women and 89% for men. Hypertension was observed in 69% and metabolic syndrome in 25% in spite of cachexia in patients with long-standing arthritis.[11] Several studies have reported a high prevalence of MetS in patients with systemic rheumatic diseases.[10, 11, 12] It is proposed that chronic inflammation can predispose to endothelial dysfunction plaque rupture and thrombosis.[13] The human leukocyte antigen-DR4 and -DRB1, and a variety of alleles called the shared epitope are considered important genetic factors. Studies have shown that additional genetic signatures increase the risk of RA and other autoimmune diseases, including STAT4 gene and CD 40 locus.[14]

It is well established that the most common cause of mortality in patients with rheumatoid arthritis is cardiovascular disease.[15] An increased level of proinflammatory cytokines can

cause endothelial dysfunction and accelerated atherosclerosis. Also, an elevated level of cytokines can make muscle and adipose tissue resistant to the effects of insulin. This will create a state of metabolic syndrome.[16] Therefore, in addition to an established cause such as endothelial dysfunction and resulting accelerated atherosclerosis, an increased prevalence of metabolic syndrome is also proposed to play an important role in the incidence of cardiovascular morbidity in patients with rheumatoid arthritis. Current studies indicate that the causes of deaths occurring in rheumatoid arthritis could be directly linked to ischemic heart disease and heart failure.[17]

Our study aimed to identify the prevalence of metabolic syndrome in patients with rheumatoid arthritis compared to age- and sex-matched controls without rheumatoid arthritis. Further, we attempted to identify the correlation between metabolic syndrome and disease activity in patients with rheumatoid arthritis.

MATERIALS AND METHODS

A case control study was conducted among patients attending rheumatology outpatient clinic, under the Department of Internal Medicine and patients admitted to medical wards of Internal Medicine, Government Medical College Hospital, Thiruvananthapuram. The study group comprised 80 patients who are diagnosed cases of rheumatoid arthritis attending rheumatology outpatient department and those admitted to the wards and 100 age- and sex-matched apparently healthy volunteers recruited from medical and paramedical staff formed the control group. Patients who had already been diagnosed with rheumatoid arthritis and who were attending the rheumatology outpatient department or had been admitted to the general medicine wards were identified. Those who satisfied the 1987 American College of Rheumatology (ACR) classification criteria were selected for the study group. Patients with rheumatoid arthritis were informed about the study in their native language. After the exclusion criteria were satisfied and informed consent was obtained, the structured pro forma was completed, with relevant data were collected. Those who belonged to the control group also provided written consent to take part in the study. Metabolic syndrome was defined according to the NCEP ATP III criteria 2001 version for which the necessary anthropometric measurements such as height, weight and waist circumference were measured. Clinical examination was conducted to record blood pressure, tender joint count and swollen joint count. Blood samples were sent to estimate fasting blood sugar, fasting lipid profile and erythrocyte sedimentation rate (ESR). Disease activity was measured using the DAS 28

calculator based on ESR which is available online from the data collected. Data analysis was done in SPSS 15. Prevalence of metabolic syndrome was estimated in both case and control group. Mean DAS 28 score was estimated in patients with rheumatoid arthritis with and without metabolic syndrome.

RESULTS

The mean age of the study population was 46.91 (sd=9.14) and 48.06 (sd=9.40) years for cases and controls respectively. The mean age for metabolic syndrome was 47.00 (sd=9.22) years among cases and 46.85 (sd=9.18) for controls, though a statistical significance was not obtained. The case group comprised 25% males and 75% females. A comparable male to female ratio was maintained in the control group, with 24% males and 76% females.

Table 1: Distribution of Diabetes Mellitus in patients with rheumatoid arthritis and control group.

Diabetes Mellitus	*Category*				*Total*	
	Case		Control			
	N	%	N	%	N	%
Present	47	58.8	33	33.0	80	44.4
Absent	33	41.3	67	67.0	100	55.6
Total	80	100.0	100	100.0	180	100.0

χ^2 =11.935 df=1 p=0.001 OR = 2.892 95% CI for OR= 1.571-5.321

Statistically significant increased prevalence of diabetes mellitus was noticed in RA group (58.8%) when compared to the control group (33%). {Odds Ratio = 2.892. 95% CI for OR= 1.571–5.321}. (Table 1).

Table 2: Distribution of BMI in study population.

BMI	*Category*				*Total*	
	Case		Control			
	N	%	N	%	N	%
Abnormal	53	66.3	43	43	96	53.3
Normal	27	33.8	57	57	84	46.7
Total	80	100	100	100	180	100

χ^2 =9.653 df=1 p=0.002 OR = 2.602 95% CI for OR= 1.415–4.787

About 66.3% of patients with RA had abnormal BMI whereas 43% in the control group had abnormal BMI. Among the RA group, 50% were overweight and 16.3% were obese, whereas

among the control group 32% were overweight and only 11% were obese. {Odds ratio 2.602. 95% CI for OR= 1.415–4.787}. (**Table 2**).

Table 3: Distribution of metabolic syndrome in study population.

Metabolic syndrome	*Category*				*Total*	
	Case		Control			
	N	%	N	%	N	%
Present	34	42.5	18	18	52	28.9
Absent	46	57.5	82	82	128	71.1
Total	80	100	100	100	180	100

χ^2 =12.986 df=1 p<0.001 OR = 3.367 95% CI for OR= 1.713–6.619

Among patients in the RA group, 42.5% were found to have metabolic syndrome when compared to 18% in the control group. {Odds ratio 3.367. 95% CI for OR= 1.713–6.619} (Table 3).

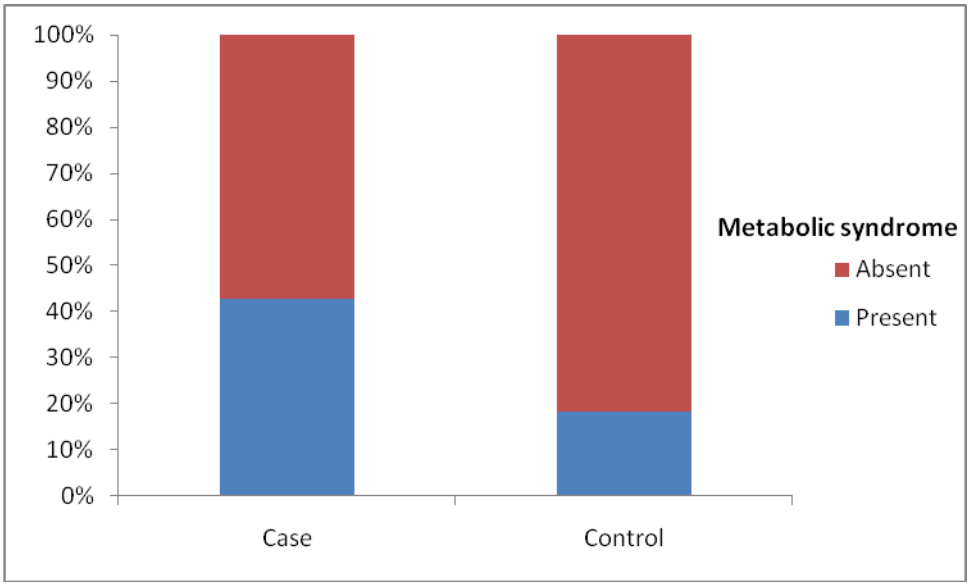

Figure 1: Distribution of metabolic syndrome in study population.

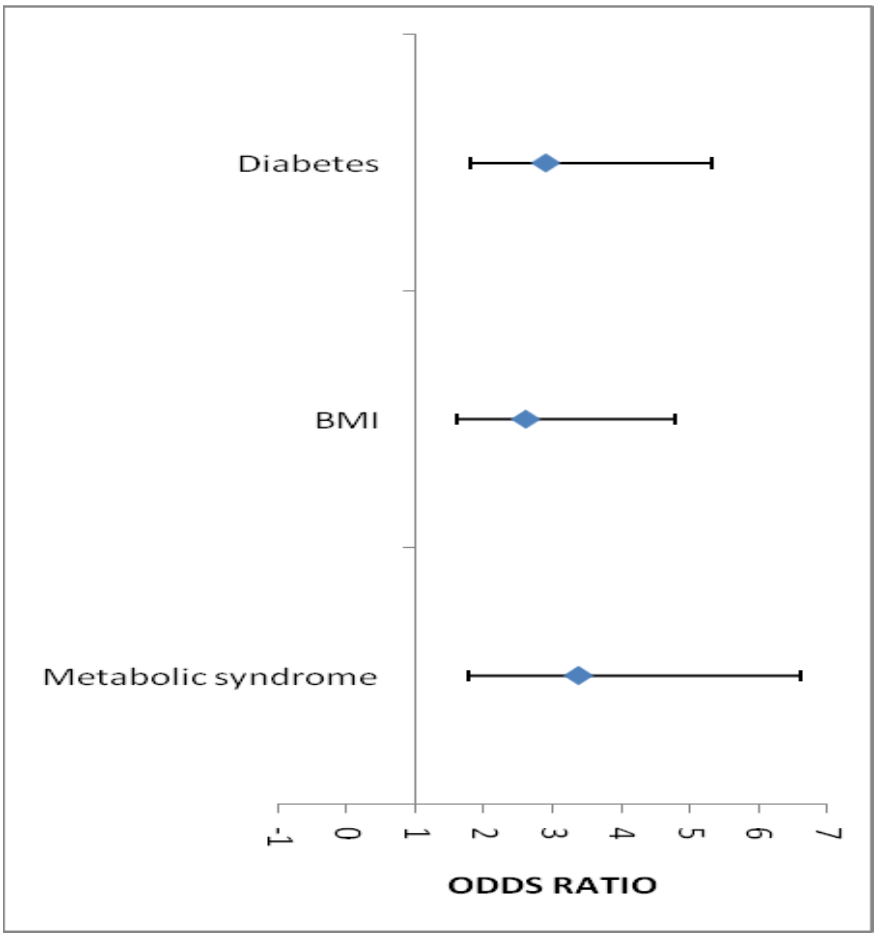

Figure 2: Forest plot describing the odds ratios of diabetes, BMI and metabolic syndrome.

Table 4: Demographical and biochemical parameters of cases and control.

	Case		Control			
	mean	sd	mean	sd	t	p
Age in years	46.91	9.14	48.06	9.40	-.824	.411
Systolic blood pressure	120.30	17.52	116.74	16.40	1.404	.162
Diastolic blood pressure	79.40	10.44	76.92	8.92	1.718	.088
BMI	26.47	3.58	24.75	3.58	3.209	.002
Waist circumference in cm	84.34	10.75	78.27	10.98	3.718	<0.001
Head circumference in cm	85.98	10.82	80.33	10.54	3.529	.001
ESR	54.94	23.31	18.65	9.46	14.184	<0.001
FBS (mg/dL)	120.89	39.08	106.73	36.87	2.492	.014
Total cholesterol (mg/dL)	161.01	22.66	162.04	22.78	-.301	.763
HDL(mg/dL)	42.78	8.93	47.73	9.47	-3.577	<0.001
LDL(mg/dL)	134.99	20.82	117.45	18.52	5.974	<0.001
VLDL(mg/dL)	34.45	7.42	28.14	6.69	5.990	<0.001
Triglyceride (mg/dL)	139.54	19.34	126.64	19.25	4.457	<0.001

Age and gender indices were similar in the control group and the patients with RA (p>0.05); BMI, waist circumference (WC), LDL, HDL, VLDL and triglyceride values of RA group were significantly higher than those of the control group (p<0.05). There was no significant difference in the prevalence of systemic hypertension between cases and control (p>0.05) (Table 4).

Table 5: Demographic and biochemical parameters of subjects with metabolic syndrome in RA group and control group.

Metabolic syndrome group	Category				t	p
	case (n=34)		Control (n=18)			
	mean	sd	mean	sd		
Age	47.00	9.22	50.22	10.92	1.125	.266
SBP	129.41	20.29	138.89	20.55	1.595	.117
DBP	84.41	12.60	90.00	10.29	1.616	.112
BMI	29.60	2.20	29.50	3.30	.201	.841
Waist circumference in cm	94.15	6.89	93.39	10.60	.312	.756
Head circumference in cm	95.94	6.22	95.33	10.36	.265	.792
ESR	66.82	19.98	18.50	8.50	9.767	<0.001
FBS	144.88	35.41	152.61	47.46	.664	.510
Total cholesterol	175.82	21.54	175.61	21.69	.034	.973
HDL	36.88	5.78	40.39	10.30	1.578	.121
LDL	144.47	18.14	135.56	15.11	1.781	.081
VLDL	38.44	6.12	32.67	8.40	2.839	.007
TG	152.35	16.26	147.44	15.78	1.046	.301

In patients with metabolic syndrome, those with rheumatoid arthritis had a higher mean value for BMI, waist circumference, LDL, total cholesterol and triglycerides, whereas a higher mean value in diastolic and systolic BP, fasting blood glucose and HDL cholesterol levels were observed in those without rheumatoid arthritis (Table 5).

Table 6: Comparison of DAS score between metabolic syndrome and non-metabolic syndrome among RA.

Metabolic syndrome	N	DAS score		t	p
		Mean	sd		
Present	34	5.47	.85	4.143	<0.001
Absent	46	4.66	.87		

Average DAS score in patients with RA and metabolic syndrome was 5.47±0.85, which was suggestive of high disease activity. In patients with rheumatoid arthritis without metabolic syndrome, the equivalent value was 4.66±.86, which indicates moderate disease activity (Table 6).

DISCUSSION

The mean age of the study population was 46.91 (sd=9.14) and 48.06 (sd=9.40) years for cases and controls respectively. Though no age is exempt, RA occurs maximally between the ages of 30 and 50 years.[18, 19] Several studies have shown that RA usually develops in the fifth decade of life.[20] Our findings correlate well with those of these studies, and the proposed causes for this phenomenon are prolonged exposure to environmental antigens causing activation of immunity, stress and thymic depression.[21] The effect of estrogen in T cell functioning could be the reason for the female predilection evidenced in our study, in correlation with other studies, which showed distribution of 25% males and 75% females, with a comparable male to female ratio maintained in the control group, with 24% males and 76% females. Similar results (3:1 male to female ratio) were observed in a study by Al-Temimi et al.[22] A statistically significant increased prevalence of diabetes mellitus was also noticed in the RA group (58.8%) when compared to the control group (33%), and this was consistent with numerous other studies. especially Jiang et al. who demonstrated the increased prevalence of type 2 diabetes mellitus in patients with rheumatoid arthritis.[23] Studies revealed that the association between diabetes and the risk of arthritis is 1.61 (95% CI: 1.14–2.28), which indicates that arthritic patients are 61% more likely to have diabetes than are those without arthritis.[24]

The risk of CVD in RA was significantly elevated compared with the general population, and comparable with the magnitude of risk in type 2 DM.[15]

The prevalence of systemic hypertension obtained in this study is 30% among cases, and 20% among controls, which is unusually low. Studies have shown that the prevalence of systemic hypertension may range from 51.7% to 73% in patients with RA.[25] The relatively low mean age of the study population could have been the reason for the low prevalence of systemic hypertension in this study. A mean SBP and DBP value was higher in the control group in this study (with a p value of 0.117 and 0.112 respectively). The increased detection of hypertension in RA with MetS seen in our study correlates well with other studies. This issue is usually less detected and undertreated in RA. It will be appropriate to plan strategies to diagnose and to give timely intervention so that the functional capacity of these patients can be benefitted.[25]

Body mass index was also observed in this study, and revealed an abnormal BMI in 66.2% of patients with RA, whereas 43% in the control group had abnormal BMI. Among the RA

group, 50% were overweight and 16.3% were obese, whereas 32% were overweight and only 11% were obese among the control group.

A statistically significant decrease of mean HDL values was observed among cases compared to controls, which increases the inflammatory burden in cases with RA and can make them more prone to increased prevalence of coronary heart disease in patients with MetS.[12, 16] Moreover, a low HDL value in patients with rheumatoid arthritis was described by Karvounaris et al.[12] The insulin resistance and dyslipidemia encountered frequently in patients with long-standing RA have important implications for the management of inflammatory arthritis which can make them more prone for increased prevalence of coronary heart disease.[27] There was an increased LDL level in the RA group compared to the controls. There was an elevated level of mean VLDL among the RA group compared with the control group. The mean triglyceride value also showed significant difference between the RA and control groups (mean value of 139 +/- 19.34 in RA group and 126.64 +/- 19.25).[28]

Although in this study MetS was defined using the NCEP ATP III criteria[5] the actual prevalence of metabolic syndrome may vary in different places and according to the definitions used.[29] Highest prevalence is observed with IDF criteria and lowest with EGIR criteria.[30] Using NCEP criteria the prevalence showed a wide range, from 17% in Mexicans to 44% in Greeks (31). Our study showed a prevalence of 18% among controls.

In this study the prevalence of MetS was found to be significantly higher in the case group compared to the control group. Similar observations were made by Karvounaris et al. revealing a higher prevalence of MetS in RA group (44%) and lower in controls (41%).[19] Similar studies by da Cunha et al. showed a prevalence of 39.2% of MetS in RA group and 19.5% in control.[32]

In another study by Crăciun Lucia et al. the prevalence and pattern of metabolic syndrome was compared in patients with rheumatoid arthritis and psoriatic arthritis. According to this study the prevalence of metabolic syndrome in patients with rheumatoid arthritis was 37.2% and 67.5% in patients with psoriatic arthritis. The proportion of those with elevated fasting glucose and elevated triglycerides were 25% and 11% respectively.[33]

Disease activity was measured using DAS 28 score based on ESR in this study. The mean DAS score was significantly higher in RA patients with metabolic syndrome (5.4656 +/-

0.85087) than with RA patients without metabolic syndrome. (4.6598 +/- 0.86646). This was consistent with reports by Dao et al. that the mean DAS 28 score was significantly higher in patients with metabolic syndrome and rheumatoid arthritis compared to RA patients without metabolic syndrome.[31] Similar observations are proposed by Iván Ferraz-Amaro, in which DAS 28 was significantly higher in RA patients with MetS than in those without (3.59 ± 1.27 versus 3.14 ± 1.53; *P* =0.01).[34]

Karvounaris et al. showed that the RA group had a low HDL cholesterol level compared to the control group (p=0.02) but an increased waist circumference and raised blood pressure value was obtained in the control group with a p value of 0.01 and 0.03 respectively. A mean low HDL value is observed in the RA group in our study with p value of 0.121.[12] In another cohort studied by La Montagna et al. with RA and 48 controls without any systemic rheumatologic disease, it was observed that the prevalence of MetS was 55.5% in patients with RA and 45.8% in patients without RA. Another factor observed was higher prevalence of insulin resistance in RA, possibly attributed to steroid therapy.[35] There is a need to carefully evaluate patients with RA for metabolic syndrome, which is often ill addressed and which can detrimentally affect the course of the disease and functional status of the patient

CONCLUSION

The prevalence of abnormal body mass index, type 2 diabetes mellitus and metabolic syndrome are significantly high among patients with rheumatoid arthritis. Disease activity is high in patients with rheumatoid arthritis and metabolic syndrome when compared to patients with rheumatoid arthritis without metabolic syndrome.

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Abbreviations

AACE: American Association of Clinical Endocrinologists

ACR: American College of Rheumatology

CRP: C Reactive Protein

DAS:Disease activity score

EGIR:European Group for the study of Insulin Resistance

ESR: Erythrocyte sedimentation rate

EUKAR:European League Against Rheumatism

IDF: International Diabetes Federation

NCEP ATP III:National Cholesterol Education Programme Adult Treatment Panel III

METs:Metabolic syndromes

RA:Rheumatoid arthritis

WHO:World Health Organization