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A Cross Sectional Study On Prevalence Of Prediabetes And Diabetes In Patients Of Rheumatoid Arthritis Attending Rheumatology Clinic In A Tertiary Care Centre In Eastern India

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Abstract:
Background: *Rheumatoid arthritis is a chronic inflammatory disease associated with elevated risk of cardiovascular diseases compared to the general population. Although there has been constant progress in management of RA with passage of time, there is still relative lack of awareness among the patients and health care providers alike regarding detection and effective management of CVD risk factors in RA patients, Diabetes Mellitus (DM) being one of the most important factors among them. Several studies have probed in to the prevalence of DM in RA patients and ended up with conflicting results. In this background, we conducted a cross-sectional study among RA patients to assess the prevalence of DM among RA patients in a tertiary care centre in eastern metropolitan area of India. (Kolkata)*
Materials and methods*: For the present study we enrolled 137 consecutive non diabetic RA patients and equal number of age and gender matched subjects suffering from non-inflammatory arthritis (fibromyalgia or osteoarthritis) attending rheumatology clinic in Medical College & Hospital, Kolkata. Following overnight fasting, blood samples were drawn for laboratory evaluation including serum glucose, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, total cholesterol, triglycerides, uric acid, high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-Cyclic Citrullinated peptide Antibodies (ACPA). Each study participant was subjected to a standard 75 g oral glucose tolerance test (OGTT) and blood sample was obtained after 2 hours for measurement of plasma glucose level.*
Result: *Prevalence of impaired fasting glucose(IFG)(15/137 vs 13/137.P=0.689), impaired glucose tolerance (IGT) (21/137 vs 17/137, P=0.483), or concomitant IFG/IGT (8/137 vs 7/137, P=0.787) was not statistically significant between the two groups but there was significantly increased prevalence of diabetes among the RA patients (17/137 vs 5/137, P = 0.008). A correlation analysis was performed between different disease related variables and fasting blood glucose and 120 minute post load glucose level which demonstrated both FBS and PPBS to be significantly positively correlated with patient age, BMI, waist circumference, SBP, DBP, DAS 28-CRP, hs-CRP, total cholesterol, LDL, triglycerides and serum uric acid level. Additionally PPBS was significantly positively correlated with ESR. Both FBS and PPBS showed significant negative correlation with serum HDL level.*
Conclusion: *As per our study there is increased prevalence of diabetes among RA patients. Increased disease activity raises the likelihood of being detected with diabetes.*
Keyword: *Rheumatoid arthritis, diabetes mellitus, cardiovascular disease*

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I.Introduction:

Rheumatoid arthritis is a chronic inflammatory disease, with usual accompanying complications of local joint deformities and varied extraarticular manifestations including the cardiovascular, respiratory and the renal system. Undoubtedly, cardiovascular disease is the most common and most feared complication of Rheumatoid arthritis.[1] The coexistence of the classic CVD risk factors including Diabetes with elevated systemic inflammatory markers may escalate the risk of adverse cardiovascular outcomes in RA patients.[2],[3]

RA is accompanied by chronic inflammation which raises the level of proinflammatory cytokines in the body like IL-6,IL-1β,TNF-α etc. Raised inflammatory markers in the circulation is associated with accelerated lipolysis which elevates level of free fatty acids (FFA) in the circulation. Free fatty acids may accelerate apoptosis of the pancreatic β cells. Hence RA may be linked with increased risk of insulin resistance and glucose intolerance. Several categories of individuals have been found to be at higher risk of diabetes. The American diabetes association (ADA) has proposed a stratification based on oral glucose tolerance test (OGTT) to detect individuals with "prediabetes". [4] ADA criteria classifies patients as normotolerant (NGT) if fasting plasma glucose (FPG) <100 mg/dl and 2 hr postload glucose <140 mg/dl and impaired glucose tolerance (IGT) if FPG<100 mg/dl and 2 hr post load glucose is 140-199 mg/dl and diabetes if FPG is >125 mg/dl and 2 hr post load glucose is >200 mg/dl; patients categorized as IFG and IGT or in combination are considered as prediabetic Prediabetic individuals are predisposed to accelerated progression to type 2 diabetes mellitus (T2DM). One study found that incidence rate of T2DM to be 47.4 per 1000 person years in case of IFG and a rate of 70.4 per 1000 persons years for combined IFG+IGT.[5] In addition to that prediabetes has been found to be independently associated with increased cardiovascular mortality.[6]

Although several groups have conducted different studies across the globe probing the relationship between RA and T2D, the results were conflicting. The difference in susceptibility to T2D in different geographical locations is a major impediment to formulate a generalization from these studies. The current study is a cross-sectional study aimed at exploring the prevalence of prediabetes and diabetes in RA patients in Eastern India.

II.Methods:

Study design and patients

Approval for the study protocol was obtained from local Ethics Committee (Ethics Committee, Medical College and Hospital,Kolkata,India). Informed consent was secured from all the participants of the study. For the present study, 137 RA patients attending the Rheumatology clinic in Medical College and Hospital,Kolkata were recruited in a consecutive fashion during a 18 months study period (Jan'2021 to June'2023). Equal number of age and gender matched subjects were recruited as controls who were referred to our clinic with musculoskeletal complains but all the autoimmune, infectious or neoplastic causes were ruled out after thorough clinical, biochemical and imaging evaluation. This group was composed of subjects with different non-inflammatory conditions like fibromyalgia (n=27), osteoarthritis (n=61) and other noninflammatory musculoskeletal conditions ((n=49).

Inclusion criteria was set as individuals >18 years of age and those satisfying the 2010 American College of Rheumatology (ACR)/EULAR classification criteria for RA. Exclusion criteria was predefined as those having past diagnosis of T2DM done by a physician prior to the onset of RA and individuals on antidiabetic medications (including oral antidiabetic drugs and insulin) before the onset of RA.

Definition of T2D,IFG & IGT:

Screening for diabetes was conducted as per 2009 American Diabetic Association (ADA) 2009 recommendation. Subjects were put on overnight fasting and then blood sample was drawn for measuring fasting plasma glucose. Subsequently 75 gm oral glucose tolerance test (OGTT) was performed on each of the subjects and blood sample was taken after 2 hours for post load blood glucose level. A patient was considered normoglycemic if fasting blood glucose (FPG) was <100 mg/dl and 2 hr post load blood glucose was <140 mg/dl. A patient was considered to have impaired fasting glucose (IFG) if FPG was 100-125 mg/dl and 2 hr post load plasma glucose <140 mg/dl. A subject was considered to have impaired glucose tolerance (IGT) if FBG <100 mg/dl and 2 hr post load glucose was 140-200 mg/dl. Subject was considered to have both impaired fasting glucose/impaired glucose tolerance (IFG/IGT) if FPG was 100-125 mg/dl and 2 hr post load glucose was 140-200 mg/dl. A person was considered diabetic (T2D) if FPG>125 mg/dl and/or 2 hr post load glucose >200 mg/dl.

Clinical severity and assessment of disease activity:

Relevant data was gathered from the subjects including RA features and disease related complications (extra articular features and/or prior history of RA related joint surgery), smoking history, demographic characteristics, associated comorbidities including metabolic syndrome, hypertension, and obesity, and related medications.

Height and weight was measured from each subject wearing light clothing without shoes. The nearest 0.1 cm was taken as value of height and nearest 0.1 kg was considered for value of weight. Body mass index was calculated applying the standard formula:

$BMI = Weight/Height^2$

Waist circumference was measured at a level midpoint between the lower margin of lowest rib and the iliac crest. Systolic (SBP) and diastolic (DBP) was measured over the left arm using well calibrated aneroid sphygmomanometer, with patient's back reclining on a chair, after resting for five minutes and arm put at level of heart. For assessment of disease activity, disease activity score including 28 joints (DAS28-CRP) was calculated. DAS28-CRP is a composite index comprising of number of swollen joints (SJC), number of tender joints (TJC), global assessment of health by patient taken on a visual analog scale (GH-VAS, range 0-100 mm), and concentration of high-sensitivity C-reactive protein (hs-CRP, mg/L).

Laboratory evaluation:

Blood sample was obtained from each individual after overnight fasting. Fasting plasma glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, serum uric acid were measured using automated chemistry analyzer. Hs-CRP was measured using immunonephelometric method. Erythrocytes sedimentation rate (ESR) was measured using capillary photometry. Serum rheumatoid factor (RF) was measured by nephelometry. Anti Citrullinated peptide antibodies were measured by chemiluminiscent immunoassay.

OGTT and case definition for insulin sensitivity:

A standard OGTT was conducted for each subject as per World health organization recommendation. Following overnight fasting, the subjects were asked to drink 75 gm of anhydrous glucose dissolved in 200 ml of water over a duration of 5 minutes; blood samples were collected at time 0 and 120 minutes following glucose load and plasma glucose concentration was measured.

Statistical analysis:

A sample size of at least 137 patients and 137 controls were estimated assuming an error of 5% on either side of the proportion of 95% confidence interval. For this calculation, population size was set at 600 individuals, corresponding to the estimated number of RA patients visiting our Rheumatology clinic with in the study period. According to a previous study prevalence of T2DM in RA patients was found to be 13.6%. The final corrected sample size was obtained by applying Cochran formula for finite population correction.

For statistical analysis data were analyzed by Statistics Package for Social Sciences (SPSS for Windows, version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentage for categorical variables. Student's *t-test* was used for comparing mean between two groups. One-way analysis of variance (one-way ANOVA) was used to compare means between three or more samples for numerical data (using the F distribution). A chi-square test (χ^2 test) or Fisher's exact test was used for comparing prevalence. A P-value of 0.05 was considered to be statistically significant.

III.Results:

General characteristics of the study participants are depicted in table 1. In comparison to the control group RA patients were found to have a significantly higher SBP (135.02 + 9.75 mm Hg vs 124.80 + 10.74 mm Hg, $P < 0.001$), higher DBP (83.08 + 4.89 mm Hg vs 78.07 + 6.64 mm Hg, $P < 0.001$), higher ESR (23.98 + 8.51 mm/h vs 12.30 + 4.95 mm/h, $P < 0.001$), higher hs-CRP (6.31 + 1.66 mg/L vs 1.74 + 0.46 mg/L, $P < 0.001$), higher serum uric acid (5.13 + 1.18 mg/dL vs 4.72 + 0.77 mg/dL, $P = 0.002$), higher FBS (97.84 + 16.50 mg/dL vs 93.48 + 15.59 mg/dL, $P = 0.025$), higher PPBS (141.42 + 39.83 mg/dL vs 127.67 + 31.78 mg/dL, $P = 0.002$), whereas no significant difference was observed for BMI, waist circumference, total cholesterol, HDL, LDL, triglycerides.

Table 1:Clinical characteristics of study population

	RA	Control	P value
Males	26	26	1.000
Age (years)	51.71 + 9.95	51.69 + 9.80	0.985
Weight (Kg)	64.52 + 10.05	63.45 + 8.89	0.350
BMI (Kg/m^2)	22.99 + 2.88	23.78 + 1.77	0.607
Waist (cm)	92.96 + 7.01	92.35 + 9.19	0.583
SBP (mm Hg)	135.02 + 9.75	124.80 + 10.74	0.000
DBP (mm Hg)	83.08 + 4.89	78.07 + 6.64	0.000
Disease duration (months)	43.34 + 22.66	-	NA
Total joint count (n)	6.48 + 2.22	-	NA
Swollen joint count (n)	2.65 + 1.54	-	NA
DAS28-CRP	4.18 + 0.70	-	NA
ESR (mm/h)	23.98 + 8.51	12.30 + 4.95	0.000
hs-CRP	6.31 + 1.66	1.74 + 0.46	0.000
Total cholesterol (mg/dL)	204.03 + 34.29	210.01 + 30.59	0.129

HDL (mg/dL)	53.02 + 7.69	53.18 + 15.25	0.912
LDL (mg/dL)	128.07 + 25.58	130.93 + 30.15	0.400
TG (mg/dL)	125.85 + 47.59	133.79 + 78.56	0.313
UA (mg/dL)	5.13 + 1.18	4.72 + 0.77	0.001
FBS (mg/dL)	97.84 + 16.50	93.48 + 15.59	0.025
PPBS (mg/dL)	141.42 + 39.83	127.67 + 31.78	0.002
BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, ESR = Erythrocytes sedimentation rate, hs-CRP = high sensitivity C reactive protein, HDL = high density lipoprotein, LDL = low density lipoprotein, TG = serum triglycerides level, UA = uric acid			

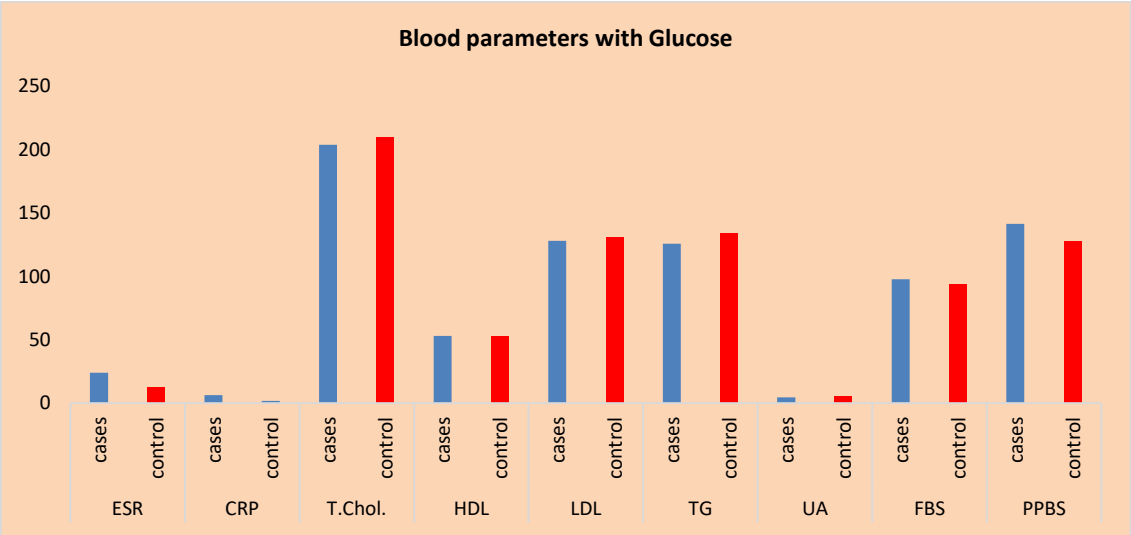

Fig 1 : Bar diagram showing the distribution of different blood parameters between cases and controls

Table 2 is showing distribution of different glycemic categories among the cases and controls. There is significant difference in prevalence of normal glucose tolerance (NGT) and T2DM among the cases and controls, although no significant difference has been noted in prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both (IFG/IGT) among the two groups.

Table 2: distribution of different glycemic categories among cases and controls:

		Group, 1=cases, 2=control		P-VALUE
		CASES	CONTROL	
category	IFG(n)	15	13	0.689
	IFG/IGT(n)	8	7	0.787
	IGT(n)	21	17	0.483
	NGT(n)	76	95	0.018
	T2DM(n)	17	5	0.008

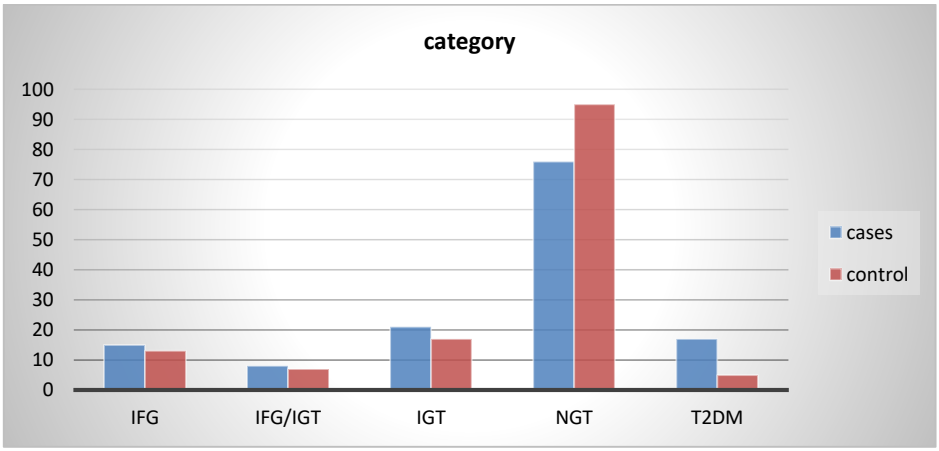

Fig.2 : Multiple bar diagram showing prevalence of different glycemic categories among the cases and the controls

Comparison was done for prevalence of different glycemic categories among different treatment arms, but no significant difference was noted.

Table 3: the distribution of cases according to administration of biologics & glycemic status:

Glycemic status	Receiving biologics?		P value
	No	Yes	
NGT	69	7	0.205
IFG	15	0	
IGT	21	0	
IFG/IGT	8	0	
T2DM	17	0	
Total	130	7	

As p value >0.05, there is no significant difference among different glycemic categories as per bDMARDs therapy.

Table 4: Distribution of cases according to synthetic DMARDs therapy and glycemic status:

Glycemic status	sDMARD name				P value
	Lefra,Hcqs,Ssz	Mtx,Hcqs	Mtx,Ssz	Mtx,Ssz,Hcqs	
NGT	4	2	2	68	0.939
IFG	1	0	0	14	
IGT	0	1	0	20	
IFG/IGT	0	0	0	8	
T2DM	1	0	1	15	
Total	6	3	3	125	

(sDMARD = synthetic disease modifying anti rheumatic drug)

There is no significant difference of glycemic status as per different sDMARDs combination therapy.

Predictors related to prediabetes and diabetes:

A correlation analysis was performed between various disease related variables and fasting blood sugar(FBS) and 120 min-Post prandial blood sugar level which showed significant correlation of age, weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, DAS28-CRP, hs-CRP, serum total cholesterol, HDL, LDL, uric acid, triglycerides with 120 min-post prandial blood glucose level.When fasting blood glucose level was deemed as dependant variable it showed significant correlation with age, weight, BMI, waist, systolic blood pressure, diastolic blood pressure, DAS28-CRP, ESR, hs-CRP, serum total cholesterol, HDL, LDL, uric acid, triglyceride level.

Table 5: showing correlation of different disease related variables with post prandial blood sugar level in RA patients:

Disease related variables	Pearson's correlation coefficient	P value
Age	0.301	0.000
Weight	0.229	0.007
BMI	0.214	0.012
Waist circumference	0.266	0.002
SBP	0.301	0.000
DBP	0.292	0.001
DAS28-CRP	0.212	0.013
hs-CRP	0.211	0.013
Total cholesterol	0.366	0.000
HDL	-0.195	0.022
LDL	0.388	0.000
Uric acid	0.356	0.000
Triglyceride	0.209	0.014

Table 6: showing correlation of different disease related variables with fasting blood sugar level in RA patients:

Disease related variables	Pearson's correlation coefficient	P value
Age	0.234	0.006
weight	0.239	0.005
BMI	0.234	0.006
Waist circumference	0.234	0.006
SBP	0.285	0.001
DBP	0.255	0.003
DAS 28-CRP	0.199	0.020
ESR	0.211	0.013
hsCRP	0.332	0.000
Total cholesterol	0.353	0.000
HDL	-0.143	0.094
LDL	0.406	0.000
UA	0.289	0.001
Triglyceride	0.194	0.023

To evaluate difference between different glycemic categories of RA patients,univariate ANOVA was performed which showed significant difference in age,BMI,waist circumference, SBP, DBP, TJC, SJC, DAS28-CRP, ESR, CRP, total cholesterol, LDL, triglyceride, uric acid among different glycemic categories. No significant difference was noted for disease duration and HDL level.

Table 7: showing clinical and laboratory differences between different categories of glucose tolerance:

	NGT (n=76)	IFG (n=15)	IGT (n=21)	IFG-IGT (n=8)	T2DM (n=17)	P value
Age	50.12 + 11	53.40 + 9.8	51.81 + 7.3	51.00 + 8.5	57.53 + 6.7	0.081
BMI	21.93 + 2.8	24.33 + 2.1	25.02 + 2.4	23.47 + 3.3	23.80 + 2.1	0.000
Waist circumference	90.63 + 6.6	93.47 + 6.6	98.00 + 7.0	95.75 + 6.1	95.41 + 5.3	0.000
sBP	131.84+ 10.4	138.93 + 7.3	139.52 + 8.9	134.75 + 5.2	140.35 + 5.2	0.000
dBP	81.87 + 4.8	82.93 + 4.3	85.43 + 5.1	83.25 + 6.7	85.65 + 2.3	0.005
TJC	5.63 + 2.1	7.27 + 1.8	7.86 + 1.9	7.63 + 1.8	7.35 + 2.1	0.000
SJC	2.05 + 1.4	3.40 + 1.1	3.38 + 1.6	3.63 + 1.6	3.29 + 1.2	0.000
ESR	22.08 + 9.5	29.47 + 8.8	24.86 + 6.1	27.63 + 5.7	24.82 + 3.8	0.016
hsCRP	5.75 + 1.5	7.46 + 1.4	6.36 + 1.6	7.84 + 2.1	6.96 + 1.12	0.000
Disease duration	43.11 + 24.7	43.20 + 19.5	36.67 + 12.6	42.00 + 18.0	53.35 + 25.7	0.271
Total cholesterol	191.93 + 34.7	217.87 + 13.3	215.86 + 33.5	202.13 + 27.7	232.18 + 23.4	0.000
LDL	118.34 + 24.1	136.87 + 16.78	138.14 + 24.7	128.63 + 19.9	151.12 + 20.8	0.000
HDL	53.86 + 8.3	53.46 + 6.4	52.01 + 7.0	51.6 + 6.5	50.65 + 7.1	0.540
Triglyceride	115.92 + 44.7	139.33 + 40.0	138.19 + 50.2	106.75 + 39.6	152.12 + 53.7	0.013
Uric acid	4.45 + 0.6	4.87 + 0.5	5.17 + 1.0	5.18 + 0.4	5.08 + 0.8	0.000

IV.Discussion:

In the current study we witnessed increased prevalence of undiagnosed diabetes among RA patients in comparison to age and gender matched control population. We noted significantly elevated level of fasting and post prandial glucose level in RA patients compared to the control individuals. However, we failed to notice any significant difference in prevalence of prediabetes in our study population. We tried to explain this surprising finding on the ground that there may be accelerated deterioration of metabolic profile in RA individuals pushing their glycaemic status in to the diabetic range much earlier from the Prediabetic range. Also the sample size was calculated on the basis of prevalence of diabetes so the present study may be underpowered to capture difference in prevalence of prediabetes. It is required to seek for early detection of diabetes in RA patients as there are ample evidence to suggest that CVD risk factors tend to play out in a synergistic way, thus elevating the risk associated with a single risk factor. To support this hypothesis, study conducted by Baghdadi et al[7] showed that the risk of having myocardial infarction was significantly elevated in RA individuals with comorbid T2DM in comparison to people with RA only. The primary finding of our study matches with that of recent literature demonstrating increased prevalence of comorbid T2DM in patients with RA. A metaanalysis of 8 cohort studies

and 11 case-control studies revealed elevated risk of T2DM in RA patients.[8] On the other hand, T2DM patients, more commonly females show an increased risk of developing RA.[9] In spite of this clearly recognized epidemiological link, the coexistence of diabetes and RA still appears to be related to poor management of diabetes and less frequent testing of hemoglobin A1c level, as well as increased rates of several underlying cardiovascular diseases and complications related to diabetes (vascular and renal).[10]

The association between RA and diabetes, however, has been present in the literature for a long time. Although initially it was ascribed to therapy with corticosteroids, subsequent studies negated significant impact of corticosteroids in pathogenesis of diabetes. [11] Recently two main theories have been put forth to explain the connection between RA and diabetes : on one hand, there is clustering of several cardiovascular risk factors (for example, smoking, consumption of alcohol, obesity) in RA patients;[12] on the other hand, presence of chronic high grade inflammation confers significantly higher diabetogenic effect.[13] Recent evidences indicate that, irrespective of corticosteroids therapy and presence of the classic cardiovascular risk factors, inflammatory state of the disease itself appers to provide the key mechanism for this elevated risk. This is attributed to the adverse influence of various inflammatory cytokines, particularly IL-6 and TNF-α, on insulin signaling and subsequent development of insulin resistance.[14] Numerous studies have revealed an increased prevalence of RA and strong connection between visceral adiposity and inflammation.[15] ,[16]

In the current study, this fact has been reflected once again by the finding that both metabolic parameters (such as BMI and waist circumference) and parameters of disease severity (such as DAS28 and hs-CRP) are significantly elevated in RA individuals with comorbid prediabetes and diabetes in comparison to the normoglycemic RA patients. Besides, both fasting blood sugar and post prandial blood sugar level has been found to be elevated in RA patients compared to the control individuals. But we did not detect significant association between disease duration and glucose intolerance in RA patients. Our sample size may not be adequate enough to capture this link between disease duration and susceptibility to develop prediabetes and diabetes.

The major limitation of our study was that the sample size was too small to enable us establishing true prevalence of prediabetes among patients with RA. We found both increased BMI and increased waist circumference in RA patients compared to the control population. The existing literature also points towards lesser muscle mass and higher visceral[17] and total fat mass[18] in RA patients. Additionally we noted higher blood pressure level in RA patients. This finding is aligned with findings in previous literature on RA which shows lesser number of people with RA are properly and timely screened for and detected with hypertension and receives adequate treatment for it. [19] Hypertension is linked to insulin resistance [20] and irrespective of the cause that gave rise to it could lead to rise in the risk of developing diabetes in patients with RA.

In conclusion, our study, despite being limited by relatively lesser number of patients, demonstrate increased prevalence of undiagnosed diabetes among RA patients and higher levels of fasting and post prandial blood sugar level in them. If this finding is firmly established on larger population across different countries, further studies will be necessary to assess the potential benefits of systematic screening for diabetes among RA patients on cardiovascular disease outcome.

V.Conclusion:

As per our study there is increased prevalence of diabetes among RA patients. Increased disease activity raises the likelihood of being detected with diabetes.

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