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Original Article

Prevalence of glucose intolerance in rheumatoid arthritis patients at a tertiary care centre in Haryana

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ABSTRACT

Aims: Recent studies have shown increasing prevalence of dysglycemia in rheumatoid arthritis (RA) patients. The present study was planned to study the prevalence of pre-diabetes and diabetes in RA patients from a tertiary care centre in Haryana, India.
Methods: 150 diagnosed cases of rheumatoid arthritis which were on follow up in Rheumatology clinic from last one year and equal number of age, sex matched controls were recruited for the study. FPG, 2 h plasma glucose level after 75 g oral glucose tolerance test and HbA1c were estimated in all the subjects. In RA patients c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and Anti-cyclic citrullinated (Anti CCP) antibodies were also measured and disease activity was assessed by using (DAS28 joint counts) and CDAI.
Results: Patients with RA had statistically significant higher waist circumference, hip circumference and BMI as compared to control group. Prevalence of glucose intolerance in RA patients and control group was 14.67% and 6.67% respectively which was statistically significant ($p = 0.025$). The prevalence of pre-diabetes was in RA group was not significant statistically. There was higher disease activity in glucose intolerant (GI) RA cases as compared to normal glucose tolerant (NGT) RA cases. The most commonly used drug combination among RA patients was MTX + HCQ + SAAZ (49 patients, 32.67%). Maximum glucose intolerance was observed in patients who were on Non-HCQ drug combinations.
Conclusions: There is elevated prevalence of glucose intolerance among RA patients that is related to high disease activity, visceral adiposity and drugs usage.

1. Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune disorder that causes chronic synovial inflammation of multiple joints affecting 0.5–1% of population all over the world [1]. It affects women three times more than the men. Recent studies have shown increasing prevalence of dysglycemia in rheumatoid arthritis patients [2]. Impaired glucose handling in RA patients is secondary to peripheral insulin resistance mediated by the inflammatory response. Role of various pro-inflammatory cytokines (including tumor necrosis factor [TNF] and interleukin-6 [IL-6]) in RA, insulin resistance (IR), and type 2 diabetes mellitus (T2DM) has been reported by several independent studies [3]. A meta-analysis of 11 case-control studies and 8 cohort studies by Jiang et al. [4] in 2014 observed an increased risk of T2DM in patients with RA. Another study done by Ursini et al. [5] in 2016 concluded that RA is characterized by an elevated prevalence of undiagnosed diabetes. There are very few Indian studies on this subject and none from Haryana [6,7]. Keeping in mind these facts, the present study was planned to study the prevalence of pre-diabetes and diabetes in RA patients.

2. Materials and methods

This was a prospective case control study conducted at the Department of Endocrinology and Rheumatology Clinic of Pt. B.D. Sharma PGIMS, Rohtak. 150 diagnosed cases of rheumatoid arthritis which were on follow up in Rheumatology clinic from last one year and equal number of age, sex matched controls were recruited for the study. Patients having co-morbid illness like diabetes mellitus, hypertension, coronary artery disease or family history of DM and patients on steroid treatment were not included in the study. An informed written consent was obtained from all participating subjects and institutional ethical committee approved the study. Subjects were advised to come overnight fasting

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(at least 8 h) and venous blood sample was collected for measurement of FPG (fasting plasma glucose) and HbA1c level. Participants were subjected to OGTT with 75 gm of anhydrous glucose powder and 2 h post glucose load venous blood sample was taken for measurement of plasma glucose level. FPG and 2 h plasma glucose level were estimated by using Glucose Oxidase method. HbA1c was estimated by high performance liquid chromatography (HPLC) method. In RA patients c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and Anti-cyclic citrullinated (Anti CCP) antibodies were also measured and disease activity was assessed by using DAS28 (Disease Activity Score using 28 joint counts) and CDAI (Clinical Disease Activity Index). Results were compared with equal number of age and sex matched controls. Among RA patient's comparison was also done between normal glucose tolerant and glucose intolerant group. The American Diabetes Association (ADA) criteria were used to categorize the subjects into prediabetes and diabetes. According to the objectives of the study, the collected data were compiled, tabulated, and analysed using appropriate statistical tests. The nonparametric tests, chi-squared test, and *t*-test were applied wherever applicable to see the association with difference among the various factors of the study. Comparison among different groups were performed using one-way analysis of variance and was considered significant at $p < 0.05$.

3. Results

The baseline anthropometric parameters of both case and control group are shown in Table 1. The mean age of RA patients was 48.53 ± 10.37 years and in control group was 46.45 ± 11.09 years with male: female ratio of 1:9 in both case and control group. Patients with RA had statistically significant higher waist circumference, hip circumference and BMI as compared to control group (Table 1).

Prevalence of glucose intolerance in RA patients and control group was 14.67% and 6.67% respectively which was statistically significant ($p = 0.025$). Although prevalence of diabetes was significantly higher in RA group (p 0.040), the prevalence of pre-diabetes was in RA group was not significant statistically (Table 2). The distribution of cases and control into various sub-categories of prediabetes (IFG, IGT, HbA1c) are summarized in Table 3. There was higher disease activity in glucose intolerant (GI) RA cases as compared to normal glucose tolerant (NGT) RA cases. ESR, DAS 28 and CDAI were 35.18 ± 21.41 and 27.50 ± 15.20 ($p = 0.042$), 5.42 ± 1.45 and 4.61 ± 1.28 ($p = 0.008$) and 28.09 ± 14.13 and 20.59 ± 11.95 ($p = 0.009$) in GI and NGT respectively (Table 4). C- reactive protein and RF positivity had no significant effect on glucose tolerance among RA patients. Anti CCP seropositive patient had higher number of patients with glucose intolerance than sero-negative patients (p 0.011). None of the patient were taking a single drug for RA treatment. The most commonly used drug combination among RA patients was MTX + HCQ + SAAZ (49 patients, 32.67%). Maximum glucose intolerance was observed in patients who were on Non-HCQ drug combinations. However, when HCQ is part of drug combinations, better glucose tolerance was seen with a p value of <0.001 (Table 5).

Table 1
Base line characteristics of cases and controls.

Variable	Cases (n = 150)	Controls (n = 150)	P value
Age(Years)	48.53 ± 10.37	46.45 ± 11.09	0.096
Sex(Female)	135(90%)	135(90%)	1.000
Weight(kg)	60.58 ± 11.01	58.46 ± 8.34	0.061
Height(cm)	156.54 ± 7.42	156.58 ± 6.26	0.953
BMI(kg/m^2)	24.64 ± 3.80	23.77 ± 2.70	0.023
Waist(cm)	84.63 ± 11.23	80.15 ± 7.04	<0.001
Hip circumference(cm)	93.64 ± 9.65	89.36 ± 8.36	<0.001
Waist hip ratio	0.90 ± 0.072	0.89 ± 0.067	0.526

Table 2
Prevalence of glucose Intolerance in cases and controls.

	Cases(n = 150)	Controls(n = 150)	P value
Glucose Intolerant	22(14.67%)	10(6.67%)	0.025
Pre-Diabetic	12(8%)	7(4.67%)	0.19
Diabetic	10(6.67%)	3(2%)	0.04

Table 3
Prevalence of prediabetes by various parameters in cases and controls.

	Cases(n = 150)	Control(n = 150)	P Value
IFG (100–125 mg/dl)	3	0	0.082
IGT(140–199 mg/dl)	0	4	0.044
HBA1C (5.7-6.4%)	4	1	0.317
IFG + IGT + HBA1C	5	2	0.251
TOTAL PREDIABETIC	12	7	0.19

4. Discussion

The present study shows that patients with RA have higher prevalence of diabetes mellitus consistent with the more recent literature, showing a high prevalence of comorbid T2DM in RA patients. In particular, a recent meta-analysis of 11 case-control studies and 8 cohort studies confirmed an increased risk of T2DM in patients with RA [4]. This can be attributed to the diabetogenic effect of high grade inflammation and metabolic factors like increased abdominal or visceral adiposity. This shift of body composition in the direction of increased visceral adiposity is independently associated with insulin resistance [8]. Patients with RA have evidence of impaired glucose handling which is secondary to peripheral insulin resistance mediated by the inflammatory response. Insulin resistance and abnormal insulin secretion are central to the development of type 2 diabetes mellitus [9]. The relationship between diabetes mellitus (DM) and rheumatic disease is of interest because relatively few studies on the risk of DM in RA have been conducted.

Simard et al. [10] in their population-based study were the first to directly address the question of an association between prevalent RA and DM. No statistically significant association was found between RA and DM. ($p = 0.46$). However another study by Ursini et al. [5] reported that although prevalence of prediabetes was similar between groups, the prevalence of diabetes was significantly higher in RA patients as compared to controls with a P value of 0.02. The findings of our study are also consistent with above study. Dubreuil et al. [11] in their study showed an increased risk of diabetes among individuals with RA compared with age and sex-matched cohorts without, adjusting for BMI, smoking, alcohol use, co-morbidities and glucocorticoids at baseline. After adjustment for BMI, smoking, alcohol, baseline glucocorticoid use and co-morbidities the difference attenuated substantially. They concluded that increased incidence of diabetes in RA is explained by obesity and lifestyle factors. In contrast, in our study we have found an increased risk of diabetes among RA patients after adjustment for confounding factors like BMI, glucocorticoid use and comorbidities. The results of our study are also in concordance with the study conducted by Cunha et al. [12], they reported a significantly higher prevalence of DM in RA cases with p value <0.001. Similarly del Rincon et al. [13] noted a significantly higher frequency of diabetes in a cohort of patients with RA compared

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