

A Study of Insulin Resistance in Rheumatoid Arthritis

Prasanta Dihingia¹, Debarun Choudhury², Sreemanta Madhab Baruah³

ABSTRACT

Introduction: Chronic activation of the immune system, as observed in the pathogenesis of rheumatoid arthritis, potentially leads to insulin resistance. Insulin resistance is a major component of type 2 diabetes mellitus and metabolic syndrome. The risk of myocardial infarction is more than twice in rheumatoid arthritis cases compared to the general population. Stratifying those at risk could direct therapies for prevention of significant morbidity and mortality.

Material and methods: This is a case-control study of 102 cases of Rheumatoid Arthritis diagnosed by ACR/EULAR 2010 and a similar number of age and sex-matched healthy controls. Insulin resistance was calculated using HOMA-IR model, those having values greater than 2.5 were considered insulin resistant. HOMA-IR values were correlated to disease activity (using the DAS28 score). Blood pressure, BMI, waist-hip ratio and lipid profile were compared between the two groups.

Results: 71.6% Rheumatoid Arthritis cases were insulin resistant whereas the same in controls was 21.4%, although the mean BMI was lower in the former (22.78±2.71 vs 23.21±3.20). Insulin resistance was more prevalent (69.8%) in those with high disease activity (DAS28>5.1). Blood pressure was lower in the control group but the lipid profile was better in the cases.

Conclusion: This study showed that the majority of patients and 1/5th of the apparently healthy population had insulin resistance. There was significant correlation between disease activity and insulin resistance. All those having insulin resistance need to be carefully monitored to prevent cardiovascular morbidity and mortality.

Keywords: HOMA-IR, Insulin Resistance, Rheumatoid Arthritis

hyperglycaemia and hyperlipidaemia. Although insulin is central to all intermediary metabolic processes, its main action is related to glucose homeostasis. Therefore, insulin resistance is typically defined as a decrease of insulin-mediated glucose delivery to insulin-sensitive tissues and increased hepatic glucose production.

Gerald M. Reaven first proposed that insulin resistance was associated with numerous cardio-metabolic abnormalities like hyperglycaemia, elevated plasma triglycerides (TG), low levels of high-density lipoprotein (HDL) cholesterol and hypertension.^{9,10,11,12} Insulin resistance is a major component of several significant cardio-metabolic abnormalities, including the metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease (CVD). However, insulin resistance is not always pathological, and may be observed in physiological states such as pregnancy and puberty.¹³ The study of insulin sensitivity or resistance associated with the underlying pathophysiology of certain diseases may favour clinical and therapeutic outcomes to retard the future development of diabetes mellitus and CVD.

A number of studies have proved that chronic activation of the immune system, as observed in the pathogenesis of RA, potentially leads to increased risk of cardiovascular disease. Several reports have discussed the association between chronic inflammatory disease states and peripheral insulin resistance (IR).^{14,15,16} Specifically, TNF α , a critical inflammatory cytokine in RA, can cause “rheumatoid cachexia” where an individual with normal BMI has decreased lean muscle mass, increased adiposity, and a theoretical propensity toward developing IR. These changes in body habitus have been well described in RA and develop independent of corticosteroid use.^{17,18,19,20,21}

Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR), a simple, cost-effective and reliable method which employs fasting insulin and glucose levels to calculate insulin resistance.

The aim of this study was to explore the proportion of

INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric inflammatory polyarthritis that mainly affects the small joints of the hands and feet. It mostly affects adults between 30-50 yrs of age and is more common in women.¹ Although RA is primarily a disease of the joints, it can affect the heart, lungs, blood vessels, eyes and nerves. Interestingly, extra-articular manifestations are more common in males.² Worldwide, the incidence of RA ranges from 0.3-1.5%³ and in India it is 0.28-0.7%.^{4,5,6,7,8}

The disease activity of RA can be evaluated by a number of scoring systems, of which the simplest is the DAS28 score. This score may range from 0 to 9.3, where a DAS28 score ≤ 3.2 is considered to reflect low disease activity and a DAS28 score > 5.1 high disease activity.

Insulin is a peptide hormone which stimulates cell growth and differentiation. Resistance to the hormone leads to

¹Associate Professor, Department of Medicine, ²Post-graduate trainee in Medicine, Department of Medicine, ³Assistant Professor, Department of Medicine, Assam Medical College and Hospital, Dibrugarh, Assam, India

Corresponding author: Dr. Sreemanta Madhab Baruah, Assistant Professor, Department of Medicine, Assam Medical College and Hospital, Dibrugarh PIN-786002, India

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insulin resistance in rheumatoid arthritis patients compared to apparently healthy population using the HOMA-IR Model and to correlate the degree of insulin resistance with disease severity using the DAS28 score.

MATERIAL AND METHODS

The present study is a hospital based case control study carried out in the Department of Medicine, Assam Medical College & Hospital, Dibrugarh for a period of one year from 1st July, 2017 to 30th June, 2018.

All rheumatoid arthritis patients of 16 years or above, diagnosed by the 2010 Rheumatoid Arthritis Classification Criteria an American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) Collaborative Initiative who attended Rheumatology clinic or were admitted in the Medicine department of Assam Medical College & Hospital, Dibrugarh were taken up into the study. After considering inclusion and exclusion criteria, a total of 102 patients and same number of age and sex-matched controls were selected. Data were collected by taking history, physical examination and relevant investigations.

Exclusion Criteria

1. Diabetics on/off medications
2. Patients on steroid therapy other than for rheumatoid arthritis
3. Pregnant women

Control Group

Healthy attendants of patients attending the outdoor of Medicine Department.

All the patients and controls were given an explanation of the study and informed written consent were taken from them or their attendants before enrolment into the study. Ethical clearance was taken from the Institutional Ethical Committee, Assam Medical College and Hospital, Dibrugarh.

Classification Criteria for Rheumatoid Arthritis (ACR/EULAR2010)

		Score
Joint Involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive Anti-CCP antibodies (3 times ULN)	1
	High-positive RF or high-positive Anti-CCP antibodies (>3 times ULN)	3
Acute-phase Reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of Symptoms	<6 weeks	0
	≥6 weeks	1

A score of ≥ 6 indicated the presence of definite RA.

Anthropometric Measurements and Disease Activity Evaluation

Height and weight were measured with patients wearing light clothing and no shoes, to the nearest 0.1 cm and 0.1 kg respectively. Body mass index (BMI) was calculated with the standard formula:

$$\text{BMI} = \text{Weight (in kg)} / \text{Height (in metres)}^2$$

Waist circumference (WC) was assessed with a flexible tape at midpoint between the lowest rib margin and the iliac crest. Blood pressure was measured on the left arm with a mercury sphygmomanometer, with the patient supine after 5 minutes of rest.

Disease Activity: Disease activity was assessed by the DAS 28. Tender joint count (TJC) and swollen joint count (SJC) was determined out of standard 28 joints. Patients global assessment of disease activity (PtGA) was assessed using a 100 mm Visual Analog Scale (VAS).

DAS28 was calculated according to the following formula:

$$0.56 \times \sqrt{(28\text{TJC})} + 0.28 \times \sqrt{(28\text{SJC})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{PtGA}$$

Remission : ≤ 2.6

Low Activity : > 2.6 to ≤ 3.2

Moderate Activity : > 3.2 to ≤ 5.1

High Activity : > 5.1

Technique of Laboratory Investigations

ESR was obtained by Westergren method, CRP by Particle Enhanced Turbidimetric Immunoassay (PETIA) technique. Rheumatoid Factor (IgG) was tested by particle-enhanced turbidimetric immunoassay using RF kit of Euro Diagnostic Systems (Synergy Bio, Premium). Anti-CCP was tested using AccuDiag™ ELISA Anti-CCP by Diagnostic Automation.

Fasting plasma glucose was analysed by glucose oxidase-peroxidase method. Fasting insulin was estimated by RIAK-1, developed by BRIT, BARC Vashi Complex, Navi Mumbai, on the principle that the radioimmunoassay method is based upon the competition of unlabelled insulin in the standard or samples and radioiodinated (I-125) insulin for the limited binding sites on a specific antibody. At the end of incubation, the antibody bound and free insulin are separated by the second antibody-polyethylene glycol (PEG) aided separation method. Insulin concentration of samples is quantified by measuring the radioactivity associated with the bound fraction of sample and standards. The normal fasting levels of insulin as laid by the manufacturer ranged from 0-30 µU/ml.

There is no universal cut-off point for diagnosing IR by its value. The different cut off points were given throughout the world in general, diabetic and/or metabolic syndrome population. In this study, a cut off value of 2.5 has been used to define insulin resistance based on previous studies.^{22,23,24}

STATISTICAL ANALYSIS

Data were analyzed using Microsoft Excel 2007, GraphPad and www.socscistatistics.com.

RESULTS

In our study, the mean age group of cases and controls were 44±11.99 years and 43.17±11.53 years respectively. Majority

	Case	Control	P-value
BMI	22.78±2.71	23.21±3.20	0.30
Waist Hip Ratio	0.83±0.04	0.82±0.03	0.04
Systolic BP	118.12±11.52	115±4.24	0.01
Diastolic BP	76.43±7.37	67±19.8	<0.001
ESR	53.85±29.05	19.67±6.69	<0.001
CRP	7.29±10.22	0.34±0.07	<0.001
Fasting Glucose	94.72±10.4	93.63±2.12	0.30
Fasting Insulin	18.85±13.65	8.44±2.33	<0.001
HOMA-IR	4.7±3.85	1.9±0.68	<0.001

Table-1: Showing comparison of some important parameters analysed in the study.

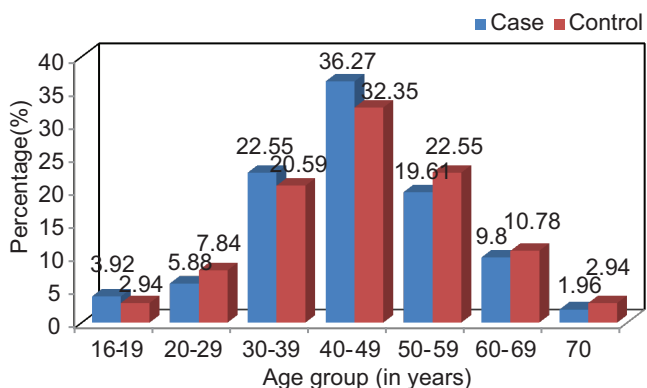


Figure-1: Showing age distribution of cases and controls.

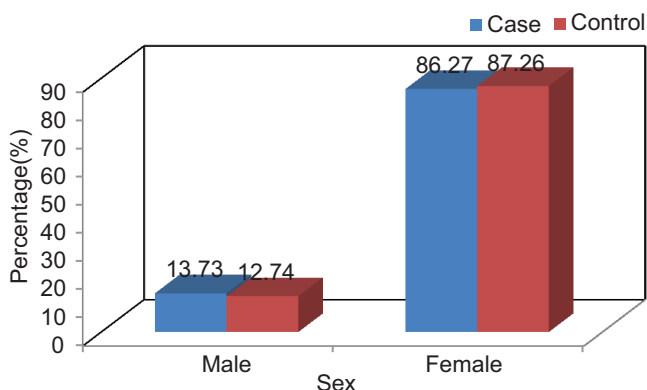


Figure-2: Showing sex distribution of both arms.

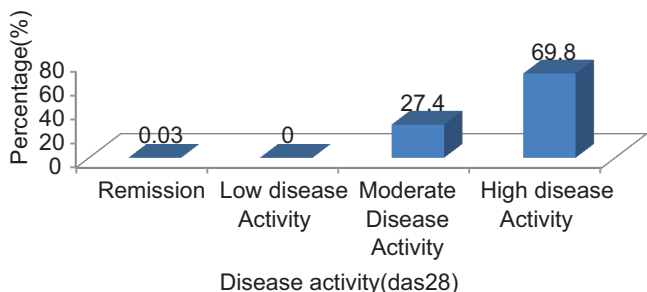


Figure-3: Showing disease activity in the cases with insulin resistance (HOMA-IR>2.5).

belonged to 40-49 year age group in both the arms (Fig. I). The ratio of males: females was 1:6.29 in cases while that in controls was 1:6.84 (Fig. II). 69.8% of patients with high disease activity had insulin resistance, while 27.4% with moderate disease activity had

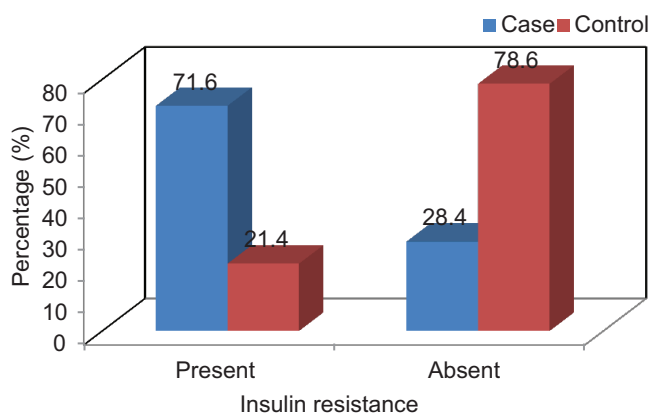


Figure-4: Showing prevalence of insulin resistance in RA cases compared to controls.

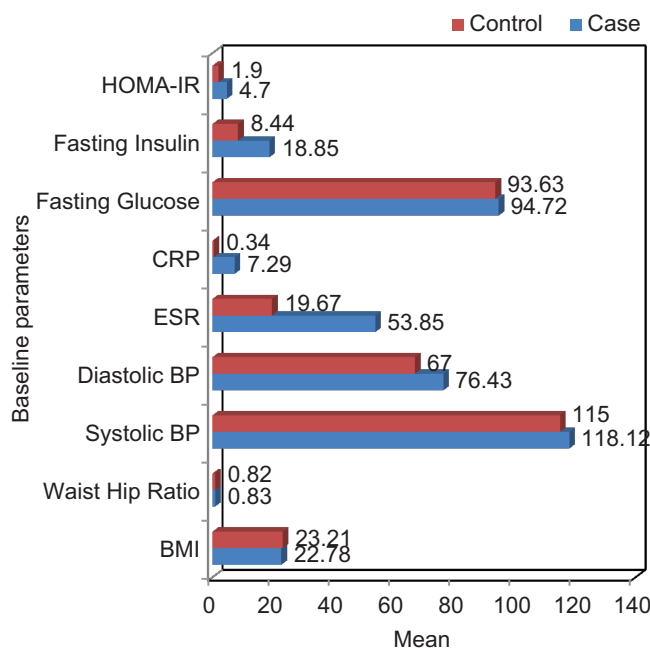


Figure-5: Showing comparison of some important parameters analysed in the study.

insulin resistance (Fig. III). In this study, 71.6% of cases had insulin resistance while 21.4% in the control group had insulin resistance (Fig IV). Although the mean BMI of cases (22.78±2.71) was less than that of controls (23.21±3.20), the result was not statistically significant. Similarly, the mean fasting glucose of cases (94.72±10.4) was found to be higher than that of controls (93.63±2.12) but not statistically significant. However, the differences of other parameters like waist-hip ratio, blood pressure, ESR, CRP and HOMA-IR between cases and controls were found to be highly significant (Table I and fig V).

DISCUSSION

The mean age group of cases in this study was 44±11.99 years. Mónica Vázquez-Del Mercado et al in 2017 had also found the mean age group was 46±12 years.²⁵ Males accounted for 13.73% and females accounted for 86.27% of the cases in a ratio of 1: 6.29. Shangyi Jin et al found the ratio was 1:4.15.²⁶

Almost 70% of patients with high disease activity had insulin resistance. Similar results were obtained by Gorica Ristic et al.²⁷

In this study, 71.6% of cases had insulin resistance while 21.4% in the control group had insulin resistance. Giovanni la Montagna et al found that 88.9% and 6.2% of cases and controls had insulin resistance respectively.²⁸ Cecilia P. Chung et al found 49% RA cases had insulin resistance.²⁹ William Bradham et al found that 53% RA cases had insulin resistance while the same was true for 15% controls.³⁰ The differences in some important parameters like BMI and waist-hip ratio are in agreement to the studies done by Yoon Kang et al³¹ and Irfan Ahamed et al.³²

This is a first of a kind study in the north-east Indian population where awareness about the disease and resources are scarce. The small sample size and omission of HbA_{1c} values as well as electrocardiographic findings due to logistic issues are definitely a shortcoming of this study. However, it can definitely give a head start to other larger studies of this nature to improve the quality of life of RA patients.

CONCLUSION

This study shows that there is a significant correlation between rheumatoid arthritis, the disease activity and insulin resistance. However, the number of diabetics with rheumatoid arthritis is very less. Probably, DMARDs have a protective effect on the glycaemic and lipid profile. These patients need to be followed up regularly to minimize cardiovascular morbidity and mortality. Further studies are required to emphasize the need for primary prevention of CVD by lifestyle modifications, anti-platelets and statins in this population.

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