ORIGINAL ARTICLE

Insulin Resistance and Inflammatory Status Among Rheumatoid Arthritis Patients in Bangladesh

Farhana Alam[1], Khademul Azad[2], Shahin Sultana[3], Taseen Habiba[4], Waheeda Nargis[5], Matira Khanam[6]

Abstract:

This study was done to evaluate the association of insulin resistance and inflammatory status in Bangladeshi population. Eighty seven subjects, collected from the outpatient department of Bangabandhu Sheikh Mujib Medical University, where 45 were rheumatoid arthritis (RA) patients and 42 controls. The RA patients showed significantly higher fasting blood sugar, fasting insulin and hs-CRP level, when compared to controls. There was no significant difference between RA subjects and controls for B-cell function assessed by Homeostasis Model Assessment (HOMA%B), insulin sensitivity assessed by Homeostasis Model Assessment (HOMA%S) and insulin resistance (IR). Among RA subjects, CRP and IR level improved after treatment. No significant correlation was found between CRP and IR, CRP and HOMA%S, and CRP and HOMA%B. In Bangladeshi RA subjects, insulin sensitivity has been found to be preserved. Insulin resistance is not a prominent feature in Bangladeshi RA subjects and CRP does not have any correlations with insulin resistance in Bangladeshi RA subjects. The improvement of the chronic inflammatory condition induced by steroid treatment seems to be associated with improved IR status.

Introduction:

Rheumatoid arthritis (RA) is a systemic immune and chronic inflammatory disease. Its prevalence is remarkably consistent worldwide. Its prevalence is 0.6% in Bangladeshi population[1] and 0.8% in western population. In addition to articular manifestations of RA, there is growing recognition of excess mortality, which is predominantly due to increased coronary artery atherosclerosis[2].

Rheumatoid arthritis is now considered as an important component of metabolic syndrome. Rheumatoid arthritis patients experience a markedly increased prevalence of cardiovascular disease[3], a comorbidity that may be partly mediated through insulin resistance[4]. An independent association of

1. Assistant Professor, Department of Biochemistry, Uttara Adhunic Medical College and Hospital, Dhaka.
2. Associate Professor, Department of Biochemistry, Shahabuddin Medical College and Hospital, Dhaka.
3. Assistant Professor, Department of Microbiology, Shahabuddin Medical College and Hospital, Dhaka.
4. Associate Professor, Department of Physiology, Shahabuddin Medical College and Hospital, Dhaka.
5. Assistant Professor, Department of Biochemistry, Uttara Adhunic Medical College and Hospital, Dhaka.
6. Assistant Professor, Department of Pharmacology, Shahabuddin Medical College and Hospital, Dhaka.

insulin resistance with carotid as well as coronary artery atherosclerosis has been reported in RA[5]. Insulin resistance seems to be the main metabolic abnormality that alters glucose metabolism, decreases the sensitivity of peripheral tissues to insulin in patients with RA and complicating rheumatic diseases via an increase in atherosclerotic disease risk and pre-diabetic state[6].

In RA, the primary site of inflammation is the synovial tissue, from which cytokines can be released into the systemic circulation. Insulin insensitivity also shows cytokine production and other markers of inflammation. Pro-inflammatory cytokines like Interleukin-1, Interleukin-6 and Tumor necrosis factor – α (TNF- α) are major modulators of these events. Under their influence, elevation of blood lipids, enhanced gluconeogenesis, catabolic hormone production and decreased insulin sensitivity occur. Similar events, however, occur during the course of inflammatory diseases such as rheumatoid arthritis[7] .The peripheral insulin sensitivity has been found to be associated with the intensity of the inflammatory reaction, as reflected by acute phase response. A more likely explanation is the inflammatory mediators either directly or indirectly affect the tissue sensitivity to insulin at the receptor or post - receptor level[8].

C-reactive protein production is part of the non-specific acute-phase response to tissue damage in RA. Many studies suggested that there is a strong and independent association of elevation in inflammatory markers, namely CRP, with decreased insulin sensitivity (SI)[9]. Significant correlations have also been found between CRP levels and dyslipidaemia, diabetes and cardiovascular disease[9]. CRP may contribute to cardiovascular disease by binding to the membranes of damaged cells, activating complement or enhancing production of thrombogenic agents and the resultant vascular inflammation may contribute to the development of insulin resistance (IR). Alternatively, IR may initiate or contribute to CRP elevation by reducing insulin induced suppression of hepatic acute-phase reactants[9].

Thus, in western population, it is evident that IR is an important feature in RA patients. So far, in Bangladesh no study has yet been done to explore the role of IR in RA patients. The present study has been undertaken to evaluate the association of IR and inflammatory status among RA patients.

Materials and method:

This study was carried out on 45 patients who met the American College of Rheumatology (ACR) criteria for RA. The RA patients were selected from the outpatient department of Bangabandhu Sheikh Mujib Medical University. The RA patients were further divided into two groups; untreated group of 19 RA patients and treated group of 26 RA patients on disease modifying anti-rheumatic agents (DMARD). Forty two apparently healthy volunteers, not having diabetes mellitus (DM) and myocardial infraction (MI), were also selected as control.

Age, height, weight, BMI, waist hip ratio, and blood pressure were recorded from all the study subjects. Informed written consent was obtained from each subject.

Fasting plasma glucose concentration was analyzed by GOD-PAP method; fasting plasma insulin concentration by Chemiluminesence based ELISA technique and serum CRP by ELISA method.

Insulin secretory capacity (HOMA%B), insulin sensitivity (HOMA%S) and IR were calculated from fasting plasma glucose (mmol/l) and fasting serum insulin (pmol/l) values by the Homeostasis Model Assessment (HOMA) model, using HOMA-2 software[10].

Statistical analysis was done using SPSS software for Window's version 12.0. Data were expressed as Mean ± SD, Median (range) or as number and percentage. Statistical significance of differences between mean and median values was assessed by Student's unpaired t-test, Mann-Whitney U-test, where appropriate. A two-tailed *p*-value of <0.05 was considered statistically significant.

Results:

Table-I shows the age, BMI, hip circumference, waist circumference and waist-hip ratio distribution of the study subjects. Table- II shows the insulin level, fasting blood sugar (FBS) level, HOMA %B , HOMA %S and IR status of the study subjects. RA patients had significantly (P<0.05) higher insulin and FBS level than the controls. No significant difference was found for HOMA %B, HOMA %S and IR status between RA patients and controls.

Table-I: Anthropometric characteristics of study subjects

Parameters	Control (n = 42)	RA patients (n = 45)	Test of significance t / p
Age in years	31.79 ± 9.22	33.89 ± 10.89	0.97 / 0.34
BMI	22.67 ± 3.7	22.17 ± 4.34	0.58 / 0.56
Hip circumference (cm)	85.21 ± 15.43	91.36 ± 8.76	2.30 / 0.02
Waist circumference (cm)	76.00 ± 9.41	83.58 ± 10.33	3.57 / 0.001
Waist Hip Ratio (WHR)	0.86 ± 0.05	0.91 ± 0.05	3.84 / 0.001

Table II: Comparison between insulin level, FBS level, HOMA %B , HOMA %S, IR and hs-CRP level between the study subjects

Parameters	Control (n = 42)	RA patients (n = 45)	Test of significance
*FBS (mmol/L)	4.85 ± 0.51	5.20 ± 0.77	2.47 / 0.02
*Insulin (pmol/L)	39.67 ± 27.67	56.51 ± 40.55	2.25 / 0.03
**HOMA % B	74.35 (43.3-198.5)	75.00 (37.8 -281.3)	-0.15 / 0.88
**HOMA % S	167.75 (30.5-287.7)	115.8 (32.4 -280.4)	-1.44 / 0.15
** Insulin resistance	0.60 (0.30 – 3.30)	0.90 (0.40 – 3.10)	-1.65 / 0.10
**hs-CRP (mg/dl)	0.04 (0.02 -5.20)	1.70 (0.03 -6.50)	-3.74 / 0.001

* values expressed as Mean ± SD and t-test done as test of significance

** values expressed as Median (range) and Mann-Whitney U-test done as test of significance

Table III: Comparison between insulin level, FBS level, HOMA %B , HOMA %S, IR and hs-CRP level between the RA patients

Parameters	Treated RA patients (n = 26)	Untreated RA patients (n = 19)	Test of significance
*FBS (m.mol/L)	5.10 ± 0.72	5.33 ± 0.85	-0.99 / 0.33
*Insulin (p.mol/L)	49.68 ± 41.34	65.86 ± 38.55	-1.33 / 0.19
**HOMA % B	68.6 (37.8 – 217.9)	87.70 (38.5 – 281.3)	-0.99/ 0.32
**HOMA % S	183.75 (32.4-280.4)	94.10 (41.6 – 268.3)	-1.56 / 0.12
**IR	0.50 (0.40 – 3.10)	1.10 (0.40 - 0 4.99)	-2.32 / 0.02
**hs-CRP (mg/dl)	0.04 (0.03 – 3.70)	2.07 (0.25 – 6.50)	-3.75 / 0.001

* values expressed as Mean ± SD and t-test done as test of significance
** values expressed as Median (range) and Mann-Whitney U-test done as test of significance

Table IV: Correlation between hs-CRP level and insulin resistance values of the RA patients

hs-CRP vs IR	Spearman's rho	*p*
RA patients (N= 45)	-0.10	0.52
Treated RA patients (N= 26)	-0.52	0.007
Untreated RA patients (N=19)	-0.17	0.49

Table V: Correlation between hs-CRP level and HOMA % B values of the RA patients

hs-CRP vs HOMA % B	Spearman's rho	*p*
RA patients (N= 45)	-0.15	0.32
Treated RA patients (N= 26)	-0.40	0.04
Untreated RA patients (N=19)	-0.03	0.91

Table VI : Correlation between hs-CRP level and HOMA % S values of the RA patients

hs-CRP vs. HOMA % S	Spearman's rho	*p*
RA patients (N= 45)	0.24	0.11
Treated RA patients (N= 26)	0.56	0.003
Untreated RA patients (N=19)	0.29	0.22

Insulin level, FBS level, HOMA %B and HOMA %S status had no significant difference between treated and untreated RA patients. Insulin resistance status was significantly ($p<0.05$) different among groups (Table-III). C-reactive protein values were significantly ($p<0.001$) higher in RA patients than controls (Table-II). CRP values also varied significantly ($p<0.001$) among treated and untreated RA patients (Table-III).

C-reactive protein values did not correlate significantly with IR, HOMA%B or HOMA%S status in RA patients. CRP also had no correlation with IR, HOMA%B or HOMA%S status in untreated RA patients (Tables- IV, V and VI). But, significant correlation was observed between CRP values and IR ($p<0.01$), HOMA%B ($p<0.05$) and HOMA%S ($p<0.01$) status in treated RA patients (Tables - IV,V and VI).

Discussion:

Insulin resistance has been considered as a main metabolic abnormality in patients with RA leading to alteration in glucose metabolism caused by decreased sensitivity of peripheral tissues to insulin. Since IR has been implicated as an inflammatory condition, the association between IR and inflammatory status in RA subjects has been evaluated in this study.

In this observational study, mean BMI of the RA patients were in the healthy range. There was no significant difference of BMI in RA subjects when compared with the controls; but significant difference was observed for hip and waist circumference. High prevalence of obesity and higher waist circumference has been reported in other studies with RA patients[7].

Fasting blood glucose level in RA patients was within normal limits, but still found higher than controls. The basal insulin level in RA patients was significantly higher. Other studies also showed increased basal and stimulated insulin levels in RA subjects[11].

In western population, it is evident that IR seems to be an important feature in RA patients[7,12]. But in this study, HOMA-2 index of insulin sensitivity and HOMA-2 index of IR showed no significant difference between RA patients and the controls. It was also observed that IR value reduced significantly in DMRD treated RA subjects. Treatment had thus improved the IR status of the RA patients. Dessein et al[7] also found that suppression of inflammation with glucocorticoids and disease-modifying agents results in decreased IR, at least in a short term.

Several studies have revealed that high-grade systemic inflammation contributes to IR in RA[8]. In this study, CRP levels, being a marker of inflammation, was significantly higher in RA subjects than the controls. After treatment, CRP status also improved significantly. This finding is reflective of the fact that treatment improved the inflammatory status of the patients.

Serum CRP concentration have been found correlated with clinical and biochemical indices of IR[11]. The relationship between increased CRP and decreased insulin action might be intrinsically determined due to IR itself[13]. But no significant correlation between CRP and IR, HOMA%S or HOMA%B was found in RA patients in this study. Reason behind such findings in Bangladeshi patients can be due to different food habit, life style etc. For conclusive results, further study with bigger population sample may be necessary.

It may be concluded that a) IR is not a prominent feature in Bangladeshi RA subjects; b) CRP does not have any correlations with IR in Bangladeshi RA subjects; and c) the improvement of the chronic inflammatory condition induced by steroid treatment seems to be associated with improved IR status.

References:

1. Haq SA. Prevalence of rheumatic disease and associated outcome in rural and urban communities in Bangladesh: A COPCORD Study. J Rheumatology 2005; 32: 552-556.
2. Dessein PH, Joffe BI, Stanwix AE. Inflammation, insulin resistance and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. Rheumatology 2003; 39: 321-324.
3. Maradit-kremers H , Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis : a population-based study. Arthritis Rheum 2005; 52: 722-732.
4. Sattar N, McCaarey DW, Capell H, McInnes IB. Expaining how 'high-grade' systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003; 108: 2957-2963.
5. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol 2006; 33: 2425-2432.
6. Top C, Tuncel A, Özkan OS, et al. The correlation of insulin resistance with serum TNF-a levels in Patients with rheumatoid arthritis. The Internet Journal of Rheumatology 2002; 1: 1528-4812.
7. Dessein PH, Joffe BI, Stanwix AE. The acute phase response does not fully predict the presence of insulin resistant dyslipidemia in inflammatory arthritis. Rheumatology 2002; 29: 462-465.
8. Svenson KL, Pollare T, Lithell H, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. Metabolism 1988; 37: 125-30.
9. Moran A, Steffer LM, Jacobs DR, et al. Relation of C - reactive protein to insulin resistance and cardiovascular risk factors in youth. Diabetes Care 2005; 28: 1763-1768.
10. Caumo A, Perseghin G, Brunani A, Luzi L. New insights on the simultaneous assessment of insulin sensitivity and ß-cell function with the HOMA2 method. Diabetes Care 2006; 29: 2733–2734.
11. Svenson KI, Lundqvist G, Wide L, Hallgren R. Impaired glucose handling in active rheumatoid arthritis; Relationship to the secretion of insulin and counter-regulatory hormones. Metabolism 1887; 36: 940-943.
12. Fernandez R, Ricart W. Insulin resistance and inflammation in an evolutionary perspective; the contribution of cytokine genotype/phenotype to thriftiness. Diabetologia 1999; 42: 1367-1374.
13. Fernandez R, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocrine Reviews 2003; 24: 278-301.