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Original Research

Circulating resistin concentration associates strongly with post-prandial plasma glucose in newly diagnosed Bangladeshi type 2 diabetic patients

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ABSTRACT

Background and Aim: Adipocytokine, resistin, has proposed link with obesity-related insulin resistance (IR) and type 2 diabetes mellitus. This study aims to evaluate serum resistin in newly diagnosed T2DM subjects with different body mass index (BMI) groups. **Subjects and Methods:** A total of 147 newly diagnosed T2DM subjects were recruited in this study. Anthropometric indices were measured using standard techniques. Insulin and resistin were measured by enzyme-linked immunosorbent assay method. Insulin secretory capacity homeostasis model assessment (HOMA) beta and insulin sensitivity (HOMA%S) were calculated using fasting glucose and insulin by HOMA-CIGMA software. SPSS for windows was used for statistical analysis. **Results:** The subjects were divided into three groups on the basis of BMI cut-off points suggested by WHO for the Asian population (Group 1: BMI 18.5-23, Group 2: BMI 23.1-27.5, Group 3: BMI >27.5). Resistin was significantly higher in Group 3 compared with Group 1 and Group 2. HOMA%S was significantly lower in Group 3 compared to Group 1 and Group 2. When the subjects were categorized in three tertiles according to resistin values, HOMA%S was significantly lower in 3rd tertile compared to 1st tertile. In multiple linear regression analysis, both BMI and post-prandial serum glucose were significantly associated with serum resistin level, but that of the latter one was stronger. **Conclusions:** (a) BMI positively and insulin sensitivity inversely associates with serum resistin concentration, and (b) post-prandial hyperglycemia shows a positive and independent association with serum resistin.

KEY WORDS: Body mass index, post-prandial glucose, resistin, type 2 diabetes

INTRODUCTION

Adipose tissue, in addition to energy storage, produces a vast array of factors, known as adipocytokines, implicated in modulating insulin sensitivity and energy balance. Such factors include tumor necrosis factor-α, interleukin-6, angiotensinogen, leptin, plasminogen activator inhibitor-1 and resistin. Resistin belongs to a family of cysteine-rich secreted proteins along with resistin-like molecule-α, also known as found in inflammatory zone (RELM-α/FIZZ 1), RELM β/FIZZ 2 [1,2]

and RELM-γ [3]. Serum resistin levels were found to be elevated in mouse models of obesity where they could antagonize insulin action; therefore, it was described as a potential link between obesity and insulin resistance (IR) [2]. However, some studies on mRNA and protein levels of resistin in different rodent models of obesity and diabetes could not clearly confirm this factor as a mediator of IR [4-9].

The relevance and physiological role of resistin in humans are even more controversial. In contrast to mice, human resistin is barely detectable in adipose tissue [10,11] and no correlation was found between resistin expression of isolated adipocytes and obesity or type 2 diabetes [10-12]. Human resistin is expressed at lower levels in adipocytes but at higher levels in circulating blood monocytes and macrophages. *In vitro*, resistin activated human endothelial cells, leading to increased expression of adhesion molecules, and induced human aortic muscle cell proliferation [13].

Previous investigations of human resistin in relation to obesity have shown higher serum resistin levels in obese subjects compared with lean subjects [14,15], which positively correlated with the changes in body mass index (BMI) and visceral fat area [16-18]. Contradictory results have also been shown in serum or plasma levels of resistin with any markers of adiposity [19-21].

In evaluating resistin and its association with insulin sensitivity in humans, several studies have identified positive correlations between resistin levels and IR *in vivo* [20] and *in vitro* [22]. In contrast, other studies have reported no associations between serum resistin levels and markers of IR in type 2 diabetes mellitus (T2DM) patients [19,23-25]. Moreover, serum and plasma resistin levels were found to be either reduced or increased in T2DM patients with no significant correlation with homeostasis model assessment for IR (HOMA-IR), waist circumference, BMI or total cholesterol [26,27].

It is however, established that the pathogenesis of T2DM is mediated through the concurrent progression of IR and sub-clinical inflammation, and obesity represents one of the foremost contributory factors leading to diabetes. Resistin, although postulated to contribute to IR, may also contribute to inflammatory responses and has been proposed to link obesity with IR and diabetes. Therefore, this study was designed to explore the association of serum resistin with insulin sensitivity in newly diagnosed Bangladeshi type 2 diabetic subjects with different degrees of BMI and hyperglycemia, which may help to gain insight about the interplay of resistin with obesity and IR in T2DM.

SUBJECTS AND METHODS

Subjects

The present cross-sectional-observational study recruited 147 newly diagnosed T2DM subjects (male 77 and female 70) purposively from the out-patient department of Bangladesh Institute of Health Sciences Hospital, Dhaka, Bangladesh. BMI of the subjects was normal to obese. Subjects were considered as T2DM using WHO guidelines [28].

Blood Sample Collection

On a prescheduled morning, subjects were requested to come after overnight fast (8-10 h) for fasting blood sample. Subjects were briefed regarding the aim of the study, and written consent was taken from the agreed volunteers. After taking blood at fasting condition, subjects were given 75 g glucose dissolved in 200 ml water and blood was taken again 2 hrs after glucose load. After centrifugation for 5 mins at 3000 rpm plasma samples were aliquoted and kept at −30°C until analysis.

Clinical and Biochemical Methods

Anthropometric and clinical parameters were measured by standard techniques and recorded using a predesigned questionnaire by standard techniques. The measurement of height and weight was done with light clothes and without shoes. The weighing scale was calibrated daily with a known standard weight. Plasma glucose, lipid profile, creatinine and glutamate pyruvate transaminase were measured by biochemistry autoanalyzer (Dimension RxL Max, USA) in a single run at three phases. Plasma insulin and resistin were measured by enzyme-linked immunosorbent assay method (Linco Research Inc, and Assaypro, USA respectively).

Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were estimated using fasting glucose and fasting insulin levels by HOMA–CIGMA software [29].

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Science version 16 for Windows (SPSS Inc., Chicago, Illinois, USA). Distributions of normality of the data were tested using Kolmogorov-Smirnov test. All data were expressed as mean ± standard deviation (SD) and/or percentage (%) as appropriate. The statistical significance of differences between the values was assessed by independent students *t*-test (as appropriate). The correlation was also observed among the parameters using Pearson's correlation and multiple linear regression analysis. A 2-tailed $P < 0.05$ was considered as statistically significant.

RESULTS

Age (years) and BMI (kg/m^2) of the study subjects were 45 ± 10 and 25.6 ± 4.2. Fasting and post-prandial (after 75 g glucose load) plasma glucose (mmol/l) of the study subjects were 10.6 ± 4.7 and 18.2 ± 5.6. Mean ± SD plasma insulin (μIU/ml) level was 12.2 ± 7.0. Mean triglyceride (mg/dl) level of the study subjects was higher than the reference range; cholesterol, high-density lipoprotein and low-density lipoprotein levels were within normal range. Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were calculated using fasting glucose and fasting insulin values using HOMA-CIGMA software and the values were 55 ± 43 and 62 ± 57, respectively.

Mean ± SD plasma resistin (ng/ml) level among the study subjects was 53±24 [Table 1].

The study subjects were categorized according to BMI cut-off points suggested by WHO for Asian population (Group 1: Normal BMI 18.5-23 kg/m^2, Group 2: Overweight BMI 23.1-27.5 kg/m^2, Group 3: Obese BMI>27.5 kg/m^2). The mean values of plasma resistin were 45.2 ± 16.2 ng/ml, 53 ± 25 ng/ml and 64 ± 26 ng/ml in Group 1, Group 2 and Group 3 respectively and the value was found to be significantly higher in Group 3 compared to Group 1 and Group 2 [Figure 1a]. The mean values of HOMA %B were 50 ± 40, 49 ± 35 and 70 ± 53 in Group 1, Group 2 and Group 3 respectively. HOMA%B was found to be significantly higher in Group 3 compared to Group 2 [Figure 1b]. The mean values of HOMA%S were 73 ± 66, 70 ± 62 and 39 ± 18 in Group 1, Group 2 and Group 3 respectively. HOMA%S was found to be significantly lower in Group 3 compared to Group 1 and Group 2 [Figure 1c].

Again the study subjects were categorized in three groups according to the ascending order of resistin concentration with 49 subjects in each group. The mean values of resistin (ng/ml) are 30 ± 6, 49 ± 7 and 81 ± 18 in 1st tertile, 2nd tertile and 3rd tertile respectively. HOMA%B and HOMA%S were reanalyzed according to these groups. The mean values of HOMA%B were 47 ± 37, 59 ± 41 and 51 ± 41 respectively. No significant difference was observed among the resistin groups [Figure 2a]. The mean values of HOMA%S were 81 ± 86, 59 ± 36 and 50 ± 28 respectively. HOMA%S was significantly lower in 3rd tertile (Group 3) compared to the 1st tertile (Group 1) [Figure 2b].

In multiple linear regression analysis [Table 2] serum resistin have shown significant positive association with BMI ($\beta = 0.208$, $P = 0.015$) and postprandial glucose ($\beta = 0.490$, $P = 0.008$).

DISCUSSION

The role of resistin in the pathophysiology of IR in humans and animals, and how it acts in muscle, liver and fat, is not clear [30,31]. Some studies have shown that resistin affects glucose transport and insulin-stimulated oxidation of glucose in L-6 skeletal muscle cells [32-35]. It also decreases the uptake and oxidation of long-chain fatty acids [36] and glycogen synthase kinase-3-β, as well as insulin-stimulated insulin receptor substrate-1 tyrosine phosphorylation [32,35] in the same cell line. Furthermore, high levels of resistin in rats leads to IR involving impaired insulin signaling in skeletal muscle, liver and adipose tissues, resulting in glucose intolerance and hyperinsulinemia [37]. A recent study suggests that resistin impairs the metabolic activation of insulin, and this impairment cannot be explained by the activity of a single enzyme [38,39]. Although some studies report positive correlations between resistin and obesity or IR, others did not agree [14,20].

Table 1: Clinical and biochemical characteristics of the study subjects (*N*=147)

Parameters	Mean±SD
Age (years)	45±10
BMI (kg/m^2)	25.6±4.2
WHR	0.97±0.02
SBP (mm-Hg)	121±15
DBP (mm-Hg)	79±9
FPG (mmol/L)	10.6±4.7
PPG (mmol/L)	18.2±5.6
TG (mg/dl)	231±137
TC (mg/dl)	173±41
HDLC (mg/dl)	36±10
LDLC (mg/dl)	95±35
ALT (U/L)	26±17
Creatinine (mg/dl)	0.96±0.30
Insulin (μIU/ml)	12.2±7.0
HOMA%B	55±43
HOMA%S	62±57
Resistin (ng/ml)	53±24

Results are expressed as mean±SD. SD: Standard deviation, BMI: Body mass index, WHR: Waist-hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, TG: Serum triglycerides, TC: Serum total cholesterol, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, ALT: Alanine aminotransferase, HOMA%B: Homeostasis model assessment beta, HOMA%S: Homeostasis model assessment sensitivity

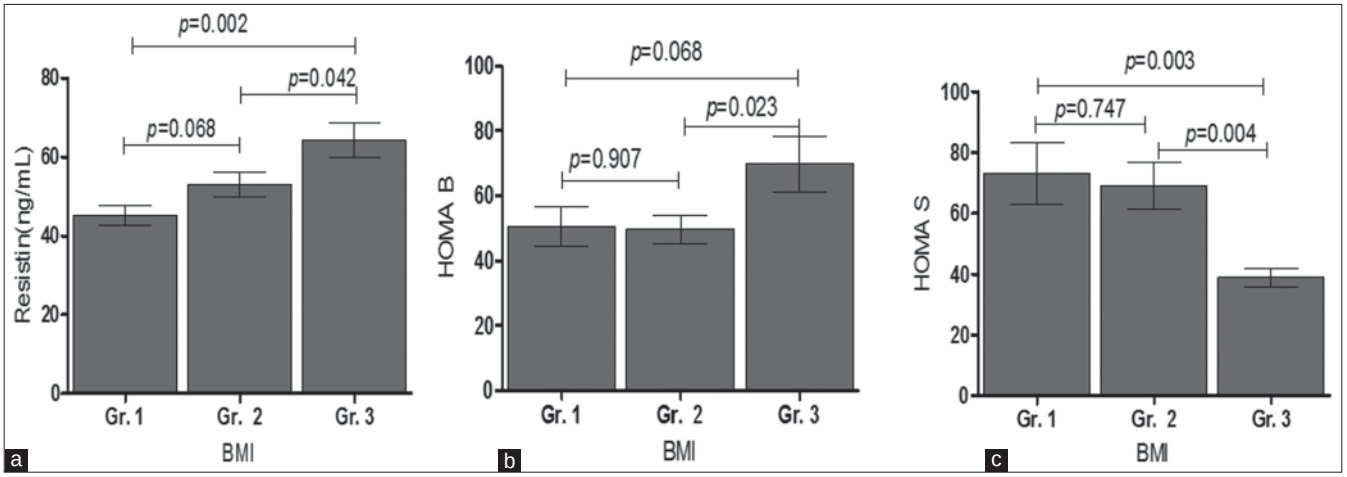

Figure 1: (a-c) Serum resistin homeostasis model assessment beta and insulin sensitivity among different body mass index (BMI) groups (Group 1: BMI 18.5-23 kg/m^2, Group 2: BMI 23.1-27.5 kg/m^2, Group 3: BMI > 27.5 kg/m^2)

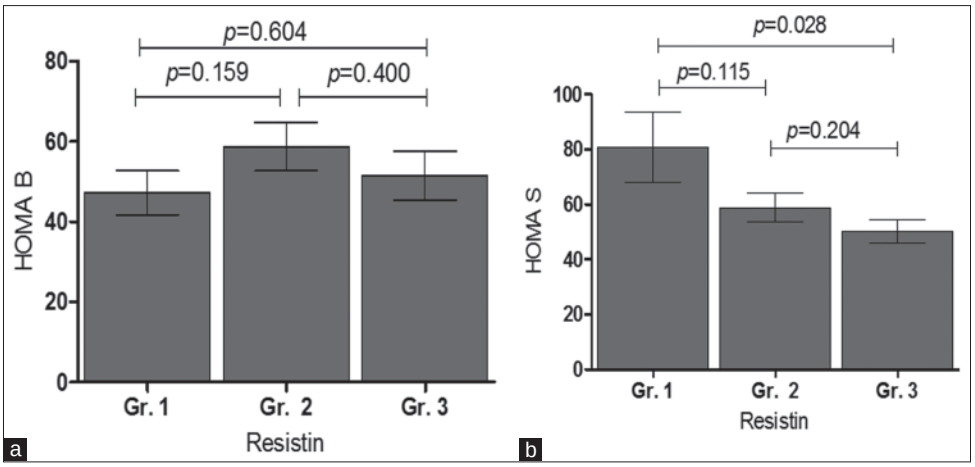

Figure 2: (a and b) Homeostasis model assessment beta and insulin sensitivity status among 1st, 2nd, 3rd tertile of resistin (Group 1, Group 2 and Group 3)

Table 2: Relationship of resistin with BMI, post-prandial glucose and HOMAS adjusted with other variables using multiple linear regression analysis

Variables	β	*P*
Age	0.150	0.070
BMI	0.208	0.015
WHR	0.053	0.518
Fasting glucose	0.315	0.080
PPG	0.490	0.008
Fasting insulin	0.101	0.260

BMI: Body mass index, WHR: Waist-hip ratio, PPG: Postprandial plasma glucose

Serum resistin concentration widely varies among different ethnic population. Serum resistin in healthy subjects of Taiwan [40] has been found as 12 ng/ml, 1.3-2.7 ng/ml in South Asians [41], whereas, in Japan [16] this value was measured as 4-20 ng/ml. In a previous study on Bangladeshi [42] healthy population the serum resistin level was found to be 9-23 ng/ml. Hence, resistin level in our population is in the range of Japanese population, but higher than other South Asian population. In another study conducted with Japanese type 2 diabetic population, it was found that serum resistin was significantly higher ($P < 0.001$) than that in normal subjects (20.8 ± 0.7 ng/ml and 14.9 ± 0.5 ng/ml respectively) [43]. On the other hand, in our study, resistin levels in type 2 diabetic subjects was 53 ± 24 ng/ml (15-131 ng/ml).

Some studies have explored resistin levels as significantly correlated with BMI in human subjects [15,16,43]. In the present study, resistin was measured in newly diagnosed T2DM subjects with different BMI levels (Group 1, BMI 18.5-23; Group 2, BMI 23.1-27.5; Group 3, BMI >27.5) and was found that serum resistin was increased with the increase of BMI. Therefore, the relationship between serum resistin levels and BMI investigated in this study was a strongly mutual inclusive relationship as other researchers mentioned. In our study, subjects with BMI >27.5 have shown significantly higher resistin levels compared to BMI <23 ($P = 0.002$) and BMI between 23 and 27.5 ($P = 0.042$) [Figure 1]. Therefore, BMI might be an important indicator for the increase of serum resistin in Bangladeshi type 2 diabetic subjects. In another study, it has been found that resistin was more correlated with BMI in girls than in boys [43], but in this study we did not find any difference in serum resistin level between male and female. Although menopausal status associated with weight gain but a cross-sectional study among healthy pre-and post-menopausal women did not find any association between serum resistin levels and menopausal status [44]. In Pearson's correlation analysis, it has been found that serum resistin was significantly associated with BMI and again when multiple linear regressions were used adjusted with other variables, resistin still showed significant association with BMI, but postprandial blood glucose was more strongly associated with resistin than with BMI. Therefore, obesity might be an important factor for the increase of resistin, and it may be ultimately involved in the complex mechanisms interplayed between IR and diabetes since obesity is related to diabetes.

When insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were analyzed according to the previously mentioned BMI groups, it has been found that HOMA%B was significantly ($P = 0.023$) increased in subjects with BMI > 27.5 kg/m^2 (Group 3) compared with Group 2 which may be because of the compensatory effect. On the contrary, HOMA%S was significantly decreased in BMI Group 3 compared to Group 1($P = 0.003$) and Group 2 ($P = 0.004$) which indicates that obesity reduces insulin sensitivity and it is the usual phenomenon. Therefore BMI 27.5 is a worsening status of overweight where β-cells of the pancreas secrete higher amounts of insulin with less functionality. The study subjects were again categorized in three tertiles according to the ascending order of resistin concentration, HOMA%S was found significantly lower ($P = 0.028$) in 3rd tertile compared to 1st tertile. It may be assumed that increased resistin could suppress some of the insulin sensitizer proteins, e.g. Peroxisome proliferator-activated receptor-γ (PPAR-γ), thereby reducing insulin sensitivity. Therefore, subjects with higher serum resistin showed decreased insulin sensitivity which interplays in increased blood glucose at least in some portion. Therefore

the viewpoints of above discussion may be summarized as: (a) BMI positively, and insulin sensitivity inversely associates with serum resistin concentration and (b) post-prandial hyperglycemia shows a positive and independent association with serum resistin.

Strength and limitation of the study: Both the obesity and type 2 diabetes were considered in the same settings to find out their relations with adipocytokine hormone, but the limitation of the study is that only resistin among all other adipokines have been analyzed.

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