Association of Adipokine Resistin With Homeostasis Model Assessment of Insulin Resistance in Type II Diabetes

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Background: Resistin is a recently discovered signal molecule that has been linked to obesity, type II diabetes mellitus (T2DM) and metabolic syndrome.
Objectives: This study aimed to assess whether serum resistin is associated with insulin resistance and glucose concentration in males with T2DM.
Patients and Methods: Thirty two adult non-trained males with type II diabetes, 34-48 years old and 88-110 kg of body weight, participated in this study by accessible sampling. Fasting blood samples were collected from all participants in order to measure serum resistin, insulin and glucose concentration. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated using fasting insulin and glucose. Relations between variables were determined by Pearson correlations.
Results: We found that serum resistin had a positive significant correlation with insulin resistance (P = 0.000, r = 0.64). No significant correlation was found between serum resistin and fasting glucose concentration in the studied patients (P = 0.21, r = 0.23).
Conclusions: Based on these data, we can argue that circulating glucose concentration is not directly affected by serum resistin in T2DM. It seems that resistin affects glucose indirectly, through insulin resistance.

Keywords: Resistin; Body Weight; Insulin Resistance; Obesity

1. Background

Increased prevalence of adipose tissue and obesity-related risk factors are closely associated with increased prevalence of cardiovascular diseases (CVD) and type II diabetes (T2DM) (1, 2). Given the importance of health and wellness, obesity and T2DM are considered today as a global epidemic. Apart from genetic factors and heredity, scientific evidence clearly supports obesity as the most important factor in the incidence of T2DM. Obesity also promotes T2DM through increasing resistance to insulin and rising blood glucose (BG) (3).

The importance of obesity on the incidence of CVD or T2DM is related to an impaired secretion of inflammatory and anti-inflammatory adipokines or cytokines. Between them, resistin is an adipokine with a molecular weight of 12.5 kDa, which is secreted in muscle, pancreatic islet, mononuclear cells, and human placenta, and also in adipocytes (4). In rodents, resistin is primarily secreted by adipocytes and is identified as a bridge between obesity and insulin resistance (5). In humans however, resistin is secreted primarily by macrophages (6), indicating that resistin is related to inflammation. On the other hand, obesity, T2DM, and CVD have recently been characterized as chronic inflammatory disorders, which can be related to secretion of pro-inflammatory cytokines, as well as adipokines, such as resistin (7).

Lee et al. found that obese mouse models have higher levels of resistin, as compared with the lean counterparts (8). Although resistin is effective in the relationship between obesity and insulin resistance in rodents, its role in humans is not known precisely. Several studies have examined the pathophysiologic significance of circulating resistin changes during the last few years. Although early studies on rodents (5) and humans (9) pointed out the potential relationship between circulating resistin levels and insulin resistance, several studies on humans denied the link between resistin and obesity and insulin resistance (10, 11). For example, no significant difference was observed in serum resistin levels between obese diabetic and non-diabetic subjects, in a recent study (12). According to the relationship of resistin with healthy obese people and not diabetics in another study, researchers pointed out that resistin is a marker of glycemic balance only in obese people and not in diabetes (13).

2. Objectives

Given the contradictory findings regarding resistin as a marker of glycemic balance in obese people and not

in diabetes, the present study aimed to determine the relationship between serum resistin, insulin resistance and blood glucose, in T2DM.

3. Patients and Methods

Subjects were 32 adult males with T2DM that participated in this study by accessible sampling. All subjects were obese, with a body-mass-index (BMI) of 30-35 kg/m², and aged 34-48 years old. The study was conducted with the approval of the Ethics Committee of Islamic Azad University, Islamshahr Branch, Islamshahr, Iran. After the nature of the study was explained in detail, informed consent was obtained from all participants. Participants were non-athletes, non-smokers and non-alcohol dependent. Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. Inclusion criteria for study subjects were determined as existing T2DM for at least 3 years. None of the participants had ongoing CVD, infections, renal diseases, hepatic disorders, use of alcohol. Those that were unable to avoid taking hypoglycemic drugs or insulin sensitivity-altering drugs for 12 hours before blood sampling were also excluded from the study.

3.1. Anthropometric Measurements

Body weight was measured in duplicate in the morning following a 12 hours fast. Height was measured on standing, while the shoulders were tangent with the wall. Abdominal circumference and hip circumference were measured in the most condensed part, using a non-elastic cloth meter. Hip circumference was measured at the maximum circumference between the iliac crest and the crotch, while the participant was standing and was recorded to the nearest 0.1 cm. The BMI was calculated as body mass (in kilograms) divided by height squared (in square meters). Visceral fat and body fat percentage were determined using a body composition monitor (Omron Electronics Oy, Esbo, Finland).

3.2. Blood Biochemistry Examination

Participants were asked to attend in hematology lab for blood sampling. Venous blood samples were collected after 10-12 hours of overnight fast between 8:00 and 9:00 AM. Subjects were asked to avoid doing any heavy physical activity during the 48 hours before blood sampling. Sera were immediately separated. Glucose was determined by the oxidase method (Pars Azmoon kit, Tehran, Iran). Insulin was determined by the enzyme linked immunosorbent assay (ELISA) method (Demeditec, Diagnostics, Gmbh, Kiel, Germany) and the intra-assay and inter-assay coefficients of variation of the method were 2.6% and 2.88%, respectively. The sensitivity of the insulin assay was 1.76 μIU/mL. The homeostatic model assessment insulin resistance (HOMA-IR)

index was calculated by the formula: HOMA-IR = fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 (14). Serum resistin was determined by ELISA method (Biovendor-Laboratoria Medicina, Brno, Czech Republic). The intra-assay coefficient of variation and sensitivity of the method were 2.8% and 0.033 ng/mL.

3.3. Statistical Analysis

Statistical analysis was done with SPSS 15.0 Software for Windows (SPSS Inc., Chicago, IL, USA). Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Pearson correlations were used to establish the relationship between serum resistin concentration and insulin resistance or glucose concentration. The results were considered statistically significant for $P < 0.05$.

4. Results

In this study, the relationships between serum resistin, glucose concentration and insulin resistance were determined in adult men with T2DM. Table 1 shows the descriptive anthropometric and biochemical features of the study subjects. All values are reported as mean ± standard deviation (SD). Based on Pearson analysis method, we found that serum resistin showed a positive significant correlation with insulin resistance in studied patients ($P = 0.000$, $r = 0.64$) (Figure 1). No significant correlation was found between serum resistin and fasting glucose concentration in the studied patients ($P = 0.21$, $r = 0.23$) (Figure 2).

Table 1. The Descriptive Anthropometric and Biochemical Features of the Studied Patients [a]

Variable	Mean ± SD
Age, y	40 ± 3.9
Weight, kg	95 ± 5.1
Height, cm	173 ± 2.9
Body mass index, kg/m²	31.7 ± 1.73
Body fat percentage	30.2 ± 1.47
Abdominal circumference, cm	105 ± 6.6
Hip circumference, cm	103 ± 4.8
AHO	1.02 ± 0.04
Serum resistin, ng/mL	1.79 ± 0.96
Insulin, μIU/mL	8.51 ± 4.76
Glucose, mg/dL	221 ± 66
Insulin resistance [b]	4.55 ± 1.30

[a] Abbreviation: AHO; abdominal to hip ratio.
[b] Homeostasis model assessment of insulin resistance index (HOMA-IR).
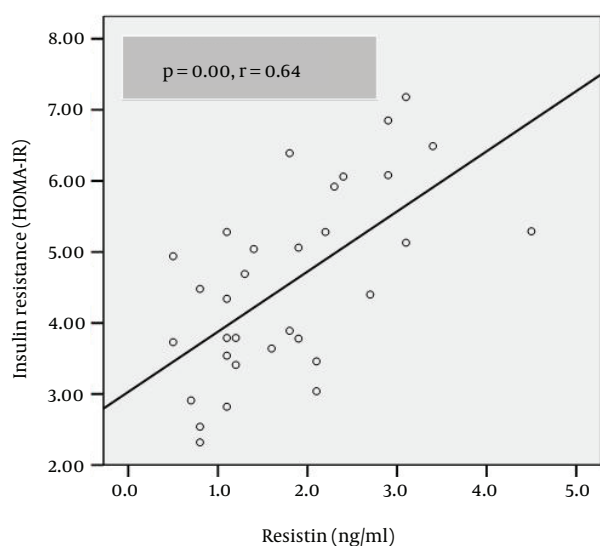
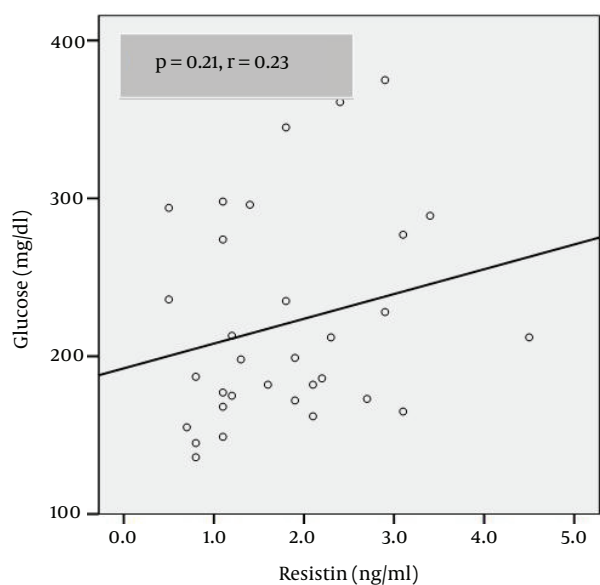**Figure 1.** The Positive Significant Correlation Between Serum Resistin and Insulin Resistance in Studied Patients (n = 32)

Figure 2. No Significant Correlation Between Serum Resistin and Glucose Concentration in Studied Patients (n = 32)

5. Discussion

A positive significant correlation was observed between serum resistin and insulin resistance in the present study. Several previous articles reported the involvement of serum resistin in obesity and insulin resistance or T2DM (15); however, conflicting evidence exists about the association of resistin with insulin resistance, because several studies reported no association of these inflammatory mediators with insulin resistance or indicators of T2DM (16-18). Therefore, according to their

observations, the researchers concluded that, due to resistin low expression in human adipocytes, its role as a link between obesity and insulin resistance is not completely understood. In fact, this protein is abundant in circulating monocytes, which release it into serum (19). The lack of association between serum resistin and glucose, hip and waist circumference, and waist-to-hip ratio is also observed in healthy individuals (20).

In humans, resistin is expressed predominantly in peripheral blood mononuclear cells and its expression increases during their differentiation into macrophages (6, 21, 22). It is known that serum resistin levels increases in obese mice, although the expression of resistin mRNA in the adipose tissue of these mice is inhibited or suppressed, so that serum resistin increases in obesity, while resistin mRNA expression reduces (23, 24). Resistin expression increases in samples of adipose tissue from obese individuals, who are prone to more leakage of macrophages into adipose tissue; they also have higher levels of resistin compared with lean subjects (22, 25). Several cross-sectional studies reported the association of resistin levels with visceral, intracardiac, and intra-aortic adipose tissue (26). It is known that impaired secretion of resistin results in disturbed insulin resistance and glucose metabolism. Academic resources have stated that increased resistin expression in mice leads to increased insulin resistance and its knockout results in decreased fasting glucose levels. Therefore, this mediator inhibits insulin function in rat liver through interference with insulin signaling pathways. Based on this evidence, resistin is introduced as an important molecular link between obesity and insulin resistance (18). Increased serum resistin occurs frequently in systemic inflammatory conditions (27) and is considered as a factor contributing to atherosclerosis, which is the most important determinant of CVD (22, 28, 29). Resistin is also introduced as a stimulator of synthesis and secretion of inflammatory cytokines (30).

In a cross-sectional study on subjects with metabolic syndrome, the researchers concluded that resistin levels have a direct relationship with insulin resistance (31). However, several studies emphasized the lack of relationship between them (4, 32). The direct effect of resistin in the incidence of T2DM has not been established with certainty in other studies (33). Despite the contradictory findings, most of them recently emphasize a significant direct correlation between resistin and insulin resistance (33-35). The findings of this study point out the close relationship between these two variables. However, in the present study, a direct nonsignificant correlation was observed between the levels of resistin and fasting glucose in studied diabetic patients, which is important form a clinical perspective. On the other hand, the lack of significant levels of resistin and glucose in the present study may be attributed to the low number of samples, which is also a limitation for this study.

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Authors' Contributions

Yahya Sokhanguei: Study concept and design, Drafting of the manuscript; Mojtaba Eizadi: Statistical analysis; Mohamad Taghi Goodarzi: Administrative, technical, and material support, writting manuscript; Davood Khorshidi: Study concept and design.

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