Serum resistin levels in patients with type 2 diabetes mellitus and its relationship with body composition

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ABSTRACT

الأهداف: تقييم العلاقة بين تركيز رزيستين مع مؤشر كتلة الجسم (BMI)، وكتلة الدهون في الجسم، وكتلة الجسم النحيل، وكتلة الجسم من البروتين لدى المرضى الذين يعانون من مرض السكري من النوع الثاني.

الطريقة: أجريت هذه الدراسة المقطعية في قسم علم وظائف الأعضاء، كلية الطب، جامعة الملك سعود، الرياض، المملكة العربية السعودية خلال الفترة من أبريل 2008 إلى مارس 2011. شملت الدراسة 229 فرد تم اختيارهم من أجل الدراسة. وجرى تقييم مكونات الجسم بواسطة محلل العوائق bioelectrical. وسجلت المؤشرات التي شملت مؤشر كتلة الجسم (BMI)، وإجمالي ماء الجسم، والدهون، والبروتين، وكتلة الجسم الهزيل. وقد تم تحليل عينات الدم من أجل قياس الهيموغلوبين، والهيموغلوبين السكري (نسبة HbA1c)، ومستويات رزيستين.

النتائج: لقد كان مؤشر كتلة الجسم في هذه الدراسة، ونسبة الخصر والورك، ونسبة الهيموغلوبين، والهيموغلوبين السكري، ومستويات رزيستين أعلى بكثير لدى مرضى السكري مقارنة مع الأصحاء. وكانت كتلة الدهون أعلى بكثير لدى مرضى السكري مقارنة مع الأفراد الأصحاء. بينما لم توجد فروقات تُذكر لكتلة العضلات، وكتلة الجسم النحيل بين المرضى والأصحاء. ولوحظ وجود ارتباط إيجابي كبير بين مستويات البلازما من الرزيستين وكتلة الدهون لدى المرضى الذين يعانون من مرض السكري من النوع الثاني (r=0.2824, p=0.0030).

خاتمة: أظهرت نتائج هذه الدراسة بأن مرضى السكري من النوع الثاني لديهم مستويات أعلى بكثير من الرزيستين والتي ترتبط بشكل إيجابي مع كتلة الدهون في الجسم، وهذا من الأدلة التي تدعم بأن الرزيستين يلعب دوراً هاماً في التسبب في السمنة ومقاومة الأنسولين.

Objectives: To assess the relationships of resistin concentrations with body mass index (BMI), body fat mass, lean body mass, and body protein mass in patients with type 2 diabetes mellitus (DM).

Methods: This cross-sectional study was conducted in the Department of Physiology, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia from April 2008 to March 2011. A total of 229 subjects were selected for the study. Body composition was assessed by bioelectrical impedance analyzer. Parameters recorded included BMI, waist hip ratio (WHR), total body water, fat, protein, and lean body masses. Blood samples were analyzed for glucose, glycosylated hemoglobin (HbA1c), and resistin levels.

Results: We found that BMI, WHR, fasting blood glucose, HbA1c, and resistin levels were significantly higher in diabetics compared to non-diabetic healthy individuals. Fat mass was significantly higher in diabetic patients compared with controls, while the difference for muscle mass and lean body mass was non-significant. A significant positive correlation was observed between plasma levels of resistin and fat mass in patients with DM (r=0.2824, p=0.0030).

Conclusion: Type 2 DM patients have significantly higher resistin levels that are positively correlated with body fat mass supporting the evidence that resistin plays an important role in the pathogenesis of obesity and insulin resistance.

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Adipose tissue was once considered to be an inert storing depot for energy. However, in the form of triglycerides, it is now known to have more complex functions as an endocrine organ that releases hormones into the blood stream to take part in their potential role in insulin resistance, obesity, and diabetes.[1] It is well known that obesity, especially visceral adipose tissue accumulation, increases the risk of developing type 2 diabetes.[2] Recent interest in adipocyte derived factors has resulted in identification of a large group of adipocyte specific proteins, such as adiponectin, acylation stimulating protein, resistin, and leptin.[3] These adipocyte derived hormones are presently under intensive investigations concerning their involvement in the regulation of adipose tissue physiology, and particularly, their potential implication in insulin resistance, obesity, and diabetes.[4] The greater risk of type 2 diabetes mellitus (T2DM) in the obese can, at least partly, be explained by changes in adipose tissue function.[5-7]

Resistin is a protein hormone secreted by adipocytes, which leads to insulin resistance (IR) in vivo and in vitro, and is considered to be an important link between obesity and diabetes.[8] Resistin has been involved in the pathogenesis of obesity-mediated IR and T2DM. It is apparent that obesity represents one of the main contributory factors leading to diabetes. In the past few years, intensive work has been carried out on the expression and functional properties of adipocytokines and their effects on metabolism, highlighting their links with human obesity and T2DM in the pathogenesis of metabolic syndrome. Some of these factors are tumor necrosis factor-α (TNF-α) interleukin-6, angiotensinogen, leptin, plasminogen activator inhibitor-1, and resistin.[9] Initial studies showed that resistin was up-regulated in rodent models of obesity and IR, and down-regulated by an insulin-sensitizer, rosiglitazone. Moreover, immune neutralization of resistin reduced hyperglycemia and improved insulin sensitivity.[10] These observations lead to the consideration of resistin as a potential etiological link between obesity and diabetes. A study by McTernan et al[11] reported the presence of resistin in adipose tissue, thus linking resistin as a possible pathogenic factor increased in central adiposity.[11] Moreover, elevated plasma free fatty acids, inflammatory markers, and altered adipokine concentrations have been observed in obese T2DM.[11,12] To date it remains unclear whether these altered plasma concentrations are related to the diabetic state or presence of obesity. Although inconsistencies remain in the data regarding the role of resistin in obesity, there is compelling evidence suggesting a role for resistin in the etiology of IR and T2DM.[13] There is scanty data on the relationship between resistin levels with body composition parameters assessed by bioimpedance analysis in normoglycemic and diabetic patients. Therefore, we aimed to study the relationship between the concentration of resistin, glycemic control, and body composition.

Methods.

Subjects. This cross-sectional study was conducted in the Department of Physiology College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia from April 2008 to March 2011. Patients were recruited from the outpatient clinic of King Khalid University Hospital. The College of Medicine and King Khalid University Hospital institutional review board approved the study. Only those individuals who agreed to participate in the study and signed the consent form were selected. A total of 229 individuals were selected for the study from a sample of 249 subjects that included 110 patients with T2DM (71 males and 39 females), and 119 healthy control subjects (75 males and 44 females).

Diagnosed cases of T2DM based on the American Diabetes Association (ADA) criteria were studied.[14] All the patients were in a stable metabolic condition. Patients with any disease such as nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis, and non-ketotic hyperosmolar coma were excluded. Those patients with a history of oral contraceptives or steroid intake, and familial hypercholesterolemia were also excluded from the study. Control subjects were matched for age, gender, and weight. Blood pressure (BP) (systolic BP/diastolic BP) was recorded in sitting position in the right arm. They were not suffering from any acute infection, or metabolic or psychological disorder. They had no family history of hypercholesterolemia or DM.

Laboratory analysis. Fasting venous blood samples were analyzed for fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), and resistin levels. The FBG was analyzed by the colorimetric method, while HbA1c was measured by a HbA1c Clover analyzer (Infopia Co. Ltd, Anyang, Korea). This instrument measures HbA1c by reflectance spectrophotometry. Human resistin immunoassay was performed by quantitative standard sandwich ELISA technique using a monoclonal antibody specific for resistin with kits supplied by R&D Systems (Abingdon, United Kingdom). Body composition was assessed by bioelectrical impedance analysis, with a commercially available body analyzer following the manufacturer's instructions (InBody3.0, Biospace, Seoul, South Korea).

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The assessment was carried out in light clothing, a fasting state, and after emptying of the bladder. Parameters recorded included height, body weight, BMI, WHR, fat mass, lean body mass, and muscle mass. Different tissues of the body have varying degrees of electrical resistance. The machine calculates the amount of each tissue with the difference in electrical impedance.[15]

Statistical analysis. Data were analyzed using the Statistical Package for Social Sciences version 19 (SPSS Inc., Chicago, IL, USA). Descriptive characteristics of the study patients were calculated as mean±standard deviation (SD) for continuous variables. The tests applied for statistical analysis were Student's t test and regression analysis. A *p*-value of <0.05 was considered statistically significant.

Results. Table 1 summarizes the descriptive characteristics and glycemic status of the control and diabetic patients. Different parameters such as BMI, WHR, FBG, and HbA1c were significantly higher in diabetic individuals compared with healthy volunteers. Similarly, serum resistin levels were significantly higher in T2DM patients than healthy subjects (*p*=0.0325). Among parameters of body composition, fat mass was significantly higher in diabetic subjects compared with controls while the difference for protein mass and lean body mass was non-significant (**Table 2**). Linear regression analysis was performed to analyze the relationship between plasma resistin concentrations and body compositions parameters. A significant positive correlation was observed between plasma levels of resistin and fat mass in patients with DM (r=0.2824, *p*=0.0030, **Figure 1a**). However, the relationship of resistin with either protein mass (r=0.0574, *p*=0.5549) and lean body mass (r=0.0953, *p*=0.3263) were non-significant (**Figures 1b and 1c**).

Discussion. The present work aimed to study the relationship of blood resistin levels with BMI, fat mass, lean body mass, and muscle mass assessed by bioimpedance analysis. Resistin levels were observed to be significantly higher in type 2 diabetics compared to control subjects as reported previously.[16]

This study revealed a significant positive correlation between plasma levels of resistin and fat mass in patients with T2DM. However, the relationship of resistin with other parameters like muscle mass and lean body mass was non-significant. In a similar report, a positive correlation of plasma resistin was observed with age, urea, creatinine, insulin, BMI, waist circumference, body fat content and homoeostasis model assessment (HOMA).[12] Similarly, another investigation suggested that plasma resistin had a role in linking central obesity and insulin resistance to type 2 DM, and resistin levels correlated significantly with BMI, waist circumference, WHR, FBS, and HOMA score.[17] However, these studies

Table 1 - Comparison of descriptive characteristics and glycemic status between control and diabetic subjects.

Characteristics	Controls n=120	Diabetics n=109	95% confidence interval of the difference		*P*-value
			Lower limit	Upper limit	
Male/Female	75/44	71/39			
Age (years)	50.13 ± 11.76	52.07 ± 11.23	-4.597	1.023	0.318
Height (cm)	167.35 ± 8.20	165.79 ± 13.54	-1.517	4.933	0.273
Weight (kg)	78.96 ± 14.17	81.19 ± 20.43	-10.247	-0.815	0.053
WHR	0.94 ± 0.11	1.00 ± 0.09	-0.088	-0.034	0.001
BMI (kg/m^2)	28.20 ± 4.84	29.67 ± 5.23	-2.793	-0.196	0.023
FBG (mmol/dl)	5.04 ± 0.91	8.80 ± 3.28	-4.426	-3.096	0.001
HbA1c (%)	5.01 ± 0.60	7.66 ±1.51	-2.987	-2.096	0.001

Differences were obtained by student's t test, WHR - waist height ratio, BMI - body mass index, FBG - fasting blood glucose, HBA1c - glycosylated hemoglobin

Table 2 - Comparison of serum resistin levels and body composition parameters between control and diabetic subjects.

Parameters	Controls n=120	Diabetics n=109	95% confidence interval of the difference		*P*-value
			Lower limit	Upper limit	
Resistin ng/ml	2.40 ± 1.14	2.75 ± 1.30	-0.528	-0.043	0.032
Protein mass (kg)	10.96 ± 1.84	11.12 ± 1.57	-0.696	0.245	0.484
Fat mass (kg)	24.17 ± 8.60	26.92 ± 10.73	-5.238	-0.286	0.029
Lean body mass (kg)	54.76 ± 9.10	56.22 ± 7.89	-3.902	0.775	0.200
Total body water (L)	40.36 ± 6.76	41.56 ± 5.86	-2.972	0.613	0.161

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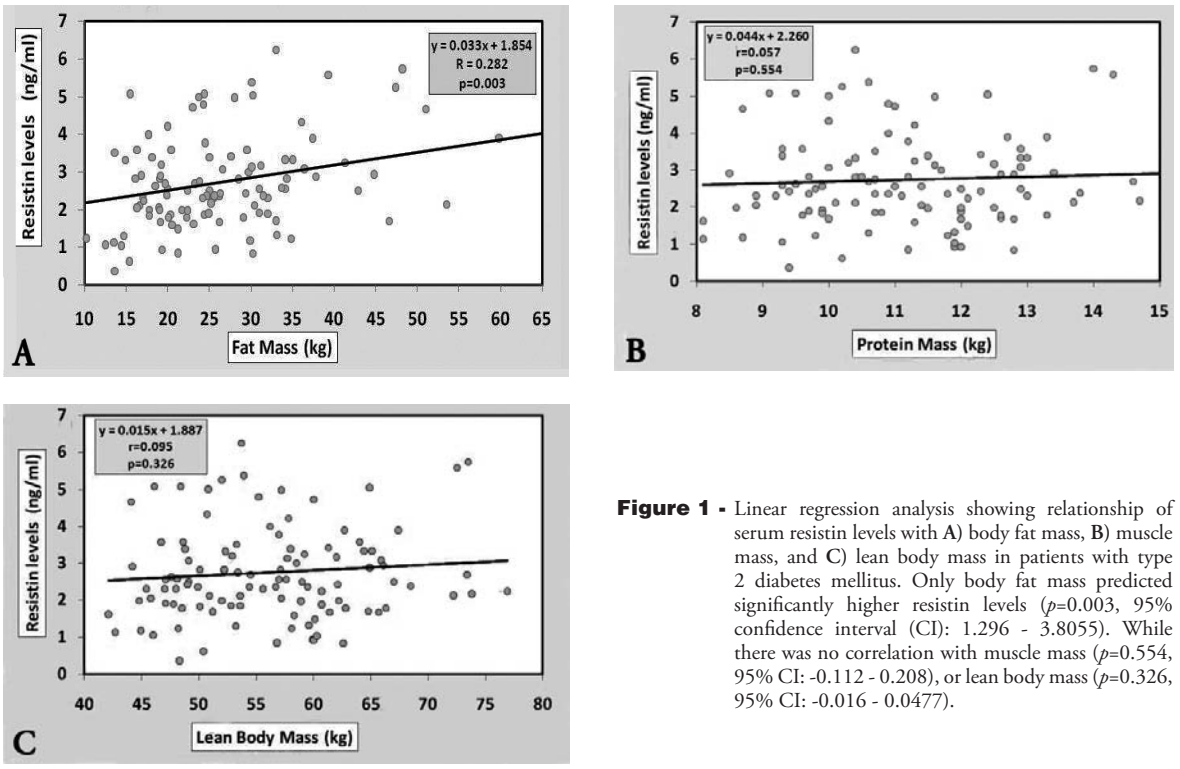

Figure 1 - Linear regression analysis showing relationship of serum resistin levels with **A**) body fat mass, **B**) muscle mass, and **C**) lean body mass in patients with type 2 diabetes mellitus. Only body fat mass predicted significantly higher resistin levels (p=0.003, 95% confidence interval (CI): 1.296 - 3.8055). While there was no correlation with muscle mass (p=0.554, 95% CI: -0.112 - 0.208), or lean body mass (p=0.326, 95% CI: -0.016 - 0.0477).

used anthropometric assessment of body composition. Although, BMI is one of the well-known methods to diagnose obesity and to evaluate weight in relation to height, it cannot be valid for all people, especially when this index is applied to athletes and muscular individuals, as they would always be considered obese due to their heavy muscle. It has also limited value in, the physically frail, pregnant women, and children. Therefore, for the true diagnosis of obesity, percentage body fat and other parameters of body composition should be considered.[18,19]

Li et al[20] reported that resistin levels are increased with central obesity, but not with simple adiposity. They observed a weak correlation of resistin with insulin resistance in Chinese children and adolescents, and revealed that central obesity was significantly related to plasma resistin levels. Waist circumference, fat mass percentage, WHR, and BMI were positively correlated with resistin in both genders.[20] In another study, resistin levels were reported to be positively correlated with changes in BMI and visceral fat areas assessed by hydro densitometry or dual-energy x-ray absorptiometry.[21] Yannakoulia et al[22] observed a positive correlation between resistin concentrations and body fat mass assessed by bioimpedance in healthy subjects. However, we did not observe this relationship in healthy subjects. A possible reason could be that their subjects were college students, 14-26 years of age and younger than our subjects.[22] Some investigations of human resistin in relation to obesity have shown higher serum resistin levels in obese subjects compared with lean subjects.[23,24] Studies in human subjects have highlighted increased resistin expression in adipose tissue,[25,26] particularly abdominal depots.[11,27]

Smith et al[28] described similar levels of resistin expressed in gluteal femoral and subcutaneous abdominal depots in non diabetic subjects without any relationship between resistin mRNA and age, body fatness, visceral adiposity, BMI and serum markers of inflammation.[28] However, in our study we observed a significant relationship between resistin levels with body fat mass in diabetic subjects

Some human studies have shown no correlation between serum or plasma levels of resistin with any markers of adiposity.[4,29]According to a report by Heilbronn et al[30] there was no relationship between resistin serum levels and percentage body fat, visceral adiposity, and BMI. This lack of significant correlation between serum resistin and increased adiposity was partly due to the confounding effects of age, because non-obese subjects were significantly younger than obese subjects in their study.[30] This study supports the evidence that resistin and body fat relationship may be an important factor in etiology and progression of type 2 DM and its cardiovascular complications.

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This report describes the relationship of body composition parameters with resistin levels assessed by bioimpedance analysis, which is cost-effective and becoming a popular method of measuring physical fitness. The limitation of this study is its cross-sectional design and limited number of subjects. Prospective studies on a larger scale are needed to further explore the role of adiposity with resistin in humans.

In conclusion, T2DM patients have significantly higher resistin levels, with a significant positive correlation with body fat mass but no correlation with protein mass or lean body mass. However, this study supports the evidence that resistin plays an important role in the pathogenesis of obesity and insulin resistance, both of which could, indirectly, contribute to the development of type 2 diabetes.

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