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Research Article

ADIPOKINE RESISTIN IS ASSOCIATED WITH INSULIN SENSITIVITY NOT INSULIN SECRETION IN DIABETIC

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ABSTRACT

A growing body of evidence supports the notion that Inflammation play a role in development of insulin resistance and type 2 diabetes mellitus (DM); however, the molecular basis of this relationship is not fully known yet. To determine whether levels of the adipocytokine resistin is associated with insulin resistance and beta cell function in diabetic patients. Fasting serum resistin, insulin and glucose were measured in twenty seven sedentary adult obese males aged 32-47 years and weight 86-107 kg with type II diabetes. Insulin sensitivity and beta cell function was assessed using the homeostasis model assessment formula derived from fasting insulin and glucose levels. Pearson correlation was used to establish the relationship between resistin concentration and insulin sensitivity and beta cell function. Serum resistin concentration were negatively correlated with insulin sensitivity ($p = 0.009$). No significant correlation was found between serum resistin and beta cell function in studied patients ($p = 0.59$). In conclusion, it is likely that serum resistin can be affect glucose homeostasis by insulin sensitivity not by beta cell function in diabetes patients.

Keywords: *Beta Cell Function, Insulin Sensitivity, Inflammation*

INTRODUCTION

Diabetes is a chronic disease, which is caused due to inability of pancreatic beta cells to produce and secrete enough insulin timely. It is also caused due to decreased sensitivity of glucose receptor cells to insulin (Wang *et al.*, 2010). It is well demonstrated that in addition to decreased insulin sensitivity, damage to pancreatic beta-cells function has a key role in the pathogenesis of type 2 diabetes, which is expected to affect over 300 million individuals by 2025 (Adeghate *et al.*, 2006). Chronic hyperglycemia can damage several tissues as well as impair insulin secretion and function (Wang *et al.*, 2010).

Mechanisms of beta-cell dysfunction in type 1 and 2 diabetes are different. In type 1 diabetes, dysfunction or damage to pancreatic beta cell due to several immune system disorders leads to decreased insulin production. In addition, inflammatory cytokines may play an important role in this process (Kawasaki *et al.*, 2001). However, beta cell dysfunction and reduced beta cell mass often increases blood circulation cytokines and free fatty acids in type 2 diabetes. This is associated with hyperglycemia (Stumvoll *et al.*, 2005). Long-term exposure of beta cells to inflammatory mediators increases production of free radicals. This is associated with inhibition of insulin secretion (Andersson *et al.*, 2001).

Resistin is among adipocytokine or cytokine secreted by adipose tissue and other tissues. It is also particularly important in the function of beta cells and other determinant components of type 2 diabetes such insulin sensitivity. Resistin is one inflammatory mediator derived from adipose tissue. It was discovered in 2002 (Steppan *et al.*, 2001). Unlike the resistin in mice, human resistin is expressed primarily in macrophages rather than adipose tissue (Tomaru *et al.*, 2009). In humans and rodents, increased serum resistin is associated with insulin resistance. Resistin is also expressed in pancreatic beta

cells. The expression of resistin in beta cells increases when insulin resistance increases. This increases beta-cell dysfunction in insulin resistance state (Minn *et al.,* 2003).

However, several studies reported that there is no association between resistin and type 2 diabetes determinants such as insulin sensitivity and resistance or blood levels of insulin (Banerjee *et al.,* 2004; Silha *et al.,* 2003; Yannakoulia *et al.,* 2003). These studies also suggested the direct effect of resistin on incidence of type 2 diabetes, which was not established with certainty in other studies (Al-Daghri *et al.,* 2005). However, it is not clear whether serum resistin levels are associated with risk factors or severity of type 2 diabetes. Hence, this study aimed to examine the relationship between serum resistin levels with beta-cell function and insulin sensitivity as two effective components in type 2 diabetes.

MATERIALS AND METHODS

Study Subjects

Subjects were aged 32–47 years, sedentary, obese (BMI 30–36 kg/m2, n=27) with type 2 diabetes that participated in this study by accessible sampling. Inclusion criteria for the test group were: aged 35 - 50 years, a history of type II diabetes at least for three years and BMI between 30 – 36 kg/m2. Participants were non-athletes and non-alcoholics. Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. We also excluded people who had any self reported physician diagnosed other chronic disease such as stroke, hypertension, cancer, heart attack, chronic cough, or bronchitis, injury and abnormal exercise electrocardiogram.

Obesity was measured by body mass index (BMI). Anthropometric measurements of height, weight, percent body fat, and circumference measurements were taken in the physiology laboratory. Height was measured without shoes on standing while the shoulders were tangent with the wall. Body weight was measured in duplicate in the morning following a 12-h fast. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m).

Biochemical Analysis

The subjects did not perform any exercise for 48 hours before the blood collection. Venous blood was collected from subjects after an overnight fast. Serum resistin and insulin were measured by ELIZA. Plasma glucose was measured with the glucose oxidase method. Insulin sensitivity and beta cell function were calculated with fasting glucose and insulin (Duncan *et al.,* 1995). Resistin was determined by ELISA method (Biovendor-Laboratoria medicina a.s. Czech) and the intra- assay and inter-assay coefficient of variation of the method were 3.4 % and 6.9 % respectively.

Data Analysis

Statistical tests were performed using SPSS Software (SPSS 15.0, free evaluation version). Whereas variables tested revealed an abnormal distribution, the Pearson correlation coefficient test was chosen for evaluating the correlations between resistin concentration and insulin sensitivity and beta cell function. A probability level of $p<0.05$ was used to indicate statistical significance.

RESULTS

In this study, the correlation in serum resistin with insulin sensitivity and beta cell function were determined in adult males with type II diabetes. Anthropometric and metabolic characteristics of the study participants are shown in Table 1. Data were expressed as individual values or the mean ± SD. The finding of Pearson correlation coefficient test showed that serum resistin is correlated negatively with insulin sensitivity ($p = 0.009$, $r = 0.49$, Table 2, Fig 1). There was no significant correlation between serum resistin and beta cell function in studied patients ($p = 0.59$, $r = 0.107$, Table 2, Fig 2)

Table 1: The descriptive anthropometric and biochemical features of the study subjects

	Minimum	Maximum	Mean	Std. Deviation
Age (year)	32	47	40.11	3.745
Height (cm)	168	181	173.67	2.948
Weight (kg)	86	107	96.59	5.786
Abdominal (cm)	94	118	106.11	6.801
Hip (cm)	97	114	104.48	4.987
WHO	.94	1.11	1.0159	.03214
BMI (kg/m2)	30	36	31.96	1.850
Body fat (%)	21	35	31.44	3.030
Visceral Fat	9	17	13.48	1.695
Resistin (ng/ml)	.5	4.5	1.904	1.0002
Insulin (µIU/ml)	6.4	11.9	8.615	1.5504
IS	.43	.58	.5004	.03311
BF	8.5	38.3	22.159	8.1300
Glucose (mg/dl)	136	380	222.52	64.029

Table 2: Correlation between serum resistin with Insulin sensitivity (IS) and Beta cell function (BF)

		Resistin (ng/ml)	IS	BF
Resistin (ng/ml)	Pearson Correlation	1	-.491**	.107
	Sig. (2-tailed)		.009	.594
	N	27	27	27
IS	Pearson Correlation	-.491**	1	.430*
	Sig. (2-tailed)	.009		.025
	N	27	27	27
BF	Pearson Correlation	.107	.430*	1
	Sig. (2-tailed)	.594	.025	
	N	27	27	27

*** Correlation is significant at the 0.01 level (2-tailed)*
** Correlation is significant at the 0.05 level (2-tailed)*

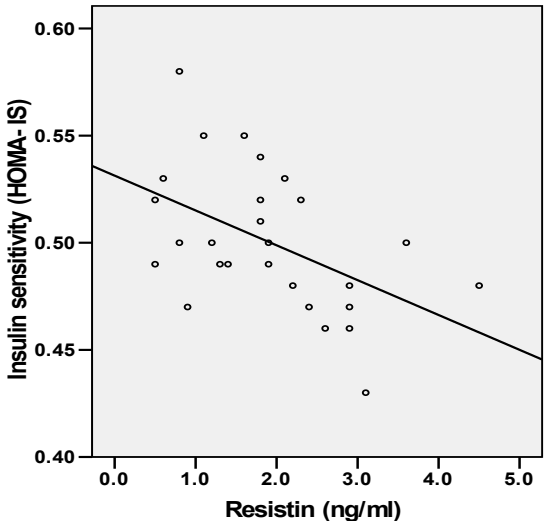

Figure 1: Relation between serum resistin with insulin sensitivity in studied patients. A negative significant correlation

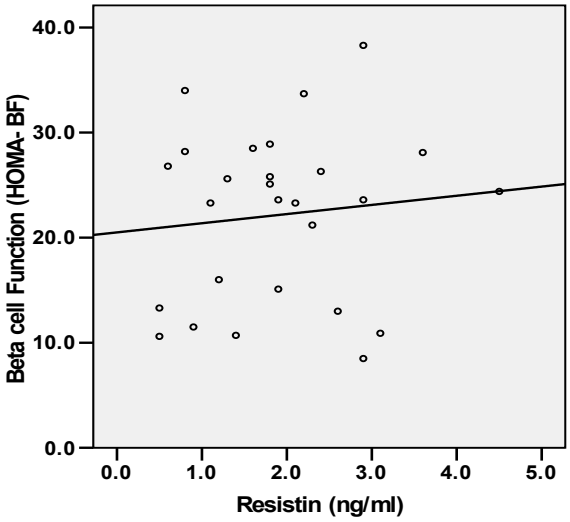

Figure 2: Relation between serum resistin with Beta cell function in studied patients. No significant correlation

DISCUSSION

It is demonstrated clearly that inflammation plays an important role in development of type 2 diabetes (Pradhan *et al.*, 2001). Although clinical data are limited in this area, the role of systemic inflammation is repeatedly addressed in incidence or severity of type 2 diabetes, particularly inflammatory or anti-inflammatory cytokine abnormalities. However, it is not clear which one of the effective factors in type 2 diabetes are affected by the peptide mediators in these patients. These factors cause hyperglycemia. The findings obtained from this study showed that serum resistin levels have an inverse and strongly significant correlation with insulin sensitivity in these patients. However, this inflammatory mediator is not associated with beta-cell function in these patients.

It is reported in several previous studies that serum resistin levels increases by twenty percent in in type 2 diabetics compared to healthy subjects (McTernan *et al.*, 2003; Fujinami *et al.*, 2004). Early studies showed that resistin increases in both obesity and insulin resistance states. This also reduces insulin sensitivity. Nevertheless, neutralization of this component leads to decreased hyperglycemia and improved insulin sensitivity (Steppan *et al.*, 2001). In this context, it is found out that insulin-dependent glucose transport is reduced in mice with hyper resistin. However, it seems that changes in glucose metabolism do not affect insulin receptor signals (Moon *et al.*, 2003). Rajela *et al* reported that resistin infusion leads to decreased insulin sensitivity. This primarily affects liver cells (Rajala *et al.*, 2003). These researchers pointed out that the resistin secreted from adipose tissue and digestive tract clearly and immediately stimulates hepatic glucose production by stimulating gluconeogenesis. This also leads to a reduction in glucose uptake by inhibiting insulin sensitivity (Rajala *et al.*, 2003).

Lack of association between resistin and beta-cell function was observed in the present study. However, several other studies showed that increased circulating resistin levels decreases insulin secretion from pancreatic beta cells in either obesity or insulin resistance states. This is also associated with degradation and dysfunction of glucose homeostasis (Wang *et al.*, 2010). Several other findings confirmed this issue and showed that resistin is expressed in pancreatic beta cells (Minn *et al.*, 2003). In addition, exposure of beta cells to high levels of resistin in obese and diabetic patients respectively leads to 70% and 60% decline in expression of insulin receptors in these individuals (Brown *et al.*, 2007). On the other hand, several studies reported that there is no correlation between resistin and insulin sensitivity and other parameters involved in type 2 diabetes (Stejskal *et al.*, 2003). Studies have shown that resistin leads to negative effects on pancreatic beta cells due to negative regulation of expression of insulin receptors. In addition, exposure of beta cells to high levels of resistin in obese or diabetic patients respectively leads to

70% and 60% decrease in expression of insulin receptors (Brown *et al.*, 2007). However, it is well demonstrated that serum resistin concentrations are correlated positively with blood glucose levels in type 2 diabetes (Al-Harithy *et al.*, 2005). Despite these observations, no correlation was observed between resistin and beta cells function in the present study.

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