International Journal of Biosciences (IJB)
ISSN: 2220-6655 (Print) 2222-5234 (Online)
Vol. 1, No. 4, p. 118-124, 2011
http://www.innspub.net

RESEARCH PAPER OPEN ACCESS

Estimation of the correlation serum resistin with metabolic syndrome

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Received: 14 July 2011
Revised: 05 August 2011
Accepted: 07 August 2011

Key words: Metabolic syndrome, obesity, serum resistin.

Abstract

Adipose tissue-derived adipokines play important role in metabolic syndrome and obesity related disease. Although the molecular mechanisms for this are less understood. In this study, we determined serum resistin in relation to metabolic syndrome determinants. For this purpose, Fasting blood samples were collected from brachial vein in 39 sedentary adult overweight - obese men aged 35 – 43 years in body mass index (BMI) ranged 28 to 33 kg/m2 in order to measuring serum resistin, lipid profile and glucose concentration. Anthropometrical indexes and blood pressure were also measured in all participants. Pearson rank correlation analysis were used for determine relationship between resistin with metabolic syndrome determinants. A p-value less than 0.05 were considered statistically significant. Serum resistin levels correlated positively with BMI, body fat percentage (BF%), Total cholesterol (TC), low density lipoprotein (LDL), age, visceral fat, waist to hip ratio (WHO), systolic and diastolic blood pressure in studied subjects. A borderline signigcant positive association was observed between serum resistin and glucose concentration. Resistin as an inflammation cytokine is associated with metabolic syndrome in obese subjects.

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Introduction

It was initially believed that adipose tissue act primarily as an energy reservoir, allowing the body to negotiate times of famine by storing triacylglycerol in times of excess, and mobilizing it in times of shortage. But, nowadays a large body of evidence suggests that adipose tissue as a metabolically active endocrine organ that is able to secrete a signigcant number of bioactive peptides that have been termed 'adipokines' such as leptin, adiponectin, Visfatin, resistin and interleukins (Kershaw *et al.,* 2004). Between them resistin is another adipose-derived cytokine first described in 2001 (Tomaru *et al.,* 2009). Unlike the expression of resistin in mouse, human resistin is expressed primarily in macrophages but not in adipose (Tomaru *et al.,* 2009). This inflammation cytokine is a 10 kDa protein of 94 amino acids, which belongs to the resistin-like molecules family and was cloned in 2001 as a thiazolidinediones (TZD)-regulated cytokine expressed in adipose tissue (Steppan *et al.,* 2001; Antuna-Puente et al., 2008). The information about resistin role in obesity and related diseases is controversial. Resistin has been linked to obesity, type 2 diabetes, inflammation and atherosclerosis but the results of animal and human studies have been at variance (Mojiminiyi *et al.,* 2007). The studies on human have highlighted increased resistin expression in adipose tissue (Savage *et al.,* 2001), particularly abdominal depots (McTernan *et al.,* 2002); furthermore, positive correlations between serum resistin and body fat content have also been reported (Zhang *et al.,* 2002). On the other hand, a number of studies have failed to demonstrate such correlations in rodents, with groups also reporting either reduced (Fukui *et al.,* 2002; Rajala *et al.,* 2002) or no alteration (Makimura *et al.,* 2002; Le et al., 2001) of resistin levels in various models of obesity. A recent study indicates a weekly correlation between resistin and body fat and these authors have not confirmed the role of resistin in metabolic syndrome (Utzschneider *et al.,* 2005).

Review of research evidence shows that Findings about the role of resistin on the metabolic syndrome indicators are conflicting and there is not a general consensus among the results. Therefore, the current study is designed to examine whether resistin s associate with the metabolic syndrome indicators such as body mass index (BMI), blood pressure and lipid profile.

Material and methods

Thirty nine sedentary adult obese men (38±5 years mean ± standard deviation) participated in the study by voluntarily. All subjects were otherwise in good health were taking no medications. All subjects had a body mass index (BMI) between 27-33 kg/m^2. An informed consent was obtained from all participants before the studies were carried out, and the Ethics Committee of Islamic Azad University, Iran approved this study. Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, orthopedic abnormalities, recent myocardial infarction, congestive heart failure, active liver or kidney disease, growth hormone deficiency or excess, neuroendocrine tumor, anemia, or who were on medications known to alter insulin sensitivity were excluded. Those that were on medications known to alter insulin sensitivity were excluded. No difference was observed in the subjects' diets 48 h before each trial**.** Subjects had neither used any medication 6 weeks prior to the study till the end nor participated in any regular physical exercise. The measurements for weight, height, abdominal and hip circumference and blood pressure were first performed. The weight and height of the participants were measured in the morning, in fasting condition, standing when the participant had thin clothes on and was wearing no shoes by using the standard hospital scales. Abdominal circumference and hip circumference were measured in the most condensed part using a non-elastic cloth meter. Visceral fat and body fat percentage was determined using body composition monitor (OMRON, Finland). Systolic and diastolic blood pressure was measured

using the left arm after the subject had been sitting comfortably for 5 min, using an oscillometric device (Alpikado, Japan). Two measurements were made every 1 minute and the average of two measurements was used for analysis. Body mass index (kg/m²) was calculated as weight (kg) divided by squared height (m²). After anthropometric measurements, the individuals in the experimental and control groups were asked to attend Hematology Lab following12 hours of overnight fasting, between the hours of 8 to 9 am for blood sampling. Fasting blood samples were collected from brachial vein in sitting position in order to measuring resistin, glucose and lipid profile. Serums were immediately separated. The subjects were advised to avoid any physical activity or exercise 48 hours before the blood sampling. Blood glucose was measured by glucose oxidase using Calorimetric method (Pars Azmoun, Tehran, Iran). Triglyceride, total cholesterol, HDL-cholesterol was measured directly with enzymatic methods (Randox direct kits) using Kobas Mira auto-analyzer made in Germany. Plasma insulin was determined by ELISA method (Demedite, German). Serum adiponectin was determined by ELISA method, using a Biovendor-Laboratorial kit made by Biovendor Company, Czech. The Intra- assay coefficient of variation and sensitivity of the method were 3.4% and 0.033 ng/mL, respectively.

Statistical analyses

Data were expressed as individual values or the mean ± SD. For the descriptive statistics after having checked the normality of the variables using the Kolmogorov-Smirnov test. The bivariate associations between serum resistin concentration with metabolic syndrome determinants were examined with the Spearman rank correlation analysis in studied subjects. Statistical analysis was performed with the SPSS software version 15.0. All statistical tests were performed and considered significant at a $P \leq 0.05$.

Results

In present study, we investigated serum resistin in relation to metabolic syndrome determinants in a group of obese men. Table 1 show the descriptive anthropometric and biochemical features of the study groups. Participant characteristics are reported as means ± SD. Anthropometrical indexes measurements showed that all participants were overweight and obese.

Table 1. Clinical and anthropometrical parameters and Pearson correlation of all variables with serum resistin.

Variables	obese group	P value
Age (year)	38 ± 5	0.013
Weight (kg)	102 ± 11	0.056
Height (cm)	176 ± 6	0.354
Body Fat (%)	30.6 ± 3.21	0.031
Body mass index (kg/m²)	32.90 ± 4.14	0.037
Waist circumference (cm)	107 ± 11	0.065
Visceral fat (mm)	14 ± 3	0.035
Hip circumference (cm)	105 ± 11	0.062
Waist to hip ratio	1.02 – 0.14	0.001
Glucose (mg/dL)	102 ± 11	0.052
Systolic blood pressure (mmHg)	128 ± 11	0.035
Diastolic blood pressure (mmHg)	89 ± 8	0.016
Insulin (µIU/ml)	8.42 ± 2.14	0.211
Insulin resistance Index		0.038
Resistin (ng/ml)	2.09 ± 0.31	------

The data of Pearson method indicates serum resistin is related with markers indicative of metabolic syndrome in obese men. Significant levels of correlation each variable with serum resistin are shown in Table 1. We observed a positive significant correlation in serum resistin and body mass index. Serum resistin also correlated positively with the other anthropometrical indexes such as body fat percentage, visceral fat and waist to hip circumference ratio. A borderline signigcant positive association was observed between fasting glucose and serum resistin that probably is due

to low number of samples. Resistin was also significant positive correlated with systolic and diastolic blood pressure. Total cholesterol and low density lipoprotein were also positive related with serum resistin.

Discussion

Our study finding showed that most indicators of metabolic syndrome have a positive relation with serum resistin in studied subjects. Metabolic syndrome is a combination of medical disorders that, when occurring together, increase the risk of developing cardiovascular disease and diabetes (Ford *et al.,* 2002). Resistin, an inflammation cytokine secreted by adipose tissue, has been demonstrated to increase insulin resistance. However, its role in human remains controversial. Resistin is a recently discovered protein that is expressed and secreted from adipocytes and is present in the circulation. Resistin belongs to a family of small cysteine-rich secreted proteins along with resistin-like molecule a and b (Steppan *et al.,* 2001; Holcomb *et al.,* 2000). Some studies have reported resistin was undetectable in serum of obese mice, with the same study indicating reductions of resistin mRNA and protein expression in obesity (Maebuchi *et al.,* 2003). This observation was in accord with another study that have reported no association of resistin expression with increased adiposity, despite observing elevated circulating levels (Lee *et al.,* 2005). How-ever, it has been suggested recently that resistin mRNA expression does not necessarily correlate with protein expression (Rajala *et al.,* 2004).

In contrast, our study showed serum resistin positively related with BMI. This finding demonstrates a high body mass index or obesity is associated with increased serum resistin. To support these data, the finding of a recent study showed that various murine models of obesity had higher circulating resistin levels compared with their lean counterparts (Lee *et al.,* 2005). These observations coincided with rodent studies another study, showing circulating resistin levels were significantly elevated and concordant with increasing levels of insulin, glucose and lipids (Rajala *et al.,* 2004); thus substantiating the initial evidence that addressed the etiology of resistin with increasing adiposity (Shuldiner *et al.,* 2001). Central obesity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between visceral fat and increasing adiposity. In present study, we also observed serum resistin was positively correlated with body fat percentage, visceral fat and waist to hip circumference. This data clearly confirms that high body weight or fat tissue lead to increase systemic resistin. These studies suggest that resistin could be a link between adipose tissue, obesity and insulin resistance.

Another finding of our study was a borderline significant correlation between serum resistin and fasting glucose. Of corese, it seems to insignificant relationship between insulin and resistin in the present study may be due to the small number of samples. It is also important to note that obesity induced by a high-fat diet, mutation of the leptin gene (ob/obmice), or mutation in the leptin receptor gene (db/dbmice) is associated with increased circulating resistin concentrations (Meier *et al.,* 2004). Resistin increases blood glucose and insulin concentrations in mice and impairs hypoglycemic response to insulin infusion. In addition, anti-resistin antibodies decrease blood glucose and improve insulin Sensitivity in obese mice (Ukkola *et al.,* 2002). Administration of resistin impaired glucose homeostasis and insulin sensitivity in wild-type mice, while neutralization of resistin in diet induced obese mice reduced blood glucose levels and improved insulin sensitivity (Steppan *et al.,* 2001). Furthermore, resistin gene expression and protein secretion were markedly reduced by the anti-diabetic TZDs (Steppan *et al.,* 2001). It was reported that Resistin suppresses insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes, and this effect is prevented by anti-resistin antibodies (Shuldiner *et al.,* 2001). Our study has also showed that resistin is positively related with insulin resistance.

Thiazoladinedione drugs reduce insulin resistance and are used to treat type II diabetes. These drugs suppress the production of resistin by adipocytes, and their antidiabetic effects may, at least in part, be achieved through this mechanism (Meier *et al.,* 2004). A number of studies have demonstrated that a decrease in fasting glucose levels, improved glucose tolerance and enhanced insulin sensitivity in resistin-gene knockout mice (Banerjee *et al.,* 2004). It was reported that the absence of resistin could allow activation of AMPK and reduce gene expression encoding for hepatic gluconeogenesis enzymes. In this area, resistin activity differed from that of the other cytokines such as leptin and adiponectin, both known to activateAMPK. Finally, resistin-deficient animalswith high-fat-diet-induced obesity and insulin resistance had reduced fasting glucose compared with matched-weight controls, suggesting that resistin interferes in hyperglycaemia and obesity-related insulin resistance (Antuna-Puente *et al.,* 2008).

Positive relation between resistin and age was another finding of present study. Metabolic syndrome affects close to half of elderly people over 50 years. The age dependency of the syndrome's prevalence is seen in most populations around the world. In our study, also a significant positive correlation was observed between serum resistin with the other metabolic syndrome determinants such as total cholesterol, low density lipoprotein, systolic and diastolic blood pressure. In this area, it is reported that resistin directly stimulates smoothmuscle cell proliferation in the human aorta (Rajala *et al.,* 2002). To support our data, study by Norata et collegous confirmed that resistin is related with lipid profile determinants (Norata *et al.,* 2007).

In a general summary, confirming some previous studies the findings of this study suggest that increased levels of body fat, particularly visceral adipose tissue have an important role in blood resistin levels. These findings support the close relationship between serum resistin levels and the presence of metabolic syndrome and its related diseases such as atherosclerosis or type II diabetes. Many components of metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol; and a trend toward increased triglycerides, blood pressure, and glucose in the genetically susceptible. Since fat tissue is the main source secreting resistin into the bloodstream, adopting appropriate mechanisms such as active lifestyle model and inclusion of exercise and physical activity in daily activities to reduce body fat levels and prevent an increase in percent body fat, play a remarkable role in reducing inflammatory cytokines secreted from adipose tissue, particularly resistin.

Acknowledgment: Hereby, the authors wish to acknowledge the Research Deputy of Islamic Azad University and all participants in this study.

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