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Human serum resistin is related to homeostasis model assessment of insulin resistance in healthy people

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Abstract

Resistin, an inflammation cytokine secreted by adipose tissue, has been demonstrated to increase insulin resistance. However, its role in human remains controversial. This study aimed to evaluate relationship between serums resistin with insulin resistance in a group of healthy adult men. For this purpose, we measured fasting serum resistin, glucose and insulin after an overnight fast in thirty nine sedentary adult men aged 38 – 43 years with body mass index between 26 – 32 kg/m2. All re participants were healthy without any chronic diseases particularly type II diabetic. Insulin resistance was calculated using fasting insulin and glucose concentration. A Pearson correlation was used to establish the relationship between serums resistin with the other variables. The statistical finding showed a positive significant relation between serum resistin and insulin resistance index (p = 0.033). A borderline signigcant positive association was observed between serum resistin and fasting glucose (p = 0.048). But insulin was not related with serum resistin (p = 0.211). Although serum resistin levels were not related to insulin, this data showed that resistin may be affect glucose and insulin resistance that is likely by mechanisms independent of insulin. Further studies are necessary to elucidate the significance of serum resistin concentration in insulin resistance pathophysiology.

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Introduction

A large body of evidence has however identified adipose tissue as a metabolically active endocrine organ that is able to secrete a significant number of bioactive peptides that have been termed 'adipokines'. These molecules include cytokines such as leptin, resistin, visfatin, adiponectin and TNF-a, hormones, growth factor (Kershaw *et al.,* 2004). Resistin, a 12.5 kDa cysteine rich adipokine, adipose-derived cytokine is an inflammatory cytokine that first described in 2001 (Kwon *et al.,* 1998). Although the expression of resistin in mice was originally restricted to adipose tissue, the principle origin of human resistin has remained somewhat contentious (Steppan *et al.,* 2001). It was reported that unlike the expression of resistin in mouse, human resistin is expressed primarily in macrophages but not in adipose (Tomaru *et al.,* 2009). Initial studies showed that resistin was up-regulated in rodent models of obesity and insulin resistance (3). Increased serum resistin level is reported in insulin resistance in rodents and human (Wang *et al.,* 2010). Elevated levels of resistin are reported in subjects with type 2 diabetes (Heilbronn *et al.,* 2004; Fujinami *et al.,* 2004; Pfutzner *et al.,* 2003), and correlate with hepatic insulin resistance (Bajaj *et al.,* 2004; Rajala *et al.,* 2003; McTernan *et al.,* 2003).

Review of research evidence shows that resistin levels in type II diabetics is much higher than non-diabetics (Stejskal *et al.,* 2003; Lu *et al.,* 2006). These findings also support a significant positive correlation between blood glucose levels and insulin resistance with systemic resistin (Lu *et al.,* 2006; Chanchay *et al.,* 2006). As based on these findings it can be concluded that increased circulating resistin levels leads to increased blood glucose concentration. A review of research findings shows that most studies have been conducted on glucose response to resistin in people with hyperglycemia or diabetes and very few studies have reported the relationship between serum levels of resistin and glucose or insulin resistance in non-diabetic and healthy individuals. This study aims to determine the relationship between serum levels of resistin with insulin resistance index in obese non-diabetic subjects.

Material and Methods

Subjects

This Study Protocol was conducted and approved by the Ethics Committee of Islamic Azad University, Iran. This semi-experimental study was conducted in order to look into evaluate relationship between resistin as inflammatory cytokine with homeostasis model assessment of insulin resistance (HOMA-IR), insulin and fasting glucose sedentary adult men aged 38 – 43 years with body mass index between 26 – 32 kg/m2.

Inclusion or exclusion criteria

All participants were healthy, none-smoker and none-athletes. Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. Subjects included individuals with no cardiovascular diseases, gastrointestinal diseases, kidney and liver disorders or diabetes. Those with type 2 diabetic were excluded from the study. An informed consent was obtained from all participants before the studies were carried out.

Anthropometrical and biomarker measurements

The measurements for weight, height, abdominal and hip circumference and blood pressure were first performed. Body weight and height were measured with a standard physician's scale and a stadiometer, respectively when subjects were in a fasting state when the participant had thin clothes on and was wearing no shoes. 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 (m^2). Blood samples were collected after an overnight fast in order to measuring serum resistin, insulin, and glucose. The HOMA1-IR index was calculated by the formula: HOMA1-IR = fasting plasma insulin (µU/ml) x fasting plasma glucose (mmol/L)/22.5 (Marita *et al.,* 2005). The blood was centrifuged immediately and serum separated. Glucose was determined by the oxidase method (Pars Azmoun, Tehran, Iran). Serum insulin was determined by ELISA method (Demedite, German). The Intra- assay coefficient of variation and sensitivity of the method were 2.6% and 2.88 µg/L, respectively. Serum resistin 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 2.8% 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 glucose, insulin and insulin resistance 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 this study we investigated serum resistin in relation to some markers indicative of type II diabetic in healthy men. The main finding of study was a positive significant relation between serum resistin with insulin resistance in studied subjects ($p = 0.033$, $r = 0.55$, Fig 1). In the other word, our finding demonstrates increased serum resistin as an inflammation cytokine is associated with increased insulin resistance. In fact, the more serum resistin, the more insulin resistance. Although the molecular mechanisms for this are less understood. Although a liner positive relation were observed between serum resistin and insulin, this relation was not significant from statistical perspective ($p = 0.211$, $r = 0.21$). Since, small number of studied participants was a limitation of this study. The insignificant relationship between insulin and resistin in the present study may be attributed to the small number of samples. Our finding also showed that serum resistin correlated negatively with total cholesterol ($p = 0.032$, $r = 0.57$), low density lipoprotein ($p = 0.041$, $r = 0.54$), age ($p = 0.013$, $r = 0.43$), systolic blood pressure ($p = 0.038$, $r = 0.46$) and diastolic blood pressure ($p = 0.036$, $r = 0.37$). Although fasting plasma glucose tended to be positively correlated with the serum resistin level after adjustment for age and BMI, this did not reach statistical significance ($p = 0.054$, $r = 0.55$). Additionally, the insignificant relationship between glucose and resistin in the present study may be attributed to the small number of samples.

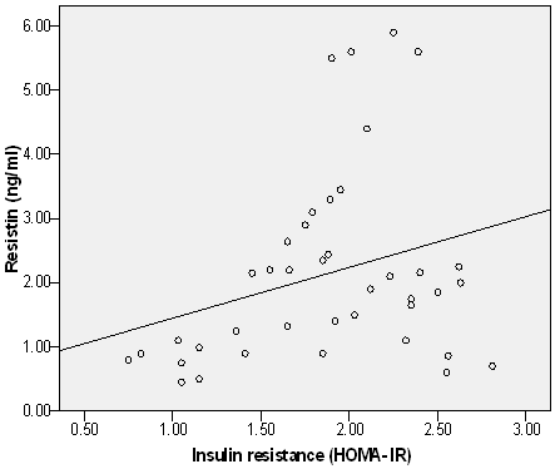

Fig 1. The correlation pattern of serum resistin in relation to insulin resistance index.

Discussion

The main study finding was a positive significant correlation between serum resistin and insulin resistin index. To support our finding, There is evidence that resistin predominantly expressed in white adipose tissue (Steppan *et al.,* 2001), reduces insulin sensitivity in adipocytes and skeletal muscles by impairing insulin-mediated glucose transport (Palanivel *et al.,* 2006; Palanivel *et al.,*

2005), and regulates fasting blood glucose by increasing hepatic glucose release (Banerjee *et al.,* 2004). However, these data do not support a role of resistin in insulin resistance (Haugen *et al.,* 2001). The role of resistin in insulin sensitivity has been reported repeatedly (Steppan *et al.,* 2001). But information and findings about insulin resistance in response to resistin is limited and controversial. In diet-induced obese rats, serum resistin levels were negatively correlated with the insulin sensitivity index (ISI). No negative correlation was found between the levels of fasting serum insulin and resistin, suggesting that insulin is not the major regulator of resistin in rodents (Feng *et al.,* 2008). But, some studies support of resistin as a potential etiological link between obesity and diabetes, with a clear functional role as a pathogenic factor contributing to insulin resistance (Steppan *et al.,* 2001). Resistin has been demonstrated as one of the adipocytokines secreted by adipose tissue and has been shown to modulate both glucose and lipid metabolism (Steppan *et al.,* 2001). It is also important to note that resistin does not alter insulin receptor signaling but affects insulin-stimulated glucose uptake, presumably by decreasing the intrinsic activity of cell surface glucose transporters (Palanivel *et al.,* 2006; Palanivel *et al.,* 2005). In mature 3T3-L1 adipocytes, resistin reduces insulin-stimulated glucose uptake by activating SOCS3, which is an inhibitor of insulin signaling (Steppan *et al.,* 2005). A number of studies have demonstrated that resistin also takes part in insulin resistance in resistin fat-specific transgenic rats by releasing free fatty acids (FFA) from adipose tissue (Pravenec *et al.,* 2006). In this area, our study also showed a positive significant relation serum resistin with total cholesterol, low density lipoprotein and body fat percentage in studied subjects.

There is considerable evidence that resistin induced insulin resistance in mice when injected into normal mice, and that treating diet-induced diabetic mice with anti-resistin antibody reduced blood glucose and improved insulin action (Feng *et al.,* 2008). It was reported that resistin is not regulated by insulin but induces insulin resistance (Banerjee *et al.,* 2004). On the other hand, some data suggests that a number of factors such as glucose, epinephrine, and somatropin can be regulating resistin secretion (Lu *et al.,* 2006; Rajala *et al.,* 2004). Therefore, insulin may regulate resistin although it is not the major regulator. It was observed that Resistin may play a role in dietinduced insulin resistance by inducing insulin resistance in hepatocytes and myotubes (Feng *et al.,* 2008).

On the other hand, there is evidence that high concentrations of resistin could possibly lead to negative effects in pancreatic beta-cells, via a down-regulation of expression of the insulin receptor (Brown *et al.,* 2007). These authors noted that when beta-cells are exposed to the kind of elevated levels of resistin which might be seen in obesity/T2D, a significant reduction in the level of insulin receptor mRNA and protein is seen, with decreases of 70% and 60%, respectively being seen (Brown *et al.,* 2007). This hypothesis that resistin can reduce insulin receptor expression in the beta-cell has profound importance. It was reported that when the insulin receptor is knocked out in a beta-cell specific manner, hyperglycaemia results due to a loss of both beta-cell mass and secretory function (Otani *et al.,* 2004), suggesting a central role for autocrine actions of insulin in maintaining pancreatic function.

On the whole, the findings of this study indicate a significant positive correlation between serum levels of resistin and insulin resistance index, but the relationship between serum insulin and resistin levels was not significant in the subjects. In fact the statistical findings of this study showed that although the relationship between serum resistin and fasting insulin was linear, this relationship was not statistically significant. The insignificant relationship between insulin and resistin in the present study may be attributed to the small number of samples. Besides; lack of correlation

between serum insulin and resistin has also been reported in some other studies. Referring to these findings, it may be concluded that apart from the functioning of insulin, serum resistin affects blood glucose levels or insulin resistance through other mechanisms. Or that these blood circulating levels of this hormone indirectly affects insulin or blood glucose through affecting other inflammatory cytokines.

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References

Bajaj M, Suraamornkul S, Hardies LJ, Pratipanawatr T, DeFronzo RA. 2004. Plasma resistin concentration, hepatic fat content, and hepatic and peripheral insulin resistance in pioglitazone-treated type II diabetic patients. Int J Obes Relat Metab Disord **28(6),** 783–9.

Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y. 2004. Regulation of fasted blood glucose by resistin. Science **303,** 1195-1198.

Brown JE, Onyango DJ, Dunmore SJ. 2007. Resistin down-regulates insulin receptor expression, and modulates cell viability in rodent pancreatic beta-cells. FEBS Lett **581(17),** 3273-6.

Chanchay S, Tungtrongchitr R, Harnroongroj T, Phonrat B, Rungseesakorn O, Paksanont S et al. 2006. Plasma resistin, insulin concentration in non-diabetic and diabetic, overweight/obese Thai. Int J Vitam Nutr Res **76(3),** 125-31.

Feng Liu, Hong-Qi Fan, Jie Qiu, Bin Wang, Min Zhang, Nan Gu et al. 2008. A paradox: Insulin inhibits expression and secretion of resistin which induces insulin resistance. World J Gastroenterol **14(1),** 95-100.

Fujinami A, Obayashi H, Ohta K, Ichimura T, Nishimura M, Matsui H. 2004. Enzyme-linked immunosorbent assay for circulating human resistin: resistin concentrations in normal subjects and patients with type 2 diabetes. Clin Chim Acta **339(1–2),** 57–63.

Haugen F, Jorgensen A, Drevon CA, Trayhurn P. 2001. Inhibition by insulin of resistin gene expression in 3T3-L1 adipocytes. FEBS Lett **507,** 105-108.

Heilbronn LK, Rood J, Janderova L, Albu JB, Kelley DE, Ravussin E. 2004. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J Clin Endocr Metab **89(4),** 1844–8.

Kershaw E, Flier J. 2004. Adipose tissue as an endocrine organ. J. Clin. Endocrinol. Metab. **89(6),** 2548–2556.

Kwon G, Corbett JA, Hauser S, Hill JR, Turk J, McDaniel ML. 1998.Evidence for involvement of the proteasome complex (26S) and NFκB in IL-1β-induced nitric oxide and prostaglandin production by rat islets and RINm5F cells. Diabetes **47(4),** 583–591.

Lu HL, Wang HW, Wen Y, Zhang MX, Lin HH. 2006. Roles of adipocyte derived hormone adiponectin and resistin in insulin resistance of type 2 diabetes. World J Gastroenterol **12(11),** 1747-51.

Marita AR, Sarkar JA, Rane S. 2005. Type 2 diabetes in non-obese Indian subjects is associated with reduced leptin levels: Study from Mumbai, Western India. Molecular and Cellular Biochemistry **275,** 143–151.

McTernan PG, Fisher FM, valsamakis G, Chetty R, Harte A, McTernan CL. 2003. Resistin and type 2 diabetes: regulation of resistin expression by insulin and rosiglitazone and the

effects of recombinant resistin on lipid and glucose metabolism in human differentiated adipocytes. J Clin EndocrMetab **88(12),** 6098–106.

Otani K, Kulkarni RN, Baldwin AC, Krutzfeldt J, Ueki K, Stoffel M, Kahn CR, Polonsky KS. 2004. Reduced beta-cell mass and altered glucose sensing impairs insulin-secretory function in betaIRKO mice. Am. J. Physiol. Endocrinol. Metab **286(1),** 41-49

Palanivel R, Maida A, Liu Y, Sweeney G. 2006. Regulation of insulin signalling, glucose uptake and metabolism in rat skeletal muscle cells upon prolonged exposure to resistin. Diabetologia **49,** 183-190.

Palanivel R, Sweeney G. 2005. Regulation of fatty acid uptake and metabolism in L6 skeletal muscle cells by resistin. FEBS Lett **579,** 5049-5054.

Pfutzner A, Langenfeld M, Kunt T, Lobig M, Forst T. 2003. Evaluation of human resistin assays with serum from patients with type 2 diabetes and different degrees of insulin resistance. Clin Lab Med **49(11-12),** 571-6.

Pravenec M, Kazdova L, Cahova M, Landa V, Zidek V , Mlejnek P. 2006. Fat-specifi c transgenic expression of resistin in the spontaneously hypertensive rat impairs fatty acid re-esterifi cation. Int J Obes Lond 30, 1157-1159.

Rajala MW, Qi Y, Patel HR, Takahashi N, Banerjee R , PajvaniU . 2004. Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes **53,** 1671-1679.

RajalaMW, Obici S, Scherer PE, Rossetti L. 2003. Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. J Clin Invest **111(2),** 225–30.

Stejskal D, Adamovská S, Bartek J, Juráková R, Prosková J. 2003. Resistin - concentrations in persons with type 2 diabetes mellitus and in individuals with acute inflammatory disease. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub **147(1),** 63-9.

Steppan CM, Bailey ST, Bhat S. 2001. The hormone resistin links obesity to diabetes. Nature (London) **409,** 307–312.

Steppan CM, Wang J, Whiteman EL, Birnbaum MJ, Lazar MA. 2005. Activation of SOCS-3 by resistin. Mol Cell Biol **25**, 1569-1575.

Tomaru T, Steger DJ, Lefterova ML, Schupp M, Lazar MA. 2009. Adipocyte-specific expression of murine resistin is mediated by synergism between peroxisome proliferator-activated receptor γ and CCAAT/enhancerbinding proteins," The Journal of Biological Chemistry **284(10),** 6116–6125.

Wang C, Guan Y, Yang J. 2010. Cytokines in the Progression of Pancreatic β-Cell Dysfunction. Int J Endocrinol. Int J Endocrinol **2010,** 515136.