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Relationship between serum resistin concentration and proinflammatory cytokines in obese women with impaired and normal glucose tolerance

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Abstract

The aim of this study was to investigate the possible role of resistin in obese women with and without insulin resistance. We compared serum concentrations of resistin with interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), soluble TNF receptors 1 and 2, and certain anthropometric and metabolic parameters in 26 obese women (body mass index [BMI], 35.8 ± 4.12 kg/m^2) and 15 healthy control women (BMI, 22.32 ± 1.89 kg/m^2). Fasting serum resistin and inflammatory cytokine levels were measured by enzyme immunoassay. Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA-R) formula. Compared with lean controls, obese women showed higher HOMA-R values and levels of insulin and increased values of TNF-α, soluble TNF receptors, and IL-6. There was no significant difference in resistin levels between the investigated groups of obese women and lean subjects. The results showed that serum resistin concentrations did not correlate with BMI, HOMA, fasting plasma glucose level, or fasting plasma insulin level. Serum resistin correlated with fat mass and IL-6 in the group with impaired glucose tolerance (obese group) ($r = 0.51$, $P < .05$, and $r = 0.37$, $P < .05$, respectively) and with low-density lipoprotein cholesterol ($r = -0.39$, $P < .05$) in the same group. The groups we examined are relatively small; it is likely that with a larger number of subjects, the correlation in other obese women groups may achieve statistical significance. It seems that resistin may be linked with inflammation and obesity and, indirectly, with insulin resistance.

1. Introduction

Obesity, especially visceral obesity, is closely linked with insulin resistance and a high risk for development of type 2 diabetes mellitus. It is commonly known that adipose tissue is an important endogenous source of lipids and that it is an endocrine organ secreting a range of adipocytokines that influence the regulation of metabolic processes and energy balance [1-4].

Proinflammatory cytokines and acute phase proteins secreted by adipocytes cause subclinical inflammation, which is a well-described mechanism of the pathogenesis of insulin resistance and type 2 diabetes mellitus [4]. In these disorders, increased levels of inflammation mediators such as C-reactive protein and the cytokine series, mainly tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [3-6], have been revealed. Both cytokines regulate hepatic synthesis and the secretion of acute phase inflammatory proteins [7]. Weight reduction in obese individuals was associated with significant decrease in TNF-α and IL-6 levels [1-5,8,9]. Soluble external domains of receptors for TNF-α are present in blood in determining concentrations; however, their role has not been fully explained. They show a greater affinity with TNF-α than the receptors connected with the cell membrane. Possibly, at higher concentrations, they demonstrate properties of inflammatory factors blocking thereafter TNF-α activity. The plasma concentrations of soluble TNF receptors (sTNFRs) appear to reflect the degree of activation of the TNF system [10,11].

The work published by Steppan et al [12] aroused much hope among scientific circles working on the pathogenesis of diabetes. They described a protein secreted by adipocytes, called resistin, which is antagonistic to insulin in both in vitro and in vivo environments. Resistin concentrations were of higher values in obese and diabetic mice. Administration of resistin increased plasma glucose levels and stimulated endogenous glucose production in rodents [12,13].

Yet, the role of resistin in human obesity still has not been explained. The problem is the translatability of the

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results obtained during the experiments on animals. The main source of resistin in rodents is adipose tissue [12]. Although human resistin is expressed in both white visceral and subcutaneous fat [13], its main source seems to be macrophages [14-16].

In early reports, resistin was proposed as a significant cytokine, which, along with other molecules, makes element linking obesity with insulin resistance and type 2 diabetes mellitus. Proof of this hypothesis was the inhibition of resistin expression by rosiglitazone acting via peroxisome proliferator–activated receptor γ both by human macrophages and by animal adipocytes [16-18].

In the light of these observations, the aim of our study was to evaluate the interaction between resistin and proinflammatory cytokines such as TNF-α, TNF receptor (TNFR) 1, TNFR2, and IL-6 in lean and obese subjects.

2. Materials and methods

2.1. Subjects

We evaluated 26 patients with obesity (body mass index [BMI] >26 kg/m^2) and 15 lean healthy volunteers (BMI <25 kg/m^2). Obese participants in the study were recruited from an outpatient obesity clinic. Healthy subjects were defined as individuals with BMI less than 25 kg/m^2 and normal glucose tolerance. None of the participating subjects had other diseases or took medication at the time of the study.

Subjects found with diabetes were excluded according to World Health Organization [19] diagnostic criteria.

Informed consent was obtained from all subjects. The study protocol was approved by local research ethics committees.

The obese group (OB group) under study was divided according to World Health Organization [19] criteria into 2 subgroups: impaired glucose tolerance group (IGT) and normal glucose tolerance group (NGT). Impaired glucose tolerance was defined as 2-hour plasma glucose levels of 140 mg/dL or greater and less than 200 mg/dL on the 75-g oral glucose tolerance test, and fasting plasma glucose level of less than 126 mg/dL.

2.2. Laboratory analysis

Fasting blood samples were drawn in the morning between 8:00 and 10:00 AM after overnight fasting. The separated serum was stored at −70°C until used in appropriate assays for adipocytokines.

The insulin resistance index from fasting serum insulin and plasma glucose levels was estimated by using the homeostasis model assessment of insulin resistance (HOMA-R) parameter: HOMA-R = fasting serum insulin (μIU/mL) × fasting plasma glucose (mmol/L)/22.5.

The resistin concentration was assayed with a commercial enzyme-linked immunosorbent assay kit (Phoenix Pharmaceuticals, Belmont, CA). The limit of detection for resistin was less than 2.0 pg/mL. The intra-assay and interassay variability were less than 5.2% and less than 9.6%, respectively.

Serum levels of TNF-α, sTNFR1, sTNFR2, and IL-6 were determined by enzyme-linked immunosorbent assay kits: Quantikine High Sensitivity TNF-α, Quantikine TNFR1, TNFR2, and IL-6 (R&D Systems, Oxford, UK). The sensitivity of assays was calculated for TNF-α, TNFR1, TNFR2, and IL-6 (values were <0.12, <3, <1.0, and <0.09 pg/mL, respectively).

The intra-assay and interassay coefficients of variance were also calculated (<6.6% and <8.4%; <6% and 5%; <8% and 4%; <5.1% and <9.8% ; and <5.55% and <9.2% for TNF-α, TNFR1, TNFR2, IL-6, respectively).

The samples were assayed in duplicate in the same assay run. Plasma glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined by commercially available test kits (Point Scientific, Lincoln Park, MI). Low-density lipoprotein (LDL) cholesterol concentration was calculated by using the Friedwald formula. Insulin level was determined

Table 1
Characteristic of the nondiabetic obese subjects and the control group

	Control group (n = 15)	OB group (n = 26)	IGT group (n = 18)	NGT group (n = 8)
Age (y)	32.57 + 8.64	30.06 ± 5.54	31.12 ± 4.58	29.0 ± 7.7
BMI (kg/m^2)	22.32 ± 1.89	35.98 ± 4.12*	36.48 ± 4.34*	34.9 ± 1.306*
Fat mass (%)	19.1 ± 2.049	42.52 ± 3.68*	43.17 ± 2.82*	41.96 ± 4.06*
Body fat mass (kg)	23.97 ± 6.28	38.68 ± 7.52*	39.87 ± 7.2*	37.88 ± 5.75*
Triglycerides (mg/dL)	81.52 ± 29.31	89.41 ± 38.42*	92.67 ± 42.7*	81.16 ± 28.1
Total cholesterol (mg/dL)	188.07 ± 33.63	203.7 ± 29.089	197.15 ± 29.09	207.72 ± 21.6
LDL cholesterol (mg/dL)	110.94 ± 33.95	124.83 ± 29.56	131.17 ± 32.80	121.38 ± 28.51
HDL cholesterol (mg/dL)	60.93 ± 14.15	54.47 ± 15.59	51.02 ± 14.95	61.8 ± 15.11
Fasting glucose (mg/dL)	92.23 ± 9.91	93.67 ± 6.97	93.35 ± 7.28	94.35 ± 6.6
Insulin (μIU/mL)	8.84 ± 4.87	16.6 ± 8.74*,†	20.21 ± 8.,32*,‡	8.92 ± 2.185
HOMA-R[a]	2.08 ± 0.97*	3.79 ± 1.82*,†	4.59 ± 1.63*,‡	2.08 ± 0.56

Values are shown as mean ± SD.

[a] HOMA = (fasting plasma glucose × fasting plasma insulin)/22.5.

* $P < .05$ vs control.

† $P < .05$, OB group vs NGT group.

‡ $P < .05$, IGT group vs NGT group.

Table 2
Serum concentration of adipocytokines in the control and obese groups

	Control group (n = 15)	OB group (n = 26)	IGT group (n = 18)	NGT group (n = 8)
TNF-α (pg/mL)	4.53 ± 2.26	8.76 ± 7.03*	8.71 ± 8.13*	8.61 ± 4.36*
TNFR1 (pg/mL)	895.75 ± 244.82	1360.45 ± 591.98*	1421.3 ± 611.49*	1231.0 ± 564.79*
TNFR2 (pg/mL)	1092.35 ± 505.38	1651.4 ± 540.27*	1721.62 ± 519.4*	1501.78 ± 588.8*
IL-6 (pg/mL)	4.70 ± 1.05	5.92 ± 1.12*	6.2 ± 1.02*	5.38 ± 1.013*
Resistin (ng/mL)	12.59 ± 4.14	14.49 ± 6.77	16.29 ± 7.44	13.49 ± 6.34

Values are shown as mean ± SD.
* $P < .05$ vs control.

by radioimmunoassay (DPC Diagnostic Products, Los Angeles, CA).

2.3. Statistical analysis

All results are presented as means ± SD.

The means of variables showing normal distribution were compared by the parametric unpaired Student *t* test, whereas the parameters whose distribution was not normal were compared by nonparametric Mann-Whitney test.

Pearson correlation and multiple regression models were used to compare the parameters studied with resistin. A *P* value less than .05 was accepted as statistically significant.

3. Results

The clinical and biochemical characteristic of the study group of patients and the control group are shown in Tables 1 and 2, whereas significant correlations between serum resistin and evaluated parameters are shown in Table 3.

Fasting serum glucose concentration in the obese groups IGT (93.35 ± 7.28 mg/dL) and NGT (94.35 ± 6.6 mg/dL) were similar to those in the control lean group (92.23 ± 9.91 mg/dL). The insulin levels and insulin resistance evaluated by the HOMA-R formula were significantly higher in the OB and IGT groups (16.6 ± 8.74 and 20.21 ± 8.32; 3.79 ± 1.82 and 4.59 ± 1.63 μIU/mL, respectively) than in the control lean group (8.84 ± 4.87 and 2.08 ± 0.97 μIU/mL, respectively). There were no significant differences among triglyceride, LDL cholesterol, HDL cholesterol, and total cholesterol serum concentrations in all groups. Indexes of obesity (BMI and fat mass) differed significantly between obese groups and the control group (Table 1).

The obese patients showed significantly higher plasma concentrations of TNF-α, sTNFRs, and IL-6 compared with the control group (Table 2).

Resistin concentrations were slightly higher in obese patients than in the control group; however, there was no statistically significant difference between them (Table 2).

A significant correlation was observed between resistin and IL-6 ($r = 0.37$, $P < .05$) and fat mass ($r = 0.51$, $P < .05$) only in the IGT group, but there was no considerably significant correlation between resistin and TNF-α and sTNF-α receptors. Resistin did not correlate with HOMA-R and BMI. LDL cholesterol correlated negatively with resistin level in the IGT group ($r = 0.39$, $P < .050$).

4. Discussion

In our report we have revealed the lack of fundamental differences between resistin concentrations in obese persons and healthy ones; in addition, we have not noticed a statistically significant correlation between resistin and HOMA-R and among resistin, glucose, and insulin. These results seem to agree with earlier suggestions that denied the existence of a close link between this cytokine and obesity and insulin resistance.

Data obtained from animal models indicated a physiologic function of resistin in the regulation of glucose. Banerjee et al [20] reported that mice lacking in the adipocyte hormone resistin exhibit low blood glucose levels after fasting. Their findings suggested that the role for resistin in mediating hyperglycemia is associated with obesity [5]. In addition, Rajala et al [13] showed that adipose resistin and serum resistin expression increased in response to hyperinsulinemia. Chronic increase in resistin led to fasting hyperglycemia, glucose intolerance, and increased hepatic glucose production [21].

However, the role of resistin in humans has still been controversial. Many reports have shown differences in resistin levels between obese and nonobese subjects and positive significant correlation with BMI [20-24] or HOMA-R [25-27]. Others, however, have reported that resistin promotes obesity, but obesity is not associated with insulin resistance [15,27]. Previous studies found no relationship between resistin gene expression and body weight or insulin sensitivity [27-30].

Our study results have shown agreement with the results of these studies. We did not find any association between resistin level and BMI and HOMA-R. However, a positive correlation between resistin and fat mass has been observed in the IGT group.

Table 3
Significant correlation between fasting serum resistin and evaluated parameters in obese groups and control group

	Control group (n = 15)	OB group (n = 26)	IGT group (n = 18)	NGT group (n = 8)
Resistin	NS	NS	Fat mass, $r = 0.51$* IL-6, $r = 0.37$* LDL, $r = -0.39$*	NS

NS indicates lack of statistically significant correlation.
* $P < .05$.

It is well known that obesity is a chronic, low-grade inflammation state [31,32]. The intensity of adipocytokine expression and production is related to the grade of obesity and insulin resistance of human obesity [2-4,33,34]. Glowinska and Urban [35] demonstrated a significant correlation between IL-6 and TNF-α and between monocyte chemotactic protein-1 (MCP-1) and BMI. Recent data have shown increased plasma concentrations of inflammatory mediators such as TNF-α and IL-6 in insulin-resistant states of obesity and type 2 diabetes mellitus [5,6,34,36].

The role of resistin in the development of inflammation and its relationship with adipocytokines remain unknown in human obesity. Previous works showed a correlation between resistin and inflammatory markers [13,37-39]. Recently, its antioxidant properties have also been shown [37].

Kaser et al [39] demonstrated that in human mononuclear cells, resistin messenger RNA expression is regulated by proinflammatory cytokines such as IL-1, IL-6, and TNF. This association signifies the relationship between resistin inflammation and insulin resistance [39]. Other investigators have demonstrated a strong correlation between resistin plasma levels of sTNFR2 in diabetic patients [11,14].

Vendredell et al [30] showed a positive association between resistin and sTNFR1 in the nonmorbidly obese, and resistin and sTNFR2 in the morbidly obese. The association between resistin and inflammation demonstrated by many studies in humans showed its increased serum level in acute inflammatory processes [14,16,40]. These results support the suggestion that resistin may play an inflammatory rather than a metabolic function in human individuals [14,15,38,41].

Muredach et al [42] found a correlation between resistin and inflammatory markers and coronary artery calcification. In subjects with the metabolic syndrome, resistin seems to be a good predictor of coronary atherosclerosis [38,43].

In both obese women subgroups that we examined we have not found a correlation between resistin concentration and TNF-α and sTNFRs. The statistically significant correlation that we found between resistin, IL-6, and fat mass in the IGT group seems to prove the role of these cytokines in the inflammatory process. This situation may be explained by the results of recently published surveys, which showed that obesity goes together with accumulation of macrophages in adipose tissue [6,31] and which also revealed that there is a relationship between resistin concentration and fat mass [42]. The increased fat macrophage infiltration in obesity will explain the increased adipose tissue cytokine expression and production and, consequently, the intensification of insulin resistance and diabetes development [6].

In their previous study, Lehrke et al [14] pointed out that induction of resistin in the adipose macrophages depends on the activation of inflammatory cascade and release of TNF-α and IL-6 and that the secretion of these cytokines is sufficient for the induction of resistin. Experimental endotoxemia in healthy volunteers induced a remarkable elevation of circulating resistin levels. The Lehrke et al data showed that hyperresistinemia in humans is indirectly regulated by an inflammatory process accompanying the obesity. Increased adipocytokine levels affect glucose metabolism. Therefore, resistin seems to be a possible mediator of insulin resistance in humans with acute inflammation [14].

In the IGT group, a negative correlation between resistin serum levels and LDL cholesterol has been observed. To our knowledge, only Jove et al [44] showed similar results. Determination of the relationship between resistin and lipid metabolism requires further examination in a larger population.

In conclusion, in our research we showed that only in the IGT group is there a correlation between resistin concentration and IL-6, and fat mass. Resistin did not correlate with any of the other investigated parameters. The groups we examined were relatively small; it is likely that a larger number of subjects would allow description of statistically significant correlations also in other obese women groups.

The results of our examination seem to confirm the hypothesis that there is a correlation between resistin, inflammation, and obesity. The role in the development of insulin resistance and diabetes in obese people does not seem to result from its direct effect on glucose metabolism but is closely connected with the intensification of inflammatory processes progressing in the adipose tissue.

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