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Serum resistin level among healthy subjects: relationship to anthropometric and metabolic parameters☆

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Abstract

Resistin is a novel adipocyte-secreted hormone that has been proposed to be the link between obesity and diabetes, although little appears to be known regarding the physiological role of resistin in human beings. We aimed to explore the relationship between serum resistin level and certain anthropometric and metabolic parameters. Seventy-one healthy subjects with a mean body mass index of 23 kg/m^2 or greater were recruited in this study. Anthropometric measurements including height, weight, body mass index, waist and hip circumferences, waist-to-hip ratio, and blood pressure were recorded. Insulin resistance was measured by homeostasis model assessment (HOMA). Fasting serum resistin, insulin and plasma glucose, lipid profiles, and uric acid levels were measured. The results revealed that serum resistin level did not correlate with any markers for adiposity, blood pressure, fasting plasma glucose, or uric acid level for either sex. Serum resistin level correlated negatively with fasting insulin level ($\gamma = -0.455$, $P = .006$) and HOMA ($\gamma = -0.455$, $P = .006$) in women but not in men. Serum resistin level only correlated negatively with high-density lipoprotein cholesterol (HDL-C) level in men ($\gamma = -0.347$, $P = .038$); there was no correlation between serum resistin level and lipid profiles in women. Multiple linear regression analysis using the logarithm of resistin as a dependent variable revealed that only HDL-C level ($\beta = -.058$, $P = .019$) was an independent significant predictor for resistin in men; however, the analysis revealed that HDL-C level ($\beta = -.044$, $P = .029$) and HOMA ($\beta = -.719$, $P = .004$) were independent significant predictors for resistin in women. In conclusion, resistin is not related to adiposity, blood pressure, insulin resistance, fasting plasma glucose level, and most lipid profiles. Resistin correlates negatively with HDL-C level for both sexes. The role of resistin in metabolic syndrome warrants further investigation.

1. Introduction

Resistin, a novel adipocyte-secreted hormone, is a member of the newly discovered family of cysteine-rich secretory proteins dually referred to as "resistin-like molecules" and proteins "found in the inflammatory zone." In 2001, Steppan et al [1] reported that resistin expression was greater in white adipose tissue than in brown adipose tissue; in fact, resistin messenger RNA (mRNA) level was barely detectable in brown adipose tissue in test mice. These authors also noted that resistin expression and plasma resistin level increased in diet-induced and genetically obese mice. Furthermore, resistin expression was down-regulated by thiazolidinediones in 3T3-L1 cells. They also noted that the administration of recombinant resistin impaired glucose tolerance in vivo in mice and ex vivo in 3T3-L1 cells. These phenomena improved after the administration of an antiresistin immunoglobulin G. Such a series of observations led these authors to conclude that resistin was the link between obesity and insulin resistance. Logically, as is suggested by its name, resistin should be related to insulin resistance, but to the best of our knowledge, and from a thorough review of the literature, it would appear that only one study [2] has actually revealed such a relationship, most studies [3-6] concluding to the contrary. Furthermore, in 2004, Seow et al [7] found that serum resistin level was similar between patients suffering

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from polycystic ovary syndrome and control subjects, although elevated serum resistin level was detected in another classic insulin-resistant disease type 2 diabetes study [8]. Because insulin resistance is the key component of metabolic syndrome [9], the relationship between resistin level and metabolic syndrome needs to be elucidated. Thus, the aim of the present study was to investigate the association between resistin level and certain parameters associated with metabolic syndrome and anthropometry.

2. Materials and methods

2.1. Subjects and measurements

Seventy-one healthy volunteers (36 men and 35 women) with a mean body mass index (BMI) of 23 kg/m^2 or greater were recruited for this study. Healthy subjects were defined as individuals with a blood pressure reading of less than 140/90 mm Hg, normal renal and liver function, a fasting plasma glucose level of less than 6.1 mmol/L, and a postprandial 2-hour plasma glucose level of less than 11.1 mmol/L; none of them were taking medication at the time of the study, and none of them were suffering from other major diseases. This study was approved by the Human Research Committee of the China Medical University Hospital. Informed consent was obtained from each volunteer.

All participating subjects presented to the outpatient clinic of the Department of Family Medicine subsequent to an overnight fasting. They were weighed in light clothing, and their heights and waist and hip-circumference measurements were recorded. Their BMI was calculated (kg/m^2) as an index of their overall adiposity. Waist circumference was measured midway between the inferior margin of the last rib and the crest of the ileum in a horizontal plane. Hip circumference was taken around the pelvis at the point of maximal protrusion of the buttocks. Circumference was measured to the nearest 0.1 cm. Waist circumference and waist-to-hip ratio (WHR) served as a measure of regional fat distribution. Blood pressure was measured from the right arm subsequent to the participant sitting at rest for a period of 20 minutes. The mean of 2 blood pressure recordings was used for statistical analysis. All the anthropometric and blood pressure measurements were performed by one observer. Fasting blood samples were drawn between 08:00 and 10:00 AM, and the separated serum was stored at −70°C until appropriate assays for resistin and insulin levels were conducted. The insulin-resistance index from fasting serum insulin and plasma glucose levels was estimated by the homeostasis model assessment (HOMA) [10] parameter: HOMA = fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5; as seen from the equation, the greater the HOMA value, the greater the level of insulin resistance.

2.2. Laboratory analysis

Plasma glucose level was determined by a glucose oxidase method (Astra-8, Beckman, Brea, Calif), and the serum insulin level was measured by a commercial radioimmunoassay kit (Diagnostic Products Corp, Los Angles, Calif). The inter-assay coefficient of variation (CV) for insulin was 8.7% and the intra-assay CV was 3.4%. Serum resistin level was assayed by a commercial ELISA kit (Biovendor Laboratory Medicine Inc, Brno, Czech Republic). The limit of detection for such a kit was 0.2 ng/mL, the intra-assay CV being 0.1% at 5.2 ng/mL and 0.9% at 10.2 ng/mL, whereas the corresponding inter-assay CV was 9.6% and 6.4%, respectively. Samples were assayed in duplicate and within the same assay run. Plasma cholesterol and triglyceride levels were determined by an enzymatic colorimetric method (Beckman Coulter Synchron LX-20, Brea, Calif) [11,12]. The high-density lipoprotein cholesterol (HDL-C) level was measured by a direct HDL-C method; HDL lipoprotein particles were solubilized by a detergent to release HDL-C which reacted with cholesterol esterase and cholesterol oxidase in the presence of chromogens to produce a color product (Beckman Coulter Synchron LX-20) [11,13]. The low-density lipoprotein cholesterol (LDL-C) level was also measured by a direct LDL-C method but used 2 kinds of detergents to solubilize the LDL particles (Beckman Coulter Synchron LX-20) [11,13]. The uric acid level was determined by a uricase-peroxidase method (Beckman Coulter Synchron LX-20).

2.3. Statistical analysis

All data are presented as mean ± SD except for log resistin$_{adj}$ (mean ± SE). Serum resistin level was logarith-

Table 1
Clinical and metabolic characteristics of the study subjects

Variables	Males (n = 36)	Females (n = 35)	*P*
Age (y)	42.3 ± 7.9	51.3 ± 11.8	<.001
Adiposity index			
BMI (kg/m^2)	25.5 ± 2.2	25.6 ± 2.4	.897
Waist circumference (cm)	90.9 ± 8.8	86.1 ± 8.6	.023
Hip circumference (cm)	99.8 ± 4.9	99.2 ± 5.0	.577
WHR	0.91 ± 0.06	0.87 ± 0.07	.011
Blood pressure (mm Hg)			
Systolic	122.3 ± 9.4	115.9 ± 12.8	.188
Diastolic	79.1 ± 6.6	73.9 ± 8.0	.003
Glucose tolerance index			
FPG (mmol/L)	5.05 ± 0.44	5.04 ± 0.34	.971
FSI (pmol/L)	90.37 ± 35.83	67.16 ± 24.01	.002
HOMA	2.83 ± 1.21	2.11 ± 0.82	.005
Lipid profile			
Total cholesterol (mmol/L)	5.39 ± 8.84	5.23 ± 10.18	.484
Triglyceride (mmol/L)	1.49 ± 0.67	1.10 ± 0.45	.006
HDL-C (mmoL/L)	1.04 ± 0.19	1.22 ± 0.25	.001
Triglyceride/HDL ratio	3.54 ± 1.96	2.21 ± 1.18	.001
LDL-C (mmol/L)	3.51 ± 0.94	3.36 ± 0.91	.500
Uric acid (mmol/L)	0.43 ± 0.08	0.32 ± 0.08	<.001
Resistin (ng/mL)	4.38 ± 3.51	4.27 ± 4.25	.902
Log resistin	1.09 ± 1.03	0.93 ± 1.18	.534
Log resistin$_{adj}$	1.06 ± 0.18	0.96 ± 0.18	.703

Values are expressed as mean ± SD. FPG indicates fasting plasma glucose level; FSI, fasting serum insulin level; and Log resistin$_{adj}$ = log resistin value adjusted for FSI and HDL-C.

mically transformed to obtain a distribution resembling a normal distribution. A Student *t* test compared the differences in parameter values between male subjects and female subjects. After adjusting for fasting serum insulin and HDL-C levels, the log resistin was analyzed by analysis of covariance. The level of correlation between log resistin and anthropometry, blood pressure, and various parameters pertaining to metabolic syndrome was assessed by Pearson correlations and partial correlation coefficient analyses. The independent effects of the metabolic parameters upon logarithmically transformed serum resistin level were identified by multiple linear regression analysis. A P value of less than .05 was considered to represent statistically significant difference between compared data sets. All analyses were performed with the SAS statistical package 8.1 (SAS Institute, Cary, NC).

3. Results

Table 1 lists the clinical and metabolic characteristics of the study subjects. Male subjects were significantly younger than female subjects. Adiposity index differed significantly between sexes, with waist circumference and WHR being greater for male subjects compared with female subjects. Male subjects also exhibited greater diastolic blood pressure than female subjects. The glucose tolerance index revealed that the fasting insulin level (range, 37.24-207.57 pmol/L in male subjects; 27.12-156.85 pmol/L in female subjects) and HOMA (range, 1.08-7.36 in male subjects; 0.75-5.18 in female subjects) for male subjects were significantly more substantial than female subjects. Furthermore, male subjects revealed greater triglyceride level and triglyceride/HDL ratio but lower HDL-C level than female subjects. There was no significant difference in serum resistin level between male subjects and female subjects (resistin 4.38 ± 3.51 vs 4.27 ± 4.25 ng/mL, $P = .902$; log resistin 1.09 ± 1.03 vs 0.93 ± 1.18, $P = .534$). After adjusting for fasting serum insulin and HDL-C levels, this result remained unchanged (log resistin_{adj} 1.06 ± 0.18 vs 0.96 ± 0.18, $P = .703$).

Table 2 shows the correlation between log resistin and anthropometry as parameters pertaining to metabolic syndrome. For male subjects, log resistin only correlated positively with HDL-C level. This correlation remained unchanged even after adjusting for either age or BMI, or age and BMI. For female subjects, log resistin correlated significantly with systolic blood pressure after adjusting for age; however, the significance of this correlation disappeared after adjusting for age and BMI. Log resistin correlated negatively with fasting serum insulin level and HOMA. This relationship remained unchanged after adjusting for either age or BMI, or age and BMI.

Multiple linear regression analysis with log resistin as a dependent variable revealed that the HDL-C level, but not the HOMA, correlated independently with resistin level, and accounted for 17.72% of the variance in serum resistin level (R^2 = 17.72%) in male subjects (Table 3); however, although HDL-C level and HOMA were significant predictors of serum resistin level, both HDL-C level and

Table 2
Correlation between log resistin, anthropometric and metabolic parameters both with and without adjustment for either age or BMI, or age and BMI

Adjustment for	Males (n = 36)				Females (n = 35)			
	–	Age	BMI	Age and BMI	–	Age	BMI	Age and BMI
Age	0.066	–	0.064	–	−0.212	–	−0.212	–
Adiposity index								
BMI	0.085	0.084	–	–	0.001	−0.005	–	–
WC	0.043	0.046	−0.079	−0.071	−0.144	−0.097	−0.185	−0.123
HC	−0.015	−0.006	−0.138	−0.126	−0.070	−0.073	−0.100	−0.098
WHR	0.093	0.091	0.045	0.042	−0.115	−0.057	−0.122	−0.059
Blood pressure								
Systolic	−0.127	−0.130	−0.142	−0.145	0.275	0.361*	0.275	0.361
Diastolic	−0.077	−0.067	−0.096	−0.086	0.184	0.216	0.190	0.223
Glucose tolerance								
FPG	0.146	0.136	0.184	0.174	−0.122	−0.067	−0.127	−0.071
FSI	−0.169	−0.158	−0.218	−0.209	−0.455**	−0.421*	−0.455**	−0.421*
HOMA	−0.135	−0.124	−0.166	−0.156	−0.455**	−0.419*	−0.456**	−0.419*
Lipid profile								
Total cholesterol	−0.037	−0.020	−0.044	−0.027	−0.315	−0.268	−0.322	−0.274
Triglyceride	0.219	0.274	0.206	0.262	−0.070	−0.083	−0.071	−0.084
HDL-C	−0.347*	−0.358*	−0.338*	−0.349*	−0.295	−0.259	−0.303	−0.267
TG/HDL ratio	0.320	0.336	0.270	0.326	0.080	0.050	0.080	0.050
LDL-C	−0.047	−0.040	−0.052	−0.045	−0.197	−0.147	−0.209	−0.154
Uric acid	0.066	0.098	0.054	0.066	0.215	0.266	0.215	0.266

WC indicates waist circumference; HC, hip circumference; and TG, triglyceride level. Other abbreviations are explained in the footnote to Table 1.

* $P < .05$.

** $P < .01$.

Table 3
Multiple linear regression analysis using log resistin as a dependent variable

Variables	Males (n = 36)			Females (n = 35)		
	EC (β)	SE	P	EC (β)	SE	P
Intercept	3.599	1.450	.019	4.379	1.109	<.001
Age	0.009	0.021	.684	0.003	0.016	.867
HOMA	−0.192	0.144	.193	−0.719	0.227	.004
HDL-C	−0.058	0.024	.019	−0.044	0.019	.029
	F = 2.30	Total R^2 = 17.72%		F = 5.01	Total R^2 = 32.65%	

EC indicates estimated coefficient. Fasting serum insulin was not included in this model because of the high degree of multicolinearity with HOMA (γ > 0.900).

HOMA correlated negatively with serum resistin level and accounted for 32.65% of the variance in serum resistin level (R^2 = 32.65%) in female subjects (Table 3).

4. Discussion

In this study, serum resistin level did not reveal any sexual dimorphism and did not appear to correlate significantly with adiposity, blood pressure, insulin resistance, fasting plasma glucose level, and most lipid profiles. Resistin level was negatively associated with HDL-C level for both sexes. Metabolic syndrome appears to be a cluster of diseases that demonstrate insulin resistance as their common etiologic factor [9]. Resistin was given its name subsequent to the original determination of its demonstrated "resistance to insulin" [1]. Four months after the discovery of resistin, however, Way et al [14] reported that resistin expression was reduced within epididymal adipose tissue deriving from 4 different murine models of obesity. Moreover, treatment of these murine models with peroxisome proliferator-activated receptor γ agonists increased adipose-tissue resistin expression in both ob/ob mice and Zucker diabetic fatty rats. Such contradictory results have also been arrived at in human studies; most previous reports [3-6] and this study have demonstrated that resistin level is not associated with insulin resistance. To the best of our knowledge, only one group has observed the existence of a significant correlation between resistin level and insulin resistance [2].

Because resistin is an adipocyte-secreted hormone, it appears reasonable to expect that it should be related to whole body or regional body adiposity; however, many human studies [2,6-8,15-19] and this study have not found any evidence of this relationship. Some studies [4,5,20], however, have reported a positive correlation between resistin level and BMI, and one particular group has demonstrated that the resistin level is associated negatively with WHR and positively with total body fat [21]. In 2001, Nagaev and Smith [22] detected only a very low level of resistin in human fat cells in 3 of 14 test subjects and also in intact adipose tissue in 4 of 14 subjects. In 2001, Savage et al [15] reported that resistin mRNA level was very low in fresh human adipocytes, but that resistin was readily detectable in mononuclear cells. In 2003, Degawa-Yamauchi et al [5] detected less resistin protein present within adipocytes than was present in the entire adipose tissue, implying that resistin was present in other cells within the adipose tissue. In 2003, Patel et al [23] found a 4-fold induction of resistin mRNA during the differentiation of monocytes to macrophages in vitro. In 2003, Wellen and Hotamisligil [24] and Xu et al [25] reported that the adipose tissue of obese subjects was characterized by macrophage infiltration. Taken together, these reports appear to imply that adipocytes are not the only source and, in fact, may not be the major source of resistin secretion in human beings. Such results may explain why no relationship between resistin level and adiposity has been noted.

Our study demonstrated no sexual dimorphism with regard to resistin level. This finding is consistent with another Chinese study [16] conducted in 2002, but is inconsistent with a number of recent Caucasian studies [2,6,21]. This discrepancy may be because of ethnic differences between study subjects. In this study, the serum resistin level did not correlate with systolic or diastolic blood pressure. This relationship was also found in subjects with hypertension [16] and those suffering from type 2 diabetes [19]. Our study has revealed that the serum resistin level is negatively associated with HDL-C level for both sexes. However, this relationship exists only when the data are analyzed by multiple linear regression and log resistin in female subjects. The biologic and physiological significance of this finding therefore needs to be proven. In 2003, Jove et al [26] reported the existence of a negative correlation between resistin mRNA level from white adipose tissue of omentum, total cholesterol, and LDL-C levels in 8 subjects subsequent to fenofibrate treatment. Those authors concluded that cholesterol regulated resistin expression within human white adipose tissue. Other studies [6,8,18], however, including our current study, have not observed any relationship between resistin level, total cholesterol, and LDL-C levels.

In summary, both leptin and resistin are adipocyte-secreted hormones. Although leptin correlates with many parameters of metabolic syndrome including BMI, waist circumference, WHR, systolic blood pressure, fasting plasma glucose level, fasting insulin level, insulin resistance, and triglyceride level [27], resistin is not associated with any markers of adiposity, blood pressure, fasting plasma glucose, insulin resistance, and most parameters of lipid profiles. Resistin level correlates negatively with HDL-C level for men and correlates negatively with HDL-C level

and HOMA for women. The specific role of resistin in HDL-C metabolism warrants further investigation.

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