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Association between serum vaspin concentrations and visceral adipose tissue in Korean subjects

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Abstract

Adipokines modulate multiple signaling pathways of insulin resistance via endocrine, paracrine, or autocrine mechanisms. Visceral adipose tissue (VAT)–derived serpin (vaspin) is a novel adipokine with potential insulin-sensitizing effects. We investigated the association between serum vaspin concentrations and abdominal adiposity. We recruited subjects (N = 150) aged 20 to 69 years who visited our hospital for regular health examinations. Abdominal VAT and subcutaneous adipose tissue areas were assessed by computed tomography. We measured serum vaspin concentrations by enzyme-linked immunosorbent assay. Statistical analysis was performed after stratification, using a homeostasis model for insulin resistance (HOMA-IR). Serum vaspin concentrations correlated positively with age ($r = 0.196$) when data from all subjects were analyzed. In the higher–HOMA-IR group, serum vaspin levels correlated more prominently with age ($r = .344$) and VAT area ($r = .327$) although these associations were not found in the lower–HOMA-IR group. In multivariate linear regression analysis, the VAT area was independently correlated with serum vaspin concentrations in the higher–HOMA-IR group. The association between serum vaspin concentrations and VAT differs according to insulin resistance. Insulin resistance might influence the correlation between serum vaspin concentration and VAT in human subjects.

1. Introduction

Obesity is often associated with metabolic complications that cluster several abnormalities, including insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease [1,2]; insulin resistance is commonly suspected as the elemental defect in the development of the condition. Apparently, accumulation of adipose tissue in the abdominal cavity, rather than excess body fat per se, is the major player in the adverse metabolic consequences of obesity [3-5]. However, the reason for this effect is poorly understood.

Adipose tissue secretes a variety of bioactive peptides that play important roles in insulin action, energy metabolism, inflammation, and cell growth through endocrine, paracrine, or autocrine routes [6-10]. Some of these adipokines may locally regulate fat accumulation by modulating growth/proliferation of adipocytes. Excess fat accumulation may in turn cause dysregulation of adipocyte function, including oversecretion of deleterious adipokines and hyposecretion of advantageous ones.

Vaspin is a novel adipokine with potential insulin-sensitizing effects. It was identified as a member of serine protease inhibitor, which was highly expressed in visceral adipose tissue (VAT) of Otsuka Long-Evans Tokushima Fatty rats at the age when obesity and insulin resistance peaked [11,12]. In these rats, the tissue expression of vaspin and its serum levels were decreased with worsening of diabetes and body weight loss; they were normalized with the treatment of insulin or insulin-sensitizing agent.

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Administration of recombinant human vaspin to obese mice improved glucose tolerance and insulin sensitivity and reversed the altered expression of genes relevant to insulin resistance in white adipose tissue [11]. In humans, expression of vaspin messenger RNA (mRNA) was also observed in human VAT and subcutaneous adipose tissue (SAT) [13]. Whereas vaspin was undetectable in lean subjects, its expression was increased from overweight to obesity. In addition, vaspin expression was more frequently detected in patients with type 2 diabetes mellitus than in individuals with normal glucose tolerance [13]. Circulating vaspin protein levels have been shown to be sex-dependent, correlated with body mass index (BMI) and insulin sensitivity [14].

Despite several reports about vaspin expression in fat tissue and serum vaspin levels in human [14,15], correlations between circulating vaspin levels and parameters of insulin sensitivity are unclear. Until now, no study evaluating the association of circulating vaspin levels with the abdominal fat accumulation has been undertaken. Therefore, we evaluated the relationship of serum vaspin concentrations with the distribution of abdominal adipose tissue as well as other metabolic variables relevant to insulin sensitivity in Korean subjects.

2. Methods

2.1. Study subjects

We recruited a total of 150 male and female subjects aged 20 to 69 years who visited the Department of Family Medicine of the Asan Medical Center, Seoul, Korea, from January 2007 to August 2008 for regular health examinations. Upon enrollment, written informed consent was obtained from each study participant. Physicians performed medical evaluation on all the individuals including full medical histories (hypertension, dyslipidemia) and physical examinations. We excluded individuals with secondary causes of obesity, those with diabetes, pregnant or lactating women, and subjects with evidence of malignancy and severe hepatic or renal diseases. Subjects taking medications that might affect weight or glucose metabolism (eg, antiobesity drugs, oral hypoglycemic agents, or insulin) were also eliminated. Finally, 77 male and 73 female subjects became enrolled for the study. This study was approved by the Institutional Review Board of the Asan Medical Center. We certify that all applicable institutional regulations on the ethical use of human volunteers were followed during this research.

2,2. Anthropometric measurements

Anthropometric measurements were taken while the subjects were dressed in light clothing, but without shoes. Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were measured using an automatic height-weight scale; BMI was calculated as weight in kilograms divided by the square of the height in meters. Percentage body fat was assessed by bioimpedance analysis (Inbody 3.0 instrument; Biospace, Seoul, Korea). Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. All anthropometric measurements were taken by a single person throughout the study to minimize interpersonal variations.

2.3. Assessment of abdominal fat distribution

The cross-sectional areas of abdominal VAT and SAT were measured by computed tomography using a Siemens Somatom Scanner (Erlangen, Germany) with an established protocol. A cross-sectional scan of 10-mm thickness centered at the L4-5 vertebral disc space, with each subject in the supine position, was obtained using a radiograph of the skeleton as a reference to establish scan position to the nearest millimeter. Area of total abdominal adipose tissue (TAT) was measured by delineation with a graph pen, followed by computation of the adipose tissue area, using an attenuation range of −190 to −30 Hounsfield units. The area of VAT was measured by drawing a line within the muscle wall surrounding the abdominal cavity, and the area of SAT was calculated by subtracting the areas VAT from the TAT area [16,17].

2.4. Measurements of metabolic variables and serum vaspin concentrations

Blood samples were obtained in the morning after a 12-hour overnight fast; serum and plasma were immediately separated by centrifugation. Plasma glucose was measured by the glucose oxidase method, and hemoglobin A_{1c} (HbA_{1c}) was by assessed immunoturbidimetric assay (Roche, Basel, Switzerland). Total cholesterol and triglyceride levels were assessed by enzymatic procedures using an autoanalyzer (Hitachi-747 instrument; Hitachi, Tokyo, Japan). The high-density lipoprotein (HDL) cholesterol fraction was measured by an enzymatic method after precipitation of apolipoprotein B–containing lipoproteins with $MnCl_2$. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation if triglyceride levels were less than 400 mg/dL. Plasma insulin levels were measured by radioimmunoassay (Dianabott, Tokyo, Japan). Insulin resistance estimation using the homeostasis model for insulin resistance (HOMA-IR) score was calculated using the following formula: fasting serum insulin (in microunits per milliliter) × fasting plasma glucose (in milligrams per deciliter)/405. *Impaired fasting glucose* (*IFG*) was defined as having fasting plasma glucose levels greater than or equal to 110 mg/dL but less than 126 mg/dL [18]. Metabolic syndrome was diagnosed in patients that met 3 of the following 5 criteria [19]: elevated blood pressure (≥130/85 mm Hg), elevated glucose (≥110 mg/dL), high triglycerides (≥150 mg/dL), low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), and abdominal obesity (≥90 cm in

men and ≥85 cm in women for Koreans) [20]. Serum vaspin concentrations were measured using a commercial enzyme-linked immunosorbent assay kit (AdipoGen, Seoul, Korea) according to the manufacturer's instructions. The assay sensitivity was 0.012 ng/mL; intra- and interassay coefficients of variance were 1.3% to 3.8% and 3.3% to 9.1%, respectively.

2.5. Statistical analysis

Data are presented as mean ± SD. Before statistical analysis, nonnormally distributed parameters were logarithmically transformed to approximate a normal distribution. In a part of data analysis, the 150 subjects were divided into 2 groups: the lower–HOMA-IR group (n = 102) and the higher–HOMA-IR group (n = 48). We defined the higher–HOMA-IR group as subjects with HOMA-IR values equal to or greater than 3.0. Comparison between 2 different groups (female/male or lower/higher HOMA-IR) were carried out using 2-tailed unpaired Student *t* test. Correlation analyses were performed using Pearson test, stratified by HOMA-IR, to examine the simple relationships of serum vaspin concentration to selected variables. To adjust for covariate effects and to identify independent relationships, multivariate linear regression analyses were performed. A *P* value < .05 was considered to be statistically significant in all tests. Statistical analyses were performed using SPSS 12.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Anthropometric and metabolic characteristics of subjects

A total of 150 male and female subjects were used for the study (Table 1). Percentage body fat, total cholesterol, and HDL cholesterol levels were significantly higher in women than in men, whereas waist circumference, VAT area, plasma glucose concentrations, and percentage of IFG were significantly higher in men. Serum vaspin concentrations tended to be elevated in women than in men; however, the difference did not reach statistical significance.

We divided 150 study subjects into lower–HOMA-IR (n = 102) and higher–HOMA-IR (n = 48) groups to examine the effect of insulin resistance on the relationship between serum vaspin concentrations and other measurements (Table 2). Body mass index, waist circumference, TAT area, VAT area, triglyceride, and plasma insulin were significantly higher in the higher–HOMA-IR group, whereas HDL cholesterol was significantly higher in the lower–HOMA-

Table 1
Basic characteristics of study subjects (N = 150)

Variables	Total (n = 150)	Female (n = 73)	Male (n = 77)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (y)	47.0 ± 12.5	49.3 ± 2.1	44.7 ± 12.6	.02
Height (cm)	165.6 ± 9.0	158.6 ± 5.2	172.2 ± 6.5	<.001
Weight (kg)	77.7 ± 16.4	69.8 ± 12.3	85.1 ± 16.4	<.001
BMI (kg/m^2)	28.2 ± 4.8	27.7 ± 4.7	28.6 ± 4.9	.27
Body fat (%)	31.9 ± 7.8	36.0 ± 6.8	28.1 ± 6.7	<.001
Waist circumference (cm)	93.3 ± 11.8	89.1 ± 10.0	97.2 ± 12.0	<.001
TAT area (cm^2)	429.6 ± 128.8	407.5 ± 119.1	451.8 ± 135.2	.09
SAT area (cm^2)	286.4 ± 109.9	288.5 ± 86.3	284.2 ± 130.2	.85
VAT area (cm^2)	143.3 ± 57.7	119.0 ± 51.3	167.5 ± 53.8	<.001
Plasma glucose (mg/dL)	105.0 ± 16.9	100.3 ± 13.2	109.4 ± 18.8	.001
HbA_{1c} (%)	5.9 ± 0.7	5.9 ± 0.6	5.8 ± 0.7	.67
Total cholesterol (mg/dL)	185.2 ± 37.5	191.9 ± 41.2	178.8 ± 32.8	.03
Triglyceride (mg/dL)	149.5 ± 86.7	140.6 ± 84.4	158.0 ± 88.5	.223
HDL cholesterol (mg/dL)	54.1 ± 14.6	59.0 ± 14.7	49.5 ± 13.0	<.001
LDL cholesterol (mg/dL)	119.3 ± 30.4	120.9 ± 31.8	117.7 ± 29.2	.52
Plasma insulin (μU/mL)	10.5 ± 9.1	9.9 ± 9.2	11.0 ± 9.1	.48
HOMA-IR	2.7 ± 2.4	2.5 ± 2.5	2.9 ± 2.4	.31
Vaspin (ng/mL)	0.52 ± 0.57	0.59 ± 0.68	0.45 ± 0.43	.13
	%	%	%	
Hypertension	28.9	27.3	30.6	.67
Dyslipidemia	33.6	30.1	36.8	.39
IFG[a]	28.0	19.2	36.4	.02
Metabolic syndrome[b]	35.4	31.8	39.3	.38

P value calculated by Student *t* test for metric variables or χ^2 test for categorical variables.

[a] *Impaired fasting glucose* was defined as having fasting plasma glucose levels ≥110 mg/dL but <126 mg/dL.

[b] Metabolic syndrome was diagnosed in patients that met 3 of the following 5 criteria: elevated blood pressure (≥130/85 mm Hg), elevated glucose (≥110 mg/dL), high triglycerides (≥150 mg/dL), low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), and abdominal obesity (≥90 cm in men and ≥85 cm in women for Koreans).

Table 2
Anthropometric and metabolic variables of study subjects according to insulin resistance

Variables	Lower–HOMA-IR group (<3) (n = 102)	Higher–HOMA-IR group (≥3) (n = 48)	*P* value
	Mean ± SD	Mean ± SD	
Age (y)	48.1 ± 12.6	44.5 ± 12.2	.095
Height (cm)	165.2 ± 9.1	166.4 ± 8.8	.452
Weight (kg)	74.1 ± 16.2	85.2 ± 14.3	<.001
BMI (kg/m^2)	27.0 ± 4.5	30.7 ± 4.4	<.001
Body fat (%)	30.8 ± 7.6	33.5 ± 7.8	.166
Waist circumference (cm)	90.2 ± 11.1	99.6 ± 10.7	<.001
TAT area (cm^2)	400.8 ± 114.1	471.2 ± 138.5	.007
SAT area (cm^2)	268.7 ± 96.5	311.8 ± 123.6	.053
VAT area (cm^2)	132.1 ± 55.1	159.3 ± 58.2	.020
Plasma glucose (mg/dL)	103.6 ± 16.9	107.9 ± 16.8	.144
HbA_{1c} (%)	5.8 ± 0.6	5.9 ± 0.7	.165
Total cholesterol (mg/dL)	186.6 ± 38.2	182.2 ± 36.4	.505
Triglyceride (mg/dL)	138.8 ± 83.0	171.9 ± 90.9	.029
HDL cholesterol (mg/dL)	56.3 ± 15.8	49.5 ± 10.2	.002
LDL cholesterol (mg/dL)	119.3 ± 30.4	119.4 ± 30.8	.988
Plasma insulin (μU/mL)	5.7 ± 2.9	20.7 ± 9.4	<.001
HOMA-IR	1.4 ± 0.7	5.5 ± 2.5	<.001
Vaspin (ng/mL)	0.50 ± 0.61	0.56 ± 0.47	.548
	%	%	
Female subjects	50	45.8	.634

P value calculated by Student *t* test for metric variables or χ^2 test for categorical variables.

IR group. Serum vaspin concentrations were not different in the lower– and higher–HOMA-IR groups.

3.2. Relationships between serum vaspin concentrations and anthropometric measurements, abdominal fat distribution, and metabolic variables

Pearson correlation analysis was performed between serum vaspin concentrations and anthropometric measurements, abdominal fat distribution, and metabolic variables (Table 3). Serum vaspin concentrations correlated weakly but significantly with age (r = 0.196) in the entire study subjects. In the higher–HOMA-IR group, serum vaspin concentrations showed positive correlations with age (r = 0.344) and VAT area (r = 0.327). On the other hand, in the lower–HOMA-IR group, serum vaspin concentrations did not correlate with any anthropometric or metabolic variable.

In the higher–HOMA-IR group, multivariate linear regression analysis was performed using the serum vaspin concentration as a dependent variable and the VAT area, age, and sex as independent variables (Table 4). The results revealed that the VAT area remained independently associated with the serum vaspin level after regression analysis in the higher–HOMA-IR group.

Table 3
Pearson correlation coefficients between serum vaspin concentration and anthropometric measurements, abdominal fat distribution, and metabolic variables

Variables	Total (n = 150)	Lower–HOMA-IR group (<3) (n = 102)	Higher–HOMA-IR group (≥3) (n = 48)
	r	*r*	*r*
Age	0.196*	0.121	0.344*
Weight	−0.017	−0.080	0.083
BMI	0.088	−0.015	0.264
Body fat	−0.102	−0.232	0.053
Waist circumference	0.035	0.030	0.038
TAT area	0.048	−0.041	0.157
SAT area	−0.037	−0.086	0.021
VAT area	0.176	0.065	0.327*
Plasma glucose	0.104	0.105	0.101
Total cholesterol	0.122	0.151	0.076
Triglyceride	0.120	0.025	0.258
HDL cholesterol	−0.001	0.106	−0.265
LDL cholesterol	0.135	0.150	0.111
Plasma insulin	0.059	0.101	0.066
HOMA-IR	0.080	0.124	0.113

The lower–HOMA-IR group and the higher–HOMA-IR group were distinguished using the HOMA-IR value of 3 as a cutoff. Triglyceride and vaspin levels were logarithmically transformed to approximate a normal distribution.

* $P < .05$ calculated by Pearson correlation analysis.

4. Discussion

In this study, we demonstrated that serum vaspin concentration was positively correlated with the VAT area as measured by computed tomographic analysis. Our results are in accordance with vaspin being a possible candidate for the connection between the visceral fat accumulation and the obesity-related metabolic disorders [21]. Notably, we found that the association varied with insulin resistance. Whereas the relationship between serum vaspin concentration and the VAT area in the lower–HOMA-IR group was not significant, the strength of the relationship was evident in the higher–HOMA-IR group.

Serum vaspin concentrations were significantly correlated with the VAT area, but not with the SAT area. This

Table 4
Multivariate linear regression analysis of serum vaspin concentration as a dependent variable and associated parameters as independent variables in the higher–HOMA-IR group

Higher–HOMA-IR group	Log serum vaspin concentration	
	β Coefficient	*P* value
VAT	0.327	.037
Age	0.210	.246
Sex	−0.203	.203

The lower–HOMA-IR group and the higher–HOMA-IR group were distinguished using the HOMA-IR value of 3 as a cutoff. Vaspin value was logarithmically transformed to approximate a normal distribution. *P* value calculated by multiple linear regression analysis.

observation suggests that the regulation of vaspin gene expression may be fat depot-specific. In contrast to OLEFT rats, in humans, vaspin mRNA expression was not restricted to visceral fat; however, vaspin mRNA expression was more often detectable in visceral fat than in subcutaneous fat [13]. Moreover, it is indicated that the induction of human vaspin mRNA expression is differentially regulated in VAT and SAT [13].

There is couple of possible explanations for the finding that circulating vaspin concentrations predominately correlate with the VAT accumulation in the presence of insulin resistance. Firstly, as previously suggested [11], the increase in vaspin concentration might be a compensatory response to antagonize the action of unknown proteases that are up-regulated in the state of insulin resistance. The reported insulin-sensitizing effect of vaspin on adipose tissue supports this possibility [11]. However, to prove this potential mechanism, further investigations including identification of the protease substrate for the induction of the protease inhibitor vaspin are required. Another possibility is that because the predominate site of vaspin production is the VAT, the circulating vaspin levels may increase with the VAT accumulation, suggesting a role of vaspin as surrogate parameter of VAT rather than an implication in the regulation of glucose homeostasis. However, in contrast to the higher–HOMA-IR group, the lack of relation between serum vaspin level and the amount of VAT in the lower–HOMA-IR group does not agree with this possibility. The inconsistency of the relation between serum vaspin levels and the VAT area is possibly derived from the difference in the studied population. Although abdominal fat distribution was not measured, it was reported in white subjects that elevated vaspin serum concentrations are associated with obesity and impaired insulin sensitivity, whereas type 2 diabetes mellitus seems to abrogate the correlation between increased circulating vaspin, higher body weight, and decreased insulin sensitivity [14].

In the present report, serum vaspin concentrations in women were higher than those in men, although statistical significance was not attained. Previous studies demonstrated sexual dimorphism in vaspin serum concentrations, with about 2-fold higher levels in female subjects compared with men [14,15]. In our study, serum vaspin concentration was positively correlated with age and VAT area in the higher–HOMA-IR group. Thus, we included sex and age as independent variables in multiple linear regression analysis.

Since the isolation of vaspin from the VAT of Otsuka Long-Evans Tokushima Fatty rats [22], there have been successive research efforts to identify its importance in insulin resistance and obesity in human. However, the relationship between circulating vaspin levels and the markers of obesity, insulin sensitivity, and glucose metabolism is still controversial in human. As in obese animal models, elevated levels of circulating vaspin [14,23] as well as increased expressions of vaspin mRNA in adipose tissues [13] have been reported in obese subjects. The previous study suggested that circulating vaspin levels correlate with BMI [14]. However, our study, using subjects with wide range of BMI, failed to find a significant positive correlation between serum vaspin concentrations and BMI.

In terms of the relationship of circulating vaspin to the markers of insulin resistance and glucose metabolism, no direct relationship was observed in the current study. However, another study reported that circulating vaspin levels significantly correlated with insulin sensitivity in subjects with normal glucose tolerance but not in patients with type 2 diabetes mellitus, showing a difference in the relationship between the 2 metabolic states [14]. In obese children, serum vaspin was positively correlated with triglycerides, fasting insulin, and HOMA-IR, suggesting a defensive role of vaspin against insulin resistance [23]. In overweight women with polycystic ovarian syndrome, vaspin circulating levels as well as its expression in omental adipose tissue were significantly elevated and were decreased by metformin treatment concomitantly with improvement in insulin sensitivity [24]. Although the serum vaspin level in type 2 diabetes mellitus was not different from that in controls, it was lower in the patients with microvascular complications [25]. Taken together, the above mentioned controversy in the association of vaspin levels with insulin resistance may be due to variability in study subjects, or other currently undefined factors that may affect vaspin or its substrate protease. Despite the controversy, majority of data suggest the protective role of vaspin in insulin resistance and glucose metabolism.

The present study has some limitations. First, the cross-sectional design makes it difficult to determine the causality of observed relationships. Second, insulin resistance was measured by the homeostasis model assessment method instead of the euglycemic-hyperinsulinemic clamp, a criterion standard technique for the determination of insulin resistance. However, it has been demonstrated that the measurements by the homeostasis model correlate significantly with those by the glucose clamp technique ($r = 0.83$, $P < .01$) [26,27]. Our measurement tool has been used in other epidemiologic studies [26,28]. In addition, our results may not be generalized because all study subjects were ethnically Korean.

In conclusion, our study showed a positive correlation between serum vaspin concentration and the VAT area in human subjects. This relationship was more prominent in patients showing higher levels of insulin resistance. The association between vaspin and visceral fat will thus vary with insulin sensitivity. The mechanism of action of vaspin and the clinical implications of elevated serum vaspin levels need to be further investigated.

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