Association between changes in serum vaspin concentrations and changes of anthropometric and metabolic variables in obese subjects after weight reduction

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Abstract: Visceral adipose tissue derived serpin (vaspin) has been regarded as a novel adipokine with potential insulin sensitizing properties. In The present study, we investigated the changes of serum vaspin concentration in response to weight reduction, and the association between changes in serum vaspin concentration and changes of anthropometric and metabolic variables in obese subjects after weight reduction. We performed a longitudinal clinical intervention study on 63 obese persons enrolled in a six-months weight reduction program that included lifestyle modification and adjuvant treatment with the anti-obesity agent. Anthropometric variables, lipid profile, fasting glucose, fasting insulin, and serum vaspin concentrations were measured. Statistical analyses were performed according to the homeostasis model assessment of insulin resistance ($HOMA_{IR}$). Serum vaspin concentration was decreased significantly in responders (≥2% reduction in baseline weight), but not in non-responders (<2% reduction in baseline weight). Changes in serum vaspin concentration were significantly correlated with body weight, BMI, waist circumference, and hip circumference in the higher, but not in the lower, $HOMA_{IR}$ group. In multivariate linear regression analysis, change in serum vaspin concentrations in the higher, but not in the lower, $HOMA_{IR}$ group was positively correlated with change in BMI and negatively correlated with initial $HOMA_{IR}$ level. The association between changes in serum vaspin concentration and changes in anthropometric and metabolic parameters differed according to insulin resistance status in obese subjects. These relationships were more prominent in the higher $HOMA_{IR}$ group. Insulin resistance may influence the correlations between changes in serum vaspin concentration and related metabolic variables.

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1. Introduction

Obesity is frequently associated with insulin resistance, type 2 diabetes, dyslipidemia, and hypertension (Jensen, 2008). In addition, adipose tissue secretes several bioactive peptides that exert paracrine and endocrine effects and play an important role in metabolic regulation (Wozniak *et al,* 2009). Thus, dysregulation of adipokine secretion may link obesity to its related metabolic disorders (Inadera, 2008).

Visceral adipose tissue derived serpin (vaspin) is a novel adipokine originally isolated from the visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty rats (Li *et al,* 2008), an animal model of type 2 diabetes (Hida *et al,* 2005). In these rats, vaspin was highly expressed at the age when obesity and insulin resistance peaked. Recombinant human vaspin administered to obese, insulin-resistant mice improved glucose tolerance and insulin sensitivity, as well as reversing the altered expression of genes relevant to insulin resistance in white adipose tissue. Thus, vaspin may antagonize the action of as yet unknown proteases, derived from fat or other tissues that impair insulin action (Hida *et al,* 2000).

Vaspin is also expressed in human adipose tissues and its expression has been shown to be higher in obese than in non-obese subjects (Kloting *et al,* 2006). Circulating vaspin concentrations have been reported to be sex-dependent and to be related to BMI and parameters of insulin sensitivity and glucose metabolism in humans. Elevated serum concentrations of vaspin are associated with obesity and impaired insulin sensitivity, whereas physical training in untrained individuals paradoxically causes increased serum vaspin concentrations with weight loss (Youn *et al,* 2008).Metformin treatment decreases serum vaspin levels in overweight women with polycystic ovary syndrome concomitant with improvement in insulin sensitivity (Tan *et al,* 2008).

However, the changes of serum vaspin concentrations according to weight change in obese subjects are still unclear. Therefore, we investigated the changes of serum vaspin concentration in response to weight reduction as well as the associations between changes in serum vaspin concentrations and anthropometric and metabolic

parameters, specifically, stratified by insulin resistance in obese subjects before and after a weight reduction.

2. Subjects and Methods

We recruited obese subjects (BMI ≥27 kg/m^2 with hypertension or dyslipidemia), aged 30–65 years, who visited the obesity clinic at National Institute for nutrition. All subjects were medically evaluated by physicians who took full medical histories and conducted physical examinations. We excluded pregnant or lactating women, subjects with secondary causes of obesity, subjects with severe hepatic or renal diseases, and subjects taking medications that might affect body weight or glucose metabolism. A total of 63 subjects were enrolled and completed a six- month's weight reduction program. All subjects underwent anthropometric measurements and blood sampling for biochemical measurements before and after the weight reduction program.

Weight reduction program:

The six months weight reduction program consisted of individual intervention sessions designed to implement behavioral strategies related to eating and physical activity, with the goal of achieving and maintaining weight loss. Participants were instructed to reduce their daily energy intake by 500 kcal. Throughout the program, participants were expected to engage in regular exercise and to visit the clinic every month for consultations. All participants were also administered 120-mg orlistat three times daily.

Anthropometric measurements:

Anthropometric measurements were taken with subjects in light clothing and without shoes. Height and weight were measured by an automatic height–weight scale, to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated by dividing weight (kg) by the square of the height (m^2). Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest and hip circumference was measured at the widest part of the hip region.

Measurements of metabolic variables and serum vaspin concentrations:

Blood samples were obtained in the morning after a 12-h overnight fast, and serum and plasma were immediately separated by centrifugation. Total cholesterol and triglyceride levels were measured by enzymatic procedures. The high-density lipoprotein-cholesterol fraction was measured enzymatically after precipitation of apo-B containing lipoproteins with $MnCl_2$. Low-density lipoprotein-cholesterol was calculated using the Friedewald equation if the triglyceride concentration was <400 mg/dl. Glucose was measured by the glucose oxidase method, hemoglobin $A_{1c.}$ and insulin by ELISA. Insulin resistance was determined by calculating the homeostasis model assessment of insulin resistance ($HOMA_{IR}$) score, using the formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl)/405 (Matthews *et al,* 1985). Serum vaspin concentrations were measured using a commercial ELISA kit according to the manufacturer's instructions.

Statistical analysis

Data are presented as mean ± S.E Prior to statistical analysis; non-normally distributed parameters were logarithmically transformed to approximate a normal distribution. Paired Student's *t*-tests were used to compare variables before and after weight reduction. To compare changes of variables according to weight reduction, participants were divided into two groups: responders, defined as those who lost ≥2% of baseline weight at the end of the six months intervention program, and non-responders. Unpaired two-tailed Student's *t*-tests were used to compare the changes in variables between the responder and non-responder groups. Subjects was also divided into those with higher (n = 32) and lower (n = 31) $HOMA_{IR}$ scores. We defined the higher $HOMA_{IR}$ group as subjects with initial $HOMA_{IR}$ values over the 50th percentile (value = 2.80). Correlations analyses were performed using Spearman's method, stratified by $HOMA_{IR}$, to examine the simple relationships between serum vaspin concentration and selected variables. To adjust for covariate effects and to identify independent relationships, multivariate linear regression analyses were performed. P values <0.05 were considered statistically significant in all tests. All statistical analyses were performed using SPSS.

3. Results:

Table (1): Anthropometric and metabolic parameters in the studied subjects before and after the six months weight reduction program

Parameter	Before	After	P-value
Body weight (kg)	88.6±1.3	82.1±1.3	< 0.01
BMI (kg/m2)	30.8 ±0.2	30.6± 0.03	< 0.01
Waist circumference(cm)	98.2 ± 0.9	95.2±1	< 0.01
Hip circumference(cm)	108 ± 0.6	106.7± 0.7	< 0.01
Total cholesterol(mg/dl)	196.4 ±3.5	189.5±4.2	0.05
Triglycerides (mg/dl)	150.5 ±12.3	157.3±13	0.63
HDL- cholesterol(mg/dl	53.3 ±1.4	48.8±1.2	< 0.01
LDL- cholesterol(mg/dl	122.2 ±3.5	117.6±3.5	0.09
Fasting glucose(mg/dl)	100 ±1.9	97.5±1.5	0.19
HbA1c(%)	5.6 ± 0.13	5.8± 0.2	0.22
Fasting insulin (µu/ml)	12.5 ± 0.7	11.3+.7	0.06
$HOMA_{IR}$	3.0 ± 0.3	2.6± 0.3	0.07
Vaspin(pg/ml)	615 ±50	530±45	0.08

- P value < 0.05 is considered to be significant.

Table (2): Changes in anthropometric and metabolic parameters in responders and non-responders after weight reduction program

Variables	Responders (n=35)		Non responders (n=28)		P-value
	Mean ± S.E	P-value	Mean ± S.E	P-value	
ΔBody weight (kg)	-4.2± 0.3	< 0.01	- 0.2± 0.2	0.18	< 0.01
ΔBMI (kg/m2)	-1.5± 0.1	< 0.01	- 0.08± 0.07	0.22	< 0.01
ΔWaist circumference (cm)	-4.4± 0.4	< 0.01	- 0.9± 0.5	0.11	< 0.01
ΔHip circumference (cm)	-2.7± 0.3	< 0.01	- 0.7± 0.4	0.07	< 0.01
ΔTotal cholesterol (mg/dl)	- 10±4.9	0.05	-1.5±3.8	0.69	0.21
ΔTriglycerides (mg/dl)	- 16.1±13.7	0.25	38.5±16.9	3	0.02
ΔHDL- cholesterol (mg/dl)	- 3.3±1.4	0.02	-5.2±1.3	< 0.01	0.35
ΔLDL- cholesterol (mg/dl)	- 6.5±4	0.12	-2.8±4	0.48	0.56
ΔFasting glucose (mg/dl)	-4.5±2	0.03	1.8±2.3	0.42	0.04
ΔHbA1c(%)	0.01± 0.05	0.8	0.1± 0.06	0.12	0.27
ΔFasting insulin (µu/ml)	-2.3± 0.7	< 0.01	0.1±1.4	0.94	0.09
Δ $HOMA_{IR}$	-0.7± 0.2	< 0.01	0.2± 0.3	0.5	0.02
ΔVaspin (pg/ml)	-12.8±7.4	0.04	33±21	0.69	0.04

- P value < 0.05 is considered to be significant.

Table (3): Spearman correlation coefficient between changes in serum vaspin concentration and changes in anthropometric and metabolic parameters after weight reduction according to $HOMA_{IR}$

Variables	Higher $HOMA_{IR\ (n=32)}$		Lower $HOMA_{IR\ (n=32)}$	
	r	P-value	r	P-value
ΔBody weight (kg)	0.477	< 0.01	- 0.005	0.98
ΔBMI (kg/m2)	0.456	< 0.01	- 0.041	0.83
ΔWaist circumference (cm)	0.525	< 0.01	- 0.116	0.54
ΔHip circumference (cm)	0.376	0.03	- 0.095	0.61
ΔTotal cholesterol (mg/dl)	- 0.003	0.99	- 0.16	0.39
ΔTriglycerides (mg/dl)	0.131	0.51	0.161	0.39
ΔHDL- cholesterol (mg/dl)	- 0.121	0.54	- 0.11	0.55
ΔLDL- cholesterol (mg/dl)	0.081	0.64	- 0.086	0.64
ΔFasting glucose (mg/dl)	0.244	0.18	0.068	0.72
ΔHbA1c(%)	- 0.079	0.69	0.002	0.99
ΔFasting insulin (µu/ml)	0.217	0.23	0.076	0.69
$\Delta HOMA_{IR}$	0.28	0.12	0.059	0.75

- P value < 0.05 is considered to be significant.

4. Discussion

It was shown here that, in obese subjects, serum vaspin concentrations decreased significantly following modest weight loss accompanied by improvements in parameters relevant to insulin resistance. Furthermore, relationships between changes in serum vaspin and changes in anthropometric parameters during the weight reduction program were modified by insulin resistance. That is, we observed strong significant correlations in the higher, but not in the lower, $HOMA_{IR}$ group. Those findings support previous results that serum vaspin concentration was independently correlated with visceral adipose tissue area in the higher $HOMA_{IR}$ group, but not in the lower $HOMA_{IR}$ group (Chang *et al,* 2010).

Circulating levels of vaspin, as well as its expression in adipose tissues, have been reported to be elevated in obese animals (Hida *et al,* 2000) and humans (Youn *et al,* 2008 and Suleymanoglu *et al,* 2009).

In obese men and women who responded to the weight reduction program, we observed significant decrease in serum vaspin level concomitant with ameliorations of insulin resistance. This observation is consistent with the hypothesis that increased vaspin may be a compensatory response to antagonize the action of unknown proteases that are up regulated in states of insulin resistance. Alternatively, vaspin concentration may simply be a surrogate parameter of obesity, because vaspin is mainly produced by adipose tissues and no mRNA transcript has yet been observed in non-adipose tissues of human and mouse organs (Hida *et al,* 2000).

In a previous intervention study, 4 weeks and 12-weeks of an intensive physical training program led to increases in serum vaspin concentrations concomitant with decreased BMI and improved insulin sensitivity (Youn *et al,* 2008, Chaston & Dixon, 2008 and Chang *et al., 2010*). Conversely, competitive sportsmen with long-term physical training had significantly lower vaspin serum concentrations than untrained age- and BMI-matched control subjects. This paradox was explained that serum concentration of vaspin was differentially regulated in the resting state and after exercise and elevated vaspin concentrations after the intensive physical training may represent a transient adaptation mechanism and that vaspin may contribute to the insulin-sensitizing effects of physical activity (Youn *et al,* 2008). In our study, weight reduction led to decrease in serum vaspin concentration with decreased BMI and improved insulin sensitivity. This discrepancy might be due to the differences of duration (short-term vs. long-term) or mode (exercise dominant vs. lifestyle modification) of weight reduction as well as exercise intensity (submaximal vs. moderate).

The present study shows that significant decrease in serum vaspin level were concomitant with reduction in waist circumference in responders group. Waist circumference is a useful index of central obesity (Pouliot *et al,* 1994) and modest weight loss has been associated with the preferential loss of visceral rather than subcutaneous fat (Smith and Zachwieja 1999). Hence, the decreased waist circumference observed in our responders may reflect the reduction in the accumulation of abdominal, particularly visceral fat. Thus, decreased vaspin concentration in the responders group may be associated with the reduction of visceral fat during the weight reduction program.

Interestingly, strong correlations between changes in serum vaspin concentration and changes in body weight, BMI, waist circumference, and hip circumference during the intervention were observed only in insulin resistant subjects. Previously, we observed that the relationship between serum vaspin concentration and visceral fat accumulation was modified by the presence of insulin resistance (Chang *et al,* 2010). In addition, multivariate regression analysis revealed that, in the presence of insulin resistance, changes in serum vaspin levels correlated positively with changes in BMI and negatively with initial $HOMA_{IR}$ after adjusting for confounding variables. Modification of the association with insulin resistance may be accounted for by the fat depot-specific regulation of vaspin production, together with the preferential loss of visceral fat, the accumulation of which is a primary risk factor for insulin resistance (Kloting *et al,* 2006).

A recent report, demonstrating a significant association between vaspin single-nucleotide polymorphism and type 2 diabetes (Kempf *et al,* 2010), supports the potential insulin-sensitizing properties of vaspin. Moreover, secretomes of primary cultures of human adipose-derived stem cells showed that adipocyte differentiation modulates the levels of expression of the serpin family of protease inhibitors (Zvonic *et al,* 2007), indicating that these molecules play a significant role in obesity and its related metabolic alterations.

Previous studies reported a sexual dimorphism in serum vaspin concentrations with higher levels in normal glucose-tolerant women compared with men (Youn *et al,* 2008 and Seeger *et al, 2008*), however, these sex differences were not observed in type 2 diabetic patients and sexual dimorphism in serum vaspin levels could be influenced by glucose tolerance or insulin sensitivity (Youn *et al,* 2008). In our study, initial serum vaspin levels were not significant different between women and men (567.87 ± 69.46 vs. 689.04 ± 97.19 pg/ml, $P = 0.274$) (data not shown). Furthermore, the change of serum vaspin concentrations after weight reduction between women and men were not different regardless of the degree of weight loss or insulin resistance state. Since our study subjects were obese, we could not exclude the possibility that our subjects might have abnormal glucose metabolism or insulin resistance and those conditions led to the absence of sexual dimorphism in our study.

The present study has several limitations. First, we defined insulin resistance by the HOMA method, instead of the glucose clamp method, the standard method used to define insulin resistance. However, estimates by the homeostasis model correlate fairly well with those by the euglycemic–hyperinsulinemic clamp ($r = 0.83$, $P< 0.01$) and have acceptable degree of reproducibility (Bonora *et al,* 2000). We also defined insulin resistance using an arbitrary criterion. Although cut-off values of $HOMA_{IR}$ may differ among study subjects and ethnic groups, the $HOMA_{IR}$ index has been widely used as a surrogate marker for insulin sensitivity after therapeutic lifestyle changes (Vogeser *et al,* 2007).

Second, we could not measure abdominal fat distribution. If we had assessed visceral and subcutaneous adipose tissue in the study subjects before and after the weight reduction program, we would have been able to analyze the decrease in serum vaspin concentrations relative to the reduction in visceral adipose tissues. Since waist circumference has been highly associated with visceral fat accumulation, we utilized waist circumference as a simple proxy anthropometric indicator of abdominal obesity (Clasey *et al,* 1999 and Lee *et al,* 2008). The change in waist circumference might reflect change in visceral fat accumulation.

Third, we could not analyze changes in serum vaspin concentrations according to the therapeutic modality of weight reduction, because we educated all subjects about lifestyle modification and prescribed a lipid absorption inhibitor (orlistat). Orlistat potently inhibits gastric and pancreatic lipases, thus limiting the hydrolysis and systemic absorption of ingested fat, and may therefore lead to changes in cholesterol and/or low-density lipoprotein-cholesterol concentration (Havizdos and Markham, 1999). However, the previous study reported that no differences in adipokine concentrations have been observed between individuals on a hypocaloric diet, with or without orlistat treatment (Bougoulia *et al,* 2006).

5. Conclusion

In conclusion, the present study revealed that modest weight loss in obese subjects resulted in a significant decrease in serum vaspin concentrations concomitant with the amelioration of insulin resistance. The associations between changes in serum vaspin concentrations and changes in anthropometric and metabolic parameters differed according to insulin resistance status in obese subjects. Insulin resistance may influence the correlations between changes in serum vaspin concentration and related metabolic variables.

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