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CLINICAL STUDY

Serum vaspin levels in type 2 diabetic women in relation to microvascular complications

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Abstract

Objective: Vaspin is a novel adipokine that has insulin sensitizing effects. The association between serum vaspin levels and diabetic complications is unknown. In this study, we aimed to evaluate serum vaspin levels as related to glycemic status and the presence of complications in a group of type 2 diabetic women.

Materials and methods: We evaluated 37 type 2 diabetic female patients and 37 control female subjects who were matched for age and body-mass index. Anthropometric measurements, insulin, hemoglobin A1c (HbA1c), C-reactive protein, and serum vaspin levels were measured in each participant. Furthermore, the patients were evaluated for diabetic neuropathy, nephropathy, and retinopathy.

Results: In diabetic patients, serum vaspin levels correlated positively with HbA1c and correlated negatively with insulin levels and homeostasis model assessment. The patients with HbA1c levels $\leq 7\%$ had lower levels of serum vaspin than patients with HbA1c levels $>7\%$ (0.11 ± 0.06 ng/ml versus 0.20 ± 0.09 ng/ml, $P<0.05$). In patients with neuropathy, retinopathy, and nephropathy, serum vaspin levels were lower than in patients without neuropathy (0.10 ± 0.07 ng/ml versus 0.17 ± 0.09 ng/ml, $P=0.041$), retinopathy (0.11 ± 0.06 ng/ml versus 0.18 ± 0.09 ng/ml, $P=0.019$), and nephropathy, (0.11 ± 0.05 ng/ml versus 0.18 ± 0.09 ng/ml, $P=0.02$). Diabetic patients receiving metformin therapy had lower vaspin levels than patients not receiving metformin.

Conclusion: Diabetic women with good glycemic control have lower levels of vaspin than those with poor glycemic control. However, presence of microvascular complications is also associated with low vaspin levels. In order to use serum vaspin levels as a marker, evaluating patients for complications and medications interfering with serum vaspin levels seems appropriate.

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Introduction

Increased visceral adiposity is associated with insulin resistance and type 2 diabetes (1–3). To investigate the link between adiposity and insulin resistance, a variety of adipokines that modulate insulin sensitivity have been demonstrated (4–8). Recently, Hida *et al*. identified a visceral adipose tissue-derived serpin (vaspin) as a member of the serine protease inhibitor family, which was expressed in visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of abdominal obesity and type 2 diabetes mellitus (9). Insulin or pioglitazone treatment normalized serum vaspin levels, and the administration of vaspin to obese mice improved their glucose tolerance and insulin sensitivity. Vaspin has been suggested as a compensatory factor against the insulin resistance state of metabolic syndrome based on the evidence from animal experiments that used recombinant vaspin protein and cross-sectional expression studies from both human visceral and subdermal white adipose tissue samples (9, 10). In OLETF rats, serum vaspin levels peaked at the age when obesity and insulin plasma concentrations reach a peak; however, vaspin levels decreased with worsening of diabetes and body weight loss (9).

A few studies were reported about vaspin expression in fat tissue and serum vaspin levels in humans and the correlation between vaspin serum levels and markers of insulin sensitivity, and glucose metabolism are unclear (11–13, 15). Until now, no study evaluating the association of serum vaspin levels with the complications of diabetes has been undertaken.

We aimed to evaluate serum vaspin levels in relation to glycemic status and the presence of complications in a group of type 2 diabetic women.

Subjects and methods

In this study, we evaluated 37 type 2 diabetic female patients and 37 control female subjects who were matched for age and body mass index (BMI). Diabetes was diagnosed using glucose cut-off values as defined by the World Health Organization.

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The study protocol was approved by the local ethical committee, and informed consent was obtained from each subject. Subjects were excluded if they had a known history of stroke or transient ischemic attack, uncontrolled hypertension, liver disease, renal disease, severe dyslipidemia (triglycerides >600 mg/dl or cholesterol >350 mg/dl), acute or chronic inflammatory disease, or any other serious, chronic disease requiring active treatment. Diabetic patients using insulin were also excluded.

Anthropometric measurements and a biochemical analysis were performed on each subject. Additionally, insulin, hemoglobin A1c (HbA1c), high sensitive C-reactive protein (CRP), and serum vaspin levels were measured for each participant. Blood pressure was measured three times in the same arm of each patient after she was seated and at rest for a minimum of 15 min. BMI was calculated as body weight (kg) divided by body height squared (m^2). Waist circumference was defined as midway between the highest point of the iliac crest and the lowest point of the costal margin and was measured on standing participants.

Diabetic nephropathy was diagnosed by the presence of microalbuminuria and overt albuminuria. Urinary albumin excretion was investigated to assess diabetic nephropathy. Urinary albumin excretion of 30–300 mg/24 h was regarded as microalbuminuria, and urinary albumin excretion of more than 300 mg/24 h was regarded as overt albuminuria. Diabetic retinopathy was evaluated by an ophthalmologist. Patients were questioned about sensory, motor, and autonomic symptoms, and their responses were recorded. A clinical history regarding any other concurrent etiology for neuropathy was also obtained. A standard neurological examination included an evaluation of knee and ankle reflex activity and feet sensation with monofilament and vibration. Neuropathy was defined as the presence of at least two of the following: symptoms, reduced vibration perception, insensitivity to monofilament at one or more of nine sites on either feet, and absent tendon reflexes.

Blood samples were collected after an overnight fast. Plasma glucose, total cholesterol, triglycerides, high density lipoprotein-cholesterol, and low density lipoprotein-cholesterol were measured using reagents from Roche Diagnostics on a Roche Modular DDP analyzer. Insulin levels were measured with an IRMA (Berthold LB 2111; Diagnostic System Laboratories, Inc., Webster, TX, USA). High-sensitivity CRP levels were measured with an immunochemical assay (Turbiquant CRP, Dade Behring, Liederbach, Germany). Serum vaspin levels were measured with a commercially available ELISA according to the manufacturers' instructions (Adipogen, Seoul, South Korea). Homeostasis model assessment (HOMA) was taken as a measure of insulin sensitivity using the following equation: fasting plasma insulin $\times$ glucose/405.

Descriptive statistics were expressed as mean $\pm$ S.D. The normality of distributions was assessed by the Shapiro–Wilk test. The differences between two groups were examined by an independent samples *t*-test. The χ^2-test or Fisher's exact test was used for the analysis of categorical variables. Associations between variables were assessed by Pearson correlation coefficients. Multiple linear regression analysis was performed to adjust for the effect of the covariates of age and BMI. Data analysis was performed by Statistical Package for Social Sciences 15.0 software package. A $P<0.05$ was accepted as statistically significant. Power calculations were assessed by NCCS-PASS 2007 software package and the power of the study was calculated as 75%.

Results

The characteristics of the patients and the controls are shown in Table 1. No difference was observed in serum vaspin levels between diabetic patients and control subjects. When all the subjects were studied, vaspin levels were negatively correlated with insulin levels ($r=-0.253$, $P<0.05$) and HOMA ($r=-0.276$, $P<0.05$). In diabetic patients, serum vaspin levels correlated positively with HbA1c ($r=0.406$, $P<0.05$), and correlated negatively with insulin levels ($r=-0.425$, $P<0.05$), and HOMA ($r=-0.405$, $P<0.05$). In the control subjects, vaspin levels correlated negatively with insulin levels ($r=-0.340$, $P<0.05$). There was no correlation between CRP levels and serum vaspin levels ($r=0.126$, $P=0.456$). In the analysis of all the subjects, multiple linear regression analysis revealed that HOMA and age remained associated with serum vaspin levels after adjustment for age and BMI. HbA1c and HOMA predicted serum vaspin levels in the diabetic patients, and insulin levels predicted serum vaspin levels in the control subjects

Table 1 Baseline characteristics of the study population.

	DM patients	Controls	*P*
Age (years)	53.6±6.8	51.9±8.7	NS
BMI (kg/m^2)	30.2±5.4	28.7±4.5	NS
Waist (cm)	99.6±12.6	92.5±11.5	0.015
Waist/hip ratio	0.90±0.08	0.87±0.07	NS
SBP (mmHg)	130.0±16.4	119.0±16.6	0.006
DBP (mmHg)	79.8±10.3	78.7±8.2	NS
FBG (mg/dl)	141.2±36.2	92.5±6.2	0.001
PPG (mg/dl)	164.2±47.6	–	–
HbA1c (%)	7.2±1.6	–	–
Insulin (μIU/ml)	15.7±7.1	9.7±2.3	0.001
HOMA	5.3±2.2	2.2±0.6	0.001
T Chol(mg/dl)	200.8±37.6	198±29.4	NS
LDL (mg/dl)	126.7±30.2	119.8±20.9	NS
HDL (mg/dl)	45.0±12.2	57.2±10.0	0.001
Triglyceride (mg/dl)	165.3±78.1	126.0±47.0	0.011
CRP (mg/dl)	0.4±0.02	0.3±0.02	NS
Vaspin (ng/ml)	0.15±0.09	0.18±0.10	NS

Data are presented as mean ± S.D. NS, not significant; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; PPG, postprandial blood glucose; T Chol, total cholesterol and CRP, C-reactive protein.

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(Table 2). When we classified HbA1c levels to indicate patients with good glycemic control ($\leq 7\%$) and patients with poor glycemic control ($>7\%$), serum vaspin levels were significantly lower in patients with good glycemic control than in patients with poor glycemic control (0.11 ± 0.06 ng/ml versus 0.20 ± 0.09 ng/ml respectively, $P<0.05$; Fig. 1). The characteristics of the patients with and without microvascular complications are given in Table 3. In patients with neuropathy ($n=10$), retinopathy ($n=14$), and nephropathy ($n=13$), serum vaspin levels were lower than in patients without neuropathy (0.10 ± 0.07 ng/ml versus 0.17 ± 0.09 ng/ml respectively, $P=0.041$), retinopathy (0.11 ± 0.06 ng/ml versus 0.18 ± 0.09 ng/ml respectively, $P=0.019$) and nephropathy (0.11 ± 0.05 ng/ml versus 0.18 ± 0.09 ng/ml respectively, $P=0.02$). Nine of the patients had all three microvascular complications. In patients with all microvascular complications serum vaspin levels were lower than those with two or fewer microvascular complications (0.09 ± 0.06 versus 0.17 ± 0.09, $P=0.021$). Multivariate regression analysis revealed that vaspin levels were correlated independently with neuropathy ($P=0.007$), retinopathy ($P=0.038$), and nephropathy ($P=0.011$) after adjusting for HOMA and HbA1c (Table 4). When we adjust the patients for BMI and age, serum vaspin levels were still correlated with neuropathy ($P=0.042$), retinopathy ($P=0.024$), and nephropathy ($P=0.028$).

Ten of the 37 patients were not on metformin therapy. The characteristics of the patients according to metformin therapy are given in Table 3. Metformin-treated patients had significantly lower serum vaspin levels than patients not taking the drug (0.26 ± 0.07 ng/ml versus 0.11 ± 0.05 ng/ml respectively, $P=0.001$). In multivariate linear regression analysis, metformin use was associated with serum vaspin levels ($P=0.001$) after adjustment for age, HbA1c, and HOMA (Table 4). After adjustment for age and BMI, vaspin levels were still correlated with metformin treatment ($P=0.001$).

Table 2 Multivariate linear regression analyses in all subjects, both diabetic patients and control subjects, after adjustment for body mass index (BMI) and age.

Independent variables	Beta coefficient	*P* value
All patients ($R^2=0.148$, $F=4.041$, $P=0.01$)		
HOMA	−0.293	0.011[a]
Age	0.255	0.028[a]
BMI	−0.144	0.208
DM patients ($R^2=0.455$, $F=6.689$, $P=0.001$)		
HbA1c	0.475	0.001[a]
HOMA	−0.529	0001[a]
Age	0.233	0.095
BMI	−0.055	0.684
Controls ($R^2=0.227$, $F=3.239$, $P=0.034$)		
Insulin	−0.323	0.043[a]
Age	0.242	0.128
BMI	−0.273	0.088

The dependent variable is serum vaspin.
[a]Indicates significant correlation.

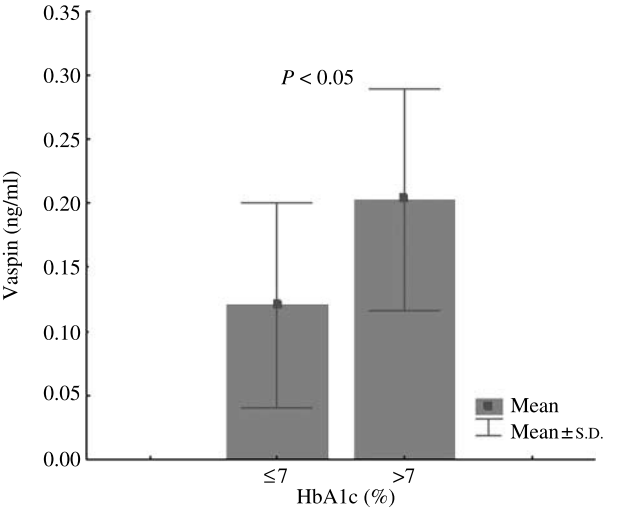

Figure 1 Serum vaspin levels of diabetic patients with good (HbA1c≤7) and poor (HbA1c>7) glucose control.

Discussion

Increased visceral adiposity is usually with a clustering of atherogenic risk factors, such as insulin resistance, hypertension, dyslipidemia, alterations in coagulation, and inflammatory cytokine profiles. As a consequence, increased visceral adiposity increases the prevalence of type 2 diabetes and cardiovascular diseases (1–3). Various adipokines have been defined in an effort to explain the relationship between visceral adiposity and increased metabolic risk (4–8).

Recently, Hida *et al.* identified a novel adipokine, vaspin, in OLETF rats (9). Vaspin mRNA was highly expressed in visceral mesenteric and retroperitoneal white adipose tissues in 30-week old OLETF rats, which corresponds with their peak in body and fat mass and hyperinsulinemia with insulin resistance. Their vaspin serum levels increased at the same age. OLETF rats progressively lost weight for the next 20 weeks along with a decline in insulin levels and a rise in HbA1c. After this period, at 50 weeks of age, vaspin mRNA expression was absent, and vaspin serum levels were markedly reduced. Insulin and thiazolidinedione treatments up-regulated vaspin mRNA and serum vaspin levels and maintained them until 50-weeks of age. The researchers suggested that the increase in vaspin may be a compensatory response to antagonize the action of other unknown proteases that are up-regulated in obesity and in states of insulin resistance; hence, this up-regulation may be a defensive mechanism against insulin resistance. Moreover, administration of vaspin to

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Table 3 Characteristics of the patients with and without microvascular complications.

	Neuropathy		Retinopathy		Nephropathy		Metformin treatment	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Age (years)	53.6±7.3	53.4±5.6	54.0±6.7	52.7±7.1	54.2±6.5	52.4±7.5	55.1±4.8	53.0±7.4
BMI(kg/m^2)	30.4±4.6	32.4±7.4	30.3±4.8	32.1±6.4	30.3±4.8	32.2±6.6	31.4±5.5	30.8±5.6
FBG (mg/dl)	134.2±32.3	159.7±41.5	137.3±33.5	147.5±40.9	135.5±33.9	151.6±39.3	146.6±41.0	139.1±34.9
Insulin (μIU/ml)	14.5±6.9	19.1±6.9	14.5±6.9	17.8±7.2	14.4±7.1	18.2±6.8	10.9±5.2[a]	17.6±7.0
HOMA	4.6±1.9[a]	7.1±1.9	4.7±2.1	6.1±2.2	4.6±2.1[a]	6.4±2.1	3.9±2.0[a]	5.7±2.1
HbA1c (%)	7.0±1.1	7.8±2.3	7.1±1.4	7.2±1.8	7.1±1.5	7.3±1.8	7.8±1.6	6.9±1.5
Vaspin (ng/ml)	0.10±0.07[a]	0.17±0.09	0.11±0.06[a]	0.18±0.09	0.11±0.05[a]	0.18±0.09	0.26±0.07[a]	0.11±0.05

Data are presented as mean±S.D.
[a]Indicates significant correlation.

diet-induced obese rats resulted in improved insulin sensitivity and glucose tolerance (9).

A few studies have been reported to identify the importance of vaspin in insulin resistance and obesity in humans. The correlation between serum vaspin levels and markers of insulin sensitivity, glucose metabolism, and obesity is still controversial. Klöting *et al.* examined vaspin mRNA expression in paired visceral and s.c. tissue from 196 patients with a wide range of obesity and glucose tolerance and found that visceral vaspin mRNA expression was correlated with BMI, percentage body fat, and 2-hour oral glucose tolerance test plasma glucose. The authors concluded that human vaspin mRNA expression in adipose tissue is regulated in a fat depot-specific manner and could be associated with parameters of obesity, insulin resistance, and glucose metabolism (11). In the current study, serum vaspin levels were correlated with insulin resistance in all patients, and in diabetic patients. In the control subjects, no correlation was observed between HOMA and vaspin levels, but insulin levels correlated with vaspin levels. By contrast, Seeger *et al.* failed to find a correlation between vaspin levels and markers of insulin sensitivity and glucose metabolism, including fasting glucose, fasting insulin, (HOMA), and adiponectin in chronic haemodialysis patients and control subjects, which included diabetic patients (12). Youn *et al.* performed a cross sectional study in 187 subjects with diabetes mellitus, impaired glucose tolerance, or normal glucose tolerance. They found a gender difference in vaspin concentrations in control subjects, but this difference was not observed in diabetic patients. They found an association between vaspin serum levels and BMI and insulin sensitivity but could not confirm this correlation in patients with type 2 diabetes (13). The controversy in the association of vaspin levels with insulin resistance may be due to different patient populations in these studies or other currently undefined factors that may affect vaspin or its substrate protease. Since vaspin is recognized as an insulin sensitizing adipokine, theoretically, we would expect a positive association between serum vaspin levels and HOMA. In our study, patients with microvascular complications had higher HOMA levels and lower serum vaspin levels than the ones without complications. Therefore, the presence of patients with microvascular complications in the study population may result in a negative correlation between serum vaspin levels and HOMA in diabetic patients and the whole study population. The administration of recombinant vaspin improved insulin sensitivity and glucose tolerance and reversed the expression of genes that may promote insulin resistance in diet-induced obese mice (9). Therefore, reasonable speculation suggests that the production of vaspin may antagonize the action of unknown proteases that impair the action of insulin (14). Further identification of potential substrate proteases may clarify the regulation of vaspin in humans.

Tan *et al.* found higher serum and adipose tissue vaspin levels in women with polycystic ovarian syndrome (PCOS) and detected significant positive associations between circulating vaspin and vaspin levels in omental adipose tissue with BMI and

Table 4 Multivariate linear regression analyses indicating the effect of microvascular complications and metformin treatment on serum vaspin levels after adjustment for HOMA and HbA1c.

Independent variables	Beta coefficient	*P* value
Neuropathy (R^2=0.428, F=8.247, P=0.001)		
Neuropathy	−0.410	0.007[a]
HbA1c	0.504	0.001[a]
HOMA	−0.238	0.090
Retinopathy (R^2=0.372, F=6.508, P=0.001)		
Retinopathy	−0.313	0.038[a]
HbA1c	0.400	0.007[a]
HOMA	−0.247	0.099
Nephropathy (R^2=0.412, F=7.717, P=0.001)		
Nephropathy	−0.365	0.011[a]
HbA1c	0.417	0.004[a]
HOMA	−0.288	0.041[a]
Metformin treatment (R^2=0.611, F=17.307, P=0.001)		
Metformin treatment	−0.648	0.001[a]
HbA1c	0.190	0.109
HOMA	−0.128	0.280

[a]Indicates significant correlation.

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waist-to-hip ratios. An interesting finding by Tan *et al*. is that 6 months metformin treatment resulted in a significant decrease in circulating vaspin and glucose levels with a concomitant improvement in insulin sensitivity and a decrease in insulin resistance indices. They hypothesized that the increased circulating and omental adipose tissue vaspin levels may be a compensatory mechanism for insulin resistance and/or glucose metabolism. Metformin treatment, possibly via its glucose lowering effect by suppressing hepatic glucose production, decreases serum vaspin levels in women with PCOS (15). In our study, no difference was observed in vaspin levels between patients with diabetes and the control subjects. However, 27 patients were taking metformin. When we compared the patients taking metformin with the patients not taking metformin, the patients on metformin therapy had lower serum vaspin levels than patients who were not taking metformin.

We found a positive correlation between serum vaspin levels and HbA1c, which may be due to a compensatory response. We divided the patients into two groups according to HbA1c levels. We learned from the United Kingdom Prospective Diabetes Study (UKPDS) and other studies that good control of diabetes is essential for decreasing microvascular complications (16–18). The current recommended target HbA1c level for diabetic patients is 7% and as close to normal ($<6\%$) as possible without significant hypoglycemia for selected individual patients (19). In patients with HbA1c levels $\leq 7\%$, serum vaspin levels were low. This may be explained by the assertion that good control of diabetes normalizes the compensatory response.

As far as we know, the association between circulating levels of vaspin and diabetic microvascular complications has not been studied to date. In patients with neuropathy, retinopathy, and nephropathy, serum vaspin levels were lower than that of patients without them. Microvascular complications lead to lower levels of vaspin. Hida *et al*. found that, in OLETF rats, vaspin levels decreased with the worsening of diabetes (9). We can speculate that the defensive mechanism of vaspin might be ceased by the development of microvascular complications. Further investigations into whether this finding is due to a vascular impairment or a consequence of other factors that leads to the worsening of the diabetic condition is necessary. The identification of a protease substrate for the induction of vaspin may clarify the role of vaspin in microvascular complications of diabetes.

The observance of low serum vaspin levels in patients under good diabetic control, high serum vaspin levels in patients with high HbA1c levels, and low vaspin levels in patients with diabetic complications raises the following question: what we will do if we observe low levels of vaspin in a diabetic patient? Our patient population is too small to answer this question, and we can not generalize the conclusions to the entire population as only women are included in the study. However, evaluating the patients for complications and medications interfering with serum vaspin levels before interpreting serum vaspin levels seems appropriate. Although vaspin levels seem to be associated with insulin resistance and glycemic status in our study, its validity as a marker is questionable at present. Further investigations are needed to understand the regulation of vaspin and its role in the development and course of diabetes.

The first limitation of the current study is that the study population is relatively small; however, the study has sufficient power to detect the influence of microvascular complications on serum vaspin levels. The second limitation is that only women are included in our study and we cannot extrapolate the conclusions to the entire population. The third limitation is that this is a cross-sectional study, and thus it is difficult to evaluate a cause-effect relationship between serum vaspin levels and microvascular complications.

In conclusion, serum vaspin levels are associated with insulin resistance in diabetic women and positively correlated with HbA1c. Serum vaspin levels are lower in patients with microvascular complications compared with those without microvascular complications. Patients on metformin therapy have low levels of serum vaspin. In order to use serum vaspin levels as a marker, evaluating the patients for complications and medications interfering with serum vaspin levels seems appropriate. An understanding of vaspin regulation with identification of its substrate protease may be helpful in deducing the mechanisms causing the interfering circumstances with serum vaspin levels and in determining the value of vaspin as a marker.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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