

Serum vaspin levels are positively associated with diabetic retinopathy in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Vaspin is linked to obesity and its metabolic abnormalities. However, the role of vaspin serum levels in diabetic retinopathy (DR) is unknown. In the present study, we investigated the association between serum levels of vaspin and both DR and vision-threatening DR.

Materials and Methods: This was a cross-sectional single-center observational study from December 2018 to September 2019. We evaluated circulating serum levels of vaspin in 372 participants with type 2 diabetes. DR was screened through detailed ocular examination. DR patients were also divided two groups: vision-threatening DR and non-vision-threatening DR. The relationship between vaspin and DR was investigated by univariate and multivariate logistic regression analyses, and the results are shown as odds ratios with 95% confidence intervals.

Results: The vaspin serum levels of 372 patients were obtained, with a median value of 1.50 ng/mL (interquartile range 0.94–2.18 ng/mL). The median age of those patients was 53 years (interquartile range 44–62 years), and 44.4% were women. Patients with DR and VDTR had significantly increased vaspin serum levels ($P < 0.001$ and $P < 0.001$). A multivariable regression model found that patients with high levels of vaspin were approximately 1.85-fold (odds ratio for per unit increase 1.85, 95% confidence interval 1.43–2.55; $P < 0.001$) more likely to experience DR, and 3.76-fold (odds ratio for per unit increase 3.76, 95% confidence interval 2.05–6.55; $P < 0.001$) more likely to experience VTDR. The predictive value of vaspin was stronger in women than in men.

Conclusion: Higher vaspin serum levels were associated with an increased risk of DR and VDTR in patients with type 2 diabetes, which showed that vaspin is an important indicator factor for DR.

INTRODUCTION

The World Health Organization report states that >422 million adults globally were suffering from diabetes in 2014, and a continuous rise in prevalence is expected¹. A cross-sectional national survey showed that the estimated prevalence of diabetes was 10.9% (prediabetes 35.7%) in the Chinese population². Diabetic retinopathy (DR) affects >30% of patients with diabetes, and remains one of the main causes of blindness in working people³.

Adipocytokines play a role in the pathogenesis of diabetes and its complications⁴. A meta-analysis confirmed that leptin

and adiponectin levels are higher in type 2 diabetes mellitus patients with microvascular complications⁵. Yilmaz *et al.*⁶ suggested that adiponectin might take part in the pathogenesis of DR. Uckaya *et al.*⁷ declared that the more advanced the DR, the higher the plasma leptin levels, suggesting leptin might play a role in the progression of human DR to a proliferative phase. In addition, circulating visfatin was increased with progressive β -cell deterioration⁸, and serum omentin-1 concentration correlated negatively with DR presence and severity in type 2 diabetes mellitus patients⁹. Jung *et al.*¹⁰ found that higher serum adiponectin was related to increased odds for diabetic nephropathy in type 2 diabetes mellitus.

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Vaspin is a novel adipocytokine produced by visceral and subcutaneous adipose tissues¹¹. Vaspin messenger ribonucleic acid expression and elevated serum levels were associated with obesity, type 2 diabetes, metabolic syndrome and atherosclerosis^{12–15}. A meta-analysis showed that significantly higher levels of serum vaspin were observed in obese individuals and type 2 diabetes mellitus patients¹⁶; however, another study showed that low serum concentration of vaspin is a risk factor for the progression type 2 diabetes mellitus¹⁷.

Furthermore, previous studies assessed the association between circulating vaspin and insulin sensitivity, yielding conflicting results^{18–19}, and the mechanisms of how vaspin might play a role in glucose metabolism and insulin sensitivity are still unknown²⁰. Interestingly, vaspin can affect vascular systems to prevent or exacerbate obesity-related vascular complications, such as diabetes-related vascular dysfunction²¹, hypertension²² and atherosclerosis²³. To our knowledge, no previous studies have clarified the relationship of serum vaspin with DR prevalence in patients with type 2 diabetes mellitus. The aim of the present study was to investigate the association between serum vaspin levels and both DR and vision-threatening DR (VTDR) in type 2 diabetes mellitus patients.

METHODS

Patients

This was a cross-sectional, single-center, observational study. A total of 506 patients with type 2 diabetes mellitus were screened from the Department of Endocrinology of Shengjing Hospital of China Medical University (Shenyang, China). The study period was from December 2018 to September 2019. The diagnosis of diabetes was based on the 1999 World Health Organization diagnostic criteria²⁴. Patients with malignant tumor, liver and/or renal insufficiency, infectious and inflammatory conditions, cardiovascular disease, psychological and/or neurological disorders, and eye infections were excluded. The research protocol of this study was reviewed and approved by the Human Studies Ethics Committee of the Shengjing Hospital of China Medical University (No. 2018-SJEC-003). No patients were included unless their written informed consent was obtained.

Data collection

Demographic information (age, sex and body mass index [BMI]), diabetes duration, hypertension, hyperlipoproteinemia, smoking habits, alcohol abuse and treatments information (insulin, lipid-lowering and blood pressure-lowering) were recorded. Intensive glucose treatment was defined as treatment with sulfonylurea or insulin or, if >120% of ideal bodyweight, metformin. DR was screened through detailed ocular examination using dilated ophthalmoscopy and slit lamp biomicroscopy. The severity of DR was defined by the Early Treatment Diabetic Retinopathy Study grading standards, which was divided into two groups: non-proliferative DR and proliferative DR²⁵. In addition, DR patients were also divided two groups: vision-

threatening DR (VTDR; included severe non-proliferative DR and proliferative DR patients) and non-VTDR (included mild and moderate non-proliferative DR)²⁶. We used the eye with the more severe symptoms to group the patients.

Laboratory testing

A fasting blood sample was collected from the cubital vein. Serum samples were separated and stored at -80°C . Serum glucose, lipids (total cholesterol, triglycerides, low density lipoprotein cholesterol, high-density lipoprotein cholesterol) and high-sensitivity C-reactive protein (Hs-CRP) were assessed using BS800M (MINDRAY, Shenzhen, China). Serum levels of vaspin and insulin were tested using commercial enzyme-linked immunosorbent assay kits, as per the manufacturers' instructions (BioVision, Inc., Milpitas, CA, USA), with intra- and interassay coefficients of variation of 4.5–8.5%/6.0–9.5% and 4.0–7.0%/5.0–8.5%, respectively. Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) index (fasting serum insulin [$\mu\text{U}/\text{mL}$] \times fasting blood glucose [mmol/L] / 22.5)²⁷.

Statistical analysis

The categorical data are presented as the number and percentage (%), whereas distributed data are presented as the median and interquartile range (IQR). The difference between groups was assessed by the χ^2 -test (categorical data) or Mann–Whitney *U*-test (distributed data). The correlation between different factors was assessed by Spearman's rank correlation test. In addition, those included patients were divided into two groups based on the vaspin levels (Q1–3 vs Q4), and the relationship between serum vaspin and other factors was analyzed.

The relationship between vaspin and DR (and VTDR) was also investigated by the univariate and multivariate logistic regression analyses (adjusted for age, sex, BMI, duration of diabetes, conventional risk factors, treatments and serum levels of glucose, lipids, insulin, and Hs-CRP), and results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). The receiver operating characteristic curve was used to elaborate the role of vaspin in diagnosing DR (and VTDR), and results are shown as the area under the curve with 95% CI. All statistical analyses were tested by IBM SPSS software (version 22.0; IBM Corporation, Armonk, NY, USA), and a $P < 0.05$ (two-sided) was considered significant.

RESULTS

Patient characteristics

We recorded 375 patients with type 2 diabetes mellitus (excluded: 8 with malignant tumor; 6 with liver and/or renal insufficiency; 12 with infectious and inflammatory conditions; 58 with cardiovascular disease; 31 with psychological and/or neurological disorders; 5 with infection in one and/or both eyes; and 11 without informed consent). The vaspin serum level was obtained for 372 patients (99.2%) with a median value of 1.50 ng/mL (IQR 0.94–2.18 ng/mL).

The characteristics of patients according to vaspin levels (Q1–3 vs Q4) are shown in Table 1. Patients with a vaspin level in the highest quartile (Q4) were more likely women and with hypertension. BMI, disease duration, HOMA-IR, serum levels of Hs-CRP, fasting serum glucose and fasting insulin were significantly greater in this group. Furthermore, patients were more likely to have DR (54.3% vs 18.6%; $P < 0.001$) and VTDR (33.3% vs 3.5%) in this group (Table 1).

Serum vaspin and other factors

A positive correlation between vaspin and BMI (r [Spearman] = 0.258, $P < 0.001$) was found (Figure 1a). Serum levels of vaspin were associated with HOMA-IR ($r = 0.518$, $P < 0.001$; Figure 1b). Furthermore, positive correlations between vaspin and Hs-CRP ($r = 0.343$, $P < 0.001$), fasting serum glucose ($r = 0.158$, $P = 0.002$), fasting insulin ($r = 0.305$, $P < 0.001$), disease duration ($r = 0.340$, $P < 0.001$) and sex ($r = 0.129$, $P = 0.013$) were shown.

Serum vaspin and DR

In the present study, 102 patients (27.4%) experienced DR, and vaspin serum levels in those patients were higher than in those patients without DR (median 2.07 ng/mL, IQR 1.23–2.73 ng/

mL vs median 1.29 ng/mL, IQR 0.90–1.88 ng/mL; $P < 0.001$; Figure 2). A multivariable regression model showed that patients with high levels of vaspin were approximately 1.85-fold (OR for per unit increase 1.85, 95% CI 1.43–2.55; $P < 0.001$) more likely to experience DR after adjustment for sex, BMI, disease duration, intensive glucose treatment, HbA1c, Hs-CRP and HOMA-IR (Table 2).

A receiver operating characteristic model showed that the optimal value of vaspin for diagnosing DR was 2.22 ng/mL (Youden's index), yielding a best value of specificity (49.0%) and sensitivity (84.8%), with the area under the curve of vaspin of 0.69 (95% CI 0.62–0.75, $P < 0.001$; Figure 3).

Serum vaspin and VTDR

Finally, 40 patients (10.8%) experienced VTDR, and vaspin serum levels in those patients were higher than in those patients without VTDR (median 2.67, IQR 2.39–2.86 vs median 1.31, IQR 0.88–1.94 ng/mL; $P < 0.001$; Fig. 4). A multivariable regression model showed that patients with high levels of vaspin were approximately 3.76-fold (OR for per unit increase 3.76, 95% CI 2.05–6.55; $P < 0.001$) more likely to experience VTDR after adjustment for sex, BMI, disease duration, intensive glucose treatment, HbA1c, Hs-CRP and HOMA-IR (Table 2).

Table 1 | Basal characteristic of diabetes patients

Characteristics	All	Vaspin (ng/mL)		P^{\dagger}
		Q1–3 (<2.18)	Q4 (\geq 2.18)	
<i>n</i>	372	280	92	–
Age (years)	53 (44–62)	54 (43–63)	53 (45–59)	0.61
Female	165 (44.4)	110 (39.3)	55 (59.8)	0.001
BMI (kg/m ²)	25.5 (23.2–27.5)	24.9 (22.6–27.0)	26.5 (25.0–28.4)	<0.001
Disease duration	8 (4–11)	7 (3–10)	10 (6–12)	<0.001
Hypertension	151 (40.6)	103 (36.8)	48 (52.2)	0.009
Hyperlipidemia	127 (34.1)	92 (32.9)	35 (38.0)	0.36
Smoking status	85 (22.8)	58 (20.7)	27 (29.3)	0.09
Alcohol intake	68 (18.3)	44 (15.7)	24 (26.1)	0.03
Intensive glucose treatment [‡]	148 (39.8)	120 (42.9)	28 (30.4)	0.03
Use of lipid-lowering medication	87 (23.4)	67 (23.9)	27 (29.3)	0.30
Antihypertensive treatment	135 (36.3)	108 (38.6)	27 (29.3)	0.11
Laboratory testing				
HbA1c (%)	7.4 (6.2–8.5)	6.9 (6.0–8.2)	8.6 (7.4–9.5)	<0.001
Hs-CRP (mg/dL)	0.41 (0.15–0.84)	0.32 (0.14–0.71)	0.75 (0.32–1.00)	<0.001
FSG (mmol/L)	6.12 (5.15–7.01)	5.94 (5.05–6.73)	7.11 (5.15–9.11)	<0.001
Fasting insulin (μ U/mL)	7.12 (5.93–8.94)	6.85 (5.76–8.32)	7.75 (6.53–9.84)	<0.001
HOMA-IR	4.33 (2.46–5.44)	3.90 (2.15–5.14)	5.32 (4.76–5.87)	<0.001
Vaspin (ng/mL)	1.50 (0.94–2.18)	1.14 (0.84–1.64)	2.72 (2.52–2.85)	<0.001
Diagnosis of DR	102 (27.4)	52 (18.6)	50 (54.3)	<0.001
PDR	25 (6.7)	6 (2.1)	19 (20.7)	<0.001
VTDR	40 (10.8)	10 (3.5)	30 (33.3)	<0.001

BMI, body mass index; DR, diabetic retinopathy; FBG, fasting blood glucose; FSG, fasting serum glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity-C-reactive protein; PDR, proliferative diabetic retinopathy; VTDR; vision-threatening diabetic retinopathy. Results are expressed as percentages or as medians (interquartile range). [†] P -values were compared by Mann–Whitney U -test or χ^2 -test as appropriate. [‡]Sulfonylurea or insulin or, if >120% of ideal bodyweight, metformin.

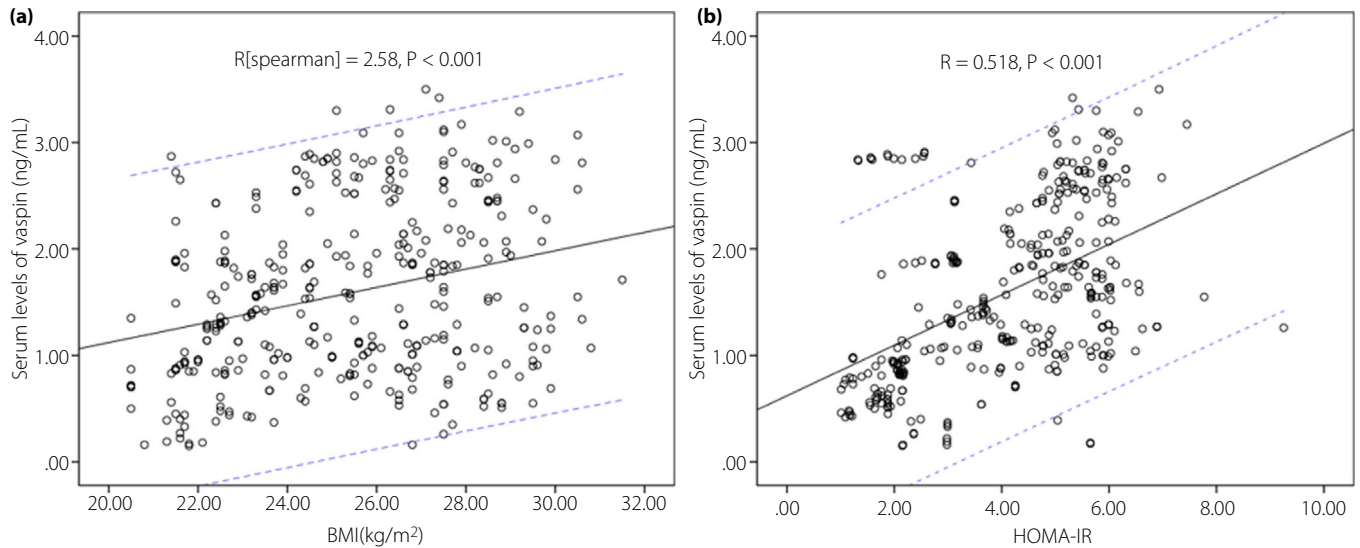


Figure 1 | The correlation between vaspin and other factors. (a) The correlation between vaspin and body mass index (BMI). (b) The correlation between vaspin and homeostasis model assessment of insulin resistance (HOMA-IR). The solid line represents the trend line and the dashed line represents the 95% confidence interval.

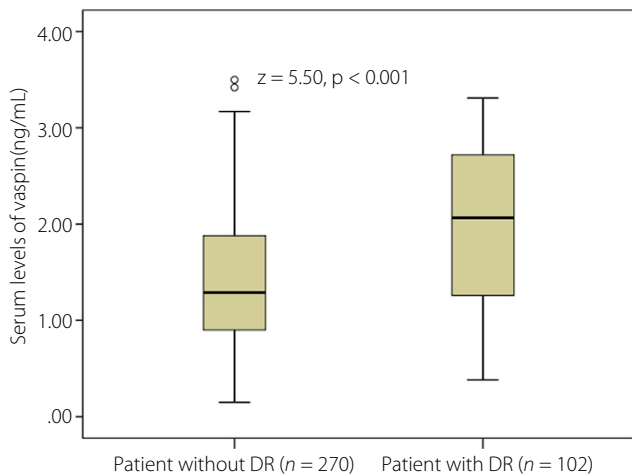


Figure 2 | Box plots of serum levels of vaspin in type 2 diabetes mellitus patients with diabetic retinopathy (DR) and without DR. The Mann-Whitney *U*-test was used. All data are medians and interquartile ranges.

A receiver operating characteristic model showed that the critical value of vaspin for diagnosing VTDR was 2.03ng/mL (Youden’s index), yielding a best value of specificity (85.0%) and sensitivity (77.7%), with the area under the curve of vaspin of 0.87 (95% CI 0.82–0.91, $P < 0.001$; Figure 5).

Subgroup analysis

We carried out analyses separately among men and women. Vaspin levels in women were higher than in men (median 1.60 ng/mL, IQR 0.95–2.53 ng/mL vs median 1.40 ng/mL, IQR

0.91–1.96 ng/mL; $P < 0.001$). Interestingly, the predictive value of vaspin to predict DR was stronger in women than in men (OR 2.01, 95% CI 1.59–2.78 vs OR 1.77, 95% CI 1.40–2.49). Similarly, the predictive value of vaspin to predict VTDR was also stronger in women than in men (OR 3.98, 95% CI 2.21–7.02 vs OR 3.31, 95% CI 1.98–6.03).

DISCUSSION

Adipokines influence vessel wall homeostasis by influencing endothelial cell function and modulating inflammation²⁸. However, the role of vaspin in DR is still unknown. In the present study, we evaluated serum levels of vaspin in Chinese patients with type 2 diabetes mellitus and investigated the role of vaspin in DR. The results showed that: (i) higher vaspin serum levels were associated with an increased risk of DR and VTDR in type 2 diabetes mellitus patients, and the specificity was relatively low to detect DR (OR for per unit increase 1.85, 95% CI 1.43–2.55), but fair specificity/sensitivity to detect VTDR (OR 3.76, 95% CI 2.05–6.55); (ii) the predictive value of vaspin to predict DR/VTDR was stronger in women than in men; and (iii) vaspin levels were positively related to BMI and HOMA-IR. The present study suggested that more frequent retinal examination should be highlighted for type 2 diabetes patients with the highest quartile range of vaspin.

Insulin resistance might influence the correlation between serum vaspin concentration and visceral adipose tissue²⁹. In the present study, vaspin was positively associated with insulin resistance. One study found that serum vaspin concentration was significantly higher in diabetes patients than that in control participants ($P = 0.020$) among women³⁰, and another study showed that vaspin might play an important role in the

Table 2 | Logistic regression model for vaspin and other predictors using diabetic retinopathy and vision-threatening diabetic retinopathy as the dependent variables

	Univariate analysis		Multivariate analysis [†]	
	OR (95% CI)	<i>P</i>	OR (95%CI)	<i>P</i>
DR				
Vaspin (increase per unit)	2.48 (1.82–3.37)	<0.001	1.85 (1.43–2.55)	<0.001
Age (increase per unit)	0.99 (0.73–1.03)	0.38	–	
Sex (female vs male)	3.17 (1.98–5.05)	<0.001	1.85 (1.43–3.02)	0.003
BMI (increase per unit)	1.15 (1.05–1.26)	0.003	1.07 (1.02–1.15)	0.009
Disease duration (increase per unit)	1.08 (1.02–1.13)	0.007	1.05 (0.95–1.21)	0.09
Hypertension (yes vs no)	1.56 (1.02–2.51)	0.075	–	
Hyperlipidemia (yes vs no)	1.22 (0.95–1.98)	0.32	–	
Smoking status (yes vs no)	1.68 (0.98–2.97)	0.58	–	
Alcohol intake (yes vs no)	2.03 (1.32–3.28)	0.13	–	
Intensive glucose treatment (yes vs no) [‡]	0.85 (0.77–0.95)	0.012	0.95 (0.88–1.06)	0.08
HbA1c (increase per unit)	1.48 (1.26–1.74)	0.001	1.32 (1.21–1.55)	0.008
Hs-CRP (increase per unit)	1.67 (1.22–2.15)	0.012	1.43 (1.15–1.94)	0.039
HOMA-IR (increase per unit)	1.14 (1.08–1.19)	<0.001	1.08 (1.02–1.15)	0.002
VTDR				
Vaspin (increase per unit)	7.65 (3.16–11.15)	<0.001	3.76 (2.05–6.55)	<0.001
Age (increase per unit)	0.98 (0.95–1.02)	0.11	–	
Sex (female vs male)	2.55 (2.01–3.16)	0.003	2.03 (1.33–2.93)	0.009
BMI (increase per unit)	1.22 (1.06–1.39)	0.004	1.15 (1.03–1.33)	0.011
Disease duration (increase per unit)	1.09 (1.03–1.18)	0.009	1.04 (1.01–1.14)	0.021
Hypertension (yes vs no)	1.72 (0.89–3.32)	0.11	–	
Hyperlipidemia (yes vs no)	1.05 (0.52–2.08)	0.82	–	
Smoking status (yes vs no)	1.32 (0.63–2.77)	0.43	–	
Alcohol intake (yes vs no)	1.87 (0.88–3.96)	0.10	–	
Intensive glucose treatment (yes vs no) [‡]	0.77 (0.63–0.92)	0.015	0.89 (0.75–1.03)	0.08
HbA1c (increase per unit)	1.60 (1.29–2.00)	<0.001	1.40 (1.14–1.92)	0.003
Hs-CRP (increase per unit)	1.44 (1.20–1.63)	0.013	1.31 (1.09–1.62)	0.04
HOMA-IR (increase per unit)	1.15 (1.09–1.22)	<0.001	1.09 (1.02–1.20)	<0.001

BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; VTDR; vision-threatening diabetic retinopathy. [†]Factors included in the multivariate analysis were confirmed in the univariate analysis [‡]Sulfonylurea or insulin or, if >120% of ideal bodyweight, metformin

pathogenesis of type 2 diabetes mellitus³¹. However, Stepan *et al.*³² did not find different circulating vaspin levels between gestational diabetes patients and control participants. In addition, circulating vaspin was not related to insulin sensitivity^{19,33}. Thus, the association between vaspin, insulin sensitivity and diabetes is more complex, and more work should be carried out to explore it further.

The role of vaspin in vascular health had been proposed. Rashad *et al.*³⁴ showed that among Egyptian type 2 diabetes patients, serum vaspin and vaspin expression levels were significantly higher in the stroke group compared with the non-stroke group, whereas another study³⁵ showed that the arterial ischemic stroke group had significantly lower vaspin levels compared with controls. One study found that serum vaspin levels correlated positively with carotid intima-media thickness (c-IMT) and atherosclerosis in humans³⁶. Hao *et al.*³⁷ suggested that vaspin correlated positively with coronary artery disease in type 2 diabetes mellitus patients. Yang *et al.*³⁸ showed that

serum vaspin levels were higher in type 2 diabetes mellitus patients without macrovascular complications than in type 2 diabetes mellitus patients with macrovascular complications ($P < 0.001$), whereas another study by Gulcelik *et al.*³⁹ also found that type 2 diabetes mellitus patients with macrovascular complications had low vaspin levels. It should be noted that Gulcelik *et al.* only evaluated 37 female type 2 diabetes patients³⁹. A small sample without male patients means the data validity is worth further study. In the present study, the data showed that the serum vaspin level was positively associated with DR and VTDR. Similarly, one study reported that vaspin levels were significantly higher in patients with cardiovascular disease than in patients without cardiovascular disease, and elevated vaspin levels were associated with a 1.7-fold increased risk of cardiovascular disease in type 2 diabetes patients ($P = 0.001$)⁴⁰. However, one study found that low vaspin levels were a risk factor for diabetic nephropathy in type 2 diabetes mellitus patients⁴¹, whereas another study showed that

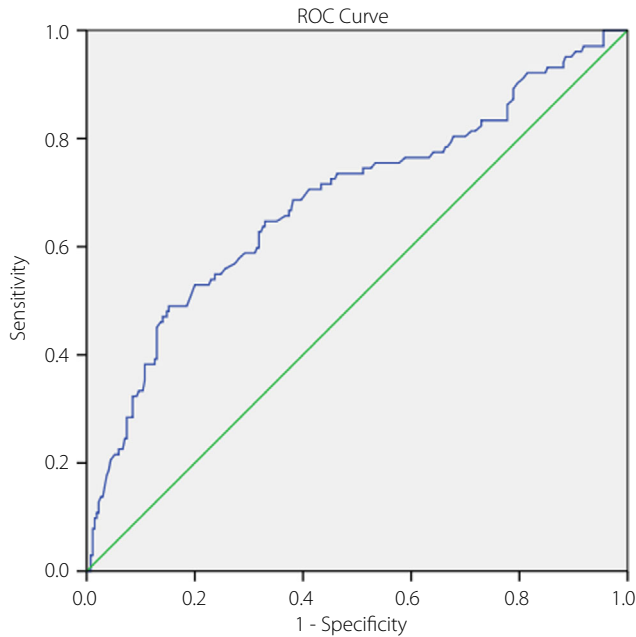


Figure 3 | The receiver operating characteristic (ROC) curve was utilized to assess the accuracy of serum vaspin levels to diagnose diabetic retinopathy.

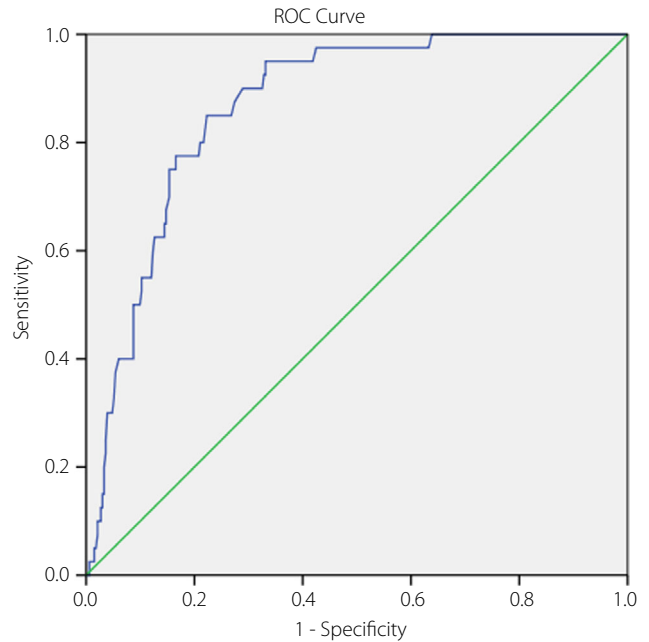


Figure 5 | The receiver operating characteristic (ROC) curve was utilized to assess the accuracy of serum vaspin levels to diagnose vision-threatening diabetic retinopathy.

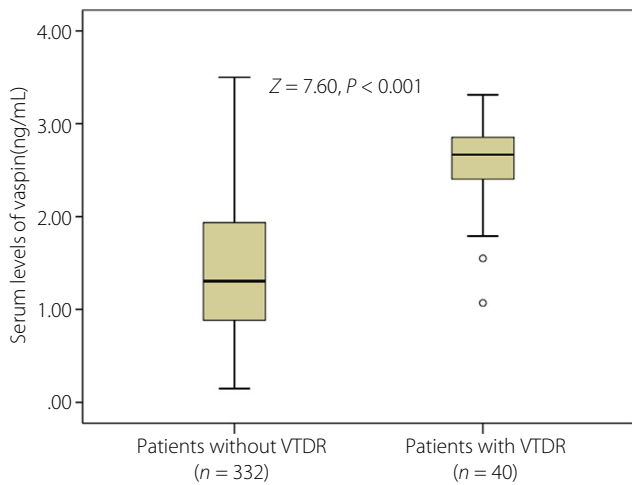


Figure 4 | Box plots of serum levels of vaspin in type 2 diabetes mellitus patients with vision-threatening diabetic retinopathy (VTDR) and without VTDR. Mann–Whitney *U*-test. All data are medians and interquartile ranges.

vaspin levels did not change within the early stages in patients with diabetic nephropathy⁴².

Vaspin serum concentrations were significantly higher in women compared with men¹⁵, which was supported by the present findings and a previous study showing sex differences in serum vaspin levels¹⁹. The sex differences in serum vaspin

levels might be caused by the sex hormone levels in men and women. However, there was no significant difference of serum vaspin levels between men and women in another study³⁰. The effect of sex on vaspin levels requires further exploration. In addition, previous studies showed that treatment with metformin could reduce vaspin serum concentrations^{18,39}. Similarly, the present results showed that low serum levels vaspin were more likely from patients receiving metformin treatment.

Vaspin, a novel cytokine, plays role in endothelial dysfunction and inflammation^{43–44}. Vaspin had been used for drug development for the treatment of obesity-related complications^{45–46}. In fact, endothelial dysfunction^{47–48} and chronic low-grade inflammation^{48–49} are the core elements in the pathophysiology of diabetes and its complications, such as DR. Thus, the role of vaspin in DR might be mediated by vascular endothelial dysfunction and inflammation. We found a positive relationship between vaspin and Hs-CRP. However, we could not test other inflammation biomarkers and endothelial dysfunction status in our participants. The direct influence of vaspin on DR through the endothelial dysfunction and inflammation in type 2 diabetes mellitus patients cannot be confirmed. Future research needs to prove this hypothesis.

Some study limitations could not be ignored. First, the present study was limited by its cross-sectional design. The relationship of causality between vaspin and DR could not be confirmed. Second, estrogen might influence the sex differences in vaspin concentrations¹⁸. However, we did not test the sex hormone levels. Third, the association between vaspin gene

variants (rs2236242) with obesity and type 2 diabetes mellitus has been proposed⁵⁰. However, we did not obtain vaspin gene variants, and the association between vaspin gene variants with vaspin serum levels and DR could not be assessed. Finally, some potential confounding factors, such as dietary intake and outdoor physical activity, might influence vaspin serum levels²⁰. However, that information was not collected in the present study.

In summary, higher vaspin serum levels were associated with an increased risk of DR and VTDR in type 2 diabetes mellitus patients, which showed that vaspin is an important indicator factor for DR, especially for VTDR. Further investigations are warranted to clarify this preliminary result.

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DISCLOSURE

The authors declare no conflict of interest.

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