IJBCS
ISSN: 2147-1428

Original Article

International Journal of Basic and Clinical Studies (IJBCS)
2020; 9(1): 65-76 Gokmen ES. et all.

Vaspin and Visfatin Levels may be a New Diagnostic Tool Regarding Insulin Resistance

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Abstract

Insulin resistance is a well-known pathogenetic mechanism in development of diabetes. In the present study, we examined the relationship between serum vaspin, and visfatin levels and insulin resistance, levels of lipid-related markers, and 25-OH-vitamine D3 in individuals without diabetes who have normal glomerular filtration rate.

A total of 146 patients without diabetes (91 males and 55 females) aged 18-65 years were enrolled in this study. Age, waist circumference, body mass index, and laboratory parameters, including biochemical tests, urine analysis, and levels of insulin, 25-OH-vitamine D3, vaspin, and visfatin were analyzed.

Of the participants, 47.3% (n=69) had insulin resistance (IR), while 23 (15.8%) had impaired fasting glucose (IFG). Serum vaspin (7.6±4.9 vs. 9.9±4.3, p=0.003) and visfatin (59.4±37.7 vs. 77.63±39.3, p=0.005; respectively) levels were significantly lower in patients with IR compared with those without IR. A significant positive correlation was noted between serum vaspin and visfatin levels (r=0.808, p<0.001). The mean serum vaspin and visfatin levels were not significantly different in patients with and without impaired fasting glucose (p>0.05).

Decreased of serum vaspin and visfatin levels may reflect insulin resistance and have a diagnosis value in patients with prediabetes.

Keywords: Overweight, Obesity, Insulin Resistance, Nicotinamide Phosphoribosyl transferase, Impaired Glucose Tolerance

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IJBCS
ISSN: 2147-1428

Original Article

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Introduction

Insulin resistance (IR) is one of the primary pathogenetic mechanisms of diabetes mellitus (DM) and may be seen months, even years before the onset of the disease (1,2). Decreased secretion of insulin from pancreatic β-cells leads to post-receptor modifications in the insulin receptors and results in diminished sensitivity to insulin (3). A growing number of studies have confirmed the predictive role of IR in the imminent development of DM (4,5).

Recent studies have changed the significance of the adipose tissue. While previously adipose tissue defined as a simple lipid storage medium, it is now regarded as an endocrine organ involved in the fat and carbonhydrate metabolism, which secretes adipocytokines (6). Vaspin is an adipocytokine that is emitted from visceral adipose tissue and related to abdominal obesity, IR, and hypertension (7). It affects the white adipose tissue and has been associated with improvements in glucose metabolism and insulin sensitivity (8,9). The overexpression of vaspin is a result of high fat-induced IR (10,11).

On the other hand, visfatin is not only an adipokine produced mainly in visceral adipose tissue, but is also isolated from subcutaneous adipocytes (12). Both the tissue expression and plasma levels of visfatin are strongly related to the degree of obesity (13). Along with its insulin-mimetic and glucose-lowering effect in obese individuals, visfatin can both bind and activate insulin receptors (12).

Further revealing the significance of vaspin and visfatin in the insulin resistance of non-diabetic patients may contribute to the elucidation of the pathological mechanisms and treatment options of this fundamental condition. In the present study, we aimed to evaluate the relationship between serum vaspin and visfatin levels in non-diabetic individuals with IR.

Methods

Study Design

A cross-sectional study was designed. The Ethics Committee of the Bagcilar Education and Research Hospital approved the study (IRB number: 357, Date: 10 February 2015). Written informed consent was obtained from all participants. The study was carried out the Declaration of Helsinki.

Setting

The study was conducted at the internal medicine outpatient clinics of the Bagcilar Education and Research Hospital between April and June 2015. The district where the hospital is settled has a population of around 735.000 people. With a staff of 1600 people and 438-bed capacity, the institution serves daily around 5.000 patients.

Participants

All applicants of the internal medicine outpatient clinics aged between 18 and 65 years were admitted during the study period. Fasting blood sugar levels were measured, and patients with diabetes (fasting blood glucose (FBG) $\geq$ 126 mg/dl or HbA1c $\geq$ 6.5%) were excluded. On the other hand, FBG values of 100-125 mg/dl were categorized as impaired fasting glucose (IFG). Patients with

thyroid disease, malignancies, pregnancy, glomerular filtration rate (GFR) <90 mL/min/1.73 m^2, or use of medications potentially affecting insulin metabolism were also excluded. None of the participants had proteinuria or microalbuminuria. The results of 146 participants were analyzed (Figure 1).

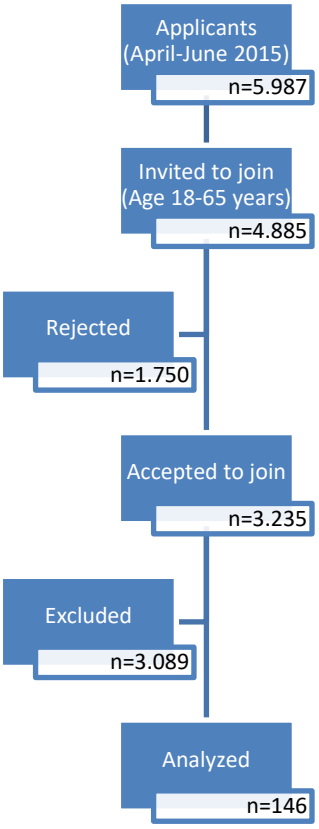

Figure 1: Participant flow diagram

The urine analysis was made via the spectrophotometric method in a Siemens Advia 1800 device. Urine albumin excretion rates exceeding 20 µg/min (30 mg/day), in the absence of uncontrolled hypertension or urinary tract infection was defined as microalbuminuria. Urinary creatinine was analyzed with an Aeroset autoanalyzer (Abbott Laboratories Inc., Abbott Park, IL, USA). GFR was calculated using the formula: eGFR = 175 x (SCr)-1.154 x (age)-0.203 x 0.742 [if female] x 1.212 [if Black]

Variables

The primary study variable was insulin resistance expressed as HOMA-IR ≥ 2.5 based on the formula HOMA-IR = [Fasting plasma insulin (U/ml) x Fasting blood glucose (mg/dl)] / 405.

Demographic data and physical examination findings were recorded. The height and weight of the participants were measured by the one researcher using the same calibrated weighting device (Seca, Germany). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). A BMI of 25–29.9 kg/m^2 and ≥ 30 kg/m^2 were defined as overweight and obese, respectively. Blood pressure was measured from the brachial artery using an aneroid device (Erka, Germany).

Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or use of any antihypertensive agent, were considered to indicate hypertension.

Blood samples were obtained from the antecubital vein after 9 hours of fasting, centrifuged at 3000 rpm, and the serum samples were stored at -80 °C.

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Serum vaspin and visfatin concentrations were analyzed using an enzyme-linked immunosorbent assay (ELISA) by commercially available kits with the antibody-coated sandwich technology. On the other hand, biochemical variables, including serum FBG, uric acid, creatinine, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride were analyzed through the photometric method using a Siemens Advia 1800 device (Siemens Healthcare Diagnostics, Kobe, Japan). Hormone variables, including insulin, were analyzed with a chemiluminescence immunoassay method in a Siemens Advia Centaur device (XE-5000, Sysmex Corp. Kobe, Japan).

Bias

To prevent selection bias, all eligible applicants during the study period were invited to participate in the research. Analysis of the data was done by an independent professional.

Study size

The required sample size was calculated based on a 47% [14] expected prevalence of IR. Given an infinite population, and a margin of error of 9%, a sample sizeof 119 cases is required to estimate insulin resistance in the study population with a confidence interval of 95% [15].

Statistical methods

The data were analyzed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). Descriptive findings were expressed as mean ± standard deviation (SD). The differences between the study groups were analyzed with the Student's t-test or the Mann-Whitney U test, while categorical data werecompared with the Chi-square test. The comparison of numerical variables between multiple independent groups was made with the one-way ANOVA or the Kruskal-Wallis test. The Pearson correlation analysis was used to evaluate the correlation between numerical variables. The specificity, sensitivity, positive predictive value, and negative predictive value of vaspin and visfatin measurements to predict highHOMA-IR was measured with the ROC analysis. A p-value < 0.05 was considered as statistically significant.

Results

Data for 146 patients were analyzed. Of the participants, 91 (62.3%) were males, and 55 (37.7%) were females. The median age was 45 years (min. 18, max. 65). Of the participants, 47.3% (n=69) had IR. Twenty-three (15.8%) had impaired fasting glucose (IFG).

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Males had significantly higher IR values than females, which were overweight and obese individuals compared to normal-weight ones (Table 1).

Table 1: Comparison of sex, BMI, and smoking status between the IR groups

		HOMA-IR category					
		<2.5		2.5 and above			
		n	%	n	%	Chi-square	p
Sex	Male	38	41.8	53	58.2	11.687	**0.001**
	Female	39	70.9	16	29.1		
BMI (kg/m2)	<25	26	83.9	5	16.1	18.107	**<0.001**
	25-30	44	48.4	47	51.6		
	>30	7	29.2	17	70.8		
Smoking	No	49	50.5	48	49.5	0.574	0.448
	Yes	28	57.1	21	42.9		

While the mean triglyceride, insulin, and glucose levels were significantly higher, serum uric acid, vaspin, and visfatin measurements were substantially lower in the high-HOMA-IR group (Table 2).

Table 2: Comparison of the numerical variables between the IR groups

	HOMA-IR category					
	<2.5		2.5 and above			
	Mean	SD	Mean	SD	t	p
TG (mg/dl)	82.82	36.14	141.07	113.13	4.281	**<0.001**
Uric acid (mg/dl)	4.49	1.28	5.65	1.31	5.386	**<0.001**
Vitamin D (ng/ml)	16.45	9.77	14.17	6.42	1.646	0.102
LDL (mg/dl)	119.52	28.37	124.91	32.69	1.067	0.288
Vaspin (ng/ml)	9.98	4.37	7.60	4.92	3.097	**0.003**
Visfatin (ng/ml)	77.63	39.34	59.48	37.70	2.867	**0.005**
Insulin (uU/mL)	7.53	2.09	20.70	15.21	7.521	**<0.001**
Glucose (mg/dl)	89.49	8.13	98.38	9.86	5.958	**<0.001**

The mean serum vaspin and visfatin levels were significantly lower in patients with IFG than without IFG (Table 3).

Table 3: Comparison of vaspin and visfatin levels between different demographic and clinical categories

			Vaspin			Visfatin		
		n	(ng/ml)	Test	p	(ng/ml)	Test	p
	<45	116	9.18±4.69	4.040	0.257ǂ	71.91±40.51	1.141	0.340‡
	45–54	20	7.63±5.05			62.98±30.55		
Age (years)	55–64	10	7.6±5.16			47.98±38.98		
	Male	91	8.69±4.74	0.913	0.361*	66.47±39.17	1.016	0.312†
Sex	Female	55	9.14±4.86			73.32±40.03		
	<25	31	9±4.84	4.841	0.238ǂ	71.32±38.88	0.845	0.924‡
Body Mass Index (BMI)	25–30	91	9.23±4.69			68.77±42.06		
(kg/m^2)	>30	24	7.28±4.89			67.2±30.51		
	<94	11	10.64±3.73	2.157	0.199ǂ	80.64±37.14	1.011	0.415‡
Waist Circumference	94–102	54	8.71±4.9			65.67±42.38		
(Male) (cm)	>102	26	7.81±4.68			62.14±32.48		
	<80	18	7.57±5.25	2.587	0.109ǂ	62.29±38.18	2.055	0.135‡
Waist circumference	80–88	25	10.73±4.02			85.1±41.17		
(Female) (cm)	>88	12	8.19±5.25			65.33±36.5		
	No	122	8.77±4.81	0.802	0.977*	69.1±40.1	0.735	0.971†
Blood pressure (mmHg)	Yes	24	9.32±4.65			68.78±37.13		
	Low	77	9.98±4.37	2.936	**0.003***	77.63±39.34	2.837	**0.005†**
HOMA-IR	High	69	7.6±4.92			59.48±37.7		
Impaired Fasting	Negative	112	9.41±4.57	1.457	0.145*	73.68±39.64	0.567	0.571†
Glucose (IFG) (mg/dl)	Positive	34	7.03±5.06			53.8±35.48		

†Independent samples t-test. ‡One way ANOVA. *Mann-Whitney U test.ǂKruskal Wallis test.

Serum vaspin levels showed significant correlations with FBG and HOMA-IR, while serum visfatin levels correlated significantly with uric acid, insulin, FBG, and HOMA-IR. Additionally, there was a significant positive correlation between vaspin and visfatin (Table 4).

IJBCS
ISSN: 2147-1428

Original Article

Table 4: Correlations of vaspin and visfatin with the measured laboratory variables

		Vaspin	Visfatin
Vaspin	Pearson r		0.808
	p		**<0.001**
TG	Pearson r	-0.053	-0.132
	p	0.527	0.114
Uric acid	Pearson r	-0.142	-0.167
	p	0.087	**0.043**
Vitamin D	Pearson r	0.020	0.076
	p	0.811	0.362
LDL	Pearson r	-0.158	-0.091
	p	0.057	0.274
Insulin	Pearson r	-0.144	-0.188
	p	0.083	**0.023**
FBG	Pearson r	-0.297	-0.292
	p	**<0.001**	**<0.001**
HOMA-IR	Pearson r	-0.171	-0.207
	p	**0.039**	**0.012**

LDL: Low density lipoprotein. FBG: Fasting blood glucose.

The ROC analysis to discriminate HOMA-IR status demonstrated an area under the curve of 0.630 and 0.633 for serum vaspin and visfatin levels, respectively (Figure 2).

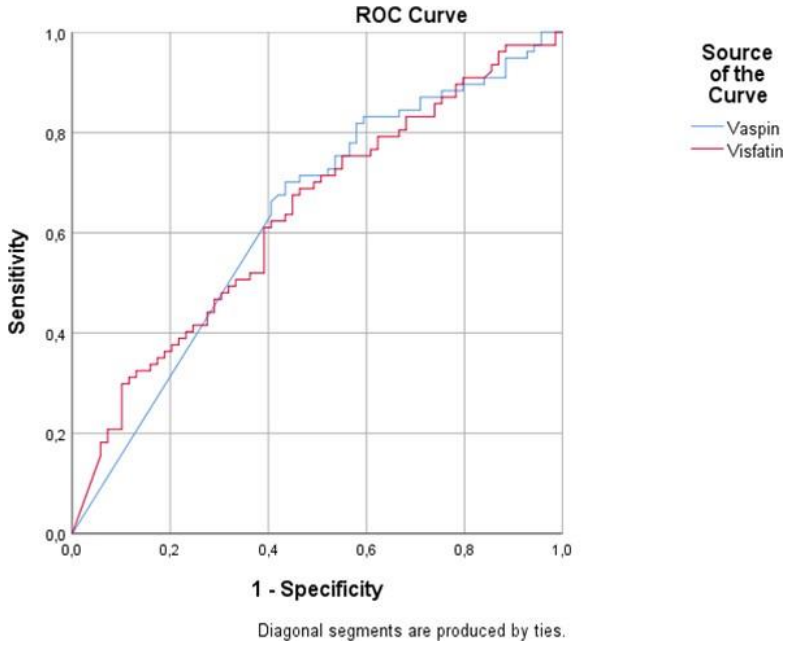

Figure 2: ROC analysis for vaspin and visfatin in predicting HOMA-IR status

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Original Article

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The best cut-off values for serum vaspin and visfatin levels were 9.43 and 69.44, respectively. The sensitivity and specificity values of the given cut-offs were 70.1% vs. 56.5% for vaspin, while 61.0% vs. 60.9% for visfatin.

Discussion

Key results

In the present study, we found serum vaspin and visfatin levels to be lower in non-diabetic patients having IR or IFG. Serum vaspin and visfatin levels were significantly correlated with FBG, HOMA-IR, and each other. Also, a significant negative correlation was determined between visfatin and uric acid, and insulin levels.

Limitations

The present study has some potential limitations. First, the study included relatively young obese and non-obese individuals without diabetes, hyperlipidemia, renal parenchymal, or cardiovascular disorders to eliminate any cumulative effect of these comorbidities on HOMA-IR. Second, the study was conducted in applicants of one hospital, which limits the generalization of the results to other populations. Finally, the single point measurement of variables may decrease the accuracy of the results.

Interpretation

Obesity is a public health burden that has been linked to increased morbidity and mortality, accounting for some 300,000 deaths per year (16). The relationship between obesity and IR has been known for more than a decade (17).

Insulin resistance is not only influenced by the degree of obesity, but also by the distribution of fat tissue. Besides being host to triacylglycerol accumulation, recent studies have found adipose tissue to have other functions, such as the secretion of adipocytokines. Vaspin and visfatin are two recent adipocytokines that have been implicated in the pathogenesis of prediabetes and diabetes mellitus (DM) (18).

In an animal model for obesity and IR, it has been demonstrated that vaspin expression was strongly associated with the degree of obesity and IR in Otsuka Long-Evans Tokushima Fatty (OLTEF) rats (10). Additionally, serum vaspin levels were positively correlated to obesity and high HbA1c levels (19,20). Although vaspin levels are predominantly higher in patients with diabetes and patients with IR, contradictions exist concerning their relationship with BMI in the obese, suggesting that increased serum vaspin levels are a result of IR rather than the high BMI (11). In the present study, serum vaspin levels were related to FBG and HOMA-IR, but not to age, gender, BMI, or waist circumference (WC).

One study is conducted by Saboori et al. indicated there was no significant association between the serum vaspin and visfatin levels. The authors also failed to determine a relationship between these two adipokines and serum concentrations of FBG, total cholesterol, LDL, and triglycerides (20). In contrast, Salama et al. noted a positive correlation between the serum vaspin and visfatin levels, which is similar to our findings (21).

IJBCS
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Original Article

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Visfatin was first introduced in 2005 by Fukuhara et al. as an adipocytokine that is expressed primarily in visceral adipose rather than subcutaneous tissue, which has insulin-mimetic effects resulting from its binding to insulin receptors (22). Additionally, visfatin is significantly correlated with HOMA-IR, but not with BMI (23,24). Other studies have reported an association between HOMA- IR and visfatin after adjusting for BMI and WC (25). Saboori et al. found no significant difference between obese and non-obese women regarding visfatin levels (20). Similarly, in the present study, we found a negative correlation between visfatin with insulin, FBG, and HOMA-IR.

Gulcelik et al. identified an association between visfatin and complications of diabetes, such as hypertension (26). Patients with diabetes and hypertension had significantly higher visfatin levels than normotensive diabetic individuals (26). In contrast, vaspin did not correlate with diastolic or systolic blood pressure in the study by Coban et al. (27). Similarly, we did not find a significant relationship between adipocytokines and blood pressure measurements in our study.

Although a relationship between low glomerular filtration rate (GFR) and high HOMA-IR has been determined in the elderly and diabetic hypertensive patients, there are some exceptions (28-30). Also, in two recent studies conducted in predialysis patients, a positive correlation was identified between serum vaspin, and visfatin levels and HOMA-IR (31,32). Seeger et al. reported an independent association between serum vaspin levels and GFR in chronic hemodialysis patients (33). Additionally, although serum vaspin levels remained within the normal range in the early stages of diabetic nephropathy (DN), they have been seen to logarithmically increase in advanced stages (34). Similarly, serum visfatin levels are significantly higher and positively correlated with HOMA-IR in patients with GFR < 50 ml/min than in healthy controls (35). In contrast to the majority of previous studies, the present study was carried out with subjects having normal GFR. We have found that a negative association between the serum vaspin, and visfatin levels and HOMA-IR, which is probably associated with preserved renal functions.

The significance of this study is that, to the best of our knowledge, it is the first study to examine serum vaspin and visfatin levels in obese or overweight individuals with preserved renal functions. All participants had GFR > 90 ml/min, and none had a urine analysis abnormality, including proteinuria, hematuria, or leukocyturia. Renal function in the obese is more impaired than in the non-obese. Therefore, obese and overweight persons with normal GFR and urine analysis in the study help eliminating any cumulative effects of decreased insulin sensitivity related to nephropathy.

Conclusion

In contrast to the majority of previous studies, we found that a significant negative relationship between HOMA-IR and serum vaspin, and visfatin levels.

That said, the fact that all of the participants in the present study had normal renal function may have had a significant impact on the negative correlation of these biomarkers with HOMA-IR. Further studies involving larger sample sizes will enable us to better understand the relationship between the IR and serum vaspin, and visfatin levels in the patients with overweight or obese nondiabetic.

Conflict of interest

The authors have no conflict of interest in this paper.

Financial disclosure

No financial support was obtained from any individual or company.

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