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RESEARCH ARTICLE

THE RELATIONSHIP BETWEEN SERUM VASPIN LEVELS AND THE PRESENCE OF MACRO VASCULAR COMPLICATIONS; ISCHEMIC HEART DISEASE AND CEREBROVASCULAR STROKE IN TYPE 2 DIABETES MELLITUS CASES

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ABSTRACT

Vaspin had been identified as a novel adipokine with high expression in adipose tissue of obese and type 2 diabetic subjects and with potentially insulin sensitizing properties. **Aim:** To assess the relationship between serum vaspin and the presence of macro vascular complications in type 2 diabetic cases. Our case control study was conducted onsixtytype 2 diabetic patients, twenty with coronary artery disease, twenty with cerebrovascular stroke and twenty diabetics without complications. Twenty healthy subjects were our control group. All participants were subjected to medical history, thorough clinical examination and lab measuring of serum Vaspin, FBG, 2hPG, HbA1c, lipid profile and microalbuminuria and had echocardiography Carotid duplex and CT brain. Serum vaspin was lower in diabetic patients with macro vascular complications than in healthy group and also significantly positively correlated with diabetes duration, lipid profile, indices of hyperglycemia and carotid intimal thickness. Vaspin might play a role in the development of diabetes and its macro vascular complications. So, it may be used in the future in the treatment strategies.

INTRODUCTION

Vaspin (a visceral adipose tissue-derived serine protease inhibitor) is a novel adipocytokine that was specifically expressed in visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats (animal model of obesity and type 2 diabetes) *(*Hida *et al., 2005&*Hida *et al., 2000)*.

In OLETF rats, the mRNA expression of vaspin in VAT increased by the increment of body fat and insulin level. Vaspin was suspected to have an insulin-sensitizing effect, which may act via normalizing the altered expression of genes relevant to insulin resistance in diet-induced obese mice *(*Hida *et al., 2005)*.

Vaspin has been identified as a novel adipokine with high expression in adipose tissue of type 2 diabetic and obese subjects and with potentially insulin sensitizing properties *(*Kempf *et al*., 2010*)*.

Diabetic subjects with good glycemic control have lower vaspin levels than those with poor glycemic control. Also, presence of microvascular complications is associated with low vaspin levels. So, the use of serum vaspin level as a marker, for evaluation of diabetic complications seems appropriate *(*Gulcelik *et al*., 2009*)*.

The present study aimed to assess serum vaspin levels in relation to glycemic status and the presence of macro vascular complications in groups of type 2 diabetic patients.

SUBJECTS AND METHODS

Our case control study was conducted on eighty subjects, sixty with type 2 diabetes mellitus and twenty volunteers as a control group. Patients were recruited in the period from diabetes out-patient clinic in Ain Shams University Hospital. This study was approved by the ethical committee. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol. They were divided into four groups: **Group 1:** Included twenty diabetic patients with ischemic heart disease (IHD) aged 52 ± 7 years and included10 males and 10 females. **Group 2:** Included twenty diabetic patients with cerebrovascular stroke (CVS) aged 53 ± 8 years

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and included 10 males and 10 females. **Group 3:** Included twenty diabetic patients without complications aged 49 ± 6 years and included 10 males and 10 females. **Group 4:** Included twenty normal subjects as a control group aged 48 ± 5 years and included 10 males and 10 females.

All subjects were subjected to full medical history emphasizing on duration of diabetes, medications and complications of diabetes, thorough clinical examination. Patients with type 1 diabetes mellitus, chronic illness like liver cell failure and renal failure were excluded from our study.

Laboratory Measurements

Laboratory tests included fasting plasma glucose (FPG), and 2 hours post - prandial plasma glucose (2hPG), HbA1c, lipid profile, micro-albuminuria by ELISA, serum vaspin level, CBC, ALT, AST, Serum creatinine and BUN. FPG and 2hPG was measured using an automated glucose oxidase method using Behring Diagnostics Reagents (SVR Glucose Test; Behring, La Jolla, CA). HbA1c was measured by Stanbio Procedure No.0350 "Quantitative colorimetric determination of Glycohemoglobin in blood". Serum lipid concentrations were assayed by quantitative enzymatic colorimetric determination for total cholesterol, high-density lipoprotein cholesterol and triglycerides in plasma (Stanbio Cholesterol Liquicolor, Procedure NO. 1010). Serum vaspin level was measured by the commercial kit (WKEA Med Supplies Corp (45011 H Ave, New York, NT 10123, USA). This kit is an in vitro ELIZA assay for the quantitative measurement of human vaspin in serum, plasma, tissue and other biological fluids.

Imaging

Also radiological assessment included echocardiography and Carotid duplex to measure intimal thickness, Computerized Tomography brain (CT brain) for patients with cerebrovascular stroke.

Statistical Analysis

Data analysis was performed using the SPSS program (version 21 2012, IBM Corporation, USA).

Data were expressed as mean ± standard deviation (SD) was used for quantitative data, whereas number and percent (%) were used for qualitative data. Independent-samples t test was used when comparing between two groups. One-way analysis of variance (ANOVA) was used when comparing between more than two groups. Post-hoc test (Tukey's) was used to detect the least significant difference (LSD) among the studied groups. Pearson's correlation coefficient (r) test was used for correlating data. Mann- Whitney U test was used to compare quantitative variables, in non-parametric data. Probability (p-value) less than 0.05 was considered significant and less than 0.01 was considered as highly significant.

RESULTS

This study was conducted on 80 subjects, 40 (50%) were males and 40 (50%) were females. They were age (p= 0.066) and sex matched ($\mathbf{X^2}$ = 0.000, p =1.00).

There was high statistical significant difference between all studied groups as regard FPG, 2hPP, HbA1c, microalbuminuria, and serum total cholesterol ($p < 0.01$). Serum vaspin levels were statistically significantly difference between all studied groups (P= 0.005). Our results showed an insignificant difference in serum vaspin level between diabetic patients with IHD or CVS (P>0.05), yet the mean of vaspin in IHD and CVS was lower than in healthy group, Data are summarized in table 1&2.

In our study, the serum vaspin level was found to be significantly positively correlated with diabetes duration where the mean diabetes duration of the subjects involved in this study was less than 10 years (P<0.01). Our results showed that there was no difference in serum vaspin level between both sexes, and also showed that there is a positive correlation between age and vaspin concentration (P<0.01).

Serum vaspin level was found to be significantly positive correlated with FBS, 2hPP & HbA1c in all studied groups (P<0.01). In addition, we recorded positive correlation between serum vaspin level & serum cholesterol, TG, LDL & HDL in all studied groups (P<0.01).

Table 1 Comparison between the different studied groups using ANOVA

	Group 1 (n=20)	**Group 2** (n=20)	**Group 3** (n=20)	**Group 4** (n=20)	**F**	**P**
Age (Years)	51.700±6.650	53.250±7.907	49.100±6.206	48.200±5.337	2.492	0.066
FBG (mg/dl)	257.000 ± 81.061	236.950 ± 69.242	119.900 ± 6.512	89.800± 11.386	48.199	<0.001**
2h PG (mg/dl)	299.550±88.626	248.750±72.731	154.100±11.083	109.250±11.238	44.987	<0.001**
HbA1c (%)	11.255±1.235	10.230±1.349	7.065±0.387	5.345±0.586	156.928	<0.001**
microalbuminuria (mg/ml)	42.250±14.194	40.350±13.496	20.900±4.254	15.950±5.615	33.075	<0.001**
T.Chol. (mg/dl)	285.150±40.067	327.900±46.089	281.850±35.769	203.650±13.476	41.298	<0.001**
TGs (mg/dl)	192.450±119.155	205.100±124.060	160.600±67.931	99.650±20.254	5.123	0.003*
HDL (mg/dl)	36.300±11.239	39.500±12.207	34.800±10.783	41.350±7.680	1.574	0.203
LDL (mg/dl)	169.800±38.960	166.950±41.214	158.650±39.149	132.300±13.526	4.734	0.004*
Vaspin (ng/ dl)	39.250±4.363	39.700±6.799	45.100±4.340	41.850±6.368	4.575	0.005*
RT IC intimal thickness (mm)	1.206±0.686	1.484±0.666	0.628±0.108	0.495±0.120	18.759	<0.001**
Percent stenosis of RT IC duplex (%)	52.600±12.102	64.650±11.940	0.000±0.000	0.000±0.000	323.808	<0.001**
LT IC intimal thickness (mm)	1.890±2.690	1.485±0.649	0.628±0.108	0.495±0.120	4.714	0.005*
Percent stenosis of LT IC duplex (%)	53.800±14.688	64.500±10.797	0.000±0.000	0.000±0.000	285.339	<0.001**

*; statistically significant, **; high statistical significant

The intimal medial internal carotid thickness & percent of stenosis on the Rt side was found to be significantly higher in diabetic cases with IHD compared to diabetic patients without complications or healthy control subjects (P<0.01). However, this difference did not reach a statistical significance on the left internal carotid artery (P>0.05), but the percent of internal carotid stenosis on either sides was significantly higher in diabetic cases with IHD compared to diabetic cases without complications & healthy control subjects. Also, there was high significant correlation between serum vaspin &Rt intimal medial internal carotid thickness & percent of stenosis on both Rt and Lt sides (P<0.01) but there was no significant correlation between serum vaspin & the left internal carotid artery in diabetic patients with IHD (P>0.05).

In the present work, Rt intimal medial thickness of internal carotid artery and percent stenosis were found to be significantly higher in diabetic cases with CVS compared to either diabetic cases without complications or healthy control group (P<0.001), table 1.However, this difference did not reach a statistical significance on the left internal carotid artery as regard intimal thickness of internal carotid artery alone, but the percent of internal carotid stenosis on either sides was significantly higher in diabetic cases with CVS compared to diabetic cases with IHD. Also, there was a high significant positive correlation between serum vaspin and intimal medial thickness of internal carotid artery on both right and left sides and also in percent of stenosis on both right and left sides in diabetic patients with CVS compared to either diabetic cases without complications or healthy control group (P<0.001), table 2.

Table 2 Correlation between vaspin and all studied parameters in different groups using Spearman's rank correlation coefficient (r):

	Vaspin							
	Group I 39.250±4.363		**Group II** 39.700±6.799		**Group III** 45.100±4.340		**Group IV** 41.850±6.368	
	r	P-value	r	P-value	r	P-value	r	P-value
Age (years)	0.913	0.000	0.897	0.000	0.922	0.000	0.940	0.000
Duration (years)	0.875	0.000	0.792	0.000	0.864	0.000		
FBS (mg/dl)	0.904	0.000	0.869	0.000	0.988	0.000	0.968	0.000
2h PG (mg/dl)	0.914	0.000	0.869	0.000	0.986	0.000	0.974	0.000
HbA1c%	0.921	0.000	0.902	0.000	0.936	0.000	0.909	0.000
microalbuminuria (mg/ml)	0.687	0.001	0.812	0.000	0.912	0.000	0.819	0.000
T.Chol. (mg/dl)	0.924	0.000	0.902	0.000	0.925	0.000	0.921	0.000
TGs (mg/dl)	0.670	0.001	0.711	0.000	0.823	0.000	0.897	0.000
HDL (mg/dl)	0.864	0.000	0.830	0.000	0.849	0.000	0.882	0.000
LDL (mg/dl)	0.883	0.000	0.853	0.000	0.874	0.000	0.907	0.000
RT IC intimal thickness (mm)	0.696	0.001	0.729	0.000	0.901	0.000	0.879	0.000
Percent stenosis of RT IC duplex (%)	0.896	0.000	0.898	0.000	--------	--------	--------	--------
LT IC intimal thickness (mm)	0.575	0.008	0.739	0.000	0.901	0.000	0.879	0.000
Percent stenosis of LT IC duplex (%)	0.876	0.000	0.908	0.000	--------	--------	--------	--------

Furthermore, our study reported a significant positive correlation between the serum vaspin level and Rt internal carotid intimal thickness and both Rt and Lt sides percent of internal carotid stenosis in patients with T2DM (P<0.01).

DISCUSSION

According to our study, vaspin level was significantly higher in diabetic patients without complications compared to diabetic patients with IHD and C.V.S, insignificant difference in serum vaspin was found between diabetic patients with IHD and CVS, yet the mean level of vaspin in IHD and CVS was lower than healthy group.These findings goes with that stated with *Kadoglou et al., 2011and Li et al., 2012*. They showed that vaspin levels are lower in coronary artery disease and cerebral stroke than in healthy subjects *(Kadoglou et al., 2011 & Li et al., 2012)*.

Regarding sex, our results found a non significant difference in serum vaspin level between both sexes. However, other studies found that females had significantly higher vaspin levels compared to males *(*Seeger *et al*., 2008*)*. Moreover, Females with normal glucose tolerance have vaspin levels up to 2.5 times higher than men *(*Youn *et al., 2008)*,but these sex differences were abrogated in Type 2 diabetic patients *(Hanaa et al., 2013)*.

Vaspin level was found to be significantly positively correlated with diabetes duration where the mean diabetes duration of the subjects involved in this study wasless than 10 years, and this concordant with *Hanaa et al., 2013*, who showed that the serum vaspin level in diabetic patients with duration <10 years was significantly positive correlatedwith diabetes duration. On the other hand, *El-Mesallamy et al., 2011*, found that the serum vaspin level decreased with Diabetes duration.

Our results showed a significant positive correlation between age and vaspin concentration. These results are in agreement with *Youn et al., 2008*, who reported that age is a predictor affecting vaspin concentration. But this was contrary to what was reported by *Nehal et al., 2014***,** who found that there is no statistical significant difference in terms of age and gender as regard serum vaspin level.

In the current study serum vaspin level was found to be significantly positively correlated with FBS, 2hPG& HbA1c in all studied groups, These results are in agreement with ***El-****Mesallamy et al., 2011 and Hanaa et al., 2013*, who found that serum vaspin levels were significantly correlated with glycemic indices such as FBG, HbA1c%.Also,*Ye et al.*, *2009*found that serumvaspin was positively associated with FPG, PP2h and HbA1c%.This goes with many other studies *(Gulcelik et al., 2009, Kukla et al., 2010 &Lee et al., 2010)*.On the other hand *Fatema et al., 2015* found that serum vaspin levels of newly diagnosed type 2 diabetes subjects without

microvascularcomplication are significantly reduced, and negatively associated with serum glucose.

In addition, our study recorded a highly significant positive correlation between serum vaspin level & serum cholesterol, TG, LDL & HDL in all studied groups, these results are in agreement with *Seeger et al., 2008*, who found an association between circulating vaspin levels and total cholesterol. However, ourresultswere in contrast to the results reported by *Handisurya et al., 2010*, who found no significant correlation between parameters of lipid metabolism with serum vaspin concentrations.

Regarding intimal medial thickness of internal carotid artery and percent of stenosis, there was a high significant positive correlation between serum vaspin and right intimal medial internal carotid thickness and percent of stenosis on both right and left sides ,these results are supported by what was reported by *(Karbek et al., 2014)*,who found that serum vaspin levels had a statistically significant association with Carotid Artery Intima-Media Thickness (CIMT) and cardiovascular risk factors and was significantly associated with coronary atherosclerosis (r=0. 365, P<0.001). Also, Carotid atherosclerosis was identified as a risk factor for CHD in the Cardiovascular Health Study *(*O'Leary *et al*., 1999*)*.Contrary to our results, *Aust et al., 2009 and Nehal et al., 2014* could not find any relation between serum vaspin levels and internal carotid artery stenosis.

There was a high significant positive correlation between serum vaspin and intimal medial thickness of internal carotid arteryon both right and left sidesand in percent of stenosis on both right and left sides in diabetic patients with CVS compared to either diabetic cases without complications or healthy control group.

A limited number of studies investigating the relation between cerebrovascular diseases and vaspin *(Cura et al., 2014)*. The relation between vaspin level and internal carotid stenos is was evaluated by *Cura et al., 2014*, who observed that when stenosis ratio increase, vaspin levels decrease gradually. Also, in a study by *Aust et al., 2009*, no relation was found between internal carotid artery stenos is and serum vaspin concentration; however, it was shown that low concentration of serum vaspin was correlated with recent ischemic events in the patients with internal carotid artery stenosis.

CONCLUSION

Despite, serum vaspin level is low in diabetic cases complicated with macrovascular complications (IHD&CVS), its level shows significant positive correlation with percent of carotid artery stenosis and intimal medial thickness. So, it may play a role in development of diabetic macrovascular complications. Serum vaspin level tends to have a positive correlation with duration of DM during the first ten years. Further studies on larger numbers of subjects with diabetic complications are needed.

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