Serum vaspin: as a predictor of ischemic heart disease in Egyptian hemodialysis patients

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Received 2 August 2017 Accepted 9 September 2017

The Egyptian Journal of Internal Medicine 2018, 30:18–22

Background

Vaspin is a compensatory adipokine with anti-inflammatory properties that can improve insulin sensitivity and plays a cardioprotective role.

Aim

The aim of this study was to evaluate the level of vaspin in patients with end-stage renal disease on hemodialysis (HD) and to determine whether it has any relation to the presence of ischemic heart disease (IHD) in these patients.

Patients and methods

The study was carried out on 45 HD patients who were divided into 15 patients with risk factors of developing IHD (group I) and 30 patients (group II) proved to have IHD by echocardiography and ECG compared with 20 healthy individuals (group III).

Results

We found that the mean±SD of serum vaspin was significantly lower in HD patients with IHD (0.57 ± 0.27) ng/ml compared with the control group (0.74 ± 0.20) ng/ml and there was a negative correlation between serum vaspin and serum creatinine in group I and group II. Also, an receiver operating characteristics study for patients with IHD (group II) yielded a vaspin cut-off value of 0.410 ng/ml with a sensitivity of 40%, a specificity of 100%, a positive predictive value of 100%, and an negative predictive value of 53%, whereas the cut-off value for serum vaspin was 0.485 ng/ml in patients at risk of developing IHD, with a sensitivity of 100%, a specificity of 85%, a positive predictive value of 83%, and an negative predictive value of 100%. **Conclusion**

Lower vaspin level is associated independently with IHD in HD patients and can be used as a predictor of IHD in patients with end-stage renal disease.

Keywords:

hemodialysis, ischemic heart disease, serum vaspin level

Egypt J Intern Med 30:18–22 © 2018 The Egyptian Journal of Internal Medicine 1110-7782

Introduction

The most common cause of death in end-stage renal disease (ESRD) patients is cardiovascular disease, accounting for 45-50% of causes of death in these patients. The mortality because of cardiovascular disease is considerably higher than that in the general population. Eighty percent of patients on maintenance hemodialysis (HD) develop cardiovascular complications [1]. Vaspin, a novel adipocytokine, was first identified in obese Otsuka Long-Evans Tokushima Fatty rats, an animal model of abdominal obesity and type 2 diabetes mellitus. Vaspin is also expressed in the skin, hypothalamus, pancreatic islets, and stomach [2]. Invitro studies have shown that vaspin exerts antiinflammatory and antiapoptotic effects. It has been found that vaspin may inhibit the proliferation, chemokines, and reactive oxygen species production of vascular smooth cells [3]. It could prevent free fatty acidinduced endothelial apoptosis; therefore, its lower levels may play an important role in the development of atherosclerosis [4]. Vaspin plays essential roles in the

development of coronary artery disease (CAD) and may serve as a biomarker for CAD.

Evaluation of vaspin levels in ESRD patients is very limited. Assessment of vaspin levels in Egyptian patients on regular HD has not been performed previously. Therefore, this study was carried out to evaluate the serum vaspin levels in Egyptian patients with ESRD treated by regular HD and its relation to the development of ischemic heart disease (IHD) and the risk of developing IHD.

Patients and methods

Patients

This case-control study was carried out in Al-Zahra University Hospital and Aswan University Hospital

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from March 2016 to October 2016, including 45 Egyptian patients on regular HD, and 20 apparently healthy control individuals without any history of IHD, renal impairment, diabetes or hypertension, and dyslipidemia (group III). Those with acute myocardial infarction, systemic infection, acute heart failure, and malignant tumor were excluded from the study. Patients included in this study were on HD for a duration between 1 and 26 years, three times per week, for 4–5 h per session using polysulfone membranes with a bicarbonatebuffered dialysate. HD patients were subdivided into 15 patients who were at risk of developing IHD (known as uncontrolled hypertension, uncontrolled diabetes, smokers, dyslipidemic, or a family history of IHD), but with normal ejection fraction, without left ventricular hypertrophy, segmental wall motion abnormalities, diastolic, or systolic dysfunction by echocardiography or ECG (group I), and 30 patients with IHD, confirmed by ECG and echocardiography (group II). Informed consent was obtained from all participants included in the study.

Methods

Five milliliter of venous blood samples were collected from each participant in the study and was left to clot; then, the serum was separated by centrifugation at 3000g for 10 min and the separated serum was stored at -20°C for determination of urea, creatinine, calcium, phosphorous, intact parathormone hormone, and vaspin. The determination of urea, creatinine, calcium, and phosphorous was carried out on a Dimension RxL Max analyzer (Siemens Healthcare GmbH, Erlangen, Germany) using colorimetric techniques. The determination of serum intact parathormone hormone was performed using an Immulite 2000 analyzer by a solid-phase two-site chemiluminescent enzyme-labeled immunometric assay (Siemens AG, Erlangen, Germany) [5]. The determination of serum vaspin was carried out using the sandwich enzyme immunoassay kit supplied by Adipogen Inc. (Songdo Techno Park, Incheon, Korea) [6].

A full assessment of history and clinical examination were performed, and BMI was calculated as body weight (kg) divided by body height squared (m²). Ecchocardiography and ECG were performed for all participants.

Results

The etiology of ESRD of both patient groups is listed in Table 1; hypertension and diabetes mellitus were the most prevalent causes.

There was no significant difference between group I, group II, and group III in age, sex, and BMI (Table 2).

Laboratory data of all patients and controls are listed in Table 3. Vaspin levels showed a significant decrease in group II compared with the control group (P=0.03).

There was a significant decrease in vaspin in group I compared with the control group (P=0.028) and there was also a decrease in vaspin levels in group II compared with those of group I (P=0.980), but this was not significant.

Comparing male and female patients in group I in terms of vaspin levels, there was a nonsignificant decrease in the mean \pm SD of vaspin (0.62 \pm 0.10) ng/ml in women compared with men of the same group (0.74 \pm 0.14) ng/ml (*P*=0.087). However, in group II, men showed a nonsignificant decrease in the mean \pm SD of vaspin (0.54 \pm 0.18) ng/ml compared with that of women of the same group (0.61 \pm 0.37) ng/ml (*P*=0.530).

There was a significant negative correlation between serum vaspin and serum creatinine in both group I and

Table	1 Perce	ntage of t	the etiol	ogy of e	end-stage	renal	disease
in the	studied	groups					

Original kidney disease	Group I (15) [n (%)]	Group II (30) [n (%)]
Hypertension	8 (53.3)	12 (40)
Diabetes mellitus	2 (13.4)	15 (50)
Glomerulonephritis	0 (0)	1 (3.3)
Chronic interstitial nephritis	4 (26.7)	3 (10)
Polycystic kidney disease	0 (0)	1 (3.3)
Systemic lupus	1 (6.7)	0 (0)
Amyloidosis	1 (6.7)	0 (0)
Unknown	0 (0)	6 (20)

Table 2	Demographic	data of the	e patients a	and control	groups	included in	the study
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	Group I (N=15)	Group II (N=30)	Group 3 (N=20)	P value
Age (mean±SD) (years)	52.53±13.76	53.40±12.49	46.85±9.06	0.15
Sex [n (%)]				
Female	5 (33.3)	13 (43.33)	9 (45)	0.75
Male	10 (66.7)	17 (56.66)	11 (55)	
Disease duration (mean±SD) (years)	7.33±6.31	6.57±4.67	-	0.64
BMI (mean±SD) (kg/m ²)	25.25±5.05	24.86±3.63	25.85±2.11	0.64

Parameters	Group I (mean±SD)	Group II (mean±SD)	Control group (mean±SD)	P value
Creatinine (mg/dl)	8.87±3.00 ^a	8.63±2.28 ^a	0.98±0.29	0.001
Urea (mg/dl)	137.73±28.00 ^a	119.30±33.08 ^a	28.92±3.3	0.001
Calcium (mg/dl)	8.73±0.95	8.61±0.88	8.98±7.90	0.315
Phosphorus (mg/dl)	4.88±1.90 ^a	4.61±1.26 ^a	3.68±5.7	0.014
iPTH (pg/ml)	589.98±484.80 ^a	470.05±470.26 ^a	41.60±5.11	0.0001
Triglycerides (mg/dl)	145.87±83.29	178.97±70.28 ^a	109.05±11.88	0.001
Cholesterol (mg/dl)	155.47±67.43	165.37±38.79	109.95±11.91	0.001
HDL (mg/dl)	32.47±5.05 ^{a,b}	27.80±4.96 ^a	44.35±3.90	0.0001
Vaspin (ng/ml)	0.69±0.13	0.57±0.27 ^a	0.74±0.20	0.034

Table 3 Laboratory data among the studied groups

HDL, high-density lipoprotein; iPTH, intact parathormone hormone. ^aVersus control. ^bVersus group II.

group II (r=-0.641, P=0.01), (r=-0.421, P=0.020) (Tables 4 and 5).

A receiver operating characteristics (ROC) study was carried out to determine the best cut-off value of vaspinbetween all patients and the control group; it was found that the cut-off value of vaspin was 0.445 ng/ml with asensitivity of 27%, a specificity of 95% (Fig. 1). However, ROC study of patients with IHD (group II) showed a vaspin cut-off value of 0.410 ng/ml with a sensitivity of 40%, a specificity of 100% (Fig. 2). In contrast, ROC study in group I showed a vaspin cut-off value of 0.485 ng/ml with a sensitivity of 100%, a specificity of 85%.

At a cut-off value of vaspin of 0.445 ng/ml, the sensitivity to detect the disease was 27%, specificity was 95%, PPV was 92%, and NPV was 37%.

At a cut-off value of vaspin of 0.410 ng/ml, the sensitivity to detect the disease was 40%, specificity was 100%, PPV was 100%, and NPV was 53% (Fig. 3).

At a cut-off value of vaspin of 0.485 ng/ml, the sensitivity to detect the disease was 100%, specificity was 85%, PPV was 83%, and NPV was 100%.

Discussion

Vaspin is one of the most recently discovered adipokines; it exerts insulin-sensitizing effects. It plays an important role in the occurrence and development of the metabolic syndrome [7]. Vaspin can inhibit the progression of atherosclerotic plaques in $apoE^{-/-}$ mice. The potential underlying mechanism is partly associated with the inhibition of endoplasmic reticulum stress-induced macrophage apoptosis. These findings confirmed that vaspin may play a beneficial role in ameliorating the progression of atherosclerosis, and provide novel insights into the protective function of

Table 4 Correlation between serum vaspin and other parameters in group I

Parameters	Vaspin r value	P value
Age	0.073	0.795
Disease duration	0.218	0.435
Creatinine	-0.641*	0.01*
Urea	-0.262	0.346
BMI	0.02	0.945
Calcium	-0.259	0.351
Phosphorus	-0.314	0.255
iPTH	0.227	0.416
Cholesterol	-0.144	0.609
Triglycerides	-0.072	0.799
HDL	0.219	0.434

HDL, high-density lipoprotein; iPTH, intact parathormone hormone. $^{\ast}P<0.05.$

Table 5 Correlation between serum vaspin and other parameters in group II

Parameters	Vaspin r value	P value
Age	-0.304	0.102
Disease duration	-0.159	0.401
Creatinine	-0.421*	0.020*
Urea	0.256	0.172
BMI	-0.094	0.62
Calcium	-0.238	0.204
Phosphorus	0.267	0.154
iPTH	0.113	0.553
Cholesterol	-0.115	0.544
Triglycerides	-0.15	0.428
HDL	0.117	0.537

HDL, high-density lipoprotein; iPTH, intact parathormone hormone. $^{\ast}P < 0.05.$

vaspin in atherosclerosis, thus suggesting that vaspin may be potentially useful for preventing vascular as well as metabolic diseases [8].

Some studies have shown that low serum vaspin is associated with CAD and unstable angina pectoris [9] as well as ischemic events in patients with carotid stenosis and coronary artery stenosis [10]. Moreover, some results have shown that low serum vaspin correlates with the severity of CAD, suggesting that vaspin may serve as a biomarker of CAD [11]. Figure 1



Diagonal segments are produced by ties.

Figure 2



Diagonal segments are produced by ties.

In the present study, we found that serum vaspin level was significantly lower in patients with ESRD on regular HD compared with the control group; this finding is in agreement with a study carried out by Inoue *et al.* [6] on Japanese patients on regular HD and the authors attributed the lower level of vaspin in their patients to extra renal elimination of vaspin from the circulation,





Receiver operating characteristic: Sensitivity and specificity of vaspin among Group I patients.

including the function of clearance receptors on the cell surface of various cells and tissues. However, and in contrast to ours and the Japanese results, Seeger *et al.* [12] did not find differences in the mean serum vaspin level between ESRD HD patients and controls. Also, in a study carried out by Yan *et al.* [13] on patients with renal impairment not on HD, they suggested that the serum vaspin levels showed no significant differences between patients with renal impairment and patients without renal impairment, and they attributed these findings to the fact that many factors might affect the serum levels of vaspin concentration.

We found that patients with IHD had the lowest vaspin levels than patients who were only at risk of developing IHD when they were compared with the control group. Kobat *et al.* [14] reported lower serum vaspin levels in patients with CAD compared with controls, and these findings are in agreement with our results. Moreover, they concluded that vaspin might be used as a predictor of CAD.

Su *et al.* [15] reported that vaspin was an independent predictor of major adverse cardiac events in a cohort of 186 patients with or without CAD. They also concluded that patients with higher levels of serum vaspin had a reduced risk for future cardiovascular events and improved left ventricular systolic function, suggesting an important cardioprotective role of vaspin.

The current study showed that serum vaspin is correlated negatively with serum creatinine in patients in both group I and group II, and this is in agreement with Inoue *et al.* [6], who reported that serum vaspin levels were correlated negatively with

Receiver operating characteristic: Sensitivity and specificity of vaspin among all patients.

Receiver operating characteristic: Sensitivity and specificity of vaspin among Group II patients.

serum creatinine levels and were significantly reduced in the Japanese chronic HD patients.

Controversies still remain on the relationship between BMI and serum vaspin. Although in the present study we did not observe any relationship between BMI and serum vaspin in the groups studied, perhaps because none of our patients were morbidly obese, Tasnim et al. [16], in contrast to our results, found a negative association between serum vaspin, BMI, and waist-hip ratio and they postulated that low vaspin levels are implicated in the development of insulin resistance and obesity leading to diabetes. Auguet et al. [17], in agreement with our results, did not observe any relationship between serum vaspin and BMI in morbidly obese women. They reported that this lack of relationship between vaspin and BMI might be attributable to racial and sex differences or some other unexplored mechanism that differentially modulates the obesity-adipokine correlation in morbidly obese women.

Receiver operating characteristics study in our patients at risk of developing IHD showed that the vaspin cut-off value was 0.485 with a sensitivity of 100%, a specificity of 85%, a PPV of 83%, and an NPV of 100%, whereas an ROC study for patients with IHD at a vaspin cut-off value of 0.410 had a sensitivity of 40%, a specificity of 100%, a PPV of 100%, and an NPV of 53%.

Su *et al.* [15] found a vaspin cut-off value for their patients at a lower level of 0.283 ng/ml compared with that in our patients, 0.410 ng/ml, which may be attributed to genetic and racial factors or may be because of the association of renal failure in our patients. There were some limitations in our study. First, the sample size was small in this study. Thus, our findings need to be confirmed in more studies with large sample sizes. Second, some medications were used by a few patients that may have influenced serum vaspin, such as statins, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker; thus, further studies are needed.

Conclusion

Serum vaspin is significantly reduced in Egyptian patients with ESRD known to have IHD and are at risk of developing IHD, compared with normal control participants, and there is a significant negative correlation between serum vaspin levels and serum creatinine levels among patients with ESRD. Also, vaspin may play an important role in the prediction of cardiovascular events in patients with ESRD. Increasing serum vaspin in patients at risk of developing IHD may play a role in the prevention of progression of the disease. Further studies on large numbers of patients are needed to confirm our results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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