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VAP-1 in peritoneally dialyzed patients*

VAP-1 a hiperglikemia u chorych dializowanych otrzewnowo

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Summary

VAP-1 (vascular adhesion protein-1) possesses semicarbazide-sensitive amine oxidase (SSAO) activity. It has also been found that serum VAP-1 was elevated in acute and chronic hyperglycemia and in patients with diabetes as well as in chronic kidney disease. Renalase, with possible monoamine oxidase activity, which breaks down catecholamines such as SSAO, is expressed in the endothelium as well as in the kidney. The aim of the study was to assess serum VAP-1 levels in peritoneally dialyzed (PD) patients and factors explaining its variability. This pilot study was performed on 25 peritoneally dialyzed patients, including 4 patients with type 2 diabetes. We found that the mean VAP-1 was significantly higher in chronic ambulatory peritoneal dialysis (CAPD) patients when compared to the control group ($p<0.05$). Dopamine was significantly lower in PD patients when compared to the healthy volunteers ($p<0.05$), whereas noradrenaline was significantly higher in PD patients relative to the healthy volunteers ($p<0.01$). There was a significant difference in the VAP-1 concentration in the group with and without residual renal function ($p<0.05$) as well as between 10 patients with hyperglycemia when compared to patients with normoglycemia ($p<0.05$). There was no effect of gender on the serum VAP-1 levels. In PD patients VAP-1 correlated with systolic blood pressure ($r=-0.4$, $p<005$), residual renal function ($r=-0.62$, $p<0.05$), and glucose ($=0.54$, $p<0.05$).
We concluded that VAP-1, elevated in patients on PD, was predominantly dependent on residual kidney function and glucose level, factors both linked to endothelial damage and cardiovascular complications.

Keywords: **VAP-1 • hyperglycemia • peritoneal dialysis**

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Introduction

Serum semicarbazide-sensitive amine oxidase (SSAO) activity has been shown to be increased in subjects with both types of diabetes [1,13], which could be one of the mechanisms leading to diabetic complications. SSAO is a monoamine oxidase which catalyzes an oxidative deamination reaction to produce aldehyde, hydrogen peroxide, and ammonia [18], known to take part in the development of diabetic complications [2]. Hydrogen peroxide is a source of oxidative stress and can contribute to the development of atherosclerotic lesions. Along with aldehyde and glucose, hydrogen peroxide can modify various proteins to generate advanced glycated end-products (AGEs), another important factor in the development of atherosclerosis [11]. Therefore, as an adhesion molecule and an enzyme, SSAO/VAP-1 can participate in the development of atherosclerosis. VAP-1 (vascular adhesion protein-1) possesses SSAO activity [13]. It has also been shown that serum VAP-1 was elevated in acute and chronic hyperglycemia and in patients with diabetes [8] as well as in chronic kidney disease [9]. On the other hand, endothelial VAP-1 can act as an adhesion molecule [12] and is involved in leukocyte rolling, adhesion, and transmigration, which are central steps during leukocyte extravasation to sites of inflammation, such as atherosclerotic lesions [11]. It was reported that mice overexpressing VAP-1 in the endothelium had increased concentrations of serum AGEs, enhanced leukocyte binding, upregulation of hepatic redox-sensitive proteins, and accelerated atherosclerosis [15].

On the other hand, renalase, with possible monoamine oxidase activity, which breaks down catecholamines like

Table 1. Clinical and biochemical characteristics of the studied populations

	Healthy volunteers	PD
Age (years)	51 (43.5-56.0)	58.5 (44-69)
Dialysis vintage (months)	NA	35.16 (9-64)
Hemoglobin (g/dL)	13.9 (13.1-14.7)	11.15 (10.5-11.5)***
Leukocyte count (x10^3/μL)	5.27 (4.72-5.98)	6.68 (5.79- 8.29)*
Platelet count (x10^6/μL)	224 (180-255)	220 (157- 253)
Residual renal function (mL)	NA	770.4 (90-1000)
Systolic blood pressure (mm Hg)	125 (113-132)	140 (122-162)*
Diastolic blood pressure (mm Hg)	70 (65-79)	89.5 (78-100)**
Cholesterol (mg/dL)	NA	189 (156-205)
LDL (mg/dL)	NA	118 (88-130)
Triglycerides (mg/dL)	NA	140 (92-165)
BMI (kg/m^2)	25.0 (23.2-26.9)	30.07 (24.25-31.15)*
ACE inhibitors (%)	NA	68
ARB (%)	NA	12
Beta-blockers (%)	NA	88
Calcium channel blockers (%)	NA	76
Diuretics (%)	NA	56
Dopamine (pg/mL)	143.23; 13.55-213.08	47.88 (35.97-64.21)*
Noradrenaline (pg/mL)	0.37 (0.28-0.56)	1.02 (0.65-1.59)
Renalase (μg/mL) ***	3.54 (3.07-4.07)	18.53 (16.16-23.33)
VAP-1 (ng/mL)	138.26 (124.71-203.24)	240.68 (211.24-320)*

Data given are median and interquartile range
*p<0.05, **p<0.01, ***p<0.001

SSAO, is also expressed in the endothelium as well as in the kidney [10]. Taking all these data into consideration and the fact that patients on PD are exposed to the glucose load in the dialysate fluid, the aim of the study was to assess serum VAP-1 levels in PD patients and factors explaining its variability.

Patients and Methods

This pilot study was performed on 25 peritoneally dialyzed patients, including 4 patients with type 2 diabetes. The mean duration of PD was 35 months (median 17, interquartile range 9-64 months). The causes of renal failure among PD patients included chronic glomerulonephritis (n=14), diabetic nephropathy (n=2), hypertensive nephropathy (n=1), autosomal dominant polycystic kidney disease (ADPKD) (n=5), others or unknown (n=3). Hypertension was diagnosed in 24 patients, coronary artery disease in 16, while 7 patients had a history of stroke. Hypotensive drugs used in this population were as follows: ACE inhibitors in 17, AT2 receptors antagonists in 3, beta-blockers in 22, alpha-blockers in 5, diuretics (furosemide) in 14 and calcium channel blockers in 19 patients. Two patients were given 5 drugs, 10 were administered 4 drugs, 7 were given 3 drugs, 5 were given 2 drugs. Statins were given to 12 patients. All patients were informed about the aim of the study and gave their informed consent. The study was approved by the Medical University Ethic Committee. Kt/v and PET (peritoneum equilibration test) were assessed according to standard methods. The presence of residual renal function was based on the 24-hour urine collection. All hypotensive drugs and other medications were collected from the individual prescription charts. The blood for the estimation of the serum VAP-1 levels and catecholamines was taken once during a routine ambulatory visit in the morning (when also BP and weight were assessed) after overnight fasting. Hyperglycemia was defined as fasting glucose over 110 mg/dL. VAP-1 was assessed using kits from BioVendor, Modrice, Czech Republic. Catecholamines were assessed by ELISA from Labor Diagnostica Nord GmbH & Co. KG, Germany. Age- and sex-matched healthy volunteers (n = 20) were included in the study to obtain normal ranges for VAP-1 and catecholamines. The data given were analyzed using Statistica 10.0. computer software (Tulsa, OK, USA). The examination of the distribution normality of variables was done using Shapiro-Wilk W test and Mann-Whitney U test for comparison of the two groups. Measurements are expressed as medians and interquartile ranges. Spearman correlations were evaluated as appropriate with $P<0.05$ considered statistically significant.

Results

VAP-1 and renalase were significantly higher in PD patients when compared to the control (Table 1). Dopamine was significantly lower in PD patients when compared to the healthy volunteers, whereas noradrenaline was significantly higher in PD patients relative to the healthy volunteers. The mean Kt/v rate in PD patients was 1.87±0.54. There were 5 anuric patients.

There was a significant difference in the VAP-1 concentration in the group with and without residual renal function (Fig. 1) as well as between 10 patients with hyperglycemia when compared to patients with normal serum glucose (Fig. 2). There was no effect of gender on the serum VAP-1 levels (325.76±185.87 ng/mL in males and 241.16±79.50 ng/mL in females). In PD patients VAP-1 correlated with systolic blood pressure (r=-0.40, p<0.05), residual renal function (r=-0.62, p<0.05), and glucose (=0.54, p<0.05).

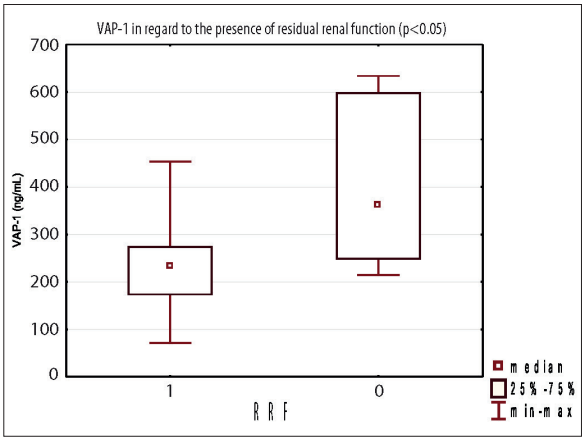

Fig. 1. VAP-1 in regard to the presence of residual renal function

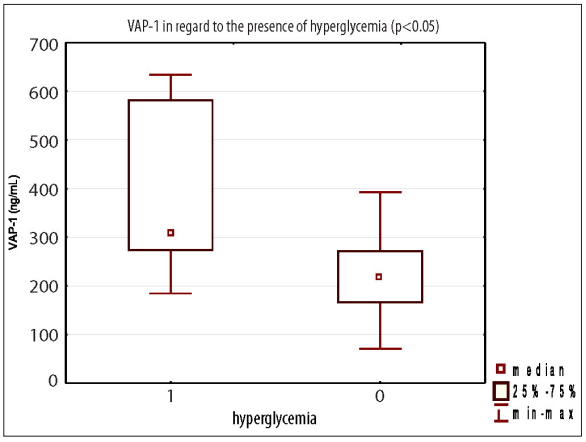

Fig. 2. VAP-1 in regard to hyperglycemia

Discussion

We reported for the first time VAP-1 levels in PD patients. In addition, in our pilot study we found that PD patients with hyperglycemia had higher VAP-1 levels than patients with normal serum glucose. In the previous study VAP-1 was related positively to the urinary albumin-to-creatinine ratio and negatively to the estimated glomerular filtration rate (eGFR) [9]. Moreover, patients with CKD stage 2 and stage 3 had significantly higher levels of serum VAP-1 than those without CKD. However, serum VAP-1 levels were not significantly different between stage 2 and stage 3 CKD. In addition, a high serum VAP-1 level was associated with the presence of CKD (OR 1.63 for 1 SD increase of VAP-1, p= 0.018). The authors did not study patients with CKD

stages 1, 4 and 5, so we could not compare our data in our PD population. In our study VAP-1 in PD was higher than that observed in their study. In addition, our control group had much higher eGFR than reported by Lin et al. [9] (102.5; 88.90-106.11 vs 69.1; 64.9–73.9). In their study in stage 2 and 3 CKD fasting glucose levels and 2 h postprandial glucose were significantly higher than in the control group. The clinical problem is to assess real fasting glucose level in PD population, since all the time the peritoneal cavity is filled with glucose (with the exception of rare cases when icodextrin is used, but this compound may also affect glucose measurement). We assessed serum glucose after an overnight fast, when patients appeared in the morning for the routine check-up visit. In our study VAP-1 was significantly higher in anuric patients, confirming the important role of residual renal function [10] and volume status [16] in PD patients with endothelial dysfunction [3]. All except 1 patient had hypertension in our PD population. Both systolic and diastolic blood pressure levels were significantly higher in the PD population relative to healthy volunteers, similarly to the study of Lin et al. [9]. The role of SSAO/VAP-1 in the pathogenesis of CKD is not well established. In an animal model (KKAy diabetic mice fed with high cholesterol diet) blocking SSAO activity by MDL-72974A and aminoguanidine could reduce albuminuria, proteinuria and the number of atherosclerotic lesions [17]. It has been thus suggested that serum VAP-1 levels or SSAO activity may be involved in the pathologic processes in the kidney. Li et al. [6] also showed for the first time that serum VAP-1 could independently predict 10-year all-cause mortality and cardiovascular mortality in subjects with type 2 diabetes. They also observed that the change in serum VAP-1 after glucose load correlated with systemic oxidative stress, AGEs, and carotid intima-medial thickness, indexes for atherosclerosis [7]. In this study VAP-1 did not differ between patients with and without coronary artery disease, but the sample size was relatively small. Selby and McIntyre [14] suggested that peritoneal dialysis is not associated with stunned myocardium, so it might be less cardiodepressive than hemodialysis and offer more hemodynamic stability. In our previous study, we found that VAP-1 was significantly higher in hemodialysis patients when compared to the healthy volunteers and related to the ejection fraction [5]. We also found that VAP-1 was significantly higher in diabetic and hypertensive patients when compared to their non-diabetic and normotensive counterparts [5]. VAP-1 was predominantly dependent on blood pressure and diabetes, factors associated with endothelial damage and cardiovascular complications. In a recent study we found that VAP-1 was elevated in kidney transplant recipients, and was predominantly dependent on endothelial damage and kidney function [4]. When we divided kidney allograft recipients according to CKD stages and compared patients with eGFR over 60 ml/min/1.73m^2 relative to eGFR below 60 ml/min/1.73m^2, we found that VAP-1 was significantly higher in subjects with at least stage 3 CKD. In addition, diabetic kidney allograft recipients had higher serum VAP-1 than non-diabetics. In this study in the PD population since there were only 4 diabetic patients we looked at the level of fasting glycemia and found that hyperglycemia was associated with higher VAP-1 levels.

Our study has several limitations due to its cross-sectional design, which makes it difficult to determine the causality between serum VAP-1 and diabetes. The small sample size and the ethnically homogeneous Caucasian PD population may be both limitations and an advantage of this study. The majority of studies in renal replacement therapy are designed for hemodialysis patients, and sometimes it is difficult to extrapolate the data into PD modality. Future prospective follow-up studies with a different population could be of value to establish the role of VAP-1 in the mechanism of diabetic and cardiovascular complications in kidney disease. In conclusion, VAP-1, elevated in patients on PD, was predominantly dependent on residual kidney function and hyperglycemia, factors linked to both endothelial damage and cardiovascular complications.

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The authors have no potential conflicts of interest to declare.