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Visfatin and apelin, new adipocytokines, and their relation to endothelial function in patients with chronic renal failure

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ABSTRACT

Purpose: Visfatin and apelin are novel adipocytokines that have recently generated much interest. The aim of the study was to assess visfatin and apelin in correlation with markers of endothelial cell injury and inflammation in 22 patients with chronic kidney disease-CKD and 22 age- and sex-matched healthy volunteers.

Methods: We assessed visfatin, apelin, markers of coagulation: TAT (thrombin-antithrombin complexes), prothrombin fragments 1+2; fibrinolysis: tPA (tissue plasminogen activator), PAI-1 (plasminogen activator inhibitor), PAP (plasmin-antiplasmin complexes); endothelial function/injury: vWF (von Willebrand factor), thrombomodulin, ICAM (intracellular adhesion molecule), VCAM (vascular cell adhesion molecule), CD146, CD40L, CD44, E-selectin, inflammation: hsCRP.

Results: Triglycerides, hsCRP, creatinine, vWF, prothrombin fragments 1+2, TAT, thrombomodulin, ICAM, VCAM, CD146, CD44, CD40L, PAI-1, PAP, visfatin and E-selectin were elevated in chronic kidney disease patients when compared with the control group. Visfatin correlated significantly in patients with chronic kidney disease, in univariate analysis, with CD40L ($r=-0.27$, $p<0.05$), apelin ($r=0.27$, $p<0.05$), ICAM ($r=0.26$, $p<0.05$), VCAM ($r=0.31$, $p<0.05$) and tended to correlate with CD146 ($r=0.21$, $p=0.10$). Apelin correlated significantly with E-selectin ($r=0.31$, $p<0.05$) and VCAM ($r=0.31$, $p<0.05$). In the healthy volunteers visfatin correlated significantly with ICAM ($r=-0.37$, $p<0.05$) and serum creatinine (0.38, $p<0.05$).

Conclusions: Elevated visfatin in CKD patients may be due to renal failure and/or inflammation. Adipocytokines related to adhesion molecules might support the importance of inflammation/endothelial cell injury in the pathogenesis of atherosclerosis and its consequences in CKD.

Key words: chronic kidney disease, adipocytokines, endothelium, inflammation, adhesion molecules

INTRODUCTION

The lifespan of patients with chronic kidney disease is markedly reduced due to premature cardiovascular death in more than 50% of this population [1]. Traditional risk factors cannot explain the high prevalence and incidence of cardiovascular disease in patients with chronic kidney disease. Therefore non-traditional factors are taken into account, such as oxidative stress, endothelial dysfunction or insulin resistance. Adipose tissue is now known to be a hormonally active organ that releases a large number of bioactive proteins regulating not only body weight and energy homeostasis, but also insulin resistance, blood lipids, endothelial health, coagulation, fibrinolysis and inflammation [2]. The pluripotent role of fat cells is still not completely understood. Fat tissue secretes a number of adipocytokines, including leptin, adiponectin, resistin, vaspin, visfatin, as well as proinflammatory cytokines such as tumor necrosis factor α and interleukin-6 [2]. However, it appears likely that reduced glomerular filtration rate can contribute to the accumulation of adipocytokines. This could explain the marked dysmetabolism in chronic kidney disease. In our previous studies we have evaluated possible relations between adipocytokines and markers of endothelial dysfunction in patients on renal replacement therapy [3-6] and conservative treatment [6]. Visfatin, also known as pre-B-cell colony-enhancing factor 1 or nicotinamide phosphoribosyltransferase (Nampt), is a ubiquitous adipokine first described by Fukuhara et al. [7] in 2005. Recently, Yilmaz et al. [8] have reported that

adiponectin and visfatin are associated with flow-mediated dilatation, a surrogate marker of endothelial dysfunction, in patients with chronic kidney disease. In our previous study, adiponectin was found to be positively related to CD146, novel adhesion molecule, in patients with chronic kidney disease [6] and hemodialyzed patients [5]. Apelin is a newly discovered adipocytokine, produced by white adipose tissue [9] and expressed in kidney, heart and endothelium [10]. Endothelial cell damage or injury is invariably associated with such clinical conditions as thrombosis, hypertension, renal failure and atherosclerosis. Taking all the data into consideration, and the fact that visfatin and apelin are considered to be novel modulators for endothelial adhesion molecules, the aim of the study was to assess visfatin and apelin in correlation with markers of endothelial cell injury and inflammation in patients with chronic renal failure on conservative treatment.

MATERIALS AND METHODS

The study was performed on 22 patients with chronic renal failure on conservative treatment (age range 26–67 years, 10 males). Inclusion criteria were: a stable clinical state, no thrombosis or inflammation (C-reactive protein within normal range), absence of cardiovascular complications (including uncontrolled hypertension), no diabetes, no oral contraception in women of child-bearing age, stable and no more than twice normal GOT and GPT activities. None of the patients investigated had received blood transfusions for at least 1.5 months and no drugs known to affect hemostasis were administered for at least 2 weeks prior the study. All the subjects were biopsied and histopathological diagnosis was established as follows: IgA nephropathy in 7 cases, membrano-proliferative glomerulonephritis in 4 cases, membranous nephropathy in 4 cases, focal segmental glomerulosclerosis in 4 cases, submicroscopic glomerulonephritis in 1 case. Biopsy was not diagnostic in 2 cases. During the study none of the patients received prednisone, anticoagulants or cytotoxic drugs. None of the patients at the time of study received antidyslipidemic medication, hormone replacement therapy or anticoagulant medication. We followed the exclusion criteria of Yilmaz et al [8] and excluded patients with diabetes, statins, ACEi/ARB.

All the patients were informed about the aim of the study and gave their consent. Blood was taken in the morning between 8.00 and 9.00 am. to avoid circadian variations and anticoagulated with 3.8% sodium citrate (volume corrected for hematocrit). The control group consisted of 22 age- and sex-matched healthy volunteers (age range 2–-64 years). Venous blood samples were collected into 3.8% sodium citrate in a ratio of 9:1 by volume. Platelet rich plasma (PRP) was obtained by centrifugation at 180 g for 20 min at room temperature. The blood was centrifuged further at 1900 g for 15 min at room temperature to yield platelet poor plasma (PPP). Samples were aliquoted and stored at -40°C before assay. We evaluated thrombin activity (thrombin-antithrombin complexes- TAT, Enzygnost TAT micro, Dade Behring, Germany, prothrombin fragments 1+2, Enzygnost F1+2 micro, Dade Behring, Germany),thrombomodulin(TM,IMUBINDThrombomodulin ELISA Kit, American Diagnostica Inc., USA) a marker of endothelial cell injury, and the degree of plasmin generation (plasmin-antiplasmin complexes PAP, Enzygnost PAP micro, Dade Behring, Germany) using commercially available kits. Markers of endothelial cell injury- von Willebrand factor and adhesion molecules: P and E-selectins, ICAM and VCAM were studied using commercially available kits from American Diagnostica, USA, R&D Systems and Quantikine, UK, respectively. Soluble CD40L, CD44 was studied using a commercially available kit from Bender, MedSystem, Austria. CD146 was assayed using commercially available kits from Biocytex, Marseille, France. Tissue plasminogen activator and its inhibitor-PAI were assayed using kits from Bioopol, Umea, Sweden. Serum apelin and visfatin were assayed using commercially available radioimmunoassays (Human Apelin RIA kit, Human Visfatin RIA kit, respectively, Linco Research, St. Charles, MO, USA). Hemoglobin, leukocyte count, creatinine, total protein, cholesterol, triglycerides and albumin concentration were measured by standard laboratory methods.

The data obtained were analyzed using the Statistica 6.0 PL computer software. Normality of variable distribution was tested using the Shapiro-Wilk W-test. Where possible, data were logarithmically transformed to achieve normal distribution (F1+2, thrombomodulin, age, P-selectin, sCD 40L, creatinine). Normally distributed measurements are reported as mean ± SD; non-normally distributed data are expressed as a median and minimal-maximal value. The Mann-Whitney rank sum U test or Student's t-test were used in statistical analysis to compare differences between groups with $P<0.05$ considered statistically significant, when appropriate. Pearson or Spearman coefficients were employed as appropriate.

RESULTS

All the biochemical and clinical data are presented in *Tab. 1*. Some hemostatic parameters and adipocytokines levels are given in *Tab. 2*. Triglycerides, hsCRP, creatinine, vWF, prothrombin fragments 1+2, TAT, thrombomodulin, ICAM, VCAM, CD146, CD44, CD40L, PAI-1, PAP, visfatin and E-selectin were elevated in chronic kidney disease patients when compared with the control group. Hemoglobin, albumin and total protein were significantly lower in chronic kidney disease patients relative to the control group.

Visfatin correlated significantly in patients with chronic kidney disease, in univariate analysis, with CD40L ($r=-0.27$, $p<0.05$), apelin ($r=0.27$, $p<0.05$), ICAM ($r=0.26$, $p<0.05$), VCAM ($r=0.31$, $p<0.05$) and tended to correlate with CD146 ($r=0.21$, $p=0.10$). Apelin correlated significantly with

Table 1. **Comparison of some biochemical parameters in patients with chronic kidney disease and the control group.**

	Healthy volunteers	CKD
age (years)	49.3±12.6	48.7 ±13.8
BMI (kg/m^2)	24.6±3.6	24.8±4.1
hemoglobin (g/dL)	14.7±0. 6	12.1±1.4***
leukocyte count (x 10^3/L)	5.7±1.9	6.2±2.5
creatinine (mg/dL)	0.88±0.13	2.89±1.65***
total cholesterol (mg/dL)	187±39	183±49
triglycerides (mg/dL)	104±36	140±58**
albumin (g/dL)	4.62±0.41	3.90±0.42*
total protein (g/dL)	7.15±0.59	6.6±0.71**

*p<0.05, **p<0.01, ***p<0.001 vs control group

E-selectin (r=0.31, p<0.05) and VCAM (r=0.31, p<0.05). In the healthy volunteers visfatin correlated significantly with ICAM (r=-0.37, p<0.05), serum creatinine (0.38, p<0.05).

DISCUSSION

Chronic renal failure has been associated with impaired immunity and subclinical inflammation involving cytokines derived from adipose tissue – adipocytokines. Deteriorating renal function may increase overall inflammatory responses because of the decreased renal clearance of factors that are directly or indirectly involved in inflammation. As an example, the serum half-lives of pro-inflammatory cytokines, tumor necrosis factor alpha and interleukin-1, are greater in animals without than with renal function [11,12]. In humans, declining renal function may also affect the levels of additional inflammatory molecules, as serum C-reactive protein (CRP), interleukin-6 and hyaluronan levels are inversely correlated with creatinine clearance [13,14]. In the present study we investigated possible correlations between visfatin, apelin and markers of endothelial damage/inflammation in patients with chronic kidney disease. In our study we excluded diabetic patients to avoid potential bias, because in previously published papers an elevated visfatin level was found in patients with type 2 diabetes mellitus [15,16]. Boucher et al. [10] identified apelin as a novel adipocyte endocrine secretion and focused on its potential link with obesity-associated variations of insulin sensitivity status. In our previous study, we found that apelin might be involved in the pathophysiology of cardiovascular disease in chronic renal failure [17]. In this study we found that apelin correlated with E-selectin and VCAM, adhesion molecules expressed on the endothelium. E-selectin is a cell surface glycoprotein that mediates the adhesion of leucocytes to vessels endothelium, an important early step in the atherosclerotic process. E-selectin has only been described on endothelial cells and may therefore represent a circulating surrogate for measurement of endothelial cell activation or damage [18]. Chronic renal disease is a highly atherogenic

Table 2. **Some inflammatory, hemostatic and endothelial cell injury markers in patients with chronic kidney disease and the healthy volunteers.**

	Healthy volunteers	CKD
Visfatin (ng/mL)	30.43±12.90	47.76±9.67**
Apelin (pg/mL)	48.98±21.81	54.58±20.82
CD44 (ng/mL)	514±129	879±145***
CD40L (ng/mL)	0.40±0.09	1.06±0.73*
CD146 (ng/mL)	319.8±101.1	379.9±140.7*
P-selectin (ng/mL)	56.89±32,87	78.03±56.71
E-selectin (ng/mL)	51.43±17.54	68.26±27.42*
hsCRP (mg/L)	0.98±0.16	4.73±2.98**
ICAM (ng/ml)	97.2±47.6	181.7±141.0**
VCAM (ng/mL)	470.3±200.2	1138.9±688.6***
thrombomodulin (ng/ml)	2.87±1.48	7.65±3.76***
vWF (%)	93.87±18.92	128.63±16.89***
tPA (ng/ml)	11.5±6.6	7.52±3.16
PAI concentration (ng/ml)	7.18±3.09	14.4±6.19*
F 1+2 (nM/l)	1.40 ±0.34	2.34±1.67***
TAT (mg/l)	1.14 ±0.26	6.86±5.92***
PAP (mg/l)	252 ±84	692 ±231***

Data given are means ± SD, * p<0.05, ** p<0.01, *** p<0.001 vs control

disease and state of subclinical systemic inflammation. It was found that altered E-selectin shedding may play a role in arterial damage and implicates this adhesion molecule in atherosclerotic complications in a high-risk condition like chronic renal failure [19]. In a recently published study, it was reported that apelin and its cognate G protein-coupled receptor APJ was widely represented in the heart and vasculature, and was emerging as an important regulator of cardiovascular homeostasis [20]. Moreover, the apelin-APJ pathway is thought to provide a mechanism for systemic endothelial monitoring of tissue perfusion and adaptive regulation of cardiovascular function [21]. To date, there are no data on possible relations between apelin and consequences of endothelial dysfunction, such as atherosclerosis. In our study apelin was not related to any parameters in the healthy volunteers. We may speculate that apelin might be involved in the possible interactions between endothelium and atherosclerosis in chronic renal failure patients; however further studies are needed to prove or disprove this hypothesis.

In our present study we found that the newly discovered adipokine, visfatin, was related to CD40L, apelin, ICAM, VCAM and tended to correlate with CD146. Vascular endothelial cells express CD40, and ligation of CD40 on endothelial cells is known to upregulate expression of the inflammatory adhesion molecules: E-selectin, VCAM-1 and ICAM-1 [22]. Slupsky et al. [23] demonstrated that ligation of CD40 on endothelial cells initiated a procoagulant phenotype which included upregulation of tissue factor and down-regulation of thrombomodulin. In our study we could observe

significantly elevated CD40L levels in CKD together with other adhesion molecules. Moreover, local ligation of CD40 on endothelial cells in the presence of increased tissue factor concentration might play a role in the thrombotic complications in CKD patients.

Visfatin, secreted by activated lymphocytes, monocytes, neutrophils, stimulates the expression of IL-6 and IL-8 in amniotic cells [24]. In CD14(+) monocytes, visfatin induces the production of IL-1beta, TNF-alpha, and especially IL-6 [25]. In the healthy volunteers we observed a positive correlation between visfatin and IL-6. Similar correlations were reported by Oki et al. [26] in Japanese Americans. They concluded that circulating visfatin might reflect inflammation status. In contrast to the study of Axelsson et al. [27] we did not observe correlations between visfatin and hsCRP or IL-6 in CKD patients. However, in their study correlations were found in the 189 patients with chronic kidney disease (CKD), comprising 149 patients with CKD stage 5 (hemodialyzed patients). In univariate analysis, visfatin level correlated with levels of GFR (rho = -0.22; P = 0.001), interleukin 6 (IL-6; rho = 0.17; P = 0.01), high-sensitivity C-reactive protein (rho = 0.14; rho < 0.05), and soluble vascular cell adhesion molecule 1 (sVCAM-1; rho = 0.39; P < 0.0001), but not total or truncal fat mass, insulin resistance, or hemoglobin A(1c) level. We confirmed a correlation between visfatin and VCAM. They reported that visfatin was associated independently with level of sVCAM-1, a marker of endothelial damage [27]. The observation of correlations only in the CKD patients may be due to the fact that a dysfunctional adipose tissue signaling-reflected by elevated visfatin may directly affect the vascular endothelium, causing its dysfunction independently of inflammation or insulin resistance, conditions commonly found in CKD [28].

The advantage of our study is the simultaneous measurement of two adipocytokines in relation to endothelial cell injury markers in the CKD patients. On the other hand, a number of limitations in this study should be mentioned. First, we exclude diabetic patients. However, in the study of Axelsson et al. [27] there were no significant differences between patients with and without diabetes, whereas in the study of Yilmaz et al. [29] (part of the former group) visfatin levels were all significantly higher in diabetics (85 incident patients with type 2 diabetes and diabetic kidney disease) than in control subjects. Second, this study is a single-centre study. Third, we could not control for a number of medications affecting vascular status, including NSAID.

CONCLUSIONS

Elevated visfatin in CKD patients may be due to renal failure and/or inflammation. Adipocytokines related to adhesion molecules might support the importance of inflammation/endothelial cell injury in the pathogenesis of atherosclerosis and its consequences in CKD.

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