RELATIONSHIP BETWEEN VISFATIN LEVELS AND ATHEROSCLEROSIS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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INTRODUCTION

Cardiovascular disease is one of the most important reasons of mortality and morbidity in patents with CKD (1). Atherosclerosis are common in patients with CKD because of endothelial dysfunction, inflammation, oxidative stress, insulin resistance etc (2,3). Adipose tissue is defined as having complex functions for body. Pro-inflammatory cytokines like visfatin, leptin, adiponectin, resistin are increased in such situations as uremic catabolic processes, systemic inflammation etc (4-6). Recent studies show that there is strong relationship between adipose tissue and endothelial dysfunction (7,8). Visfatin is among pre-B cell colony-enhancing factors. It is produced by adipose tissue, skeletal muscle, liver, bone, lymphocyte and mesangial cell (9-12). In CKD patients, increases in severity of inflammation and visfatin accumulation occur by decrease in glomerular filtration rate (GFR) (13-16). In the present study, we aim to test the hypothesis that increase in level of visfatin is associated with endothelial dysfunction and accelerated atherosclerosis in CKD patients.

SUBJECTS AND METHODS

Patients

Fifty patients with CKD from nephrology clinic in Uludag University (22 females, 28 males) and thirty one healthy volunteers (18 females, 13 males); totally eighty one subjects were recruited. All patients were diagnosed as having stage 4 or 5 CKD as defined by National Kidney Foundation K/DQOI Guidelines 2013. All of them were over 18 year old. GFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula [GFR = 186 × Pcr (Plasma creatinine)-1.154 × age-0.203 × 1.212 (if black) × 0.742 (if female)] (17). Patients with congestive heart failure, valvular heart disease, hypertension, arrhythmia, smokers, infection, and patients taking angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins or nonsteroidal anti-inflammatory drugs were excluded. In addition, patients with a prior diagnosis of diabetes, current use of oral antidiabetic medication or insulin, or with a fasting glucose level greater than 126 mg/dl were also excluded.

Body mass index (BMI) is calculated as body mass (kg) divided by the square of height (m^2).

Laboratory measurements

After 12 hours of fasting, blood samples were collected from patients and healthy individuals. Serum samples were separated by centrifuging at 3000 r/min for 10 minutes at 37 ºC. Plasma visfatin (Eastbiopharm, China); IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2 and CPR (Siemens, Germany) and PCT (Biomerieux, France) levels were determined by an ELISA kit. Serum lipids, glucose, albumin, urea, creatinine, calcium, phosphorus, alkaline phosphatase, iron and total iron-binding capacity were analyzed by auto biochemical analysis equipment (Architect c16000; Abbott; USA). Hemoglobin was analyzed by Cell dyn 3700 (Abbott, USA). Transferrin saturation is the ratio of serum iron and total iron-binding capacity, multiplied by 100. Parathyroid hormone (PTH), erythropoietin and ferritin were analyzed by immunoradiometric assay.

Ultrasonography assessment

Radiological examination of the patient was performed by a radiologist in the supine position, head hyperextension and neutral neck position. Measurements were made by a single observer using a Doppler ultrasound (Aplio SSA 770, Toshiba, Japan) with a linear 7-MHz prob. The far wall of the CCA, 10 mm proximal to the carotid bulb, was used for the measurement of intima-media thickness on both sides by magnification of captured image. 0.8 mm and higher values were accepted as diagnostic in terms of atherosclerosis (Mannheim carotid intima-media thickness and plaque consensus**).**

Statistical analysis

Non-normally distributed variables were expressed as median (minimum-maximum) and normally distributed variables were as mean ± SD as appropriate. Categorical variables were expressed as frequency and the corresponding percentage value. Between-group comparisons were assessed for ordinal variables with independent samples t test and Mann Whitney U test. Between-group comparisons were assessed for nominal variables with Fisher's exact test and Yates corrected chi square test. Relationships between variables were tested using simple (Pearson's *r* correlation coefficient) linear regression analysis. A P value <0.05 was considered to be statistically significant. The data was statistically processed by IBM SPSS version 22 software (IBM Acquires SPSS Inc., Somers, NY, USA).

RESULTS

The characteristics of both groups are given in Table 1. There were statically significant differences between patients and the controls according to the age, BMI. Distribution of sex between groups was similar.

Table 2 shows laboratory and vascular assessment according to groups. Levels of hemoglobin (Hgb), HDL, albumin, Ca and total iron-binding capacity were lower and levels of P, ferritin, urea, creatinine, visfatin, CRP, PCT, ALP, PTH, IgG2 were significantly higher (p<0.001) in patients with CKD than those of the controls. Level of CRP were higher in patients. As expected, in CKD group, visfatin, CRP, PCT and CIMT levels were significantly higher in patients with atherosclerosis than patients without atherosclerosis (p<0.001) (Table 3).

In CKD groups; age was positively and HDL cholesterol levels were negatively correlated with CIMT (r=0.53, p<0.001 for age; r=-0.29, p=0.039 for HDL levels). CRP levels were positively correlated with CIMT (r=0.46, p<0.001). We also found negative correlation between albumin levels and CIMT (p=0.023. r=-0.32). Creatinine and triglyceride levels were positively correlated with visfatin level (r=0.30, p=0.032 for creatinine level; r=0.34, p=0.016 for triglyceride level) (Table 4). In control group; creatinine, urea, triglyceride, ferritin level, and BMI were significantly positively correlated with CIMT (r=0.42, p=0.002; r=0.39, p=0.03; r=0.50, p=0.004; r=0.41, p=0.02; r=0.39, p=0.031, respectively). Age was significantly correlated with CIMT and visfatin level (r=0.37, p=0.042 for CIMT; r=0.43, p=0.016 for visfatin) (Table 5). Visfatin was performed as dependent variable and GFR, total cholesterol, CRP, procalcitonin, age, triglyceride, albumin, creatinine, LDL cholesterol were used as independent variables in multivariate analysis. Multiple linear regression was performed with backward method. The coefficient of determination of the final model was determined as R^2 =0.27 with the p value of (p<0.001) regression model. And the final model was constructed as Visfatin= 18.157+1.607 (creatinine) +1.83 (CRP).

DISCUSSION

Visfatin is one of the most important cytokines secreting by adipose tissue. It is also secreted by bone, liver, muscle tissue and active lymphocyte, monocyte, neutrophils while inflammatory processes (9, 10, 19-21). Visfatin acts on the early stages of B cell synthesis. It increases the effect of stem cell factor and IL-7 by stimulating phosphoribosyl transferase enzyme-rate limiting enzyme of the synthesis of nicotinamide adenine dinucleotide (NAD) and provides maturation of vascular smooth muscle. Furthermore, visfatin increases IL-1β, IL-6 and TNFα secretion acting as extracellular cytokine. There are also insulinomimetic effects of visfatin, by binding to the insulin receptor (22). Visfatin levels increase because GFR and renal clearance of it decrease in patients with CKD (11, 15). Studies report that increase in visfatin levels is a predictor of atherosclerosis (11, 14). In our study we also detected high levels of visfatin in patient group. While it is known that CKD patients suffer higher risk of CV morbidity and mortality, the reasons for this is unclear. Progression of CKD is associated with decreased endothelial function, increased prevalence of atherosclerosis, and vascular media calcification, all of which have been associated with mortality (22-26). According to the registry reported in Turkey, CV diseases are the most common cause of death in hemodialysis and peritoneal dialysis patients; 53.45% and 43.24%, respectively. In United States of America, 42.9% of CKD patients had atherosclerotic heart disease, and mortality rate of CVD was 46% in CKD patients (27, 28). In a report from japan 117 patients (with stage 4 and 5 CKD) of total 167 subjects were studied. In patient group, CIMT was significantly higher (29). In another study from japan, in 68 patients with CKD, there was significant relationship between visfatin level and abdominal aortic calcification (assessed by computed tomography) (22). Marinelli *et al.* (30) showed that calcification in superficial femoral artery was increased significantly in 153 patients with CKD (105 had stage IV CKD and, 48 had hemodialysis).In present study, the patients with CKD had higher CIMT. Our results extend these reports. CRD effects immunity and immune response. It stimulates systemic inflammatory processes by cytokines. While renal clearance decreases, lots of toxins increases in blood. Some of these toxins trigger inflammatory processes directly or implicitly (19-21, 31).

IL-6, CRP, visfatin and adiponectin are some of the biomarkers giving information about these processes. Visfatin is defined as pre-b colony enhancing factor 1 (22). In our study, inflammatory markers like CRP, PCT were higher in CKD patients. In CKD patients, changes in visfatin levels are observed due to protein energy malnutrition, uremia and appetite status. In CKD patients who have anorexia and decreased appetite, visfatin levels are increased (??) There are significant correlation between visfatin levels and triglycerides, albumin and HDL levels (32) In our patient group, we found increased triglyceride levels and decreased HDL and albumin levels. In CKD patients, triglyceride levels and visfatin levels were positive correlated in our study. In conclusion, because inflammation is triggered in CKD, visfatin accumulates in patients with especially end stage renal disease. It is among the risk factors for atherosclerosis. It should be considered as a predictor marker for atherosclerosis in CKD patients.

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Table 1: Clinical Characteristics of the Groups

	Patient Group	*Volunteer Group*	*p values*
Age (years)	46.5 (22-79)	32 (23-54)	p<0.001
Sex (Female / Male)	22 / 28	18 / 13	p=0.316
BMI (kg/m²)	29.39±2.81	25.5±4.62	p<0.001

BMI: Body mass index.

Table 2: Laboratory and vascular assessment according to groups

	Patient Group	*Volunteer Group*	*p values*
GFR (ml/min/1.73 m²)	8.48±4.46	110.32±12.08	p<0.001
Hgb (g/dL)	11.632±1.908	14.100±1.315	p<0.001
WBC (K/µL)	7.529±2.344	6.6042±1.787	p=0.064
PLT (K/µL)	228.032±86.112	265.032±59.105	p=0.025
Glucose (mg/dL)	88±22.908	84±18.344	p=0.163
Urea (mg/dL)	107±41.415	25±7.835	p<0.001
Creatinine (mg/dL)	7.659±2.964	0.780±0.138	p<0.001
Total cholesterol (mg/dL)	188.58±50.706	194.94±41.786	p=0.560
HDL cholesterol (mg/dL)	37.34±12.495	46.774±8.739	p<0.001
LDL cholesterol (mg/dL)	114.05±40.34	119.1±40.16	p=0.119
Triglyceride (mg/dL)	190.42±135.01	116.52±70.19	p=0.003
Total protein (g/dL)	6.8±0.688	7.4±0.329	p<0.001
Serum albumin (g/dL)	3.66±0.5	4.26±0.2	p<0.001
Visfatin (ng/mL)	32.45±15.83	21.06±8.14	p<0.001
CRP (mg/dL)	1.39±0.37	0.41±0.05	p=0.005
PCT (ng/mL)	0.34±0.41	0.05±0.001	p<0.001
IgA1 (mg/dL)	165.85±113.455	146.9±54.38	p=0.487
IgA2 (mg/dL)	48.7±26.787	46.5±21.167	p=0.907
IgG1 (mg/dL)	718±277.828	649±144.1	p=0.2
IgG2 (mg/dL)	316.540±112.911	425.806±138.543	p=0.198
IgG3 (mg/dL)	74.25±47.126	46.4±31.588	p=0.003
IgG4 (mg/dL)	37.25±11.97	51.1±9.38	p=0.254
IgM (mg/dL)	80.6±49.227	109±68.898	p=0.095
Ca (mg/dL)	8.726±0.761	9.3 ±0.369	p<0.001
P (mg/dL)	4.55±1.289	3.5±0.676	p<0.001
PTH (pg/mL)	237.95±61.856	51.2±24.567	p<0.001
ALP (IU/L)	93±24.74	55±19.462	p<0.001
Ferritin (ng/mL)	390±81.39	35.97±6.11	p<0.001
Fe (µg/dL)	64.15±38.3	84.5±29.962	p=0.021
TIBC (µg/dL)	213.5±63.162	309±59.407	p<0.001
Transf Sat	27.197±20.468	28.622±11.607	p=0.884
CIMT (mm)	0.75±0.23	0.49±0.13	p<0.001

GFR: Glomerular filtration rate. Hgb: Hemoglobin. WBC: Leukocyte. PLT: Platelet. HDL cholesterol: High density lipoprotein cholesterol. LDL cholesterol: Low density lipoprotein cholesterol. CRP: C-reactive protein. PCT: procalcitonin. Ig:

Table 3: Laboratory assessment according to atherosclerosis.

Variable	Carotid atherosclerosis (+) n=30	Carotid atherosclerosis (-) n=51	p value
Visfatin, ng/mL	38.2±14.6	20.4±9.6	<0.001
CRP, mg/dL	1.88±3.31	0.49±0.39	<0.001
PCT ng/mL	0.38±0.49	0.13±0.16	<0.001
CIMT, mm	0.89±0.17	0.57±0.15	<0.001

CRP: C-reactive protein. PCT: procalcitonin. CIMT: Carotid intima media thickness.

Table 4: Patient Group Regression Analysis

	VISFATIN		*CIMT*	
	r value	p value	r value	p value
Age	0.04	0.77	0.53	<0.001
PTH	-0.36	0.010	-0.35	0.013
Serum albumin	0.03	0.864	-0.32	0.023
CRP	0.19	0.18	0.46	0.001
PCT	0.12	0.398	0.01	0.928
Creatinine	0.3	0.032	-0.04	0.797
Triglyceride	0.34	0.016	0.14	0.331
HDL cholesterol	-0.36	0.011	-0.29	0.039
LDL cholesterol	0.1	0.482	-0.04	0.806
BMI	0.23	0.107	0.26	0.067
Hgb	0.05	0.708	0.1	0.503
WBC	0.17	0.248	-0.02	0.878
PLT	0.3	0.034	0.18	0.201
Glucose	-0.05	0.741	0.15	0.297
Urea	0.07	0.621	-0.01	0.969
Total cholesterol	0.14	0.320	-0.04	0.793
Total protein	0.06	0.67	-0.08	0.606
IgA1	0.04	0.766	0.36	0.01
IgA2	0.10	0.484	0.34	0.018
IgG1	-0.09	0.541	0.01	0.937
IgG2	0.02	0.884	0.04	0.79
IgG3	0.06	0.672	0.21	0.152
IgG4	0.05	0.753	0.12	0.408
IgM	0.04	0.804	-0.04	0.76
Ca	0.13	0.359	-0.01	0.961
P	-0.16	0.26	-0.14	0.329
ALP	0.00	0.995	0.07	0.630
Ferritin	0.2	0.154	0.35	0.012

Table 5: Volunteer Group Regression Analysis

	VISFATIN		*CIMT*	
	r value	p value	r value	p value
Age	0.43	0.016	0.37	0.042
PTH	-0.36	0.047	0.02	0.923
Serum albumin	-0.01	0.964	-0.01	0.956
CRP	0.09	0.624	0.00	0.987
PCT	-0.24	0.195	-0.13	0.479
Creatinine	0.15	0.438	0.42	0.002
Triglyceride	0.06	0.735	0.5	0.004
HDL cholesterol	0.15	0.408	-0.13	0.489
LDL cholesterol	0.02	0.936	-0.07	0.72
BMI	0.14	0.465	0.39	0.031
Hgb	0.12	0.523	0.10	0.599
WBC	0.02	0.904	-0.12	0.533
PLT	-0.04	0.831	-0.03	0.869
Glucose	0.09	0.645	0.25	0.173
Urea	0.34	0.061	0.39	0.03
Total cholesterol	0.03	0.86	0.01	0.946
Total protein	0.08	0.673	-0.18	0.336
IgA1	0.08	0.668	0.02	0.932
IgA2	0.02	0.899	-0.06	0.744
IgG1	0.08	0.684	-0.08	0.664
IgG2	0.09	0.648	-0.14	0.468
IgG3	-0.19	0.300	-0.05	0.773
IgG4	-0.14	0.45	-0.14	0.46
IgM	-0.12	0.536	-0.52	0.003
Ca	0.05	0.782	0.14	0.447
P	0.06	0.734	0.26	0.152
ALP	-0.03	0.881	0.21	0.249
Ferritin	0.05	0.793	0.41	0.021
Fe	-0.01	0.944	-0.16	0.385
TIBC	0.00	0.991	0.06	0.732
Transf Sat	0.02	0.906	-0.13	0.488

BMI: Body mass index. GFR: Glomerular filtration rate. Hgb: Hemoglobin. WBC: Leukocyte. PLT: Platelet. HDL cholesterol: High density lipoprotein cholesterol. LDL cholesterol: Low density lipoprotein cholesterol. CRP: C-reactive protein. PCT: procalcitonin. Ig: Immunoglobulin. Ca: Calcium. P: Phosphorus. PTH: Parathyroid hormone. ALP: Alkaline phosphatase. Fe: Iron. Transf sat: Transferrin saturation. TIBC: Total iron binding capacity. CIMT: Carotid intima media thickness.

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