THE RELATIONSHIP BETWEEN VISCERAL ADIPOSE TISSUE AND INTIMA-MEDIA THICKNESS IN PATIENTS WITH KIDNEY DISEASE

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ABSTRACT

***Introduction**: Increase in visceral adipose tissue (VAT) is associated with cardiovascular risk. However, the relationship between atherosclerosis and VAT has not yet been adequately studied in chronic kidney disease (CKD). The aim of this study was to assess the relationship among VAT, adipokines, and atherosclerosis in patients with CKD.*

***Materials and methods**: 45 healthy control, 53 predialysis patients, and 52 hemodialysis patients have been enrolled in the study. Intima media thickness (IMT) of the carotid artery, and VAT measurements were evaluated via ultrasonography.*

***Results**: IMT (p:0.002), VAT (p:0.021), adiponectin (p<0.001) and pentraxin-3 (p:0.003) were higher in predialysis patients than healthy controls. The values of IMT (p<0.001), VAT (p:0.0014), adiponectin (p:0.005), pentraxin-3 (p: <0.001), C reactive protein (CRP) (p:0.009), triglyceride (p: <0.001) and parathyroid hormone (PTH) (p<0.001), were higher in hemodialysis patients than healthy controls. VAT was positively correlated with CRP(r: 0, 23 p: 0.005), IMT (r: 0.347 p<0.001), body mass index (BMI) (r: 0.33 p<0.001), and negatively correlated with creatinine clearance (R: -0.245 p: 0.003). VAT is independently related with adiponectin (β:-0.213 p: 0.008), BMI (β: 0.369, P<0.001), and CRP (β:0.164, P:0.032) in multiple regression analysis. IMT was positively correlated with VAT (r: 0.347 p<0.001), CRP (r: 0.186 p: 0.022), age (r: 0.333 p<0.001), BMI (r: 0.444 p<0.001) in all participants.*

***Conclusion**: These findings show that VAT is a strong risk factor for atherosclerosis in patients with CKD. However IMT was not correlated with adiponectin, pentraxin-3, and leptin in patients with CKD. Also sonographic measurement of VAT could be useful to stratify the risk of cardiovascular disease in patients with CKD.*

***Keywords**: visceral adipose tissue, intima media thickness, adiponectin, leptin, Pentraxin-3, Chronic Kidney Disease.*

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Introduction

Mortality is related with cardiovascular disease in approximately 50 percent of patients with chronic kidney disease (CKD)[1,2]. Many traditional and non-traditional risk factors cause cardiovascular events in these patients. Traditional risk factors such as hyperlipidemia, hypertension, and diabetes alone are insufficient to explain the high cardiovascular morbidity and mortality in patients with CKD. Increasing evidences bring the role of non-traditional risk factors to the fore such as oxidative stress and inflammation[3].

The perception in which adipose tissue is known as storage location of fatty acids has changed in recent years. It has been figured out that gradually increasing evidences show that adipose tissue mass is directly related with both systemic inflammation and cardiovascular risk increase with number of cytokines such as adiponectin, leptin, pentraxin-3 playing a central role in glucose and lipid metabolism[4, 5]. Adiponectin is a very sensitive indicator of prediction for cardiovascular events[6]. It has been shown that serum leptin, and pentraxin-3 levels are closely related with stroke, chronic heart failure, acute myocardial infarction, coronary heart disease[7,

[8]. It has been demonstrated in previous study that visceral adipose tissue (VAT) has increased in patients with CKD, and associated with atherosclerosis[9]. However, the relationship between VAT and atherosclerosis is still unknown exactly. The aim of this study was to assess the relationship among VAT, cytokines originating from visceral fat such as adiponectin, leptin, and Pentraxin-3, and atherosclerosis in patients with CKD.

Material and methods

The study protocol was approved by the Pamukkale University Ethical Committee. A control group of 45 healthy individuals (Group-1), 53 predialysis patients (Group-2), and 52 hemodialysis patients (Group-3) have been enrolled in the study. The study was performed in Pamukkale University Faculty of Medicine between February, 2011 and November, 2011. Exclusion criteria included those under 18, and above 80, who had active infections, coronary artery disease, history of percutaneous or surgical revascularization, congenital heart disease, inflammatory diseases, malignancy, and diabetes mellitus. The glomerular filitration rate (GFR) of the patients with chronic renal failure is between 60-15 ml/min. All of the hemodialysis patients had been receiving hemodialysis 3 times per week with bicarbonate dialysate solution at least for one year. Systolic and diastolic blood pressure was measured in each individual twice, following a 5-minute rest, with erka brand sphygmomanometer using an appropriate cuff width. Those with blood pressure ≥ 140/90 mmHg and using anti-hypertensive drugs are accepted as hypertensive patients. Those with serum total cholesterol ≥ 200 mg/dl and/or triglycerides ≥ 150 mg/dl and using lipid-lowering drugs are accepted as hyperlipidemic patients.

Laboratory analysis

Blood samples were collected in all subjects in the study at 8 in the morning after 12 hours of fasting. Blood samples were collected in hemodialysis patients prior to dialysis treatment. Imaging technique was carried out within 2 hours after blood samples had been collected. The adiponectin plasma levels (RD195023100, Human Adiponectin, Elisa Bio Vendor Laboratory Medicine Inc., Brno, Czech Republic), the leptin plasma levels (RD 191001100 Human leptin ELISA kit, Bio Vendor GmbH, Heidelberg, Germany), and human Pentraxin-3/TSG-14 plasma levels (Quantikine ELISA kit, R&D Systems, Minneapolis, Minn, Catalog Number DPTX30)were measured with immunoassay. Immulite 2000 analyzer was used for the measurement of Insulin; Sysmex XT 2000I analyzer was used for the measurement of complete blood; Modular P and Roche/Hitachi analyzer was used for the measurement of others parameters. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting blood glucose (FBG) and fasting insuline (FI) levels using the following formula; {FBG (mg/dl) × FI (mu/ml)}/405 (10). Also GFR was calculated with The Modification of Diet in Renal Disease method (MDRD) in all individuals in the study. MDRD was calculated as GFR (ml / min / 1.73 m 2) = 186 x (Scr) -1154 x (Age) -0203 x (0.742 if you are a woman).

Carotid intima media thickness measurement

IMT of the carotid artery as an indicator of subclinical atherosclerosis was measured. Carotid artery ultrasounds of all groups were applied by a single radiologist in Pamukkale University Department of Radiology, Medical Faculty Hospital. Toshiba aplio XY high-resolution B-mode ultrasonography with 7.5 MHz linear probe was used in the measurements. The measurement in between two echogenic lines seen between intima lumen interface and media adventitia interface was described as IMT measurement[11]. Posterior wall was used in the measurement as performed in the axial and longitudinal plans in views. Imaging techniques were performed within 2 hours after blood is collected from patients.

Visceral adipose tissue measurement

VAT measurements of all groups were applied by a single radiologist in Pamukkale University Medical Faculty Hospital, Department of Radiology. Toshiba aplio XY high-resolution B-mode ultrasonography with 3.5 MHz convex probe was used in the measurements. Measurements were performed via 3.5 MHz convex probe placed 1 cm beyond umbilicus after an overnight fast while patients lying supine. By means of taking 3 samples from the distance in between skin and rectus abdominis, the average value of these samples was accepted as subcutaneous adipose tissue. By means of taking 3 samples from the distance in between inner fascia of rectus abdominis and front fascia of the abdominal aorta the average value of these samples was accepted as VAT[12].

Statistical analysis

Statistical analyses were carried out using the Statistical package for Social Sciences for Windows version 10.0 (SPSS, Chicago, IL, USA) in Pamukkale University School of Medicine Department of Biostatistics. Descriptive statistics for each variable were determined. Results for continuous variables were demonstrated as mean± standard deviation. Pearson's correlation coefficient, Spearman correlation coefficient, Mann Whitney U test, two of the difference between the means test, chi-square test, kruskal-wallis ANOVA, one-way analysis of variance, and Bonferroni correction Mann-Whitney U test were used for comparing the studied groups. Statistical significance was defined as $P< 0.05$

Results

The study groups consisted of a control group (n: 45), a predialysis group (n: 53), and a dialysis group (n: 52). The basal characteristics and labora-

	Control Group	Predialysis Group	Dialysis Group	P	Statistical differences between groups		
					K-PD	K-D	D-PD
Gender(M/F)	23/22	28/25	26/26	>0.05	>0.05	>0.05	>0.05
Age (year)	48.66±9.40	53.26±11.37	50.36±11.12	>0.05	0.334	0.736	0.736
Duration of CKD	0	49.64±47.14	93.53±63.09	<0.001	<0.001	<0.001	<0.001
BMI	27.57±3.82	26.02±3.81	25.18±3.06	0.005	<0.001	<0.001	0.389
Triglyceride (mg/dl)	156.63±99.51	169.13±107.45	183.34±106.15	>0.05	0.981	0.577	0.861
LDL (mg/dl)	120.54±31.49	110.22±43.25	104.77±33.96	>0.05	0.782	0.181	0.802
HDL(mg/dl)	44.97±9.2	49.39±17.02	46.20±14.56	>0.05	>0.05	>0.05	>0.05
T. cholesterol (mg/dl)	193.75±34.53	195.99±54.69	187.67±47.55	>0.05	0.995	0.921	0.836
CRP (mg/dl)	0.42±0.29	1.11±1.89	1.71±4.37	0.037	0.081	0.009	0.59
Glucose (mg/dl)	96.08±15.24	100.73±27.80	96.85±17.84	>0.05	0.992	0.998	0.999
HOMA-İR	2.24±1.55	4.23±5.042	3.85±3.15	>0.05	0.698	0.116	0.775
Sist. B.P. (mmHg)	119.77±12.87	125.94±17.70	121.25±12.04	>0.05	0.08	0.959	0.193
Diast. B.P. (mmHg)	77.66±9.02	79.90±11.201	75.57±7.77	>0.05	0.66	0.702	0.133
Calcium (mg/dl)	9.16±0.36	8.89±0.66	8.92±0.71	0.066	0.076	0.141	0.955
Phosphor (mg/dl)	3.41±0.60	4.1±0.75	4.8±1.02	<0.001	<0.001	<0.001	<0.001
Albumin (mg/dl)	4.56±0.23	4.10±0.57	4.1±0.50	<0.001	<0.001	<0.001	>0,05
Duration of smoking (year)	5.84±12.75	10.62±14.52	8.26±12.18	>0.05	0.041	0.227	0.227
Creatinine Clearance (ml/mn)	116.20±29.07	32.22±12.52	8.76± 3.87	0.0001	<0.001	<0.001	<0.001
PTH (pg/ml)	59.36±20.29	191.28±161.14	501.00±594.31	0.0001	0.474	<0.001	0.001
Ferritin (ng/dl)	58.71±47,35	138.52±126.37	519.35±450.60	0.0001	0.364	<0.001	<0.001
Hemoglobin (g/dl)	13.42±1.68	11.62±1.58	11.41±1.61	0.0001	<0.001	<0.001	0.965
İMT (MM)	0.66±0.11	0.76±0.14	0.84±0.12	0.0001	0.002	<0.001	0.048
Adiponectin (µg/mL)	6.17± 3.21	11.52± 8.22	10.46± 5.73	0.0001	<0.001	0.005	0.542
Leptin (ng/mL)	24.48 ± 22.22	22.78 ± 18.98	22.53 ± 22.51	>0.05	0.999	0.97	0.993
Pentraxin-3 (ng/mL)	0.36 ± 0.25	0.79 ± 0.65	0.96± 0.73	0.0001	0.003	<0.001	0.849
SAT	20.33± 6.02	19.86± 8.39	20.10 ± 7.045	>0,05	0.965	0,999	0,998
VAT	51.25± 51.25	63.06± 22.72	63.78± 20.41	0.004	0.021	0.014	0.998

Table 1: The basal characteristics and laboratory parameters of the control group, predialysis group, and dialysis group.
Abbreviations: Duration of CKD: Duration of chronic kidney disease, BMI: Body mass Index, LDL: Low density lipoprotein, HDL: High density lipoprotein T. cholesterol: Total cholesterol , CRP: C reactive protein, HOMA-İR: The threshold value for insulin resistance, Sist. B.P.: Systolic blood pressure Diast. B.P.: Diastolic blood pressure PTH: Parathyroid hormone, Cr. Cl: Creatinine clearance, İMT: Carotid Intima-Media Thickness, SAT: subcutaneous adipose tissue, VAT: visceral adipose tissue

tory parameters of the control group, predialysis group, and dialysis group are shown in table 1.

The values of age, sex, triglycerides, low density lipoprotein (LDL), High density lipoprotein (HDL), total cholesterol, HOMA-IR, systolic blood pressure, diastolic blood pressure, duration of smoking, leptin, and subcutaneous adipose tissue were not detected to be significantly different among three groups (table 2).

	Control	Predialysis	Dialysis	P
Antihypertensive medication use.	6/45(%13)	30/53(%65)	10/52(%28)	>0,05
Statin medication use	3/45(%14)	9/53(%16)	10/52(%19)	>0,05

Table 2: Antihypertensive and statin medication use in the study groups.

The values of IMT (p: 0.002), VAT (p: 0.021), adiponectin (p<0.001), pentraxin-3 (p: 0.003), creatinine clearance (p<0.001), hemoglobin (p<0.001), albumin (p p<0.001), phosphorus (p<0.001), BMI (p<0.001), and duration of CKD were detected to be significantly higher in predialysis patients than in healthy control group. The values of IMT (p<0.001), VAT (p:0.0014), adiponectin (p: 0,005), pentraxin-3 (p<0.001), CRP (p: 0,009), creatinine clearance (p<0.001), PTH (p<0.001), duration of CKD (p<0.001), albumin (p<0.001), phosphorus (p<0.001), Ferritin (p<0.001), were detected to be significantly higher in hemodialysis patients than group of healthy control. The values of duration of CKD (p<0.001), phosphorus (p<0.001), and PTH (p: 0.001) were detected to be significantly higher in hemodialysis patients than group of predialysis patients. The values of BMI (p<0.001), and hemoglobin (p<0.001), were detected to be significantly lower in predialysis patients than group of healthy control. The values of BMI (p<0.001), and hemoglobin (p<0.001), were detected to be significantly lower in dialysis groups than in predialysis patients (table 1). No significant difference was detected in the frequency of statin and antihypertensive drug use among three groups (table 2).

VAT was significantly positively correlated with CRP (r: 0.23p: 0,005), IMT (r: 0,347 p<0.001), BMI (r: 0,33 p<0.001), and negatively correlated with creatinine clearance (r: -0,245 p: 0,003) in all participants in the correlation analysis. It was detected that IMT was significantly correlated with VAT (r: 0,347 p<0.001), CRP (r: 0.186 p: 0.022), age (r: 0.333 p<0.001), BMI (r: 0.444 p<0.001), and in a negative correlation with creatinine clearance (r: -0,451 p<0.001), in all participants in the correlation analysis (table 3). IMT was not correlated with adiponectin, pentraxin-3, and leptin levels in patients with CKD. It was shown that adiponectin was in a negative correlation with VAT in all patients with CKD (r: -0.233 P: 0.017) (table 4).

	İMT		VAT	
	R	P	R	P
Age (year)	0.333*	<0.001	0.15	0.067
BMI(kg/cm^2)	0.444*	<0.001	0.33*	<0.001
Cr. Cl. (ml/mn)	-0.451*	<0.001	-0.245*	0.003
T. cholesterol (mg/dl)	-0.0129	0,115	0.052	0.53
Triglyceride (mg/dl)	-0.008	0,924	0.148	0.072
LDL (mg/dl)	-0.147	0,073	0.049	0.549
CRP (mg/dl)	0.186*	0,022	0.23*	0.005

Table 3: Correlation analysis of visceral adipose tissue and carotid intima media in all study groups.

	Adiponectin		Pentraxin-3		Leptin	
	R	P	R	P	R	P
Age (year)	-0,024	0,81	-0,034	0,73	0,047	0,638
BMI(kg/cm^2)	-0,16	0,103	0,149	0,128	0,035	0,724
Cr. Cl. (ml/mn)	0,165	0,092	0	0,997	0,112	0,257
T. cholesterol (mg/dl)	0,021	0,832	0,033	0,736	0,151	0,124
Triglyceride (mg/dl)	-0,037	0,704	0,089	0,368	0,161	0,102
LDL (mg/dl)	-0,036	0,718	0,02	0,839	0,074	0,456
İMT (mm)	-0,068	0,493	-0,028	0,777	-0,156	0,112
VAT (mm)	-0,233*	0,017*	0,14	0,153	-0,088	0,372
SAT (mm)	-0,084	0,397	1		-0,13	0,185

Table 4: Correlation analysis of adiponectin, Pentraxin-3, and leptin in all patients of chronic kidney disease.
*Abbreviations: BMI: Body mass Index, LDL:low density lipoprotein, HDL:High density lipoprotein T. cholesterol: Total cholesterol, Cr. Cl.: Creatinine clearance, İMT: Carotid Intima-Media Thickness.VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue, *: p<005*

	B	Std. Error	Beta	p	95% CI (Lower - Upper)
Bmi	0,704	0,151	0,369	0,0001*	0,405 - 1,002
Adipo	-0,673	0,249	-0,213	0,008*	-1,164 - 0,182
crp	1,201	0,555	0,164	0,032*	0,104 - 2,297

Table 5: Multiple regression analysis of markers affecting visceral adipose tissue in all groups.
Model p: 0.00001; R^2:0.185; Adj. R^2: 0.168; 95% CI :95% confidence interval; BMI: Body mass Index; CRP: C-reactive protein

Upon the assessment of variables effecting VAT such as BMI, HOMA-IR, triglycerides, CRP, pentraxin-3, adiponectin, leptin, age, creatinine clearance in all the patients in our study via multiple regression analysis, it was detected that VAT is independently in a negative correlation with adiponectin (β: -0.213 p: 0.008), and in a positive correlation with BMI (β: 0.369, P: 0.004) and CR P (β:0.164, P:0.032) in multiple regression analysis (Table 5).

Discussion

In our study, we showed that VAT, IMT, adiponectin, and pentraxin-3 were higher in patients with CKD and hemodialysis patients, and also that VAT is significantly correlated with IMT and CRP and is in a negative correlation with creatinine clearance, and adiponectin.

In accordance with our study, Odamaki et. al. showed that VAT was higher in hemodialysis patients[13]. It was demonstrated in the PREVEND study that creatinin levels were negatively correlated with central obesity in 7676 patients without diabetes mellitus[14]. In a change reaction, increase in VAT leads to an increase in the production of angiotensin in adipose tissue[15]. Respectively, this increase in angiotensin causes increase in blood pressure[16], endothelial dysfunction, and finally a decrease in GFR[17]. Also, increased VAT contributes renal damage and a reduction in GFR as cause intra renal pressure via to physically compress kidney[18].We showed in our study that VAT was related with IMT in hemodialysis and patients with chronic renal failure. It has been shown in the recent studies that VAT is correlated with IMT and coronary artery calcification in patients with chronic renal failure[19, 20, 21]. These findings have shown that increase in VAT induces atherosclerosis. It has been shown that the increase of VAT is related with strong cardiovascular risk factors such as inflammation[22] oxidative stress[23, 24], and increased small dense LDL particles[25, 26]. In accordance with literature, VAT had a correlation with CRP in our study, as well. In the recent studies, it has been shown that a great number of inflammatory cytokines which can increase atherosclerosis risk are secreted from VAT[27, 28].

In our study, adiponectin and pentraxin-3 were detected to be higher in kidney failure patients in comparison with healthy males and females. We did not detect a significant difference in the leptin levels of kidney failure patients and control group individuals. In accordance with our study, it was detected that adiponectin level was higher in patients with chronic renal failure[29, 30, 31]. Still in accordance with our study, it was shown that adiponectin was in a negative correlation with VAT[32, 33].

In our study, we did not detect a statistically significant correlation between adiponectin and IMT. In accordance with our study, Nakanishi et al, and Rubio et al did not detect any correlation between adiponectin and IMT in patients with diabetes mellitus[34], and hypertension[34, 35]. The reason why we did not detect a significant correlation between adiponectin and IMT may be due to the changes in adiponectin metabolism, posttranslational modifications, or abnormal accumulation of metabolites in CKD[36].

In accordance with our study, Maloponte et al. showed that PTX3 plasma level is higher in uremic patients[37]. Boheme et al. detected that PTX-3 plasma level increased in hemodialysis patients[38]. Also, it was shown that PTX-3 level was higher in patients with chronic renal failure[39]. In accordance with our study, any statistical difference in the leptin levels of healthy control individuals and chronic renal failure patients was not detected in some studies such as Heimburger et al[40] and Stevinkel et al[41].

In our study, it was detected that upon the analysis of parameters effecting IMT in CKD patients, there happened to be a relationship among age, CRP and VAT. Age is one of the independent risk factors in coronary artery disease. In accordance with our study, it was demonstrated in the literature that IMT was positively correlated with age[42, 43]. As is in previous studies in literature[44, 45], it was also shown in our study that CRP was in a positive correlation with IMT and that CRP was positively correlated with IMT.

Usually, VAT was measurement via tomography in the literature. Ultrasonography is harmless, relatively inexpensive, available, and there is no ionizing radiation.Our findings show that sonographic measurement of VAT could be useful to stratify the risk of cardiovascular disease in patients with CKD.

Our findings showed that increase in VAT is in a relation with the decrease in creatinine clearance, inflammation, and the increase of atherosclerosis risk. This positive relation points out to the fact that inflammatory cytokines caused by VAT take a role in accelerated atherosclerosis. Finding out the relation among the accelerated atherosclerosis, VAT,

and inflammation in CKD can shed light on the new approaches in the treatment to prevent high cardiovascular mortality, the most important problem in these patients.

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