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## Relationship between adiposity and cardiovascular risk factors in prevalent hemodialysis patients

George A. Kaysen<sup>1,2,3</sup>, Peter Kotanko<sup>1,4</sup>, Fansan Zhu<sup>1</sup>, Shubho R Sarkar<sup>1,5</sup>, Steven B. Heymsfield<sup>6</sup>, Martin K. Kuhlmann<sup>1</sup>, Tjien Dwyer<sup>2</sup>, Len Usvyat<sup>1</sup>, Peter Havel<sup>7</sup>, and Nathan W. Levin<sup>1</sup>

<sup>1</sup> Renal Research Institute NY NY

<sup>2</sup> Division of Nephrology Department of Medicine and Department of Biochemistry and Molecular Medicine University of California, Davis Davis CA

<sup>3</sup> Research Service VA Northern California Health Care System

<sup>4</sup> Krankenhaus der Barmherzigen Brueder, Graz, Austria

<sup>5</sup> Weil Cornell Medical Center Department of Medicine, New York, NY

<sup>6</sup> St. Lukes Hospital New York Obesity Research Center NY NY

<sup>7</sup> Department of Molecular Biosciences School of Veterinary Medicine and Department of Nutrition University of California, Davis, Davis CA

### Abstract

Increased Body Mass Index (BMI) is associated with reduced all cause and cardiovascular (CV) mortality in hemodialysis patients (HD), while CV risk increases with BMI in the general population. In the general population obesity is associated with inflammation, decreased HDL, increased LDL and triglycerides (TGs), all risk factors for CV disease. LDL does not predict CV risk in HD, whereas increased C-reactive protein (CRP), interleukin-6 (IL-6), low HDL or apo AI and increased fasting triglycerides (TG) do predict risk. Renal failure is associated with dyslipidemia and inflammation in normal weight patients. We hypothesized that effects of obesity may be obscured by virtue of renal failure in HD. We explored the relationship between adipose tissue pools and distribution, i.e., subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (measured by MRI) and measures of inflammation (CRP, IL-6, ceruloplasmin and  $\alpha$  1 acid glycoprotein) HDL and LDL cholesterol, total TGs, apo A I, apo B, apo C II (an activator of lipoprotein lipase (LPL)) and CIII (an inhibitor of LPL) and the adipokines, leptin and adiponectin in 48 patients with prevalent HD. Total TG concentrations were positively correlated with VAT controlled for age, sex and weight. Both apo C II and apo C III correlated only with VAT. Adiponectin was inversely correlated with VAT and leptin was positively associated with SAT. CRP and  $\alpha$  1 acid glycoprotein were weakly associated with SAT while ceruloplasmin was strongly associated with VAT by multiple regression analysis. In contrast, apo B, LDL, apo A I and HDL, and IL-6 were not correlated with any measure of body composition potentially mitigating the effects of obesity in HD

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Address correspondence to: George A. Kaysen M.D. Ph.D. FASN, Chief, Division of Nephrology, University of California Davis, One Shields Ave, TB 136 Davis CA 95616, USA, gakaysen@ucdavis.edu.

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## Keywords

Inflammation; Apo A I; Apo C II; Apo C III; adipokines; leptin; adiponectin; HDL; LDL; triglycerides; ceruloplasmin

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## Introduction

While the relative risk of mortality is high among dialysis patients, one factor that predicts survival is having a higher BMI (1,2,3). BMI is imprecise as a measure of body composition and does not distinguish between muscle and fat mass. Nevertheless, the lack of an increase in mortality among a population with a very high BMI ( $>35 \text{ kg/m}^2$ ) strongly supports a hypothesis that adiposity either in some way protects dialysis patients from mortality or that risk factors normally associated with adiposity may not be associated with adiposity among dialysis patients. Indices associated with lean body mass, such as total body water, approximated by the volume of distribution of urea (V) independently predict survival (4,5). Similarly, total body potassium, a measure of intracellular volume, predict survival in a variety of chronic diseases (6,7,8). While the positive association between lean body mass and survival can be explained by better preserved nutritional reserves or lower co-morbidities, the basis for improved survival among obese patients is not obvious, although a similar survival advantage is observed in patients with other chronic diseases (9).

Several cardiovascular risk factors are linked metabolically to body composition among subjects having normal kidney function (10). LDL cholesterol levels and triglyceride levels are positively associated with adiposity while HDL is inversely associated with adiposity among subjects having normal kidney function (11). Inflammation, as assessed by plasma CRP or IL-6 concentrations are also important cardiovascular risk factors both in dialysis patients as well as in subjects with normal kidney function (12,13,14). CRP and IL-6 levels are thought to be associated with adiposity in subjects with normal kidney function as a result of inflammation within or caused by increased visceral adipose mass (15,16). A third set of risk factors that are associated with adiposity both in the population having normal kidney function as well as in patients having kidney failure are the adipokines, leptin and adiponectin.

While some risk factors that predict cardiovascular disease among populations not having kidney failure are no longer predictive in dialysis patients, such as hypertension and Low Density Lipoprotein (LDL) cholesterol (17), other risk factors preserve their predictive values, such as C reactive protein (CRP), IL-6 (12,13,18), and low levels of High Density Lipoprotein cholesterol (HDL) (17,19).

Elevated triglycerides (TG) are also associated with mortality among dialysis patients (19). While TG levels are associated with adiposity among subjects having normal kidney function, TG levels are also increased in dialysis patients by factors that may not be linked to body composition, such as increased levels of lipoprotein lipase inhibitors such as apolipoprotein C III (apo C III) (20,21) which is also linked both to insulin resistance and to increased body adiposity

A third cluster of risk factors associated with body composition modulating cardiovascular risk are adipokines (22,23). Leptin is secreted by adipocytes, and additionally is increased in dialysis patients beyond what would be anticipated by total fat mass, primarily because of reduced renal clearance of leptin (24,25), although the relationship to adiposity persists within populations of patients having renal failure (24,25). Leptin is associated with insulin resistance and increased circulating leptin has been directly associated with vascular disease

(26,27,28,29). Circulating concentrations of a second adipokine, adiponectin, are inversely proportion to fat mass (30), and specifically inversely related to the important visceral adipose tissue mass (31,32). Adiponectin, like HDL has been reported to be inversely associated with vascular disease in subjects with normal renal function (33). The relationship between adiponectin levels and cardiovascular risk in patients having kidney disease is controversial. High levels have been associated with increased cardiovascular risk in some studies of dialysis patients (23) as well as in patients having stage 3 and 4 chronic kidney disease (34) while high levels have been reported to be protective in other studies (22).

In the present study, we measured body adipose tissue compartments and lean body mass using MRI in a cohort of hemodialysis patients to investigate the relationship between the relationship between adiposity and a number of risk factors for cardiovascular disease.

## Methods

Institutional Review Board approval was obtained and all subjects signed an informed consent prior to participation. Forty-eight prevalent hemodialysis patients consisting of 20 women and 28 men over the ages of 18 years were chosen so as to encompass a wide range of body mass indices and ages. Thirty-seven patients were African American, 3 were non black Hispanic, 3 were white, and 2 were Asian and 3 were other. Sixteen patients had diabetes mellitus. For analysis of the effect of race patients were coded as black or non black because of the small numbers in the other groups. All but one subject had been on maintenance hemodialysis for at least 3 months prior to study. One subject had been on dialysis for 2 months. They were studied on the day of a regularly scheduled hemodialysis session approximately 3 hours prior to initiation of a dialysis treatment.

Following an overnight fast, body weight was measured to the nearest 0.1 kg (Weight Tronix, New York), and height was measured to the nearest 0.5 cm by using a stadiometer (Holtain, Crosswell, United Kingdom). Whole-body MRI scans were prepared by using a 1.5 Tesla scanners (6X Horizon; General Electric, Milwaukee) to evaluate muscle and fat mass (35).

All assays were performed on serum obtained while the patient was in the fasting state. The inflammatory markers C-reactive protein (CRP) interleukin-6 (IL-6), the long lived acute phase proteins ceruloplasmin and  $\alpha$  1 acid glycoprotein ; the adipokines leptin and adiponectin, and the apolipoproteins (Apo) apo A I, apo C II, apo C III, apo B, triglycerides, total cholesterol and high density lipoprotein (HDL) low density lipoprotein (LDL) cholesterol were measured. CRP, ceruloplasmin, apo A I apo B and  $\alpha$  1 acid glycoprotein were measured with rate nephelometry using a Beckman Array automated nephelometer (36). Apo C II and apo C III were measured nephelometrically using a Hitachi chemical analyzer, leptin and adiponectin were measured by RIA (Millipore, St. Charles, MO). All nephelometric measurements were made in duplicate in each of two optical systems. The average of these values was used for calculations.

## Statistical analysis methods

Data are presented as mean, standard deviation, median and range. Distribution of variables for normality was assessed by Kolmogorov-Smirnov test (37). Variables that were non-normally distributed were log transformed. Multivariate analysis employed multiple linear regression analysis, with backward elimination ( $P < 0.1$  for parameter retention in the model) with biochemical markers as dependent variables. The independent variables were subcutaneous adipose tissue mass (SAT) or visceral adipose tissue mass (VAT) or total adipose tissue mass (TAT) measured by MRI adjusted for age, sex, presence of diabetes,

weight and race. We also analyzed the effect of VAT on cardiovascular risk factors using VAT as a categorical variable. We divided the population into tertiles and performed an analysis of variance using Tukey's test for significance. We controlled for the effects of age, race, and sex. A two-sided P-value < 0.05 was considered significant. JMP 5.0.1 (SAS Campus Drive Cary, NC 27513 USA) was used for statistical analysis.

## Results

Median BMI was 27.3 kg/m<sup>2</sup> (19.4-46.6), median age was 54.5 years (33-80), median weight 78.1 kg (43.1-120). Median total adipose tissue mass was 24.3 kg (6.2-57.9), median subcutaneous adipose tissue mass was 20.3 kg (5.8-50.8), median visceral adipose tissue mass was 3.25 kg (0.13-8.88), median skeletal muscle mass (SMM) was 23.3 kg (12.2-36.9). Vintage ranged from two months to 15.3 years with a median vintage of 2.8 years. Residual renal function expressed as urea clearance ranged from zero to 7.7 ml/min. Only 9 patients had any urine output. Among those 9 the median residual clearance was 1.4 ml/min. Median and range of risk factor are shown in Table 1.

### Inflammatory Markers

By simple linear regression analysis, CRP was positively associated with SAT ( $r^2 = 0.11$ ,  $P = 0.03$ ), ceruloplasmin positively associated with VAT ( $r^2 = 0.16$ ,  $P = 0.01$ ) and SAT ( $r^2 = 0.2$ ,  $P < 0.005$ ) and  $\alpha 1$  acid glycoprotein was positively associated with SAT ( $r^2 = 0.11$ ,  $P = 0.03$ ) (Table 2). After adjustment for demographic variables the association that remained significant were between both  $\alpha 1$  acid glycoprotein and log CRP and SAT and between ceruloplasmin and VAT (Table 3). IL-6 was not significantly related to any measure of adiposity.

### Lipid Markers

By univariate analysis triglycerides correlated with VAT ( $r^2 = 0.27$ ,  $P = 0.0006$ ) (Figure 1) (Table 2). By multiple regression analysis, TGs were significantly correlated only with VAT after controlling for age, sex, and race (Table 3). When VAT was used as a categorical variable, TGs were significantly greater in tertiles 3 and 2 when compared with patients in the lowest tertile of VAT.

Apo C II correlated with VAT ( $r^2 = 0.24$ ,  $P = 0.001$ ) and SAT ( $r^2 = 0.18$ ,  $P = 0.006$ ) by univariate analysis (Table 2). By multiple regression analysis apo C II correlated either with VAT after adjustment for age, sex and race, (Table 3). Apo C II was significantly greater in patients in the upper two tertiles of VAT compared to tertile I.

Similarly, apo C III correlated with VAT ( $r^2 = 0.22$ ,  $P = 0.0016$ ) (Figure 2) and TAT ( $r^2 = 0.2$ ,  $P = 0.003$ ) by univariate analysis (Table 2). By multiple regression analysis apo C III correlated positively with VAT after adjustment for age, sex, race, (Table 3). Apo C III was significantly greater in patients in the upper two tertiles of VAT compared to tertile I.

Neither HDL cholesterol nor apo A I nor LDL cholesterol correlated with any measures of body composition. In contrast to other lipid markers the  $r^2$  values were approximately zero suggesting no effect of body composition on HDL or apo A I levels in these subjects.

### Adipokines

Adiponectin was significantly and inversely associated with SAT ( $r^2 = 0.20$ ,  $P = 0.0027$ ) and VAT ( $r^2 = 0.37$ ,  $P < 0.0001$ ). By multiple regression analysis, adiponectin was only negatively associated with VAT ( $P < 0.00001$ ) and was not affected by sex or any other anthropometric measurements (Table 3). The relationship between adiponectin and VAT

(Figure 3) was essentially identical between men and women. Adiponectin was significantly greater in patients in the first tertile of VAT compared with the second ( $P < 0.01$ ) and was significantly greater in the first tertile than in either the 2<sup>nd</sup> or the 3<sup>rd</sup> tertile.

Leptin (following log transformation) was positively associated with SAT ( $r^2 = 0.766$ ,  $P < 0.0001$ ), VAT ( $r^2 = 0.47$ ,  $P < 0.001$ ) (Table 2) by univariate analysis but only with SAT by multivariate analysis ( $r^2$  for the model 0.766,  $P < 0.0001$ ) (Table 3).

## Discussion

Mortality is increased with increasing BMI after a minimum mortality at BMIs between 23 and 26 in normal subjects (38,39). Adiposity, especially visceral adiposity, is associated with cardiovascular disease (39,40), hypertension (41) and other cardiovascular risk factors (increased triglycerides, LDL cholesterol, decreased HDL cholesterol and inflammation (10) in patients with normal kidney function. Obesity identified as waist to hip ratio is also a risk factor for incident chronic kidney disease (CKD) (42). Among those patients who develop CKD, waist to hip ratio also was a risk factor for cardiovascular events (43). However, the mean GFR in this cohort was 51.1 ml/min, so that extrapolation of risk to that of prevalent dialysis patient population may not be applicable.

The causal link between cardiovascular mortality and adiposity is proposed at least in part to be a consequence of alterations in blood lipid levels and in inflammation (15,16,44). In contrast to patients having normal renal function, BMI is associated with increasing survival among dialysis patients even at BMI values greater than 39 (1). Thus, obesity in dialysis patients must either contribute some beneficial effect, or specific risk factors linking mortality and adiposity must be mitigated.

We found that components of this relationship, especially the linkage between HDL cholesterol and Apo A I, and to a lesser extent, the relationship between IL-6 and CRP and elements of adiposity were obscured among dialysis patients. By contrast the relationship between VAT and triglyceride-rich lipoproteins was essentially preserved as was the relationship between adiposity and adipokine levels.

The dyslipidemia of CKD, specifically of the apo-B containing lipoproteins, is characterized by reduced clearance (45). Decreased clearance of these lipoproteins is due in part to intrinsic defects in the capacity of triglyceride-rich lipoproteins to act as appropriate substrates for lipolytic enzymes (21) consistent with the presence of an intrinsic structural change in lipoproteins making them less susceptible to lipolysis by LPL. Apo C III is an inhibitor of the action of LPL on TG rich lipoproteins (46,47) and is increased in dialysis patients (20). However while the levels of apo C III were significantly greater than reported for normal subjects (48,49), we found that apo C III levels were associated with VAT within these subjects, similar to the relationship described in patients without renal failure (50). By contrast, LDL cholesterol was low for this population as a whole and was not significantly associated with adiposity.

Inflammation is common among dialysis patients (51) and is well above levels observed in non-dialysis populations (3,12). Inflammation is associated with the malnutrition, inflammation, atherosclerosis (MIA) syndrome (52) providing a basis for inflammation in non obese subjects, potentially obscuring an effect linked to adiposity. Among subjects having normal kidney function, the association between adiposity and either CRP and IL-6 is quite strong, however the median values are significantly lower than we report for here for dialysis patients (53). The upper tertile of CRP found among patients not having kidney disease begins at 3 mg/L (54), a value below the median value among the dialysis patients whom we studied. Similarly median IL-6 values were also well above the upper quartile (>

2.28 pg/ml) among the non dialysis population (14). Axelsson reported an association between truncal fat mass and serum IL-6 levels, however the  $r^2$  value was 0.044 (55). By contrast we found a strong association between the more long lived acute phase protein ceruloplasmin and VAT. Ceruloplasmin has been associated with central obesity in patients not on dialysis (56). Serum IL-6 and CRP values are highly variable temporally in hemodialysis patients, far more so than are the levels of  $\alpha$  1 acid glycoprotein or ceruloplasmin (57) possibly contributing to the decrease in association between these more variable proteins and the adipose pools. Thus, while inflammation and low HDL were indeed found in this population, the risk was either not linked to adiposity at all or only weakly linked to adiposity (CRP), primarily because of low HDL and increased inflammation, at least as reported by short lived makers of inflammation, among lean dialysis patients. The risk factors were present regardless of adiposity and present at a level associated with the highest level of cardiovascular risk in populations not having kidney failure. It is possible that other factors that we have not controlled for have obscured any effects of body composition.

Adiposity remained associated with triglycerides and with the cardiovascular risk factor Apo C III and visceral adiposity was inversely associated with adiponectin. In contrast to patients without kidney failure, adiponectin has been found to be directly associated with mortality in dialysis patients by some investigators, (23), indeterminate by some, (58), while a protective effect has been noted by others (22). It is indeed possible that adiponectin is not in the causal pathway linking body composition to outcome and is simply reflecting adiposity, thus explaining the apparent salutary effect of high adiponectin in the population of patients not having renal failure with a possible deleterious effect observed by some investigators among populations of patients having kidney failure (23).

We previously established in a much larger group of patients (approximately 26,000) that the relationship between HDL cholesterol and BMI was effaced as eGFR declined (59). The main limitation of the current study is that it is small, however we have directly measured both VAT, which is strongly associated with insulin resistance and dyslipidemia, as well as SAT and found that many, but not all risk factors associated with increased adiposity are increased in prevalent hemodialysis patients, regardless of total adiposity or visceral adipose mass. If indeed these risk factors are on the causal pathway to cardiovascular mortality, incremental risks imposed by these factors are not increased among obese dialysis patients. However, other risk factors, specifically associated with triglyceride-rich lipoproteins (TG and apo C III levels) retain the same qualitative relationship to body composition in dialysis patients as they do in subjects having normal renal function. Why obese dialysis patients avoid increased mortality risk despite the residual association between adiposity and these risk factors remains to be established.

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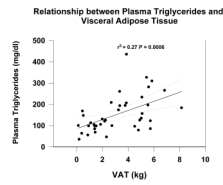
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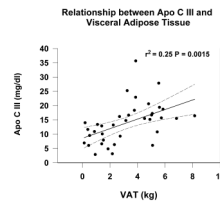


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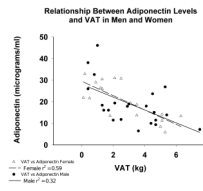
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**Figure 1.** Relationship between serum triglycerides and visceral adipose tissue (VAT) measured by MRI in prevalent hemodialysis patients.



**Figure 2.** Relationship between serum apo C III and visceral adipose tissue (VAT) measured by MRI in prevalent hemodialysis patients.



**Figure 3.** Relationship between serum adiponectin level and VAT measured by MRI in prevalent hemodialysis patients by sex. Men are represented by the open circles and women by the open triangles.

**Table 1**  
**Median and range of Risk Factors Among Dialysis Patients**

CRP g/L	5.0(0.1-260)
IL-6 (pg/ml)	5.5 (1-22)
$\alpha$ 1 AG (mg/dl)	106(46-187)
Ceruloplasmin (mg/dl)	42(23-73)
HDL Cholesterol (mg/dl)	43 (8-79)
Apo A I (mg/dl)	131(89-239)
Triglycerides (mg/dl)	133(36-436)
Apo C III (mg/dl)	15.0(2.9-35.7)
Apo C II (mg/dl)	3.2(0.45-7.66)
LDL Cholesterol (mg/dl)	66(13-142)
Remnants Chol (mg/dl)	3.7(2.1-9.1)
Total Cholesterol (mg/dl)	157(83-236)
Apo B (mg/dl)	60.9(14.9-120)
Adiponectin ( $\mu$ g/ml)	18.4(5.9-59.4)
Leptin (ng/ml)	9.85(0.2-127.2)

Median and range of risk factors in hemodialysis patients.

**Table 2**  
**Relationship between body composition and cardiovascular risk factors in hemodialysis patients**

Relationship between acute phase proteins and body composition by univariant analysis		
	VAT	SAT
Log CRP	NS	P = 0.03 *
Log IL-6	NS	NS
$\alpha$ 1 AG	NS	P = 0.03 *
Ceruloplasmin	P = 0.01	P = 0.005
Relationship between adipokines and body composition by univariant analysis		
	VAT	SAT
Log Leptin	< 0.0001	< 0.0001
Log Adiponectin	< 0.0001*	0.003
Relationship between lipids and body composition by univariant analysis		
	VAT	SAT
Total Cholesterol	NS	0.012 *
Triglycerides	0.0003 *	0.03
LDL	NS	NS
HDL	NS	NS
Apo C II	0.001 *	0.006
Apo C III	0.002 *	0.007
Apo B	NS	NS
Apo A I	NS	NS

Univariant relationship between groups of risk factors, inflammatory markers, adipokines, lipoprotein levels and and measures of adipose mass, visceral adipose tissue (VAT), subcutaneous adipose tissue and (SAT) in hemodialysis patients. All tissue compartments are in kg and were measured by magnetic resonance imaging.

**Table 3**  
**Multivariate analysis of relationship between body composition and cardiovascular risk factors in hemodialysis patients**

Dependent variable	Independent variable	$\beta$	Std. Error	t	P.	Adjusted R <sup>2</sup>	Excluded variables
<b>Log_CRP</b>	Constant	-0.709	0.169	-4.187	.000		Race, sex, age, VAT
	SAT	0.016	0.007	2.314	.026	0.092	
<b><math>\alpha</math>1AG</b>	Constant	85.987	9.670	8.892	.000	0.087	Race, sex, age, VAT
	SAT	.913	0.405	2.254	.029		
<b>Ceruloplasmin</b>	Constant	20.937	5.955	3.516	.001	0.300	Sex, Age, SAT
	VAT	3.181	.809	3.933	.0001		
	Race (black)	14.543	5.011	2.902	.006		
<b>Apo C II</b>	Constant	1.072	.706	1.519	.137	.275	Age, SAT, sex
	VAT	.491	.120	4.077	.0001		
	Race (black)	1.123	.576	1.949	.059		
<b>Apo C III</b>	Constant	9.114	1.714	5.317	.0001	.219	Race, sex, SAT, age
	VAT	1.571	.450	3.491	.001		
	Constant	85.400	21.689	3.938	.000	.262	Race, SAT, sex, age
<b>Triglycerides</b>	VAT	21.965	5.769	3.808	.001		
	Constant	1.618	.079	20.480	.000	.429	Sex, SAT, age
	VAT	-.078	.013	-5.850	.0001		
<b>Log_Adiponectin</b>	Race (black)	-.133	.065	-2.056	.046		
	Constant	-.189	.110	-1.719	.093	.766	Race, age, sex
	SAT	.047	.006	7.388	<.0001		
<b>Log_Leptin</b>	VAT	.053	.030	1.735	.090		