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Abstract

Rationale and Objectives: Adiposity and physical fitness levels are major drivers of cardiometabolic risk, but these relationships have not been well-characterized in chronic kidney disease (CKD). We examined the associations of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intrahepatic fat and physical function with inflammation, insulin resistance, and adipokines in patients with CKD.

Study Design: Prospective cohort study

Setting and Participants: Participants with Stage 3–5 CKD not receiving chronic dialysis, followed at one of 8 clinical sites in the Chronic Renal Insufficiency Cohort study, and who underwent MRI of the abdomen at an annual CRIC Study visit (n=419)

Predictors: VAT volume, SAT volume, intrahepatic fat, body mass index (BMI), waist circumference (WC), and time taken to complete the 400 m walk test (physical function)

Outcomes: Markers of inflammation (IL1-beta, IL-6, TNF-R1, and TNF-R2), insulin resistance (HOMA-IR), and adipokines (adiponectin- total and high molecular weight [HMW], resistin, and leptin).

Analytical Approach: Multivariable linear regression of VAT and SAT volume, intrahepatic fat and physical function, with individual markers (log-transformed values) adjusting for relevant covariates

Results: Mean age of the study population was 64.3 years; 41% were females, and the mean eGFR was 53.2 (+/− 14.6) ml/min/1.73 m^2. Over 85% were overweight or obese, and 40% had diabetes. Higher VAT volume, SAT volume, and liver proton density fat fraction, were associated with lower levels of total and HMW adiponectin, higher levels of leptin and insulin resistance, lower HDL cholesterol and higher serum triglycerides. A slower 400m walk time was associated only with higher levels of leptin, total adiponectin, plasma IL-6 and TNFR-1 and did not modify the associations between fat measures and cardiometabolic risk factors.

Limitations: Lack of longitudinal data and dietary details

Conclusions: Various measures of adiposity are associated with cardiometabolic risk factors. Physical function was also associated with the cardiometabolic risk factors studied and does not

modify the associations between fat measures and cardiometabolic risk factors. Longitudinal studies of the relationship between body fat and aerobic fitness with cardiovascular and kidney disease progression are warranted.

Keywords

Obesity; fat; physical function; kidney disease; cardiometabolic risk factor

Introduction

In the general population, regional fat distribution rather than overall obesity is recognized as a key factor in the link between obesity and cardiovascular disease[1]. Central abdominal obesity is a better predictor of cardiovascular disease than overall obesity as assessed by body mass index (BMI). Importantly, various abdominal fat compartments and distributions have different associations with cardiometabolic risk factors in those without kidney disease[2–7]. However, such relationship in the setting of CKD have not been explored previously. Experimental studies have explored multiple mechanisms underlying the development and progression of kidney disease in the setting of obesity[8]. In both overweight and obesity, increases in renal plasma flow and glomerular hyperfiltration leading to an increased interglomerular pressure are noted. . Furthermore, through the renin-angiotensin-aldosterone system, adipose tissue also contributes to glomerular arteriolar modulation with changes in intraglomerular pressure and filtration fraction[9].

Pro-inflammatory adipokines including adiponectin have been linked to increased urinary protein excretion and cardiovascular disease in patients with obesity[10]. Leptin, a 16-kDa peptide plays a key role in food intake and energy expenditure and may contribute to the progression of kidney disease secondary to the proliferation of endothelial cells and mesangial cell hypertrophy[11]. Data indicate that there may be a differential relationship between visceral and subcutaneous fat and inflammatory adipokines in the general population but whether these associations are similar among those with CKD is unknown. In addition, we know relatively little about the role of physical fitness and cardiovascular risk in CKD. In diabetic and non-diabetic populations (with preserved kidney function), higher physical fitness levels (independently) among those with higher BMI are associated with a lower prevalence of cardiovascular risk factors and mortality compared to those with normal BMI and lower fitness level[12–14]. Indeed, fitness and adiposity may have independent or synergistic relationships with mechanistic pathways for adverse outcomes, individual cardiometabolic risk factors, and clinical outcomes in CKD. Therefore, we examined the associations of visceral adipose tissue (VAT)/subcutaneous adipose tissue (SAT) (assessed using MRI), other obesity measures, and physical function (measured using 400 m walk test, a surrogate measure of physical fitness) with inflammation, insulin resistance, adipokines and lipid parameters among individuals with CKD participating in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods

CRIC study

In the first phase of the CRIC study (2003–2008)-an ongoing multicenter observational cohort study, 3939 adults aged 21–74 years with an eGFR of 20–70 ml/min/1.73 m^2 were recruited from 13 discrete clinical research sites. Later in 2013 (phase 3), an additional 1560 individuals with mild-moderate CKD were recruited and are also currently being followed. Details of the CRIC study have been published previously[15].

CRIC VAP study

We enrolled 449 patients for the CRIC Visceral Adiposity and Physical function (CRIC VAP) study from 8 clinical sites, as an ancillary to the parent CRIC study. CRIC participants aged 21–79 years with an eGFR 25–74 ml/min/1.73 m^2 who were enrolled in Phases 1 and 3 of CRIC were eligible for inclusion. Participants who were on dialysis or had received a kidney transplant, had severe osteoarthritis or peripheral vascular disease precluding participation in a 400 m walk test and/or could not undergo an MRI exam (with metallic implants, pacemaker, claustrophobia, etc.) were excluded. All eligible participants who participated in a 400 m walk test to assess physical functional status and had an MRI to quantify visceral, subcutaneous and intrahepatic fat content. The study protocol was approved by the Institutional Review Board at each of the participating sites. All study participants were consented at their primary sites prior to enrollment.

Covariates

Age, sex, race, smoking, alcohol intake details, comorbid conditions and medication use were obtained at routine study visits. BMI was calculated as weight in kilograms divided by height in meters squared, and waist circumference was measured at the uppermost lateral border of the iliac crest with a Gulick II tape measure.

400 m walk test

A 400 m walk test was administered during routine CRIC study visits to assess physical function and as an indicator of aerobic capacity[16,17]. The test was administered in an open corridor of the clinical unit with two cones spaced 20 m apart. Participants walked 10 laps around the cones for a total of 400 m and were given standard encouragement at each lap. Heart rate was recorded for each lap, and blood pressure was measured at the end of the test. Completion time for the 400 m walk was recorded in seconds. If the participant felt a need to stop and rest, they were allowed to stand in one place and rest. Participants could not lean against a wall, table or elsewhere. Stopping criteria for the test included: (1) if the participant reported chest pain, tightness or pressure in the chest, shortness of breath, feeling faint, lightheaded or dizzy, or severe leg pain, or (2) test duration over 15 minutes.

MRI imaging

Visceral and subcutaneous adipose tissue volume were assessed by magnetic resonance imaging using a standardized protocol. Images of the abdominal cavity were obtained using a Siemens, GE or Philips MR system based on availability at the participating sites. The

quantitative 6-point Dixon proton density fat fraction (PDFF) measurement consisted of multiple 3D axial acquisitions spanning the dome of the liver to the symphysis pubis using 5mm slices. Typically, three breath-hold 3D slabs (obtained at end expiration) were needed to cover this distance, with a minimum of 2 slabs and a maximum of 4 slabs used. Images were reconstructed, combined, and post-processed automatically using the FDA approved commercial PDFF software for each MR system. VAT and SAT volume were quantified using an automated algorithm described in more detail by Addeman et al[18], with a trained observer correcting errors when applicable. The automated segmentation algorithm applies a three-stage process to identity and segment VAT and SAT using fat, water, and PDFF images collected with 6-point Dixon MR technique. Using the combined fat and water image series, the dataset is pre-processed to identify the torso volume from background noise using adaptive k-means clustering. Adipose tissue was then identified by applying the torso volume to the PDFF image and filtering for PDFF values above 70% followed by a region growing algorithm to identify connected partial-volume adipose tissue above 50% PDFF. Finally, SAT and VAT were separated by fitting a 3D surface to the muscles that are proximal to the subcutaneous adipose. Intrahepatic fat content (% PDFF) was obtained by a trained observer placing a circular region-of-interest on a single slice in the PDFF image series and documenting the average PDFF value within the region of interest. A healthy volunteer scan was obtained prior to the study initiation to implement corrective measures to ensure consistency/accuracy of the protocol at each site.

Metabolic Assessments

Blood samples were obtained to determine fasting glucose, insulin, leptin, resistin, total/high molecular weight adiponectin, IL-6, IL-1 beta, TNFR1, and TNFR2 concentrations. Plasma insulin was determined via radioimmunoassay (EMD Millipore, Billerica, MA, USA) and insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR)[19]. IL-6, IL-1 beta, TNFR1, TNFR2, resistin, leptin, total and high molecular weight adiponectin were analyzed via ELISA (R&D systems, Minneapolis, MN, USA). All samples were stored at −80°C, and assays were performed at the time of initial thawing. All assays were performed in duplicate, and mean values were used in the analysis.

Statistical analysis

Clinical and demographic characteristics of the study cohort were tabulated (Table 1). Continuous (biomarkers) variables were checked for skewness and log transformed if they were not normally distributed. We examined SAT and VAT volume within various categories of BMI (18.5–24.99, 25–29.9, and >30) and WC (high or normal: < 88cm in women and <102 cm in men) using Kruskal-Wallis tests. The associations between SAT and VAT and categories of both BMI and WC were examined separately for men and women using the Kruskal-Wallis test. Boxplots were created for SAT and VAT based on stages of kidney disease (stage 3a, 3b and 4) and based on time to complete the 400 m test by quartiles of SAT and VAT. Spearman correlations of VAT, SAT, liver PDFF, BMI, WC and 400 m walk time were performed with each of the cardiometabolic risk factors.

A separate multivariable regression model was constructed for each SD increase in VAT, SAT, intrahepatic fat (liver PDFF), and 400 m walk time as the independent variable and each of the cardiometabolic risk factors as the dependent variable. Cardiometabolic markers were log transformed except for LDL-cholesterol. We did not fit regression models for IL-1 beta as more than half of participants had undetectable levels. We adjusted each model for age, sex, race, diabetes, hypertension, hypercholesterolemia (except for outcomes- HDL, LDL and triglycerides), cardiovascular disease, eGFR and proteinuria. Regression models for 400 m walk test were also adjusted for BMI. Due to co-linearity between BMI and VAT/SAT/intrahepatic fat, we did not adjust for BMI in the multivariable models of VAT/SAT. We also examined VAT/SAT as categorical variables (as quartiles) and studied their relationship with the same cardiometabolic factors. We evaluated 2-way interactions between predictors that were statistically significant in the primary models and sex, and diabetes. We also evaluated the previously mentioned SAT and VAT models including an interaction with physical activity. Covariate data were missing for: BMI (n=1), eGFR (n=2), and urine protein:creatinine ratio (n=26). We used multiple imputation (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain to impute 5 datasets with complete covariate data. All regression models were performed on each of the 5 imputed datasets and parameter estimates were combined with SAS MI analyze.

All statistical analyses were conducted with Linux SAS version 9.4 (SAS Institute, Cary, NC) and graphs were created using R 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p-value of 0.05 was used to determine statistical significance.

Results

Baseline characteristics

Of the 449 participants consented, 432 completed the 400 m walk test; 419 completed the MRI scan, and 409 subjects completed both the walk test and MRI assessment. The 419 participants who completed the MRI exam are included in this study (Figure S1). Mean age of the study population was 64.3 ± 8.5 years; 41% were female, 47.5% were non-Hispanic blacks. Over 85% of participants were overweight or had obesity (BMI >25 kg/m^2), and 40% had diabetes. Mean eGFR was 53.2 ± 14.6 ml/min/1.73 m^2 with a mean urine protein excretion of 0.56 g per day. Other baseline characteristics are presented in Table 1. Median (25^{th}–75^{th} percentile) VAT volume was 5993 mL (3987, 8768) mL, SAT volume was 9405 (6057, 13715) mL and intrahepatic fat was 4.3 (2.7, 7.4) %. All participants completed the 400 m walk test and the median (25^{th}-75^{th} percentile) time taken to complete the test was 384 (334,441) seconds. Details of the baseline lipid parameters, adipokines and inflammatory marker are outlined in Table 1. Baseline VAT and SAT levels based on BMI and WC categories and stratified by gender are presented in Table S1.

Correlations between VAT, SAT, Physical function and other adiposity measures

Time taken to complete the 400 m walk test among those with different levels of SAT and VAT are shown in Table S2. Spearman correlations of VAT, SAT, intrahepatic fat, BMI, WC and 400 m walk test time with metabolic risk factors are displayed in Table 2. VAT, SAT and intrahepatic fat were inversely correlated with total and HMW adiponectin. VAT and

intrahepatic fat were also inversely correlated with HDL cholesterol. VAT, SAT and liver fat were positively correlated with leptin, HOMA-IR, and triglycerides. Similar correlations were also noted for BMI and WC with the cardiometabolic factors. On the other hand, higher levels of physical function was correlated only with leptin, resistin and inflammatory markers.

Associations of adiposity measures and physical function with cardiometabolic factors

Continuous variables—The results of the multivariable-adjusted linear regression analyses for the association of VAT and SAT volume, intrahepatic fat and physical function with continuous metabolic risk factors are summarized in Table 3. Each SD higher VAT and SAT volume and intrahepatic fat were associated with lower levels of total and HMW adiponectin and HDL cholesterol, and higher levels of leptin, insulin resistance and serum triglyceride levels. Each SD higher 400m walk time was associated only with higher levels of total adiponectin, leptin, plasma IL-6 and TNFR-1.

Categorical variable—The results of the multivariable-adjusted linear regression analyses for the association of VAT, SAT or liver PDFF as categorical variables (quartiles) with metabolic risk factors are summarized in Table S3. These results were qualitatively similar to the results of the continuous analyses.

Effect modifiers—The relationship between VAT and log transformed total adiponectin varied by sex (interaction term p= 0.04) suggesting that while the relationship between VAT and adiponectin was significant for both sexes, it was stronger for women than for men (women estimate per 1 SD higher −0.44, SE 0.09, men estimate −0.25, SE 0.05). The association of hepatic PDFF and log transformed HOMA-IR also varied by sex. There also was a significant interaction between liver PDFF and sex on log transformed HOMA-IR, (p=0.01) while higher liver PDFF was associated with higher HOMA-IR in both sexes, the association was stronger for women (women estimate per 1 SD higher 0.39, SE 0.07, men estimate 0.13, SE 0.06). No other significant interactions were noted with sex. No significant interactions were noted with diabetes. There was a significant interaction between VAT and 400 m walk time on log leptin (p=0.008). When we explored the interaction categorizing VAT above and below the median, the interaction was no longer significant, but a longer 400m walk time was associated with an additional increase in log leptin for those with visceral fat above the median VAT.

Discussion

In a cohort of men and women with varying degrees of CKD, a higher VAT volume, SAT volume and visceral fat deposits reflected by intrahepatic fat were associated with higher inflammatory burden, insulin resistance, altered adipokines profile and lower HDL cholesterol and higher triglyceride levels. These associations were similar to the relationship of other traditional measures of adiposity such as BMI and WC, with inflammation, insulin resistance and adipokines. Physical fitness was assessed by time taken to complete the 400 m walk test and was associated only with higher levels of leptin and higher inflammatory burden, and not with other adipokines and insulin resistance. Higher levels of physical

fitness did not modify the associations between adiposity measures and cardiometabolic risk factors in CKD.

Adverse consequences of visceral fat have been attributed to several different mechanistic pathways as follows[3]. The increase in visceral fat is likely a response to an inability to increase SAT in the setting of positive caloric balance. Previous epidemiological investigations in the general population have shown a relationship between various fat depots and cardiometabolic risk factors. Data from the Framingham Heart Study demonstrated that both higher VAT volume and SAT volume were negatively correlated with total adiponectin and resistin, but were positively associated with systemic inflammation (IL-6, C-Reactive protein)[4,20]. In the Dallas Heart study, higher VAT was associated with lower adiponectin, enhanced insulin resistance, and abnormal HDL cholesterol levels. In contrast, SAT was associated with increased leptin and inflammatory markers, but not with insulin resistance, dyslipidemia and other cardiovascular risk factors[21]. Similar findings were also noted by the Jackson Heart Study investigators[6]. In contrast to the general population, the role of SAT/VAT with adipokines, inflammation and insulin resistance have not been examined in those with CKD. Our findings extend our understanding of these critical associations by characterizing them among a large cohort of individuals with CKD. Further, within this population, these relationships seem to be consistent across the sexes unlike what has been noted in the general population[22,23]. It is critical to note that our cohort is older (mean age 64 years vs 46 years in FHS and 44 in the DHS) and also had higher comorbidity burden unlike other study cohorts. Whether the differential associations of VAT and SAT noted in younger populations change with aging and development of comorbidity burden (as noted in our study) is unclear.

Similar to our findings, data from other community-based cohorts also observed higher correlation for both VAT and SAT with BMI/WC, and the association between VAT/SAT with the cardiometabolic factors were independent of overall adiposity[21,24]. We didn't adjust for BMI/WC in the multivariable models due to high collinearity in the models. CKD *per se* is associated with higher CV disease burden, which is mediated in part, by greater inflammation, oxidative stress and insulin resistance. In the Framingham Heart Study, both VAT/SAT were associated with incident cardiovascular risk factors (hypertension, diabetes, HDL cholesterol) during a follow-up of 6 years[25]. We were unable to study this prospective relationship in our study population without pre-existing cardiovascular disease. Whether such a phenomenon exists in CKD is unknown and merits further investigation.

Finding that all metrics of adiposity assessed in our study had similar associations with cardiometabolic risk factors is notable. While MRI metrics are not readily available in clinical settings, BMI and WC can be easily measured. It is important to note that in both dialysis and non-dialysis dependent CKD, higher levels of BMI, but not WC have been associated with a lower risk of mortality[26,27]. Our observation that higher levels of BMI, WC, VAT and SAT were associated with a higher burden of cardiometabolic risk argues for longitudinal studies to assess if these observations will translate to higher CV events and mortality. Body fat distribution varies even within the same BMI range with some having a higher VAT while some with lower level[28]. Whether higher levels of VAT within different

categories of SAT are associated with altered metabolic profile is of interest and warrants further study.

Data from the Framingham Health Study noted that intrahepatic fat was associated with cardiometabolic risk factors including an abnormal lipid profile and elevated BP; however data linking intrahepatic fat with adipokines and inflammatory markers are limited[29]. Our study provides novel data about the relationship between intrahepatic fat and metabolic risk factors in CKD. Higher liver PDFF was associated with several cardiometabolic risk factors including serum triglycerides in this cohort. Even though the exact mechanism for these observed associations are unclear, this may be because VAT and liver PDFF often influence both glucose regulation and lipid metabolism[30]. Higher VAT increases lipolytic activity leading to an increased delivery of hepatic fatty acids to the liver via the portal vein. The increased hepatic fatty acid load in turn increases serum triglyceride levels and contributes to hepatic insulin resistance.

Conflicting data exist regarding the relationship between various fat deposits and the risk of decline in kidney function. Data from the Framingham Offspring study shows that VAT and SAT are associated with CKD when eGFR was calculated using the cystatin C based equation, but not with MDRD[31]. In the Health ABC cohort, SAT, VAT, IMAT ((Intermediate Muscular Skeletal Assessment and Treatment), BMI, and WC (per SD increase) were significantly associated with a decline in kidney function and the authors concluded that anthropometric measures of body fat appear to provide an estimate of the risk of kidney function decline that is consistent with estimates based on CT measures of VAT, SAT[32]. We did not observe any correlation between baseline kidney function and VAT, SAT and liver PDFF in those with established CKD. Thus, whether these have any differential associations with kidney function decline will require future study.

Contrary to our hypothesis, performance on the physical function test did not alter the associations between fat measures and cardiometabolic factors. However, a higher level of physical fitness was associated with higher leptin and adiponectin levels in our cohort. Both in community-dwelling older men and women, higher leptin is associated with increased risk of impaired physical function[33]. Older adults with sarcopenic obesity (especially those with CKD) are also at higher risk of impaired physical function due to a loss of skeletal mass and strength from chronic inflammation and oxidative stress. The association between adiponectin and physical function has been attributed to a decline of skeletal muscle function[34,35]. While we did not formally assess skeletal muscle function, our observations are consistent with this observation.

Strengths of our study include a relatively large sample of patients with clinically diagnosed chronic kidney disease, the use of MRI to precisely quantify VAT, SAT and intrahepatic fat, and a validated protocol to assess aerobic fitness in patients with kidney disease. Further, fidelity of the MRI measure was assured by using the same standardized protocol at each site. We did not restrict the study to those with obesity and enrolled patients with different levels of BMI thereby increasing generalizability. Despite its strengths, we acknowledge limitations. Given the cross-sectional associations, causal relationship among adiposity measures, and cardiometabolic risk factors cannot be established. We enrolled patients who

are being followed in health systems (actively seeking care) and hence whether these data are applicable to those with CKD in the community is unclear.

In summary, different adiposity measures such as BMI, WC, VAT and SAT are associated with various cardiometabolic risk factors highlighting the harmful effects of obesity in CKD. Physical function, as assessed by a 400m walk test was associated with some, but not all cardiometabolic risk factors studied. Notably, level of physical function did not modify the associations between fat measures and the cardiometabolic risk factors. A deeper understanding of the reasons for these differential associations may lead to new approaches to management of patients with CKD. Longitudinal studies addressing the relationship between measures of body fat and aerobic fitness with cardiovascular and kidney disease progression are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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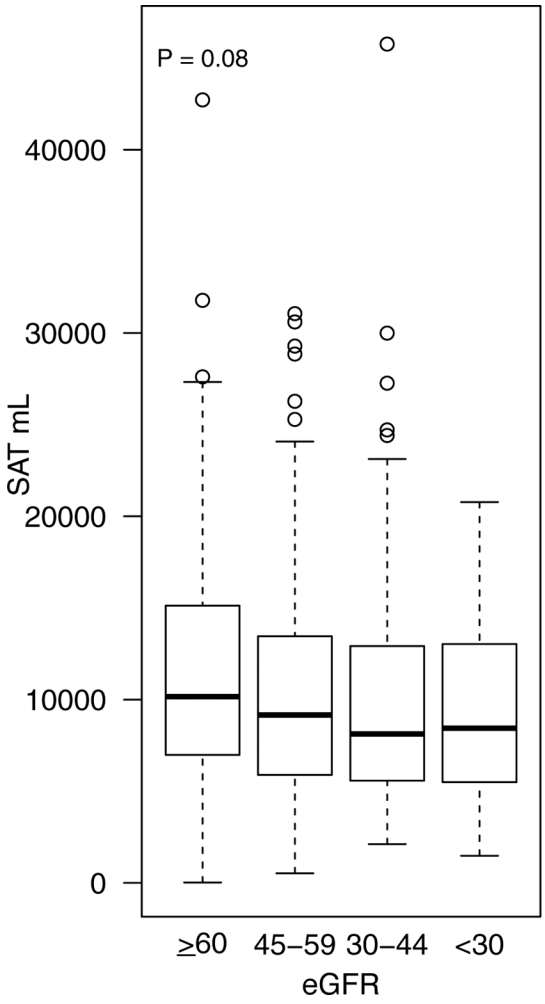
PLAIN-LANGUAGE SUMMARY

Obesity as assessed by body mass index is associated with an increased risk of heart disease and progression of kidney disease in those with chronic kidney disease (CKD). In this cohort of patients with CKD, we studied whether different obesity measures such as intra-abdominal fat, liver fat and sub cutaneous fat (obtained using an MRI scan) were associated with known cardiometabolic risk factors. We further assessed whether physical function (measured using a 400 m walk test) was independently associated with the same cardiometabolic risk factors. Our analysis suggests that all measures of higher fat content were associated with an increased level of cardiometabolic risk factors. While slower walk time were associated with an increased level of cardiometabolic risk factors, it did not modify the associations between fat measures and these risk factors. In summary, these data highlight that various abdominal fat measures and lower physical fitness levels are associated with a higher cardiovascular risk in those with CKD.



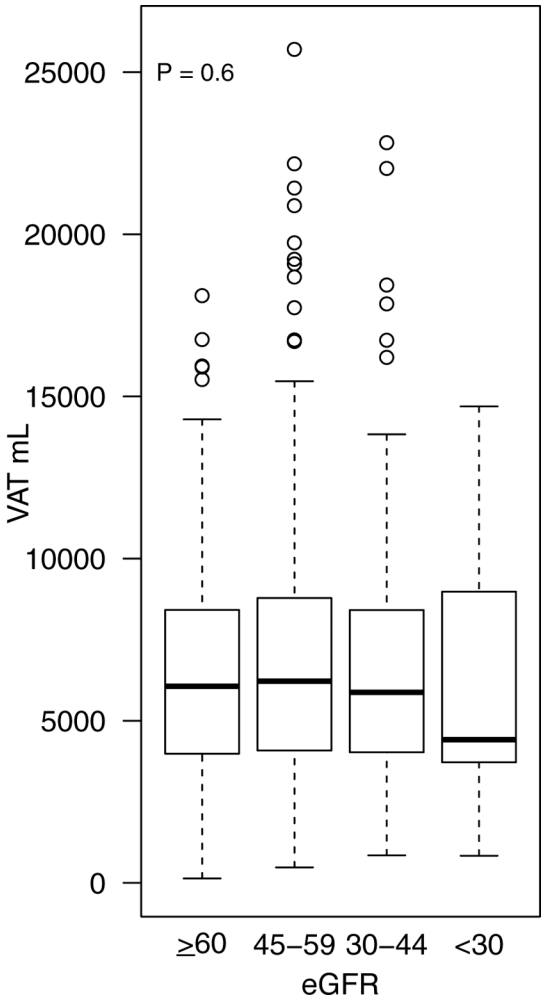


Figure 1—.
Boxplot of SAT and VAT by stage of CKD

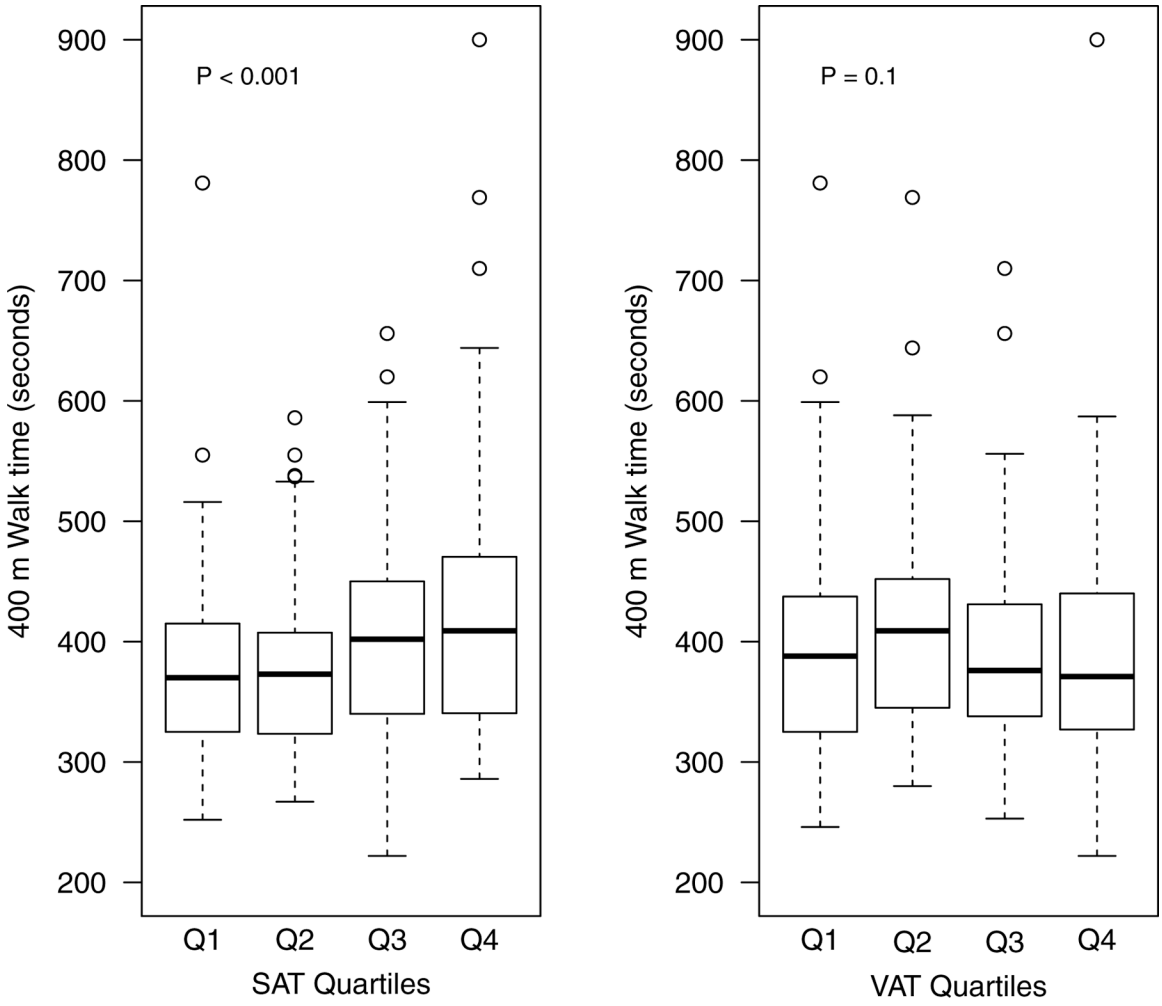


Figure 2—.
Boxplot of 400 m walk test time by quartiles of SAT and VAT

Table 1.

Baseline characteristics of study population

Factor	Total (N=419)
Age (years)	64.3±8.5
Female, N (%)	170(40.6)
Race, N (%)	182(43.4)
Non-Hispanic White	
Non-Hispanic Black	199(47.5)
Hispanic	28(6.7)
Other	10(2.4)
Education category, N (%)	
Less than high school	48(11.5)
High school graduate	72(17.2)
Some college	109(26.0)
College graduate or higher	190(45.3)
BMI (kg/m^2), N (%)	
18.5–24.9	61(14.6)
25–29.9	150(35.9)
30–39.9	179(42.8)
>40	28(6.7)
Weight (kg)	89.2±18.7
Waist Circumference (cm)	104.6±14.6
Systolic BP (mmHg) *	126.7±18.6
Diastolic BP (mmHg) *	69.7±12.0
eGFR (ml/min/1.73 m^2) *	53.2±14.6
CKD stage (ml/min/1.73 m^2, %), N (%)	
≥90	4(0.96)
60 – <90	125(30.0)
45 – <60	174(41.7)
30 – <45	93(22.3)
15 – <30	19(4.6)
<15	2(0.48)
Urine Protein/Creatinine Ratio (g/g)	0.17[0.07,0.59]
Hemoglobin A1C (%)	6.5±1.4
Chronic medical conditions, N (%)	
Atrial fibrillation/other arrhythmia	64(15.3)
Cardiovascular disease	98(23.4)
Congestive heart failure	20(4.8)
Peripheral vascular disease	16(3.8)

Factor	Total (N=419)
CVA	38(9.1)
Chronic Obstructive Pulmonary Disease	48(11.6)
Diabetes	166(39.6)
Family History of CAD	19(4.5)
Hyperlipidemia	345(82.3)
Hypertension	393(93.8)
Smoking (both previous and current)	190(45.3)
Alcohol Use	266(64.1)
Use of ACE Inhibitors or ARBs (%)	278(66.3)
Lipid-lowering drug use (%)	264(63.0)
Glucose (mg/dl)	118.0±45.7
Total cholesterol (mg/dl)	178.0[147.5,208.5]
LDL cholesterol (mg/dl)	101.0[77.0,130.0]
HDL cholesterol (mg/dl)	44.0[36.0,55.0]
Triglycerides (mg/dl)	125.0[89.0,179.0]
Adipokines, inflammatory markers	
Total adiponectin ng/ml	6840[4247,12429]
HMW adiponectin ng/ml	3795[2147,6455]
Leptin pg/ml	29363[13252,59090]
Resistin ng/ml	13.0[9.4,18.4]
TNFR1 pg/ml	2429[1888,3308]
TNFR2 pg/ml	4086[3147,5607]
IL1 beta pg/ml	0.00[0.00,0.21]
IL-6 pg/ml	2.4[1.6,3.9]
MRI data	
Visceral adipose tissue volume, L	5.99[3.98,8.76]
Subcutaneous adipose tissue volume, L	9.40[6.05,13.71]
Intrahepatic fat (PDFF %)	4.3(2.7, 7.4)
400 m walk time (seconds)	384 [334, 441]

*Data not available for all subjects. Missing values: Body Mass Index (kg/m) = 1, Diastolic BP (mmHg) = 5, eGFR - CKD EPI Equation (ml/min/1.73m) = 2, Glucose (mg/dL) = 2, Height (cm) = 1, Urine Protein/Creatinine Ratio from spot sample = 26, Serum Albumin (g/dL) = 2, Systolic BP (mmHg) = 4, 24H Urine Protein (g/24H) = 303, History of Chronic Obstructive Pulmonary Disease (emphysema) = 6, Statistics presented as Mean ± SD, Median [P25, P75], or column %.

Table 2a.

Spearman correlation between cardiometabolic risk factors, VAT, SAT, and intrahepatic fat

Factor	N	VAT rho (95% CI)	p-value	N	SAT rho (95% CI)	p-value	N	Intrahepatic fat rho (95% CI)	p-value
Total Adiponectin	402	−0.39 (−0.47, −0.30)	***<0.001***	402	−0.20 (−0.29, −0.10)	***<0.001***	402	−0.41 (−0.49, −0.33)	***<0.001***
HMW Adiponectin	402	−0.40 (−0.48, −0.31)	***<0.001***	402	−0.19 (−0.28, −0.09)	***<0.001***	402	−0.44 (−0.52, −0.36)	***<0.001***
Leptin	403	0.15 (0.05, 0.24)	***0.003***	403	0.66 (0.60, 0.71)	***<0.001***	403	0.24 (0.15, 0.33)	***<0.001***
Resistin	402	0.04 (−0.06, 0.14)	0.4	402	−0.02 (−0.12, 0.08)	0.6	402	−0.10 (−0.19, 0.00)	0.05
HOMA-IR	373	0.27 (0.17, 0.36)	***<0.001***	373	0.24 (0.14, 0.33)	***<0.001***	373	0.31 (0.22, 0.40)	***<0.001***
IL1B	402	0.17 (0.07, 0.26)	***<0.001***	402	0.17 (0.07, 0.26)	***<0.001***	402	0.04 (−0.06, 0.14)	0.4
IL6	403	0.07 (−0.03, 0.17)	0.2	403	0.15 (0.06, 0.25)	***0.002***	403	0.12 (0.02, 0.21)	***0.020***
TNFAR1	403	0.02 (−0.08, 0.11)	0.8	403	−0.11 (−0.20, −0.01)	***0.03***	403	−0.09 (−0.18, 0.01)	0.08
TNFAR2	402	−0.03 (−0.12, 0.07)	0.6	402	−0.08 (−0.18, 0.01)	0.095	402	−0.03 (−0.13, 0.07)	0.5
HDL cholesterol	376	−0.35 (−0.44, −0.26)	***<0.001***	376	−0.01 (−0.11, 0.09)	0.8	376	−0.24 (−0.33, −0.14)	***<0.001***
LDL cholesterol	375	−0.09 (−0.19, 0.01)	0.07	375	0.13 (0.03, 0.23)	***0.01***	375	−0.06 (−0.16, 0.04)	0.2
Triglycerides	375	0.34 (0.24, 0.42)	***<0.001***	375	0.14 (0.04, 0.24)	***0.006***	375	0.37 (0.28, 0.46)	***<0.001***

Table 2b.

Spearman correlation between cardiometabolic risk factors BMI, WC and physical function

Factor	N	BMI rho (95% CI)	p-value	N	Waist Circumference rho (95% CI)	p-value	N	400m walk time rho (95% CI)	p-value
Total Adiponectin	401	−0.31 (−0.40, −0.22)	***<0.001***	362	−0.33 (−0.42, −0.23)	***<0.001***	392	0.05 (−0.05, 0.14)	0.4
HMW Adiponectin	401	−0.31 (−0.40, −0.22)	***<0.001***	362	−0.35 (−0.43, −0.25)	***<0.001***	392	0.01 (−0.09, 0.11)	0.8
Leptin	402	0.60 (0.54, 0.66)	***<0.001***	363	0.44 (0.35, 0.52)	***<0.001***	393	0.35 (0.26, 0.44)	***<0.001***
Resistin	401	0.05 (−0.05, 0.14)	0.4	362	0.02 (−0.09, 0.12)	0.7	392	0.18 (0.08, 0.27)	***<0.001***
HOMA IR	372	0.38 (0.29, 0.46)	***<0.001***	337	0.38 (0.29, 0.47)	***<0.001***	363	0.07 (−0.03, 0.17)	0.2
IL1-Beta	401	0.04 (−0.05, 0.14)	0.4	362	0.05 (−0.06, 0.15)	0.4	392	−0.01 (−0.11, 0.09)	0.9
IL6	402	0.28 (0.19, 0.37)	***<0.001***	363	0.28 (0.18, 0.37)	***<0.001***	393	0.34 (0.25, 0.43)	***<0.001***
TNFAR1	402	−0.01 (−0.11, 0.08)	0.8	363	0.03 (−0.08, 0.13)	0.6	393	0.26 (0.16, 0.35)	***<0.001***
TNFAR2	401	−0.01 (−0.10, 0.09)	0.9	362	−0.03 (−0.13, 0.08)	0.6	392	0.15 (0.06, 0.25)	***0.002***
HDL cholesterol	375	−0.19 (−0.28, −0.09)	***<0.001***	340	−0.27 (−0.36, −0.16)	***<0.001***	366	−0.02 (−0.12, 0.08)	0.7
LDL cholesterol	374	−0.00 (−0.10, 0.10)	0.9	339	−0.10 (−0.21, 0.00)	0.05	366	−0.03 (−0.13, 0.07)	0.5
Triglycerides	374	0.16 (0.06, 0.26)	***0.001***	339	0.17 (0.06, 0.27)	***0.002***	366	−0.01 (−0.11, 0.09)	0.8

Table 3.

Multivariable linear regression of adipokines, insulin resistance, inflammatory markers (log-transformed) and lipid profile with VAT, SAT, intrahepatic fat, and physical function

Outcome	N	Estimate (per 1 SD increase)	StdErr	Probt
VAT				
Total adiponectin	402	−0.30	0.04	**<0.001**
HMW adiponectin	402	−0.31	0.04	**<0.001**
Leptin	403	0.48	0.05	**<0.001**
Resistin	402	0.05	0.03	0.09
HOMA	373	0.22	0.05	**<0.001**
IL6	403	0.04	0.05	0.3
TNFAR1	403	−0.00	0.01	0.9
TNFAR2	402	0.01	0.02	0.7
HDL cholesterol	376	−0.07	0.02	**<0.001**
LDL	375	1.3	2.3	0.5
Triglycerides	375	0.16	0.03	**<0.001**
SAT				
Total adiponectin	402	−0.21	0.04	**<0.001**
HMW adiponectin	402	−0.22	0.04	**<0.001**
Leptin	403	0.61	0.05	**<0.001**
Resistin	402	0.03	0.03	0.2
HOMA	373	0.17	0.05	**<0.001**
IL6	403	0.08	0.04	0.07
TNFAR1	403	0.00	0.01	0.8
TNFAR2	402	−0.00	0.02	0.9
HDL cholesterol	376	−0.05	0.02	**0.007**
LDL	375	2.7	2.2	0.2
Triglycerides	375	0.07	0.03	**0.009**
Intrahepatic fat				
Total adiponectin	402	−0.31	0.04	**<0.001**
HMW adiponectin	402	−0.36	0.04	**<0.001**
Leptin	403	0.35	0.05	**<0.001**
Resistin	402	0.01	0.03	0.8
HOMA	373	0.25	0.04	**<0.001**
IL6	403	0.11	0.04	**0.007**
TNFAR1	403	0.01	0.01	0.5
TNFAR2	402	0.02	0.02	0.3
HDL cholesterol	376	−0.08	0.02	**<0.001**
LDL	375	−2.7	2.2	0.2
Triglycerides	375	0.19	0.02	**<0.001**

Outcome	N	Estimate (per 1 SD increase)	StdErr	Probt
400 m walk time				
Total adiponectin	392	0.09	0.05	**0.05**
HMW adiponectin	392	0.05	0.05	0.3
Leptin	393	0.10	0.05	**0.04**
Resistin	392	0.04	0.03	0.2
HOMA	363	−0.06	0.05	0.2
IL6	393	0.13	0.05	**0.006**
TNFAR1	393	0.06	0.02	**<0.001**
TNFAR2	392	0.01	0.02	0.7
HDL cholesterol	366	−0.03	0.02	0.2
LDL	366	−2.4	2.5	0.3
Triglycerides	366	−0.03	0.03	0.4

*Adjusted for age, sex, race, diabetes, hypertension, hypercholesterolemia (except for outcomes HDL, LDL and triglycerides), cardiovascular disease, PVD, eGFR, proteinuria.

Models with walk total seconds are also adjusted for BMI.

Estimates obtained from 5 datasets with imputed covariate values created with multiple imputation and MI analyze.