Association of Visceral and Subcutaneous Adiposity with Kidney Function


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Background and objectives: Obesity is a risk factor for incident chronic kidney disease (CKD). Visceral (VAT) and subcutaneous adipose tissue (SAT) may confer differential metabolic risk profiles. The relations of VAT and SAT were analyzed with CKD as estimated by creatinine- and cystatin-based estimating equations.

Design, setting, participants, & measurements: Participants from the Framingham Offspring Study who underwent abdominal computed tomography for VAT and SAT quantification were included (n = 1299; 53% women; mean age 60 yr). CKD was defined as estimated GFR < 60 ml/min per 1.73 m², as estimated using creatinine (n = 89) in the Modification of Diet in Renal Disease (MDRD) formula or by cystatin C (n = 136). Regression models evaluated the cross-sectional relations between VAT and SAT with CKD and cystatin C, with age and gender adjustment and cardiovascular risk factor adjustment.

Results: Neither VAT nor SAT was associated with CKD as estimated by the MDRD equation. In contrast, both VAT and SAT were associated with CKD when defined using cystatin-based equations. The estimated decrease in estimated GFR by cystatin C per 1-SD increase of VAT was 1.9 ml/min per 1.73 m² and for SAT was 2.6 ml/min per 1.73 m² in a multivariable-adjusted model.

Conclusions: VAT and SAT were associated with CKD when defined using cystatin C estimating equations but not when using a creatinine-based estimating equation. Mechanisms linking adipose tissue to cystatin C warrant further research.


Chronic kidney disease (CKD) is common and affects 13.1% of adults in the United States and continues to increase (1). As a consequence of CKD, risk for all-cause and cardiovascular mortality is increased (2). Obesity is a risk factor for CKD, although the mechanisms are poorly understood (3,4). Given the current epidemic of obesity (5), it is important to understand potential mechanisms that link obesity to CKD.

Several studies have suggested that visceral adiposity, as measured by computed tomography (CT) scan, may be a better predictor of cardiovascular disease (CVD) risk factors as compared with traditional clinical anthropometric measures such as body mass index (BMI) and waist circumference (6–8). Whereas clinical anthropometric measures offer easily obtainable measures of central adiposity, they do not allow for the differentiation between subcutaneous and visceral fat. One previous study suggested that central obesity as estimated by waist-to-hip ratio was inversely associated with level of kidney function (9). Because of the inability of waist-to-hip ratio to detect subcutaneous as compared with visceral fat, it is uncertain whether there is a differential association between abdominal fat compartments and kidney function.

Given the previous literature suggesting strong associations between metabolic risk factors with both visceral fat and CKD, we hypothesized that community-dwelling individuals with more visceral abdominal adiposity would be more likely to have CKD, using creatinine-based estimating equations. We also sought to relate cystatin C, a novel marker of kidney function, and cystatin C–based estimation of GFR to visceral (VAT) and subcutaneous adipose tissue (SAT).

Materials and Methods

Study Sample

Participants were drawn from the Framingham Offspring Study, a community-based study of the children and their spouses of the original Framingham Heart Study participants. Framingham participants were 99.7% white (10). Multidetector CT was conducted on 1418 participants who participated in a CT substudy from 2002 through 2005. Inclusion criteria were men age at least 35 or nonpregnant women at least age 40 yr. All patients had to weigh <160 kg. Inclusion in this CT substudy was weighted toward participants from larger Framingham

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ISSN: 1555-9041/306–1786
families and toward those who resided in the Northeast. Exclusion criteria from this analysis were missing VAT and/or SAT measurements (n = 41), missing creatinine at examination 7 (n = 43), missing cystatin C at examination 7 (1998 through 2001; n = 32), missing BMI data (n = 1), and BMI <18.5 (n = 2), resulting in 1299 participants who were part of this study.

The institutional review boards of Massachusetts General Hospital and Boston University Medical Center approved this study. Written consent was obtained from all participants. The authors had full access to and take full responsibility for the integrity of the data.

Adipose Tissue Volumetric Imaging and Measuring
Participants had an abdominal multislice CT scan covering 125 mm above the level of S1 using a slice collimation of 8.0 × 2.5 mm (120 kVp, 300 mA, rotation time 500 ms) for quantification of VAT and SAT. VAT and SAT were quantified using pixel measurement (Aquarius 3D Workstation; TeraRecon Inc., San Mateo, CA). The image display window width of −195 to −45, with a center window of −120 Hounsfield units identified fat-containing pixels. The abdominal wall separating VAT and SAT was traced manually. Two independent readers assessed interreader reliability on 100 random participants. VAT interclass correlation was 0.992, and SAT interclass correlation was 0.997 (11). CT scans were done on average 4.5 yr after biochemical data were obtained.

Kidney Measurements
CKD was defined as estimated GFR (eGFR) <60 ml/min per 1.73 m². Serum creatinine was measured by colorimetric Jaffe reaction (Roche Hitachi 911; Roche Diagnostics Corporation, Indianapolis, IN). Intra-assay coefficient of variation (CV) was 4.0%, and interassay CV was 2.8%. Serum creatinine was statistically indirectly calibrated to Third National Health and Nutrition Examination Survey (NHANES III) data (12,13). Creatinine-based GFR (eGFRcys) was estimated by the four-variable Modification of Diet in Renal Disease (MDRD) equation: eGFRcys = 186 × Pcr⁻¹.154 × age⁻⁰.²⁰³ × 1.212 (if black) × 0.742 (if female) (14). Serum cystatin C was measured by nephelometry on previously frozen samples, which were stored at −80°C (Dade Behring Diagnostic, Marburg, Germany). The CV intra-assay was 2.4%, and interassay was 3.3%. The detection range was 0.29 to 7.22 mg/L. Cystatin C–based GFR (eGFRcys) was estimated using a recently derived, validated equation (eGFRcys = 76.7 × Scys⁻¹.¹⁸) (15).

Covariates
Covariates were selected on the basis of our previous work in examining risk factors for the development of CKD over time (12). Fasting morning laboratory measurements were assessed at the examination cycle. BMI was measured as the weight in kilograms divided by the height squared in meters. BP was obtained by a physician using a sphygmomanometer, with participants seated. The average of two BP readings was used. Hypertension was defined as the average systolic BP ≥140 mmHg, average diastolic BP ≥90 mmHg, or antihypertensive medication use. Diabetes was defined as fasting blood glucose level ≥126 mg/dL, taking oral hypoglycemics, or using insulin. Current tobacco use was defined as at least one cigarette daily for the past year. Postmenopausal status was defined as >1 yr without a menses. High alcohol consumption was defined as ≥14 drinks weekly for men and ≥7 drinks weekly for women (16).

Statistical Analyses
SAT and VAT were standardized to a mean of 0 and SD of 1 to facilitate direct comparison of regression coefficients. The association between VAT or SAT and CKD was evaluated with logistic regression, using eGFR <60 ml/min per 1.73 m², estimated by both the MDRD creatinine-based equation and the cystatin C–based estimating equation. For assessment of relations between VAT or SAT and cystatin C concentration, eGFRcys was modeled as a continuous dependent variable using linear regression.

All models were first age and gender adjusted, and then multivariable adjusted (age, gender, systolic BP, hypertension treatment [yes/no], HDL cholesterol, lipid treatment [yes/no], diabetes [yes/no], prevalent CVD [yes/no], tobacco use [yes/no], menopausal status [yes/no], hormone replacement therapy [yes/no], and excess alcohol use [yes/no]). In a secondary analysis, we tested for effect modification with gender. A two sided P < 0.05 was considered statistically significant for all results.

Results
The mean age of the sample was 60 yr, and 53% were women. The prevalence of CKD on the basis of the MDRD estimation was 6.9% (n = 89). The prevalence of CKD on the basis of eGFRcys was 10.5% (n = 136); overall, 54 people were defined as having CKD by both measures. Study participant characteristics, creatinine, and cystatin C data are presented in Table 1. The age- and gender-adjusted correlation between VAT and SAT was 0.58. Mean BMI was 28.3 kg/m², and 30% of participants were obese. The correlation of VAT with BMI and waist circumference was 0.65 and 0.67, respectively (P < 0.001); the correlation of SAT with BMI and waist circumference was 0.78 and 0.81, respectively (P < 0.001) (17).

Associations between VAT, SAT, and CKD
Neither VAT nor SAT was associated with CKD when using the MDRD equation. In age- and gender-adjusted analyses, the odds ratio of CKD per 1 SD of VAT was 1.05 (95% confidence interval [CI] 0.82 to 1.34; P = 0.72). Results were similar after multivariable adjustment (OR 0.90; 95% CI 0.68 to 1.18; P = 0.45). Similar results were observed for SAT in age- and gender- and multivariable-adjusted models (Table 2).

VAT and SAT were associated with CKD when determined by eGFRcys. An increase in 1 SD of VAT was associated with a 48% increase in the odds of CKD (OR 1.48; 95% CI 1.24 to 1.78; P < 0.001) in an age- and gender-adjusted model. In the multivariable-adjusted model, 1 SD of VAT was associated with a 35% increase risk for CKD (OR 1.35; 95% CI 1.10 to 1.65; P = 0.006). Similar results were observed for SAT. Upon adjustment for BMI and waist circumference, findings were attenuated (P > 0.55).

Associations between VAT, SAT, and eGFRcys
VAT and SAT were associated with eGFRcys also when evaluated as a continuous analysis (Table 3). The estimated decrease in eGFRcys per 1-SD increase of VAT was 2.6 ml/min per 1.73 m² (95% CI 1.9 to 3.4; P < 0.001) in an age- and gender-adjusted model and 1.9 (95% CI 1.0 to 2.8; P < 0.001) in a multivariable-adjusted model. Findings were similar for SAT (Table 3). In secondary analyses, we tested for effect modification by gender with CKD as defined by creatinine and cystatin; no significant interactions were observed (all P > 0.21).
Potential Mechanisms

Inflammation, insulin resistance, endothelial dysfunction, and activation of the renin-angiotensin system, all of which may be interrelated, may explain the link between adipose tissue and cystatin C (26–30). Visceral adiposity is a key regulator of numerous adipokines and cytokines, including leptin, cystatin C, and other adipokines. This indicates that visceral adiposity may be a key mediator in the development of renal dysfunction. Cystatin C has been independently associated with obesity and waist circumference in multivariable regression models (20–22). Adipocytes have been shown to secrete cystatin C (23). The Health ABC study found that cystatin C was associated with both BMI and lean body mass, suggesting that cystatin C may be associated with underlying metabolism (24). Age, gender, height, weight, tobacco use, and even C-reactive protein have been associated with cystatin C, despite adjustment for creatinine clearance (22). Also, cystatin C was increased by administering corticosteroids, supporting the concept that cystatin C may not be purely a marker of kidney function (25); therefore, our findings may be due to extrarenal sources of cystatin C and may not solely represent a pathologic association between adipose tissue and cystatin C as a marker of kidney function. Despite this, most studies have shown that iothalamate GFR is the primary determinant of cystatin C (18,19); however, if fat mass is associated with cystatin C, then cystatin C–based GFR estimating equations may be confounded by increasing adiposity. It is likely that these two explanations are not mutually exclusive, and both may be partly true.

Context within the Current Literature

Obesity, as measured by BMI, has been associated with kidney disease, independent from other comorbidities. A large cohort study of Kaiser Permanente patients found that higher BMI was associated with increasing odds for developing ESRD (4). The Physicians’ Health Study found that participants with higher baseline BMI were more likely to have CKD after 14 yr of follow-up (3). The cross-sectional Prevention of Renal and Vascular End-stage Disease (PREVEND) study of 7676 participants without diabetes found that a central pattern of fat distribution, as determined by waist-to-hip ratio, was associated with increased risk for decreased eGFR, in obese people as well as normal-weight people (9). Our findings that VAT and SAT are associated with higher levels of cystatin C may support the concept that central adiposity, including both abdominal visceral adiposity and subcutaneous fat in the abdominal area, is associated with CKD.
adiponectin, and resistin (31), and has also been associated with insulin resistance, metabolic syndrome, and diabetes (32–34), all physiologic processes that have been connected with incident CKD. Despite the literature linking VAT with metabolic processes, recent work also suggested that SAT is an important correlate of metabolic risk factors (17,35), as well as markers of inflammation and oxidative stress (36). These associations may help to explain our findings that both VAT and SAT are similarly associated with cystatin C.

Limitations

The limitations of the study include the cross-sectional design and lack of longitudinal data; therefore, causality cannot be inferred. Our sample was nearly all white, and it is uncertain whether these findings would be generalizable to other ethnic groups. Biochemical tests and weight were collected 4.5 yr before the CT scan assessment; however, this would not explain the differential association between VAT, SAT, and cystatin C as compared with CKD. Because cystatin C and eGFR are measured at the same time, this should not affect our detection of differences in the relationship between these variables and adipose tissue. Creatinine may be a better measure of kidney function, although it likely underestimates glomerular filtration. Cystatin C estimating equations overestimate glomerular filtration (15), which would not explain the results of our study. Another limitation was that we had relatively few participants with CKD and had only modest power to detect an association. Also, although the differences in eGFR are statistically significant, in absolute terms, they are small. The severity of CKD in our sample was moderate; therefore, it is unclear whether our findings are generalizable to samples with more severe CKD. However, our results are generalizable to stage 3 CKD, which is the largest group of patients with kidney disease in the United States (13).

Implications for Further Research

Given the epidemic of obesity and type 2 diabetes (5) and the increasing burden of CKD in the American population (1,37), understanding the cause of obesity-related CKD is of critical importance. Previous literature suggested that VAT and SAT convey differential risk (31). Given the complex nature of this relationship, mechanistic studies, as well as prospective studies, are needed to elucidate further the complex interplay of risk factors. Interventions may therefore be targeted to the appropriate population and risk factors. In addition, the potential impact of adipose tissue on cystatin C production needs to be further elucidated, given the implications for cystatin C–based GFR equations.

Conclusions

Both VAT and SAT were associated with CKD but only when defined as eGFR <60 ml/min per 1.73 m² as estimated by

<table>
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<tr>
<th>Exposure</th>
<th>Model Adjustment</th>
<th>OR per 1 SD VAT or SAT</th>
<th>95% CI</th>
<th>P</th>
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<td>1.34 to 1.70</td>
<td>0.0020</td>
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<sup>a</sup> CI, confidence interval; OR, odds ratio.
<sup>b</sup> Multivariable models adjusted for age, sex, systolic BP, hypertension treatment, HDL cholesterol, lipid treatment, diabetes, prevalent CVD, tobacco, menopausal status, hormone replacement therapy, and alcohol use.

<table>
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<th>Exposure</th>
<th>Model</th>
<th>Decrease per 1 SD VAT or SAT</th>
<th>95% CI</th>
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<td>1.8 to 3.4</td>
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<td>2.6</td>
<td>1.8 to 3.3</td>
<td>&lt;0.001</td>
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<sup>a</sup> β Coefficients are expressed in ml/min per 1.73 m<sup>2</sup>.
<sup>b</sup> Multivariable models adjusted covariates listed in Table 2 legend.
cystatin C, not creatinine. Higher levels of VAT or SAT were associated with higher cystatin C concentrations. Mechanisms linking adipose tissue to cystatin C warrant further research.

Acknowledgments

This study was supported by the National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195). R.S.V. is supported in part by 2K24HL04334 (National Heart, Lung, and Blood Institute’s Framingham Heart Study (N01-HC-25195). R.S.V. is supported in part by 2K24HL04334 (National Heart, Lung, and Blood Institute’s Framingham Heart Study). None.

Disclosures

None.

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