Epidemiology/Population Science

Fatty Kidney, Hypertension, and Chronic Kidney Disease
The Framingham Heart Study

Meredith C. Foster, Shih-Jen Hwang, Stacy A. Porter, Joseph M. Massaro, Udo Hoffmann, Caroline S. Fox

See Editorial Commentary, pp 756–757

Abstract—Ectopic fat depots may mediate local and systemic disease. Animal models of diet-induced obesity demonstrate increased fat accumulation in the renal sinus. The association of renal sinus fat with hypertension, chronic kidney disease, and other metabolic disorders has not been studied in a large, community-based sample. Participants from the Framingham Heart Study (n=2923; mean age: 54 years; 51% women) underwent quantification of renal sinus fat area using computed tomography. High renal sinus fat (“fatty kidney”) was defined using sex-specific 90th percentiles in a healthy referent subsample. Multivariable linear and logistic regression was used to model metabolic risk factors as a function of fatty kidney and log-transformed renal sinus fat. Multivariable models were adjusted for age, sex, and outcome-specific covariates and then additionally adjusted for body mass index or abdominal visceral adipose tissue. The prevalence of fatty kidney was 30.1% (n=879). Individuals with fatty kidney had a higher odds ratio (OR) of hypertension (OR: 2.12; P<0.0001), which persisted after adjustment for body mass index (OR: 1.49; P<0.0001) or visceral adipose tissue (OR: 1.24; P=0.049). Fatty kidney was also associated with an increased OR for chronic kidney disease (OR: 2.30; P=0.005), even after additionally adjusting for body mass index (OR: 1.86; P=0.04) or visceral adipose tissue (OR: 1.86; P=0.05). We observed no association between fatty kidney and diabetes mellitus after adjusting for visceral adipose tissue. In conclusion, fatty kidney is a common condition that is associated with an increased risk of hypertension and chronic kidney disease. Renal sinus fat may play a role in blood pressure regulation and chronic kidney disease. (Hypertension. 2011;58:784-790.) • Online Data Supplement

Key Words: renal sinus fat ■ hypertension ■ chronic kidney disease ■ blood pressure ■ computed tomography ■ epidemiology

Obesity continues to be an important global public health problem. Current estimates indicate that more than two thirds of American adults1 and 1.3 billion adults worldwide2 are either overweight or obese. The impact of obesity on cardiovascular and metabolic diseases, including diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and cardiovascular mortality, is well established.3 In addition, obesity is now recognized as a risk factor for the development of renal dysfunction, with a growing body of evidence supporting the association of higher body mass index (BMI) with chronic kidney disease (CKD).4–6

BMI is a good measure of general adiposity, but it captures both lean and fat mass and does not distinguish between patterns of fat distribution. Abdominal adiposity, independent of generalized obesity, is associated with CKD.7,8 The association of regional fat deposition with CKD suggests a potential role for ectopic fat.9 This is particularly relevant for the kidneys, which are surrounded by abdominal visceral adipose tissue (VAT) and have the potential to accumulate ectopic fat in the renal sinus.

The accumulation of renal sinus fat is important because the renal vein and artery pass through the renal sinus and may be compressed by ectopic fat. Renal vein constriction has been shown to increase kidney volume and renal interstitial pressure and to decrease sodium excretion in animal models.10–13 Human studies and animal models have demonstrated fat accumulation in the renal sinus9,14,15 and renal parenchyma.16–19 Concomitant structural and functional changes in the kidney and renal vasculature have been observed in animal models.14,17–19 However, whether these...
renal changes are associated with diseases of the kidney in humans is uncertain. The association of renal sinus fat with hypertension, CKD, and other metabolic traits has not been characterized previously in a large, community-based sample. Thus, the aim of this study was to evaluate the association of renal sinus fat accumulation, or “fatty kidney,” quantified using computed tomography with these cardiometabolic and renal traits in the Framingham Heart Study. We hypothesized that renal sinus fat would be independently associated with measures of blood pressure and renal function and not with other cardiometabolic traits, after accounting for abdominal VAT as a measure of abdominal adiposity.

Methods

Study Sample

Participants were drawn from the Framingham multidetector computed tomography (MDCT) cohort, which consists of 3529 participants from the Framingham offspring (n=1418) and third-generation (n=2111) cohorts who underwent MDCT between June 2002 and March 2005, as described previously.20 Eligible participants included 2923 participants who attended the eighth offspring or first third-generation examination with an interpretable abdominal MDCT scan. A subsample consisted of 1210 offspring participants with serum cystatin-C measured during the seventh offspring examination. Participants provided written informed consent, and this study was approved by the Boston University Medical Center and Massachusetts General Hospital institutional review boards.

Renal Sinus Fat Quantification

Abdominal MDCT scans were captured using an 8-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI), covering 125 mm in the abdomen with 25.0-mm slices above the S1 level (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1), and were interpreted using the Aquarius 3D Workstation (TeraRecon, Inc, San Mateo, CA). Renal sinus fat was quantified in a single MDCT slice within the right kidney. Briefly, renal sinus fat (in centimeters squared) was measured by 1 reader manually tracing the right kidney from the abdominal MDCT scan after applying a selection rule to a set of candidate slices selected based on visual inspection. Adipose tissue was identified using MDCT pixel density in Hounsfield units (HU) centered on −120 HU with a window width of −195 to −45 HU. The interclass correlation coefficients were 0.93 and 0.86 for intrareader and interreader reproducibility, respectively. Our complete protocol appears in the supplementary methods in the online Data Supplement (please see http://hyper.ahajournals.org).

Outcome Assessment

Systolic (SBP) and diastolic (DBP) blood pressures were measured by the examining clinic physician using the mean of 2 readings. Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or current use of prescription hypertension medication. Imputed blood pressure values were calculated by adding 10 mm Hg to SBP and 5 mm Hg to DBP if a participant was currently using hypertension medication.21 Serum creatinine was measured using the modified Jaffé method (interassay coefficient of variation [CV]: 2.8%; intra-assay CV: 4.0%; Roche Hitachi 911, Roche Diagnostics, Indianapolis, IN) and indirectly calibrated to the Third National Health and Nutrition Examination Survey serum creatinine values as described previously.22 Cystatin C was measured using nephelometry on previously indirectly calibrated to the Third National Health and Nutrition Examination Survey serum creatinine values as described previously.22 Cystatin C was measured using nephelometry on previously calibrated creatinine samples. Urinary creatinine was quantified using a Tina-quant albumin immunoturbidimetric assay (interassay CV: 3.1%; intra-assay CV: 2.1%; Roche Diagnostics). Urinary creatinine was quantified using a modified Jaffé method (interassay CV: 1.9%; intra-assay CV: 1.0%; Roche Diagnostics). The urinary albumin:creatinine ratio was calculated by dividing the amount of urinary albumin (in milligrams) by the amount of urinary creatinine (in grams). Microalbuminuria was defined as a urinary albumin:creatinine ratio >25 mg/g in women or >17 mg/g in men. Serum levels of fasting plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined using a fasting blood sample from the clinic examination. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL or current use of oral hypoglycemic treatment or insulin. High triglycerides were defined as serum triglycerides ≥150 mg/dL or current use of lipid-lowering medication. Low HDL cholesterol was defined as HDL cholesterol <50 mg/dL in women and <40 mg/dL in men.

Covariate Assessment

Height and waist circumference at the umbilicus were recorded to the nearest quarter inch and weight to the nearest pound by trained clinic staff. BMI was defined as weight divided by height2 (in kilograms per meter squared). Abdominal VAT volume was assessed by MDCT.20 Current smoking was defined as smoking ≥1 cigarette per day in the past year. High alcohol intake was defined as >7 drinks per week among women and >14 drinks per week among men based on self-report. Physical activity was determined by calculating a physical activity index based on a structured questionnaire.

Statistical Methods

Fatty kidney was defined as the presence of high renal sinus fat based on sex-specific 90th percentiles in a healthy referent subsample, defined using the following exclusion criteria: (1) BMI ≥30 kg/m2; (2) hypertension, high triglycerides, low HDL cholesterol, impaired fasting plasma glucose, or diabetes mellitus; (3) CKD_eGFR or microalbuminuria; (4) current smoking; (5) BMI <18.5 kg/m2; and (6) missing covariates described in the previous exclusion steps and other model covariates. The healthy referent sample consisted of 400 women and 213 men, with 90th percentile renal sinus fat cut points of 0.445 cm2 in women and 0.710 cm2 in men.

Renal sinus fat measurements below the observed lower limit of detection (0.0048 cm2) were set to 0.0040 cm2 in statistical analyses. Age- and sex-adjusted partial Pearson correlation coefficients were used to assess the correlation of log-transformed renal sinus fat with continuous covariates. Renal sinus fat was modeled dichotomously as fatty kidney and continuously with a natural-log transformation, standardized to a sex-specific mean of 0 and SD of 1. Linear and logistic regression was used to model continuous and dichotomous outcomes as functions of renal sinus fat. Models were initially adjusted for age and sex and then underwent further multivariable adjustment. Multivariable models of hypertension, imputed SBP, and imputed DBP, were adjusted for age, sex, current smoking, high alcohol intake, and physical activity index. Multivariable models of eGFR and CKD were adjusted for age, sex, diabetes mellitus, hypertension medication use, SBP, current smoking, and HDL cholesterol. Multivariable models of HDL cholesterol were adjusted for age, sex, current smoking, high alcohol intake, and lipid lowering medication use. Multivariable models of triglycerides were adjusted for age, sex, and current smoking. Finally, multivariable models were separately adjusted for BMI and abdominal VAT. To help disentangle the potential association of renal sinus fat and abdominal VAT with blood pressure and eGFR, we examined trends across sex-specific renal sinus fat tertiles within sex-specific abdominal VAT tertiles. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).
Secondary Analyses
As a secondary analysis, we recreated the healthy referent sample excluding individuals with BMI ≥25 kg/m² instead of BMI ≥30 kg/m² (“lean healthy referent”) and determined the sex-specific 90th percentile cut points. The lean healthy referent sample included 282 women and 100 men; the 90th percentile cut points were 0.420 cm² in women and 0.455 cm² in men.

Results

Overall Study Sample Characteristics
Renal sinus fat ranged from the lower limit of detection in 133 participants to 4.89 cm² with a median value of 0.31 cm². The prevalence of fatty kidney (renal sinus fat ≥0.445 cm² in women and ≥0.710 cm² in men) was 30.9% in the overall sample (n = 879). Individuals with fatty kidney were older, had a higher BMI, and had a more adverse metabolic risk factor profile when compared with individuals without fatty kidney. The prevalence of hypertension, CKDcrea, CKDcys, and microalbuminuria was also higher among those with as compared with those without fatty kidney (Table 1). Age- and sex-adjusted correlations of renal sinus fat with adiposity measures and continuous covariates are presented in Table 2. Renal sinus fat was correlated with all of the covariates examined (P ≤0.03) except urinary albumin:creatinine ratio (P = 0.18), with the strongest correlations observed for other adiposity measures and age.

Renal Sinus Fat and Hypertension
Individuals with fatty kidney had a higher odds ratio (OR) for hypertension (Table 3; OR: 2.12; P < 0.0001), which persisted after adjustment for BMI (OR: 1.49; P < 0.0001) or VAT (OR: 1.24; P = 0.049). Individuals with fatty kidney also had higher imputed SBP (4.8 mm Hg) and DBP (2.3 mm Hg) compared with those without fatty kidney (Table 3; both P < 0.0001). In models with continuous renal sinus fat as the exposure, estimates were similar (Table S1, please see the online Data Supplement).

Renal Sinus Fat and Renal Function
Among participants with cystatin C measurements (n = 1210), 5.9% (n = 71) had CKDcrea. Fatty kidney was associated with an increased OR for CKDcrea (Table 3; OR: 2.30; P = 0.005), which persisted after adjustment for BMI (OR: 1.86; P = 0.04) or VAT (OR: 1.86; P = 0.05). Fatty kidney was associated with an increased OR for CKDcrea after age and sex adjustment (OR: 1.49; P = 0.04) but not after multivariable adjustment (Table 3; OR: 1.14; P = 0.53).

The prevalence of microalbuminuria was 13.4% among individuals with fatty kidney and 6.0% among those without fatty kidney (Table 1). Fatty kidney was associated with an increased OR of microalbuminuria in age- and sex-adjusted models (OR: 1.45 [95% CI: 1.08–1.94]; P = 0.01), which was attenuated and no longer statistically significant after multivariable adjustment (OR: 1.17 [95% CI: 0.86–1.59]; P = 0.31).

Renal Sinus Fat and Additional Metabolic Risk Factors
Fatty kidney was associated with an increased OR for diabetes mellitus after age and sex adjustment (OR: 2.26; 95% CI: 1.74–2.93; P < 0.0001; Table 4), which was attenuated after adjustment for VAT (OR: 1.09; P = 0.62); similar results were observed for fasting plasma glucose (Table 4). Similarly, fatty kidney was associated with an increased OR for high triglycerides (Table 4; OR: 1.88; P < 0.0001) but not after adjustment for VAT (OR: 1.04; P = 0.69).

Abdominal Fat Distribution Patterns and CKD
The prevalence of CKDcrea and CKDcys by fat distribution pattern category is presented in the Figure. The highest prevalence of both conditions was observed among individuals with fatty kidney and high VAT. The prevalence of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fatty Kidney (n = 879)</th>
<th>No Fatty Kidney (n = 2044)</th>
<th>Age- and Sex-Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 ± 13</td>
<td>51 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Women, %</td>
<td>42.7 (375)</td>
<td>54.6 (117)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Renal sinus fat, cm²†</td>
<td>0.97 (0.73, 1.34)</td>
<td>0.18 (0.06, 0.33)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.3 ± 5.7</td>
<td>26.6 ± 4.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Visceral adipose tissue, cm³</td>
<td>2557 ± 1040</td>
<td>1456 ± 842</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>106 ± 14</td>
<td>94 ± 14</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>52 ± 15</td>
<td>57 ± 18</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL †</td>
<td>117 (82, 165)</td>
<td>91 (66, 134)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>129 ± 17</td>
<td>120 ± 15</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75 ± 11</td>
<td>75 ± 9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57.8 (508)</td>
<td>26.6 (543)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Use of antihypertensive medication, %</td>
<td>46.2 (406)</td>
<td>18.6 (381)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>14.6 (128)</td>
<td>4.2 (86)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current smoking status, %</td>
<td>10.5 (92)</td>
<td>12.6 (257)</td>
<td>0.17</td>
</tr>
<tr>
<td>High alcohol intake, %‡</td>
<td>9.2 (123)</td>
<td>11.2 (228)</td>
<td>0.003</td>
</tr>
<tr>
<td>Physical activity index, 17</td>
<td>36 ± 7</td>
<td>37 ± 7</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFRcrea, mL/min/1.73 m²</td>
<td>84.9 ± 19.8</td>
<td>90.9 ± 17.8</td>
<td>0.40</td>
</tr>
<tr>
<td>CKDcrea, %</td>
<td>9.2 (81)</td>
<td>2.8 (57)</td>
<td>0.04</td>
</tr>
<tr>
<td>eGFRcys, mL/min/1.73 m²‡</td>
<td>81 ± 17</td>
<td>89 ± 16</td>
<td>0.0005</td>
</tr>
<tr>
<td>CKDcys, %§</td>
<td>9.1 (53)</td>
<td>2.8 (18)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Urinary albumin:creatinine ratio, mg/g†</td>
<td>5.4 (3.1, 11.1)</td>
<td>4.5 (2.8, 8.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
<td>13.4 (118)</td>
<td>6.0 (123)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Sex-specific cut points for fatty kidney are ≥0.710 cm² in men; ≥0.445 cm² in women.
†Data are presented as median (25th, 75th percentiles).
‡Data show >7 drinks per wk in women, ≥14 drinks per wk in men.
§Cystatin C levels were collected during the offspring seventh examination cycle (n = 1210; fatty kidney: n = 561; no fatty kidney: n = 649).

P < 0.0001; Table 4), which was attenuated after adjustment for VAT (OR: 1.09; P = 0.62); similar results were observed for fasting plasma glucose (Table 4). Similarly, fatty kidney was associated with an increased OR for high triglycerides (Table 4; OR: 1.88; P < 0.0001) but not after adjustment for VAT (OR: 1.04; P = 0.69).
Fatty kidney is a common condition, present in nearly one third of our community-based sample. Fatty kidney is associated with both hypertension and CKD based on cystatin C. These associations persisted after accounting for measures of generalized or abdominal adiposity, suggesting that renal sinus fat may have an independent association with renal function. In contrast, the observed associations of renal sinus fat with other cardiometabolic traits were generally attenuated after accounting for overall VAT, which is consistent with the hypothesized localized impact of renal sinus fat and provides further support for the potential unique role of this fat depot in hypertension and renal dysfunction.

The association of obesity with the development of CKD has been observed in small imaging studies of children \( n = 6 \)27 with normal renal function. The association of obesity with the development of CKD and hypertension25 is well established, although the pathogenic mechanisms are not fully understood. Ectopic fat accumulation is one of several mechanisms proposed to explain these associations. Renal sinus fat accumulation has been observed in small imaging studies of children \( n = 15 \)26 and adults \( n = 6 \)27 with normal renal function. The association of renal sinus fat with hypertension and creatinine clearance was studied recently in 205 participants from the Pulmonary Edema and Stiffness of the Vascular System Study, a study designed to assess predictors of congestive heart failure in older individuals.15 In this study, patients with SBP \( \geq 160 \) mm Hg or DBP \( \geq 100 \) mm Hg had higher levels

Secondary Analyses

Using lean healthy referent cut points, the prevalence of fatty kidney was 38.9% (26.9% of women and 51.4% of men). Among participants not currently using hypertension medication \( n = 2129 \), results from models of SBP and DBP as functions of fatty kidney were essentially unchanged (data not shown). Results from blood pressure, renal function, and lipid models remained consistent in diabetes mellitus–free subsamples from the overall \( n = 2702 \) and cystatin C subgroups \( n = 1103 \).

Discussion

Table 2. Age- and Sex-Adjusted Partial Pearson Correlations \((r)\) With Log-Transformed Renal Sinus Fat

<table>
<thead>
<tr>
<th>Variable</th>
<th>( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Visceral adipose tissue</td>
<td>0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subcutaneous adipose tissue</td>
<td>0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>−0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log(triglycerides)</td>
<td>0.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>log(UACR)</td>
<td>0.02</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFRcrea</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>eGFRcys</td>
<td>−0.10</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

*eGFRcrea indicates estimated glomerular filtration rate using the modified Modification of Diet in Renal Disease Study equation; eGFRcys indicates estimated glomerular filtration rate using the cystatin C only Chronic Kidney Disease Epidemiology Collaboration equation; UACR, urine albumin:creatinine ratio.

*Data show the sex-adjusted partial Pearson correlation.

Table 3. Imputed Blood Pressure and Renal Function Outcomes Modeled as Functions of Fatty Kidney Status

<table>
<thead>
<tr>
<th>Model Outcome of Interest</th>
<th>Age and Sex</th>
<th>Multivariable*</th>
<th>Multivariable + BMI</th>
<th>Multivariable + VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>4.9 (0.7) ( P&lt;0.0001 )</td>
<td>4.8 (0.7) ( P&lt;0.0001 )</td>
<td>2.2 (0.7) ( P=0.002 )</td>
<td>1.2 (0.7) ( P=0.11 )</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>2.4 (0.4) ( P&lt;0.0001 )</td>
<td>2.3 (0.4) ( P&lt;0.0001 )</td>
<td>0.8 (0.4) ( P=0.07 )</td>
<td>0.5 (0.5) ( P=0.31 )</td>
</tr>
<tr>
<td>eGFRcrea, mL/min/1.73 m²</td>
<td>−3.27 (0.89) ( P=0.0002 )</td>
<td>−2.20 (0.89) ( P=0.01 )</td>
<td>−0.64 (0.90) ( P=0.48 )</td>
<td>−0.90 (0.96) ( P=0.35 )</td>
</tr>
<tr>
<td>eGFRcys, mL/min/1.73 m²</td>
<td>0.61 (0.72) ( P=0.40 )</td>
<td>0.57 (0.72) ( P=0.43 )</td>
<td>0.05 (0.75) ( P=0.95 )</td>
<td>−0.27 (0.78) ( P=0.72 )</td>
</tr>
<tr>
<td>Dichotomous outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.13 (1.77–2.57) ( P&lt;0.0001 )</td>
<td>2.12 (1.75–2.56) ( P&lt;0.0001 )</td>
<td>1.49 (1.22–1.83) ( P&lt;0.0001 )</td>
<td>1.24 (1.00–1.53) ( P=0.049 )</td>
</tr>
<tr>
<td>CKDcrea</td>
<td>2.68 (1.51–4.75) ( P=0.0007 )</td>
<td>2.30 (1.28–4.14) ( P=0.005 )</td>
<td>1.86 (1.02–3.42) ( P=0.04 )</td>
<td>1.86 (1.00–3.46) ( P=0.05 )</td>
</tr>
<tr>
<td>CKDcys</td>
<td>1.49 (1.01–2.20) ( P=0.04 )</td>
<td>1.14 (0.76–1.72) ( P=0.53 )</td>
<td>1.16 (0.76–1.78) ( P=0.49 )</td>
<td>1.20 (0.77–1.86) ( P=0.43 )</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; eGFRcrea estimated glomerular filtration rate using the modified Modification of Diet in Renal Disease Study equation; eGFRcys estimated glomerular filtration rate using the cystatin C only Chronic Kidney Disease Epidemiology Collaboration equation; VAT, abdominal visceral adipose tissue volume; CKDcrea, chronic kidney disease status based on eGFRcrea; CKDcys, chronic kidney disease status based on eGFRcys. Sex-specific cut points for fatty kidney are \( \geq 0.710 \) cm² in men and \( \geq 0.445 \) cm² in women. Increments in the outcome when fatty kidney is present (SI shown in parentheses) are presented for continuous outcomes. Odds ratios (95% CIs) comparing those with fatty kidney to those without fatty kidney are presented for dichotomous outcomes.

*Multivariable models are adjusted for age and sex, as well as covariates listed below by outcome: eGFRcrea, eGFRcys, CKDcrea, CKDcys, diabetes mellitus status, current hypertension medication use, systolic blood pressure, current smoking status, and high-density lipoprotein cholesterol level. Imputed systolic blood pressure, diastolic blood pressure, hypertension: current smoking status, high alcohol intake, and physical activity index.
of renal sinus fat, quantified by MRI, than in those with blood pressure \(<160/100\) mm Hg, although associations with SBP, DBP, and renal function were not observed, possibly because of the small sample of highly selected individuals.

Animal models of diet-induced obesity provide additional insight into potential mechanisms involved in the pathogenesis of renal sinus fat. Rabbits with diet-induced obesity undergo a 61% increase in renal sinus mass, primarily driven by increases in fat within the renal sinus. This increase in renal sinus mass is observed concomitantly with increases in blood pressure. It has been hypothesized that renal sinus fat deposition leads to increases in renal interstitial pressure through the compression of vessels exiting the kidney, including the renal vein and lymph vessels. This potential mechanism is supported by studies in dog and rat models in which renal vein compression leads to increased renal interstitial pressure, kidney volume, and, in the presence of volume expansion, increased sodium reabsorption in the loop of Henle and decreased sodium excretion. Increased tubular reabsorption and retention of sodium is also observed in the dog model of obesity-related hypertension, a model for the development of obesity-related hypertension in humans.

Alternative animal models of obesity reported lipid accumulation within the renal parenchyma, supporting proposed mechanisms of obesity leading to kidney damage and hypertension through lipotoxicity, oxidative stress, inflammation, and fibrosis. Obese mice fed a high-fat diet developed lipid accumulation in the glomeruli and proximal tubules in addition to albuminuria, increased SBP and oxidative stress, and a larger glomerular tuft area and mesangial matrix when compared with mice fed a low-fat diet. Zucker diabetic fatty rats exhibit greater lipid accumulation in the renal cortex when compared with pair-fed lean controls. Lipid accumulation within the renal parenchyma has also been described in humans.

Overall, evidence from animal models supports the presence of obesity-related increases in renal lipid accumulation with concomitant structural and functional changes in the kidney and vasculature. However, it is uncertain whether these changes are specifically because of renal fat accumulation as compared with generalized weight gain and adiposity. Higher levels of BMI are among the strongest correlates of many ectopic fat depots. We have attempted to dissect the specific role of renal sinus fat as compared with generalized markers of adiposity and ectopic fat through our modeling structure and serial adjustment for BMI and VAT. Although our findings are attenuated after accounting for each of these adiposity-related variables, the residual statistical significance suggests a potential independent association.
of renal sinus fat with hypertension and CKD. We have also addressed this issue by evaluating the trends in SBP and eGFRcys with increasing renal sinus fat within narrower ranges of abdominal VAT; these findings further support an independent association with renal sinus fat. Finally, we did not observe an association with the presence of diabetes mellitus after accounting for abdominal VAT, which is in contrast to our previous work demonstrating consistent associations with VAT, liver fat, and upper body subcutaneous fat. This suggests that potential mechanisms for the association of renal sinus fat with hypertension and CKD are unlikely because of high correlations among different fat depots and provides support for a unique and specific association between renal sinus fat and hypertension and CKD.

Similar to our previous findings investigating abdominal VAT and CKD, we observed in the present analysis that fatty kidney is associated with CKD when using cystatin C–based eGFR but not creatinine-based eGFR. One potential explanation is that cystatin C may be a more sensitive marker for assessing renal function as compared with serum creatinine in older populations, given that serum creatinine is predominately derived from muscle tissue and that overall muscle mass is lower in older individuals. However, our results may also reflect potential confounding because of the independent association of cystatin C with nonrenal factors, including BMI. Cystatin C is secreted by adipose tissue, and the prevalence of cystatin C–based CKD may be overestimated in overweight and obese individuals when compared with the prevalence based on the Modification of Diet in Renal Disease Study equation. Although it is important to consider the role of adiposity in cystatin C production, if our association observed for fatty kidney and cystatin C–based CKD was solely attributed to confounding by overall adiposity, the association would have been completely attenuated after adjusting for BMI or abdominal VAT. Conversely, we observed a significant residual association on further adjustment. Therefore, secretion of cystatin C by adipocytes is unlikely to fully explain our observations.

The Framingham MDCT cohort is a large, well-characterized, community-based sample with multiple measures of adiposity, allowing for adjustment of several important confounders and further adjustment for generalized and central adiposity. Using computed tomography, we were able to develop a noninvasive, reproducible method to quantify renal sinus fat accumulation in a community-based setting. Some limitations warrant mention. This is an observational study, which limits our ability to assess the causality of our findings. Given the cross-sectional design, we were also unable to assess the temporality of our observed associations. Our study sample is composed of white participants. Based on this, our findings may not be generalizable to populations consisting of other racial or ethnic groups.

**Perspectives**

Fatty kidney is a common condition associated with an increased risk of hypertension and CKD. Our results suggest that renal sinus fat may be associated with blood pressure regulation and CKD in humans and provides additional insight into the pathophysiologic role of adiposity in renal dysfunction. Further research is necessary to evaluate the longitudinal associations of renal sinus fat with markers of renal function and metabolic risk factors.

**Sources of Funding**

The Framingham Heart Study is supported by the National Heart, Lung, and Blood Institute (N01-HC-25195).

**Disclosures**

None.

**References**


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Meredith C. Foster, Shih-Jen Hwang, Stacy A. Porter, Joseph M. Massaro, Udo Hoffmann and Caroline S. Fox

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FATTY KIDNEY, HYPERTENSION, AND CHRONIC KIDNEY DISEASE:
THE FRAMINGHAM HEART STUDY

Meredith C. Foster MPH$^{1,2,3}$, Shih-Jen Hwang PhD$^{1,2}$, Stacy A Porter MA$^{4}$,
Joseph M. Massaro PhD$^{5}$, Udo Hoffmann MD MPH$^{6}$, Caroline S. Fox MD MPH$^{1,2,7}$

Affiliations:
1. NHLBI’s Framingham Heart Study
2. Division of Intramural Research and the Center for Population Studies,
   NHLBI, NIH
3. Department of Epidemiology, Harvard School of Public Health
4. Harvard Medical School
5. Department of Biostatistics, Boston University School of Public Health
6. Department of Radiology, Massachusetts General Hospital
7. Division of Endocrinology and Metabolism, Brigham and Women's Hospital,
   Harvard Medical School

Short Title: Fatty kidney, hypertension and CKD
### Table S1. Imputed blood pressure and renal function outcomes as functions of log-transformed renal sinus fat. Increments in outcome per standard deviation increase in log-transformed renal sinus fat (standard errors shown in parentheses) are presented for continuous outcomes. Odds ratios (95% confidence interval) for a standard deviation increase in log-transformed renal sinus fat are presented for dichotomous outcomes.

<table>
<thead>
<tr>
<th>Model outcome of interest</th>
<th>Age and sex</th>
<th>Multivariable†</th>
<th>Multivariable + BMI</th>
<th>Multivariable + VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>2.8 (0.3)</td>
<td>2.7 (0.3)</td>
<td>1.2 (0.3)</td>
<td>0.7 (0.4)</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.0005</td>
<td>p=0.045</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.6 (0.2)</td>
<td>1.5 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.6 (0.2)</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.0007</td>
<td>p=0.005</td>
</tr>
<tr>
<td>eGFR&lt;sub&gt;cys&lt;/sub&gt;</td>
<td>-1.82 (0.52)</td>
<td>-1.13 (0.52)</td>
<td>-0.0005 (0.54)</td>
<td>-0.15 (0.58)</td>
</tr>
<tr>
<td>(mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>p=0.0004</td>
<td>p=0.03</td>
<td>p=0.99</td>
<td>p=0.80</td>
</tr>
<tr>
<td>eGFR&lt;sub&gt;crea&lt;/sub&gt;</td>
<td>0.70 (0.33)</td>
<td>0.59 (0.34)</td>
<td>0.33 (0.35)</td>
<td>0.14 (0.38)</td>
</tr>
<tr>
<td>(mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>p=0.03</td>
<td>p=0.08</td>
<td>p=0.36</td>
<td>p=0.71</td>
</tr>
<tr>
<td><strong>Dichotomous outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.59</td>
<td>1.57</td>
<td>1.26</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>(1.43 – 1.76)</td>
<td>(1.42 – 1.75)</td>
<td>(1.12 – 1.41)</td>
<td>(0.99 – 1.26)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.08</td>
</tr>
<tr>
<td>CKD&lt;sub&gt;cys&lt;/sub&gt;</td>
<td>2.33</td>
<td>2.07</td>
<td>1.67</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>(1.48 – 3.67)</td>
<td>(1.30 – 3.28)</td>
<td>(1.04 – 2.67)</td>
<td>(1.01 – 2.81)</td>
</tr>
<tr>
<td></td>
<td>p=0.0003</td>
<td>p=0.002</td>
<td>p=0.03</td>
<td>p=0.045</td>
</tr>
<tr>
<td>CKD&lt;sub&gt;crea&lt;/sub&gt;</td>
<td>1.04</td>
<td>0.85</td>
<td>0.82</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>(0.82 – 1.32)</td>
<td>(0.66 – 1.08)</td>
<td>(0.63 – 1.07)</td>
<td>(0.62 – 1.08)</td>
</tr>
<tr>
<td></td>
<td>p=0.75</td>
<td>p=0.19</td>
<td>p=0.14</td>
<td>p=0.15</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index; eGFR<sub>crea</sub>=estimated glomerular filtration rate using the modified MDRD study equation; eGFR<sub>cys</sub>=estimated glomerular filtration rate using the cystatin-C only CKD-EPI equation; VAT=abdominal visceral adipose tissue volume; CKD<sub>crea</sub>=chronic kidney disease status based on eGFR<sub>crea</sub>; CKD<sub>cys</sub>=chronic kidney disease status based on eGFR<sub>cys</sub>.

*Sex-specific cut points for fatty kidney: ≥0.71 cm<sup>2</sup> in men; ≥0.445 cm<sup>2</sup> in women.
†Multivariable models are adjusted for age and sex as well as covariates listed below by outcome: eGFR<sub>cys</sub>, eGFR<sub>crea</sub>, CKD<sub>cys</sub>, CKD<sub>crea</sub>: diabetes status, current hypertension medication use, systolic blood pressure, current smoking status, high-density lipoprotein cholesterol level. Imputed systolic blood pressure, diastolic blood pressure, hypertension: Current smoking status, high alcohol intake, physical activity index.
Figure S1. (A) Mean imputed systolic blood pressure (SBP) and (B) mean cystatin-C-based estimated glomerular filtration rate (eGFR<sub>cys</sub>) across tertiles of renal sinus fat within tertiles of abdominal visceral adipose tissue (VAT).

S1. (A) Mean imputed systolic blood pressure (SBP) and (B) mean cystatin-C-based estimated glomerular filtration rate (eGFR<sub>cys</sub>) across tertiles of renal sinus fat within tertiles of abdominal visceral adipose tissue (VAT).
Supplemental Methods

Framingham Heart Study Renal Sinus Fat Measurement Protocol

1) Before performing the first renal sinus fat measurement during a session, open the Aquarius 3D Workstation software and confirm that the Fat template has the correct settings. This can be checked by opening the 3D Setting and confirming that the settings in A and B match the settings in Protocol Figure 1 below (WW = 160, WL = -120, Opacity = 1.00).

Protocol Figure 1: Aquarius 3D Workstation W/L, Opacity, and Color Settings for the renal sinus fat measurement protocol.

2) Select scan from the patient name column.
3) Select 30-slice option from the box at the lower left of the screen.
4) Use the 30-slice scout to identify the renal sinus in the right kidney, based on the following steps:
   i. **Identify the end slice:** Find first slice in which the opening of the renal sinus is visualized record slice number (slice n). Select slice n+1 as the end slice. For example, if slice 10 is the first slice in which the renal sinus opening is visualized, then select slice 11 as the end slice.
   ii. **Identify the start slice:** Find last slice in which the opening of the renal sinus is visualized and record slice number (slice m). Select slice m-1 as the start slice. For example, if slice 3 is the last slice in which the renal sinus opening is visualized, then select slice 2 as the start slice. If the opening of the renal sinus is visualized in slice 1, then select slice 1 as the start slice.
5) Click on 3D tab at the top of the screen.
6) Select the template tab and use the mouse to double-click on the FAT 3 icon.
7) On mask tab, select curve.
8) On mask tab, select axial.
9) Respond “yes” to “Do you want to reset the current mask?”
10) **Final slice selection and renal sinus fat measurements**
a. Of the range of selected slices (slice numbers \( n \) through \( m \)) in the renal sinus, identify the slice/slices of 'maximum fat' based on visual inspection. These slices should appear similar visually, with the renal sinus containing the largest amount of black coloring on the CT scan.

b. If an odd number of slices are identified in step 10a, then select the middle slice within the range of selected slices for the measurement. If an even number of slices are identified in 10a, then identify the two middle slices within the range of selected slices and choose from these two slices the slice that anatomically superior for the measurement.

   i. If only one slice is identified in step 10a, then select this slice for the renal sinus fat measurement.

c. Scroll to the slice selected in step 10b for the measurement and use the mouse cursor while holding down the mouse left-click button to trace around edge of the kidney. Make sure that the tracing is just within the boundary of the kidney such that surrounding visceral fat is not accidentally captured in the measurement.

d. The opening of the renal sinus will be present in the CT scan. Use a straight line to trace across the opening of the renal sinus. The boundary between inside and outside the renal sinus used for measurements should be based on anatomical characteristics where a dimple forms at the edge of the renal sinus opening (See Figure 2 below for an example of tracing across the renal sinus).

e. Only trace the kidney on the one slice selected for measurement.

f. Once the kidney has been traced, use right-click button on mouse to keep the traced area; the green line traced around the kidney will turn red after using the right-click button (Protocol Figure 2).

Protocol Figure 2: Abdominal CT scan with a manual tracing of the right kidney in red.
11) Check the tracing surrounding the right kidney in the measurement slice. If a mistake in the tracing is identified, then the measurement must be performed again, starting from Step 2 in the protocol.

12) Once the tracing of the right kidney slice is completed, select **Keep Region**. The red outlined region (**Protocol Figure 2**) will now be shaded green (**Protocol Figure 3**).

**Protocol Figure 3**: Abdominal CT scan with the selected region based on the manual tracing of the right kidney highlighted in green after selecting **Keep Region** in step 12.

13) Drag icon in **Box A** to **Box B** and click “Reverse.” The green shading on the CT scan will now be reversed, as shown in **Protocol Figure 4**.

**Protocol Figure 4**: Abdominal CT scan with the selected region based on the manual tracing of the right kidney highlighted in green.
14) Under the **mask** tab, click the **3D** tab at the bottom of the screen. When selected, the fat accumulation within the renal sinus will be visualized in pink (Protocol Figure 5).

**Protocol Figure 5**: 3D visualization of fat within the renal sinus selected using this protocol.

15) Select **measure** and then **volume**. A set of measurements will appear on the lower left corner of the screen (Protocol Figure 6).

**Protocol Figure 6**: Volumetric measurement of renal sinus fat in the measurement slice.

a. The measurement for “Object #2” is the renal sinus fat volume in cubic centimeters (Protocol Figure 6).

b. If “Object #1” and “Object #2” do not appear in the output on the lower left of the screen, then the fat measurement is below the limit of detection. This value will be coded as 0.004 in the final dataset.

16) Select **output** at the top of the screen. After selecting **output**, if a picture is already present in the output window, delete it before proceeding to step 17.
17) Select **capture** on bottom left of screen.
18) Use the mouse to left-click on the image. This image will show up on the output screen after this left-click.

Select “**save file**” and save the file as a .jpg.