Volumetric evaluation of renal sinus adipose tissue on computed tomography images in bilateral nephrolithiasis patients

Peng Lin1 · Zeng Min2 · Gong Wei1 · Hu Lei1 · Zeng Feifei1 · Zha Yunfei1

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Abstract
Purpose To compare renal sinus fat volume (RSFV) separately within the right and left kidneys between bilateral nephrolithiasis patients and healthy controls.

Methods This cross-sectional study analyzed patients who underwent unenhanced abdominal computed tomography (CT) divided into nephrolithiasis (n = 102) and healthy control (n = 130) groups. Age, sex, blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], estimated glomerular filtration rate (eGFR), body weight, and height of each participant were extracted. Volumetric renal sinus adipose tissue was measured separately for both kidneys on CT images. Urea, serum creatinine (Scr), uric acid (UA), total serum cholesterol (TCH), serum triglyceride (TG), and serum high- and low-density lipoprotein (HDL and LDL, respectively) cholesterol levels were obtained.

Results Overall, 232 participants (mean age 47 years, 50% women) were enrolled. There were no differences in sex, DBP, urea, and LDL-cholesterol between the two groups (all p > 0.05). However, nephrolithiasis patients had higher age, BMI, SBP, and RSFV; higherScr, UA, TCH, and TG serum levels; and lower HDL-cholesterol level and eGFR. Average left RSFV was significantly higher than right RSFV in healthy controls (4.56 ± 2.29 versus 3.34 ± 1.90 cm³, p < 0.001). A significant relationship between bilateral RSFV, age, BMI, SBP, and eGFR was noted in bilateral nephrolithiasis patients. Multivariate linear regression analysis showed age, BMI, and LDL-cholesterol to be independent predictors of left RSFV, and only BMI was an independent predictor of right RSFV.

Conclusions Our data showed renal sinus adipose tissue accumulation and the relationship among RSFV, age, BMI, and LDL-cholesterol in bilateral nephrolithiasis patients.

Keywords Renal sinus fat · Computed tomography · Nephrolithiasis · Ectopic fat deposition · Vascular calcification

Introduction
Nephrolithiasis is one of the most common urological conditions with a high recurrence rate. It has been thought to be related to diet and abnormal renal handling of electrolytes over the last several decades. However, recently a large number of epidemiologic studies showed a consistent link between nephrolithiasis and other systemic disorders including cardiovascular disease (CVD), metabolic syndrome (MS), and atherosclerosis (AS) [1–3]. Despite this rationale, the pathogenic mechanism underlying nephrolithiasis is still debated. A recently formulated vascular theory argues that a significant pathological process occurs in the renal interstitium in a pattern similar to that of atherosclerotic plaque formation [4]. Both vascular calcification (VC) and kidney stone can be defined as extraosseous sites of abnormal calcium deposition. Moreover, VC and bone demineralization coexist in nephrolithiasis, suggesting the possibility of common potential pathways leading to increased extraosseous calcium depositions in the kidneys and blood vessels [5].

Increasing evidence suggests that ectopic fat deposition or fat accumulation within and around non-adipose tissues and organs plays an essential role in the development of adjacent anatomical organ dysfunction and systemic disorders [6]. Epicardial adipose tissue (EAT) accumulation is associated with myocardial steatosis, development of atrial fibrillation, and ventricular dysfunction [7–9]. Perivascular...
adipose tissue (PVAT) accumulation has a pro-inflammatory phenotype, leading to atherosclerosis and hypertension [10–12]. The kidneys are surrounded by the intra-abdominal, retroperitoneal fat depot and tend to accumulate ectopic fat in the renal sinus (RS). RS fat is considerably affected by visceral adipose tissue volume and has characteristics of PVAT [13]. As a new index of ectopic fat depots, RS fat accumulation may also mediate local and systemic effects through excessive mechanical pressure and paracrine effects of locally released adipocytokines or lipotoxicity [14, 15]. It has been previously shown that RS adipose tissue may have an independent association with increased risk of hypertension [16] and chronic kidney disease (CKD) [17, 18] even after accounting for other adiposity measures. Furthermore, a recent study has demonstrated the relationship between RSFV in middle-aged patients suspected to have coronary artery disease and coronary artery calcification [19].

To the best of our knowledge, to date, RS fat has not been evaluated in patients with nephrolithiasis. Thereby, the hypothesis explored in this study was that RS fat accumulation is more prevalent in nephrolithiasis. The present study aimed to determine (1) whether patients with nephrolithiasis have more RSFV than healthy controls and (2) whether RSFV is related to other possible variables in nephrolithiasis.

Materials and methods

Participants

The retrospective study sample comprised patients from the Renmin Hospital of Wuhan University, Wuhan, China who underwent unenhanced abdominal computed tomography (CT) between October 2017 and April 2019.

Patients with bilateral punctiform calculi (stones with diameter < 0.5 cm) without obvious clinical symptoms were included. Patients with an underlying cause of urinary calculi, certain systemic metabolic diseases causing abnormal calcium and phosphorus metabolism, hydronephrosis or renal cyst affecting the measurements, congenital anatomical abnormalities of the kidneys, liver disease, chronic intestinal disease, and merging of the tumor were excluded from the analyses. Further, kidney transplant recipients, patients with any autoimmune disease, known coronary artery disease, previous coronary revascularization, chronic diarrhea, or inflammatory bowel disease and patients with a history of stroke were also excluded from the study. According to the inclusion and exclusion criteria, 232 participants (115 men and 117 women; mean age 47 ± 13.6 and 48 ± 12.8 years, respectively) were analyzed. The control group consisted of healthy adults with no kidney stones and signs or symptoms of systematic diseases. All participants provided written informed consent at enrollment. All investigations were performed following institutional guidelines with approval from the institutional ethics review board.

Protocol development

Unenhanced abdominal CT images were captured using a General Electric medical systems Lightspeed 64-slice CT spiral CT scanner. The CT scanning range covered the abdomen with 0.625-mm slices above the S1 level (tube voltage, 120 kV; tube current, 400 mA; and gantry rotation time, 500 ms). All imaging analyses were performed on a dedicated Advantage Workstation (version 4.7, GE Healthcare). RS fat quantification was performed in a semi-automated method that required a slice-by-slice manual definition of borders on CT axial images, and the total volume of RS fat was obtained. According to Foster et al. [20] protocol, the boundary of RS was defined as a straight line tracing across both dimples at the edge of the RS opening based on visual inspection such that the surrounding abdominal adipose tissue would be excluded from this measurement. Owing to the anatomical differences, a total of 12–18 layers of images were delineated. Pixel density in Hounsfld units (HU) were used to identify RS adipose tissue based on a window width of − 195 to − 45 HU, centered on − 120 HU. RSFV was measured separately within the right and left kidneys (Fig. 1).

Repeated measurements were performed in 22 arbitrarily selected patients by another experienced radiologist to determine the inter-observer variability in RSFV measurements. Inter-observer variability was evaluated using Pearson’s correlation coefficient for these measurements on identical images.

Data collection

Age, sex, body weight, and height of each participant were recorded after their admission. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m²). Blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] measurements were performed by a professional medical assistant. The estimated glomerular filtration rate (eGFR) was estimated in all subjects using the abbreviated modification of diet in renal disease study equation [21]. Laboratory data included a metabolic panel. Urea, serum creatinine (Scr), uric acid (UA), total serum cholesterol (TCH), serum triglycerides (TG), and serum high- and low-density lipoprotein (HDL and LDL) cholesterol levels were obtained from the clinical examination of a fasting blood sample within 7 days of the CT examination in the Clinical Laboratory of the Renmin Hospital of Wuhan University.
Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows version 23.0 (SPSS, Chicago, IL). Dependent variables were analyzed to determine whether they were normally distributed using the Kolmogorov–Smirnov test. Means and standard deviations were calculated for continuous variables. Linear associations between continuous variables were assessed using the Spearman correlation test. Differences between the nephrolithiasis and control groups were tested by Student’s t test for continuous variables and Chi-square analyses for categorical variables. The right and left RSFVs were compared using paired Student’s t test in the control group. In the linear regression models, univariate associations between RSFV and other variables (age, BMI, SBP, Scr, UA, TCH, TG, HDL-cholesterol, and eGFR) were explored. Multivariate linear regressions were performed to determine significant associations between RSFV and other variables (age, BMI, SBP, Scr, UA, TCH, TG, HDL-cholesterol, and eGFR), adjusted for potential confounders. Bland–Altman plots were utilized to assess potential systematic biases within the repeated measurements. Statistical significance was set at \( p < 0.05 \).

Results

Variables measured between the nephrolithiasis and control groups

Intra-reader and inter-reader RSFV measurements are plotted in Fig. 2. Pearson’s product-moment correlation coefficient for the RSFV in a sample of 22 patients was \( r = 0.99 \) for intra-observer variability and \( r = 0.98 \) for intra-observer variability.

The baseline characteristics of 102 bilateral nephrolithiasis patients and 130 healthy subjects are shown in Table 1. There were no differences in sex, DBP, urea, and LDL-cholesterol between the nephrolithiasis and control groups. However, bilateral nephrolithiasis patients were older and had higher age, BMI, and SBP; higher serum levels of Scr, UA, TCH, and TG; and lower HDL-cholesterol and eGFR than healthy subjects.

Bilateral RSFVs were significantly higher in bilateral nephrolithiasis patients than in healthy subjects (left RSFV: \( 5.47 \pm 3.50 \) cm\(^3\) versus \( 4.56 \pm 2.29 \) cm\(^3\), \( p = 0.02 \); right RSFV: \( 4.14 \pm 3.12 \) cm\(^3\) versus \( 3.34 \pm 1.90 \) cm\(^3\), \( p = 0.01 \)). Moreover, the average left RSFV was significantly higher than the right RSFV in the control group (\( 4.56 \pm 2.29 \) cm\(^3\) versus \( 3.34 \pm 1.90 \) cm\(^3\), \( p < 0.001 \)) (Fig. 3).

Correlation analysis between bilateral RSFVs and other variables in the nephrolithiasis group

There was a statistically significant relationship between bilateral RSFVs, age, BMI, SBP, and eGFR in the nephrolithiasis group (left RSFV: \( r = 0.36, p < 0.01 \); \( r = 0.43, p < 0.01 \); \( r = 0.28, p < 0.01 \); \( r = -0.23, p = 0.02 \) and right RSFV: \( r = 0.33, p < 0.01 \); \( r = 0.44, p < 0.01 \); \( r = 0.28, p < 0.01 \); \( r = -0.21, p = 0.03 \), respectively) (Table 2).

The multivariate linear regression analysis revealed that age, BMI, and LDL-cholesterol were independent predictors of left RSFV, and only BMI was an independent predictor of right RSFV. The regression analysis results are shown in Table 3 and Fig. 4.
Discussion

There were four principal findings in this study. First, bilateral RSFV was higher in the nephrolithiasis group than in the control group. Second, bilateral nephrolithiasis patients had higher age, BMI, and SBP; higher serum levels of Scr, UA, TCH, and TG and lower HDL-cholesterol level and eGFR than healthy subjects. Third, RSFV significantly correlated with age, BMI, SBP, and eGFR in bilateral nephrolithiasis patients. Lastly, age, BMI, and LDL cholesterol were found to be independent predictors of left RSFV, and only BMI was an independent predictor of right RSFV.

Multiple imaging modalities can be used to assess the development of renal lesions in humans, including renal sinus fat accumulation, such as ultrasonography, CT, and magnetic resonance imaging [22–24]. Further, CT has been used to develop a feasible and reproducible measurement protocol for characterizing the distribution of RS fat in a sample from the Framingham MDCT cohort [20]. We delineated the RS area on axial CT images slice-by-slice and obtained the total volume of RS fat semi-automatically. The RSFV measurements theoretically might be affected by an operator-associated bias; however, we noted high intra-class and inter-class correlations, thereby ensuring the reproducibility of the results.

Our study confirms conclusions from many previous studies. Caglar et al. [25] demonstrated that RSFV and age were positively correlated for both kidneys in normal subjects, although this correlation appeared to decline after 70 years of age. Similarly, in this study, left RSFV was positively correlated with age in bilateral nephrolithiasis patients. This may allow clinicians to estimate the age-related RS fat volume changes better and help decision making. In addition, consistent with previous studies [26, 27], the right RSFV was significantly lower than left RSFV in normal subjects. This asymmetry predisposes the left RS to higher RS adipose tissue deposition. We speculate that, first, asymmetrical RS adipose tissue accumulation could be a result of the anatomical differences between the left and right renal veins. The right renal vein receives blood from only the right kidney, whereas the left renal vein receives blood from the left gonadal and adrenal veins in addition to the vein from the left kidney. The mean left renal blood flow was on average significantly lower than the right mean renal blood flow. Second, there was a wide variation in calyceal orientation, as the calyceal angles in the right and left kidneys differ. We hypothesized that a significantly higher RS adipose tissue
Deposition in the left kidney could possibly be an inborn structural phenomenon that might cause asymmetrical renal blood flow.

In this study, RSFV was associated with higher SBP and lower eGFR. These associations disappeared in the multivariate linear regression analysis. However, we noted a significantly higher SBP and lower eGFR in the nephrolithiasis group supporting previously published findings demonstrating that people with high BP have an increased risk of developing kidney stones, and those with kidney stones have an increased risk of developing high BP [28]. In addition, Wagner et al. [18] concluded that perivascular adipose tissue in the RS may play a role in the

| Table 1 | Demographic and biochemical parameters between the nephrolithiasis and control groups |
|---------|-------------------------------------------------------------|
| Variables | Nephrolithiasis group (n = 102) | Control group (n = 130) | p value |
| Age (years) | 49.9 (14.0) | 45.4 (12.1) | <0.01 |
| BMI (kg/m²) | 22.4 (2.0) | 20.8 (2.2) | <0.01 |
| SBP (mmHg) | 127.4 (15.7) | 118.6 (5.4) | <0.01 |
| DBP (mmHg) | 78.9 (11.6) | 77.7 (4.9) | 0.26 |
| Urea (mmol/L) | 5.38 (1.66) | 5.10 (1.24) | 0.15 |
| Scr (µmol/L) | 74.8 (21.9) | 67.8 (16.8) | 0.01 |
| µUA (µmol/L) | 354.5 (91.0) | 316.9 (53.7) | <0.01 |
| TCH (mg/dL) | 4.54 (0.77) | 4.97 (0.86) | <0.01 |
| TG (mg/dL) | 1.51 (0.92) | 1.25 (0.35) | 0.03 |
| HDL-cholesterol (mg/dL) | 1.16 (0.37) | 1.25 (0.28) | 0.04 |
| LDL-cholesterol (mg/dL) | 2.63 (0.67) | 2.47 (0.60) | 0.07 |
| eGFR (ml/min/1.73 m²) | 93.93 (20.16) | 110.11 (10.95) | <0.01 |
| Left RSFV (cm³) | 5.47 (3.50) | 4.56 (2.29) | 0.02 |
| Right RSFV (cm³) | 4.14 (3.12) | 3.34 (1.90) | 0.01 |

All of the participants in the study sample are Chinese
Continuous variables are presented as mean ± SD, and dichotomous variables are presented as %
Data are expressed as mean ± standard deviation (SD). Significance set at p < 0.05
BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, Scr serum creatinine, UA uric acid, TCH total cholesterol, TG triglycerides, HDL-cholesterol serum high density lipoprotein cholesterol, LDL-cholesterol low density lipoprotein cholesterol, eGFR estimated glomerular filtration ratio, RSFV renal sinus fat volume

| Table 2 | Associations of the left and right RSFVs in the nephrolithiasis group with other indices in the univariate regression analysis |
|---------|-------------------------------------------------------------|
| Variables | Left RSFV | Right RSFV |
|          | r       | p value | r       | p value |
| Age       | 0.36** | <0.01  | 0.33** | <0.01  |
| BMI       | 0.43** | <0.01  | 0.44** | <0.01  |
| SBP       | 0.28** | <0.01  | 0.28** | <0.01  |
| Scr       | 0.10   | 0.34   | 0.06   | 0.52   |
| UA        | 0.09   | 0.37   | 0.10   | 0.33   |
| TCH       | 0.02   | 0.81   | 0.06   | 0.56   |
| TG        | 0.01   | 0.97   | 0.03   | 0.80   |
| HDL-cholesterol | 0.05 | 0.60 | 0.05 | 0.60 |
| LDL-cholesterol | 0.17 | 0.08 | 0.14 | 0.17 |
| eGFR      | −0.23* | 0.02   | −0.21* | 0.03   |

BMI body mass index, SBP systolic blood pressure, Scr serum creatinine, UA uric acid, TCH total cholesterol, TG triglycerides, HDL-cholesterol serum high density lipoprotein cholesterol, LDL-cholesterol low density lipoprotein cholesterol, eGFR estimated glomerular filtration ratio, RSFV renal sinus fat volume
**p < 0.01; *p < 0.05
Table 3  Multivariate linear regression analysis with bilateral RSFVs as the dependent variable in the nephrolithiasis group

| Variables          | Coefficient | SE  | β (beta) | p value | 95% CI       |
|--------------------|-------------|-----|----------|---------|--------------|
|                    | L-RSFV      | R-RSFV | L-RSFV | R-RSFV | L-RSFV | R-RSFV | L-RSFV | R-RSFV | L-RSFV | R-RSFV |
| Age                | 0.07        | 0.04 | 0.03     | 0.03    | 0.28** | 0.17    | 0.04    | 0.21    | 0.04    | 0.14    | −0.02   | 0.10    |
| BMI                | 0.73        | 0.65 | 0.16     | 0.15    | 0.42** | 0.42**  | <0.01   | <0.01   | 0.40    | 1.05    | 0.35    | 0.95    |
| SBP                | −0.01       | 0.01 | 0.02     | 0.02    | −0.02  | 0.02    | 0.87    | 0.88    | −0.06   | 0.07    | −0.04   | 0.04    |
| Scr                | 0.01        | −0.02 | 0.03   | 0.03    | 0.04   | −0.14   | 0.86    | 0.51    | −0.08   | 0.04    | −0.08   | 0.04    |
| UA                 | 0.01        | 0.01 | 0.01     | 0.01    | 0.08   | 0.13    | 0.46    | 0.25    | −0.01   | 0.02    | −0.01   | 0.01    |
| TCH                | −0.69       | −0.36 | 0.51   | 0.46    | −0.15  | −0.09   | 0.18    | 0.44    | −1.70   | 0.31    | −1.27   | 0.56    |
| TG                 | −0.15       | −0.31 | 0.35   | 0.32    | −0.04  | −0.03   | 0.67    | 0.73    | −0.86   | 0.55    | −0.75   | 0.53    |
| HDL-cholesterol    | 0.69        | 0.40 | 0.93     | 0.84    | 0.07   | 0.05    | 0.46    | 0.64    | −1.16   | 2.53    | −1.27   | 2.08    |
| LDL-cholesterol    | 1.13        | 0.73 | 0.53     | 0.48    | 0.22*  | 0.16    | 0.03    | 0.13    | 0.09    | 2.12    | −0.22   | 1.68    |
| eGFR               | −0.01       | −0.02 | 0.04   | 0.03    | −0.01  | −0.15   | 0.97    | 0.47    | −0.07   | 0.07    | −0.09   | 0.04    |

BMI body mass index, SBP systolic blood pressure, Scr serum creatinine, UA uric acid, TCH total cholesterol, TG triglycerides, HDL-cholesterol serum high density lipoprotein cholesterol, LDL-cholesterol low density lipoprotein cholesterol, eGFR estimated glomerular filtration ratio, L-RSFV left renal sinus fat volume, R-RSFV right renal sinus fat volume, CI confidence interval, SE standard error, β (Beta) standardized beta coefficient

*p < 0.05; **p < 0.01

Fig. 4 Correlation analysis in the nephrolithiasis group. a Between the left RSFV and age. b Between the left RSFV and BMI. c Left RSFV and LDL-cholesterol. d Right RSFV and BMI
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