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Renal sinus fat volume in type 2 diabetes mellitus is associated with glycated hemoglobin and metabolic risk factors

Ling Lin [a,*], Ilona A. Dekkers [a], Lu Huang [b], Qian Tao [a], Elisabeth H.M. Paiman [a], Maurice B. Bizino [a], Ingrid M. Jazet [c], Hildo J. Lamb [a]

[a] Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands
[b] Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Qiaokou District, Wuhan, Hubei, China
[c] Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands

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ABSTRACT

Aims: We aimed to compare renal sinus fat volume assessed by MRI between patients with type 2 diabetes and healthy volunteers, and investigate the association between renal sinus fat and metabolic traits.
Methods: In this cross-sectional study, renal sinus fat and parenchyma volumes measured on abdominal MRI were compared between patients and controls using analysis of covariance. Associations of renal parameters with clinical characteristics were analyzed using linear regression analysis.
Results: A total of 146 participants were enrolled, consisting of 95 type 2 diabetes patients (57.2 ± 8.8 years, 49.5% male) and 51 controls (54.0 ± 9.2 years, 43.1% male). Patients with diabetes demonstrated larger sinus fat volumes (15.4 ± 7.5 cm^3 vs. 10.3 ± 7.1 cm^3, $p < 0.001$) and sinus fat-parenchyma ratio than controls. In the total population, renal sinus fat was positively associated with HbA1c, abdominal VAT, cholesterol and triglycerides, after adjustment for age, sex, ethnicity and type 2 diabetes. In type 2 diabetes patients, increased sinus fat volume was significantly associated with urinary albumin-to-creatinine ratio.
Conclusion: Renal sinus fat volume is positively associated with several metabolic risk factors including HbA1c level and urinary albumin-to-creatinine ratio in type 2 diabetes patients, indicating a potential role of renal sinus fat in the development of diabetic nephropathy. Future studies are needed to investigate whether sinus fat volume can serve as an early biomarker for diabetic nephropathy.

1. Introduction

Diabetic nephropathy has a cumulative incidence of 25–40% in patients with type 2 diabetes mellitus (T2DM) and increases the risk of death.[1,2] The diagnosis of diabetic nephropathy is based on the values of urinary albumin excretion and estimated glomerular filtration rate (eGFR).[2] However, pathophysiological changes such as glomerular hyperfiltration,[3] morphological changes such as renal hypertrophy[4] and histological lesion such as glomerulopathy, tubular atrophy and interstitial fibrosis[5] may exist when urinary albumin and eGFR remain normal. As the progression of diabetic nephropathy can be reversed or delayed at an early stage,[2] there is an increased interest in early renal morphological changes in T2DM. The Framingham Heart Study revealed the association of high total kidney volume with diabetes.[6] This study also demonstrated that increased eGFR was a predictor of increased total kidney volume, indicating the association between glomerular hyperfiltration and kidney enlargement.[6] However, kidney size is related to age, sex, renal function, anthropometric parameters and chronic nephropathy risk factors such as obesity and diabetes in the general population,[7–9] which makes it complicated to interpret individual renal parenchyma volume in clinical settings.

Renal sinus fat is an ectopic perivascular fat depot around renal hilum, which is in close contact with renal vasculature, lymphatic vessel, renal pelvis and calyces. The Framingham Heart Study demonstrated an association between “fatty kidney” (defined by renal sinus fat>90th percentile in a sex-specific healthy referent subsample), and an increased odds ratio of microalbuminuria.[10] The accumulation of renal sinus fat has been reported to be associated with hypertension and renal dysfunction.[10,11] Another study suggested that renal sinus fat is associated with visceral adipose tissue (VAT), and may have a role in obesity-

* Corresponding author at: Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands.
E-mail address: l.lin@lumc.nl (L. Lin).

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induced renal damage.[12] There has been an increased interest in renal sinus fat in diabetes patients as well. Larger renal sinus fat volume has been reported to be associated with lower GFR and increased renal vascular resistance in T2DM patients.[13] However, compared with renal parenchyma volume, little is known about the characteristics of renal sinus fat in the general population as well as in patients with diabetes.

Ultrasound-derived renal size or areas of renal sinus fat and parenchyma derived from single-slice computed tomography (CT) or magnetic resonance imaging (MRI) have been frequently used instead of renal volumes.[7,10,11,13–19] Although ultrasonography is the first-line diagnostic tool, it is operator-dependent and tend to underestimate kidney size.[20] Volumetric analysis of renal sinus fat and renal parenchyma by CT and MRI has also been reported.[6,8,9,12,20–24] While MR is preferred over CT due to non-radiation and excellent tissue contrast, volumetric analysis of renal volumes based on MRI could be compromised by large slice thickness with slice gaps, and the utility of contrast agents in previous studies.[20–22] Dixon technique for water-fat separation has been widely used in clinical applications, which can generate water-only and fat-only images based on chemical shift in MRI.[25] The increasing application of three-dimensional (3D) high resolution Dixon imaging in clinical settings has provided the potential for accurate measurements of renal volumes, especially sinus fat volume.

In this study, we aimed to characterize renal sinus fat and parenchyma volume in patients with T2DM and healthy volunteers based on 3D segmentation in high resolution DIXON images. We hypothesize that renal sinus fat volume is larger in T2DM patients compared with healthy controls, and is associated with glycaemic control and metabolic risk factors.

2. Material and methods

2.1. Study design and participants

This was a cross-sectional analysis of the baseline data of the single-center MAGNA VICTORIA studies (ClinicalTrials.gov NCT01761318,[26] NCT02660047[27]). Written informed consent was obtained from each participant prior to inclusion. The present study was performed according to the revised Declaration of Helsinki and was approved by the institutional review board.

Inclusion criteria for T2DM patients were initially defined disregarding ethnicity. However, the inclusion criteria for South Asian T2DM patients were adjusted due to insufficient number of patients in this group. Ethnicity was based on self-identified and self-reported origin of both biological parents and their ancestors. In addition, healthy controls of West European and South Asian decent were prospectively enrolled.[28] Therefore, the final inclusion criteria respectively for West European and South Asian T2DM patients were: age 18–70 years and 18–75 years, BMI $\geq$25 kg/m^2 and $\geq$23 kg/m^2, glycated hemoglobin (HbA1c) was $\geq$53.0 and <86.5 mmol/mol ($\geq$7.0 and $\leq$10.0%) and $\geq$47.5 and <96.5 mmol/mol ($\geq$6.5 and $\leq$11.0%), systolic and diastolic blood pressure was <150/85 mmHg and <180/110 mmHg, eGFR was >60 mL/min/1.73m^2 and >30 mL/min/1.73m^2, no history of coronary artery disease for the West European T2DM patients and no acute coronary accident in the preceding 30 days for the South Asian T2DM patients. Exclusion criteria were: history of heart failure (New York Heart Association class III-IV), significant valvular disease, abnormalities on rest echocardiography and any contra-indication for MRI.[26,27]

For healthy controls, the inclusion criteria were: age 40–70 years, no history of cardiovascular disease and no medication use. Exclusion criteria were: diabetes or prediabetes (fasting plasma glucose $\geq$6.1 mmol/L, or 2-h plasma glucose $\geq$7.8 mmol/L in glucose tolerance test, or HbA1c $\geq$39 mmol/mol), metabolic syndrome (definitions have been described previously),[28] contra-indications for MRI, abnormalities upon physical examination, plasma tests (blood count, liver and kidney function) or rest echocardiography.[28]

2.2. Data collection

Potential patients and healthy volunteers were enrolled after a screening visit. Clinical examinations and MR scanning were scheduled either in the morning after an overnight fast or evening ($\geq$6 h fasting). At the start of study, fasting blood samples were taken, and weight and blood pressure were measured for each participant. Glycated hemoglobin (HbA1c) was measured with ion-exchange high-performance liquid chromatography (HPLC; Tosoh G8, Sysmex Nederland B.V., Etten-Leur, the Netherlands). Serum creatinine, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol (Friedewald formula) were measured in all the participants. Urinary albumin-to-creatinine ratio (UACR) of each patient was obtained from urine samples. Bioelectrical impedance analysis was used to estimate total body fat percentage. The eGFR was calculated from serum creatinine (mg/dl) and age according to the CKD-EPI equation.[29] Detailed information of the collection of clinical data has been reported in a previous publication.[28]

2.3. MRI protocol and measurements of renal volumes and abdominal adipose tissue

Abdominal MRI was performed using a clinical 3 Tesla whole-body MR system with a dStream Torso anterior coil and a FlexCoverage posterior coil, with up to 32 coil elements for signal reception (Ingenia, Philips Medical Systems, Best, the Netherlands). The water-only and fat-only images were acquired by a two-point modified Dixon sequence with the following parameters: repetition time 3.5 ms, first/second echo time 1.19/2.3 ms, flip angle 10°, slice thickness 4 mm with slice overlap of 2 mm, acquired voxel size 0.9 × 0.9 × 2 mm^3.

Renal sinus fat and renal parenchyma volumes of the left kidney were measured using an open source software (ITK-SNAP 3.6.0, www.itksnap.org).[30] Firstly, renal parenchyma was labeled on fat-only images by the semi-automatic threshold-based 3D segmentation module. Secondly, renal sinus fat was labeled based on the label of parenchyma, and was defined by a straight line tangent to the margins of parenchyma beside the renal hilum in axial slices. Finally, renal pelvis, calyces, vasculature and cysts were manually discarded from the volumes of interest based on the water-only images (Fig. 1). Renal sinus fat volume and parenchyma volume were automatically calculated by summation of the volumes of all the labeled voxels. Renal sinus fat-parenchyma ratio is sinus fat volume divided by parenchyma volume. All the measurements of renal volumes were blindly performed by the same radiologist with four years' experience of abdominal MRI (LL). Repeating measurements in 20 randomly selected cases were performed one month later by the same radiologist and by another radiologist with six years' experience of abdominal MRI (LH), to determine the inter- and intra-observer agreements.

Abdominal visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) were measured using the same modified Dixon sequence but on three reformatted transverse slices at the fourth to fifth lumbar vertebrae level, with slice thickness of 10 mm and slice gap of 12 mm. VAT and SAT areas were semi-automatically labeled based on pixel intensity thresholding and were quantified as the mean area in squared centimeters of all three slices (MASS 2015-EXP, Leiden University Medical Center, Leiden, The Netherlands).

2.4. Statistical analysis

Inter- and intra-observer reproducibility was evaluated using Bland-Altman plots and intraclass correlation coefficients (ICCs). Clinical characteristics, abdominal adipose parameters and renal volumes were presented as mean ± standard deviation, median (interquartile ranges) or numbers (percentage). Distribution of the data was visually assessed by histograms and Q-Q plots. Differences in renal parameters between T2DM patients and controls were assessed initially using Student's *t*-test, and then using analysis of covariance (ANCOVA) with adjustments for

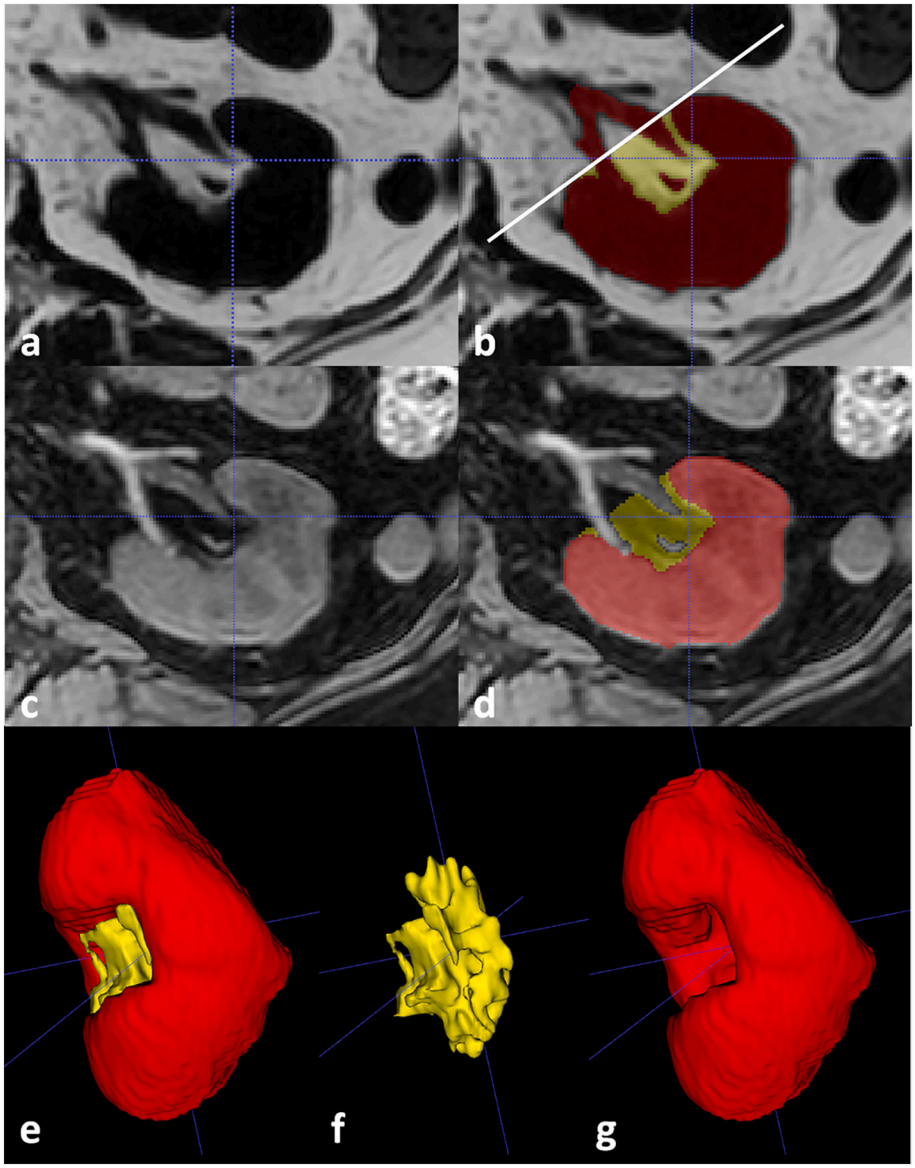

Fig. 1. 3D segmentation of the renal sinus fat and parenchyma using Dixon images. (A) The fat image of the left kidney of one patient. (B) Renal parenchyma was labeled based on (A) using the semi-automatic segmentation module in ITK-SNAP. Renal sinus fat was labeled based on the label of parenchyma, and was defined by a straight line tangent to the margins of parenchyma beside the hilum in axial slices (the white line). (C) The water image of the left kidney in the same patient. (D) The segmentation in (B) was loaded upon (C), where the renal pelvis, calyces and vasculatures were discarded. (E–G) 3D view of the segmentation of the whole kidney, the sinus fat and the parenchyma.

age, sex and ethnicity. The interactions by age, sex and ethnicity on the associations between renal parameters and T2DM were also examined using ANCOVA. Renal parameters in hypertension patients and non-hypertension participants were compared using student *t*-test and ANCOVA. Renal sinus fat volume between patients with and without lipid-lowering drug was compared using ANCOVA. Pearson or Spearman correlation was applied to assess the correlations among renal parameters and clinical characteristics. The associations of renal sinus fat and sinus fat-parenchyma ratio with metabolic traits were further examined by multivariable linear regression analysis. Models were initially adjusted for age, sex, ethnicity and T2DM. Then the association with HbA1c was further determined with additional adjustment for abdominal VAT, triglycerides and total cholesterol. Lastly, body surface area was adjusted additionally for both sinus fat volume and sinus fat-parenchyma ratio. Association between renal sinus fat and UACR was tested in T2DM patients using multiple linear regression. UACR was transformed by square root to meet the assumption of normality. All statistical analyses were performed using SPSS 25.0 (IBM Corp, New York, United States), with two-tailed $p < 0.05$ as the significance threshold.

3. Results

One hundred and one diabetic patients and 53 healthy controls were registered originally. Three patients were excluded due to claustrophobia. One patient was excluded because of type 1 diabetes. Two patients and two healthy controls withdrew from the trial. The present analysis consisted of 146 participants, including 95 T2DM patients (mean age of 57.2 ± 8.8 years; range 31–74 years; 50% males) and 51 healthy controls (mean age 54.0 ± 9.2 years; range 31–71 years; 43% males). The 95 T2DM patients consisted of 48 Western Europeans and 47 South Asians, and the healthy controls of 30 Europeans, 21 South Asians. A flow diagram of the included participants is presented in Fig. 2.

Measurements of renal sinus fat volume and parenchyma volume demonstrated excellent intra- and inter-observer agreement (Fig. 3). For intra-observer agreement, the mean differences were 0.32 ± 1.21 cm^3 for sinus fat volume and -0.29 ± 2.43 cm^3 for renal parenchyma volume. ICC for sinus fat volume was 0.966 (95% CI: 0.919–0.987). ICC for parenchyma volume was 0.998 (95% CI: 0.994–0.999). For inter-observer agreement, the mean differences were 1.15 ± 1.82 cm^3 for sinus fat volume, and -0.18 ± 2.64 cm^3 for parenchyma volume. ICC was 0.903 (95% CI: 0.698–0.905) for sinus fat volume and 0.997 (95%

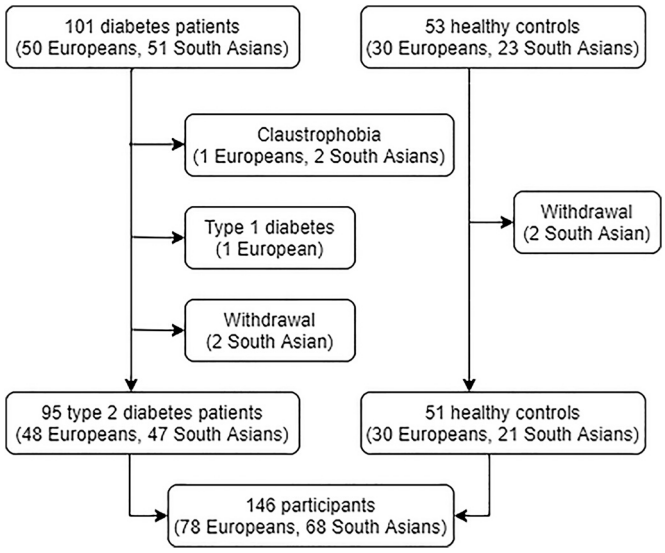

Fig. 2. Flowchart of the enrollment of the participants. Three patients were excluded due to claustrophobia. One patient was excluded because of type 1 diabetes. Two patients and two healthy controls withdrew from the trial. A total of 146 participants were enrolled in the current analysis, including 95 type 2 diabetes patients and 51 healthy controls.

CI: 0.993–0.998) for parenchyma volume.

3.1. Clinical characteristics and abdominal adipose parameters

The clinical characteristics of all the participants are demonstrated in Table 1. The T2DM patients had higher body weight, BMI, BSA, waist circumference, hip circumference and waist-hip ratio, higher blood pressure and serum lipids than the healthy controls. Regarding adipose parameters, T2DM patients had higher total body fat percentage and larger abdominal VAT and SAT than healthy controls, with all p values smaller than 0.001. No statistical difference was found in serum creatinine ($p = 0.152$) or eGFR ($p = 0.213$) between patients and controls. UACR was below 300 mg/mmol in all the patients.

3.2. Renal volumes and comparisons with and without adjustment for confounders

Renal sinus fat volume, parenchyma volume and sinus fat-parenchyma ratio in T2DM patients and healthy controls are presented in Table 2. T2DM patients demonstrated statistically larger renal sinus fat volume, parenchyma volume and sinus fat-parenchyma ratio (15.4 ± 7.5 cm^3, 170.1 ± 39.0 cm^3 and 0.09 ± 0.04) than those of healthy controls (10.3 ± 7.1 cm^3, 135.1 ± 25.0 cm^3 and 0.07 ± 0.05, see Table 2 and Fig. 4). The statistical significances in sinus fat volume and parenchyma volume persisted after adjustment for age, sex and ethnicity in ANCOVA (Table 2). No interaction by age, sex or ethnicity was found in the associations of renal parameters with T2DM status.

In the whole cohort, participants with hypertension ($n = 71$, all were patients) demonstrated larger renal sinus fat volume (16.1 ± 7.6 vs. 11.3 ± 7.2, $p < 0.001$), parenchyma volume (172.0 ± 40.0 vs. 144.5 ± 32.3, $p < 0.001$) and higher sinus fat-parenchyma ratio (0.095 ± 0.040 vs. 0.076 ± 0.043, $p = 0.01$) than those without hypertension ($n = 75$). However, the differences lost statistical significances after adjusting age, sex, ethnicity and T2DM.

The T2DM patients on lipid-lowering therapy ($n = 76$) had larger sinus fat volume (16.5 ± 0.8 vs. 11.3 ± 1.6, $p = 0.007$) and sinus fat-parenchyma ratio (0.096 ± 0.005 vs. 0.074 ± 0.009, $p = 0.028$) than those without lipid lowering drugs. However, the differences lost statistical significance after adjustment of age, sex and ethnicity.

3.3. Associations between renal parameters and clinical characteristics

Pearson's correlation coefficients between renal parameters and the clinical characteristics are listed in Table 3. In the whole cohort, renal sinus fat volume was associated with parenchyma volume. Renal sinus fat and sinus fat-parenchyma ratio were positively correlated with HbA1c, VAT, waist-hip-ratio and serum triglycerides. Renal parenchyma volume was positively correlated with eGFR, while no statistical correlation was found between sinus fat volume and eGFR (Table 3).

Multivariable linear regression results for sinus fat and sinus fat-parenchyma ratio are presented in Table 4. The positive association between sinus fat volume and HbA1c level persisted after additional adjustments for abdominal VAT, total cholesterol, triglycerides and BSA. The positive association between sinus fat-parenchyma ratio and HbA1c level also remained significant after adjustment for VAT, total

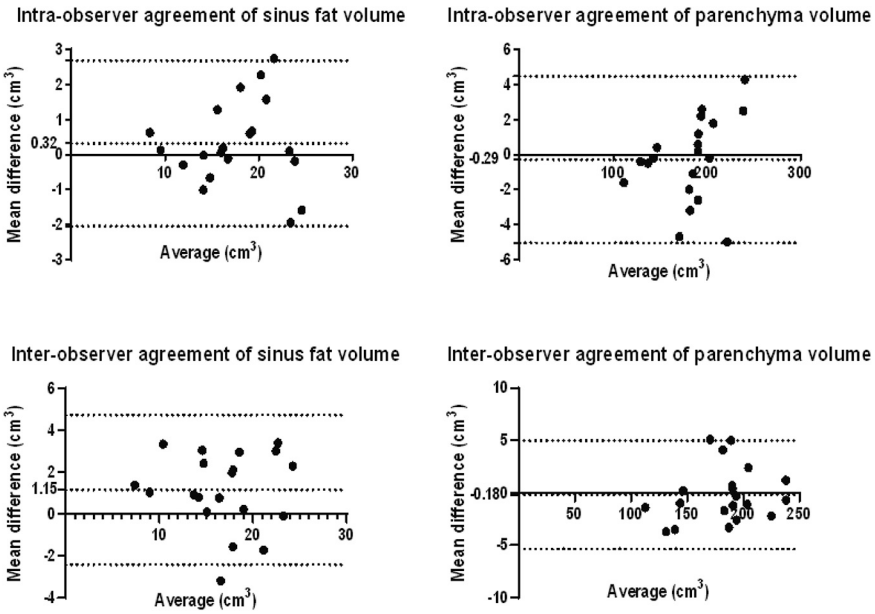

Fig. 3. Bland-Altman plots of the intra- and inter-observer agreement of the renal volumes in 20 participants.

Table 1
Clinical characteristics and abdominal adipose tissue of the participants.

Characteristics	T2DM patients (n = 95)	Healthy controls (n = 51)
Age (year)	57.2 ± 8.8	54.0 ± 9.2
Sex, male (%)	47 (50%)	22 (43%)
Ethnicity (%)		
European	48 (51%)	30 (59%)
South Asian	47 (49%)	21 (41%)
Height (cm)	168.9 ± 9.7	169.8 ± 9.3
Weight (kg)	88.1 ± 15.2	69.3 ± 11.4
BMI (kg/m^2)	30.8 ± 4.1	24.0 ± 3.2
BSA (m^2)	2.03 ± 0.22	1.80 ± 0.18
Waist circumference (cm)	105.7 ± 10.3	84.7 ± 8.7
Hip circumference (cm)	105.8 ± 7.9	96.9 ± 6.9
Waist-hip ratio	1.00 ± 0.08	0.87 ± 0.08
Systolic blood pressure (mmHg)	142.9 ± 18.3	125.1 ± 12.7
Diastolic blood pressure (mmHg)	86.0 ± 9.5	80.2 ± 9.5
Triglycerides (mmol/L)	1.7 (1.1, 2.6)	0.9 (0.7, 1.1)
Total cholesterol (mmol/L)	4.5 ± 1.0	5.5 ± 1.0
HDL-cholesterol (mmol/L)	1.2 ± 0.3	1.7 ± 0.4
LDL-cholesterol (mmol/L)	2.3 ± 0.9	3.4 ± 0.9
Fasting glucose (mmol/L)	8.0 ± 2.7	5.1 ± 0.4
HbA1c (mmol/mol)	66.7 ± 11.1	35.5 ± 2.5
Diabetes durations (years)	14.2 ± 9.0	–
Metformin, n (%)	93 (97.9%)	–
Insulin, n (%)	67 (71%)	–
Insulin dose (units/day)	60.0 (40.0; 95.0)	–
Lipid lowering drugs: n (%)	76 (80%)	–
Antihypertension drugs, n (%)	71 (75%)	–
Diuretics	37 (39%)	–
AT2 antagonist	31 (33%)	–
Beta blocker	22 (23%)	–
Calcium antagonist	18 (19%)	–
ACE-inhibitors	30 (32%)	–
UACR (mg/mmol)	1.1 (0.4; 5.3)	–
Serum creatinine (μmol/L)	70.6 ± 18.8	75.0 ± 15.4
eGFR (mL/min per 1.73 m^2)	92.0 ± 16.2	89.0 ± 13.0
Total body fat (%)	36.9 ± 9.2	29.2 ± 7.6
Male	28.9 ± 3.9	22.3 ± 3.4
Female	44.5 ± 4.5	34.1 ± 5.7
Abdominal VAT (cm^2)	187.0 ± 68.8	74.1 ± 32.1
Male	196.1 ± 61.5	88.2 ± 29.7
Female	178.0 ± 74.8	63.4 ± 30.0
Abdominal SAT (cm^2)	333.6 ± 123.1	217.4 ± 90.7
Male	279.6 ± 97.4	178.0 ± 73.2
Female	386.5 ± 123.4	247.4 ± 92.3

Data are presented as n (%) or mean ± SD or median (interquartile range).
BMI: body mass index; BSA: body surface area; HbA1c, Glycated hemoglobin A1c; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; AT2 antagonist: angiotensin II type 2 receptors antagonist; ACE-inhibitors: Angiotensin-converting enzyme inhibitors; UACR: urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate based on CKD-EPI equation; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue.

cholesterol, triglycerides and BSA. The adjusted coefficients of determination (adjusted R^2) of the multivariable models of sinus fat-parenchyma ratio were lower than those of renal sinus fat volume. Fig. 5 is the standardized residual plots demonstrating the associations of sinus fat volume with HbA1c, total cholesterol and abdominal VAT after adjustments for age, sex, ethnicity and T2DM.

In the T2DM patient group, after adjustment for age, sex and ethnicity, both sinus fat volume (standardized $\beta = 0.27$, $p = 0.016$) and sinus fat-parenchyma ratio (standardized $\beta = 0.28$, $p = 0.007$) were positively associated with UACR (Fig. 5). Total cholesterol (standardized $\beta = 0.23$, $p = 0.036$) and triglycerides(standardized $\beta = 0.40$, $p < 0.001$) were also associated UACR after adjustment of age, sex and ethnicity.

4. Discussion

In this study, both renal sinus fat volume and sinus fat-parenchyma ratio were larger in T2DM patients compared with healthy controls, and were associated with higher level of HbA1c. The associations persist after adjustments for metabolic and anthropometric characteristics. In T2DM patients, higher urinary albumin-to-creatinine ratio was also associated with increased renal sinus fat and sinus fat-parenchyma ratio.

HbA1c level reflects the average plasma glucose level over the previous 8 to 12 weeks.[31] Higher HbA1c indicates poorer control of blood glucose over time, and is strongly associated with increased risk of diabetic complications, such as diabetic nephropathy.[32] In this study the association between sinus fat and HbA1c remained significant even after additional adjustment for other metabolic risk factors. To our knowledge, this association has not been reported before. As a marker of kidney damage, UACR is used for screening of diabetic nephropathy. Similar to our study, an earlier study found a trend for the association of renal sinus fat area with UACR.[19] Another study reported an association of renal sinus fat with exercise-induced albuminuria in a non-diabetic cohort at diabetic risk.[17] The findings in our study suggested that sinus fat might be associated with preclinical kidney injury in circumstances of poor blood glucose control.

The underlying mechanism can be conceived from previous studies and the association of sinus fat with metabolic risk factors in this study. Earlier studies suggest that perivascular fat is strongly associated with insulin sensitivity,[33] and insulin resistance is a strong marker of incident impairment of renal function.[34] Renal sinus fat as an ectopic perivascular fat has the paracrine effect of secreting inflammatory cytokines and vasoconstrictive factors,[35] which could lead to local inflammation, oxidative stress, lipotoxicity and fibrosis.[10,36] It has been reported that renal sinus fat is associated with kidney injury molecule-1 and fibroblast growth fator-21 levels in a healthy population.[12] Excessive renal sinus fat accumulation might also mechanically compress the vasculatures in the renal hilum, thereby directly increase intra-renal pressure and stimulate the renin-angiotensin-aldosterone system.[35] This mechanism was proposed in several studies demonstrating the associations of increased renal sinus fat with hypertension and decreased eGFR or gold-standard GFR.[10,13,19,37] However, we did not find an association between renal sinus fat and eGFR in this study (Table 3). This disparity might be caused by the poor correlation between eGFR and true GFR when serum creatinine is within the normal range,[38] which is the case in the majority of our participants.

Table 2
Comparisons of renal sinus fat volume, parenchyma volume and sinus fat-parenchyma ratio between T2DM patients and healthy controls.

Renal volume	All participants (n = 146)		Student t	ANCOVA		P values of interactions		
	T2DM patients (n = 95)	Healthy controls (n = 51)	P value	Adjusted mean difference (95% CI)[a]	P value	By age	By sex	By ethnicity
Sinus fat (cm^3)	15.4 ± 7.5	10.3 ± 7.1	<0.001	4.8 (2.6, 7.1)	<0.001	0.769	0.844	0.639
Parenchyma (cm^3)	170.1 ± 39.0	135.1 ± 25.0	<0.001	40.3 (30.9, 49.8)	<0.001	0.210	0.907	0.939
Sinus fat-parenchyma ratio	0.09 ± 0.04	0.07 ± 0.05	0.020	0.012 (−0.001, 0.026)	0.079	0.664	0.544	0.186

T2DM, type 2 diabetes mellitus; ANCOVA, analysis of covariance.
[a] adjusted for age, sex and ethnicity.

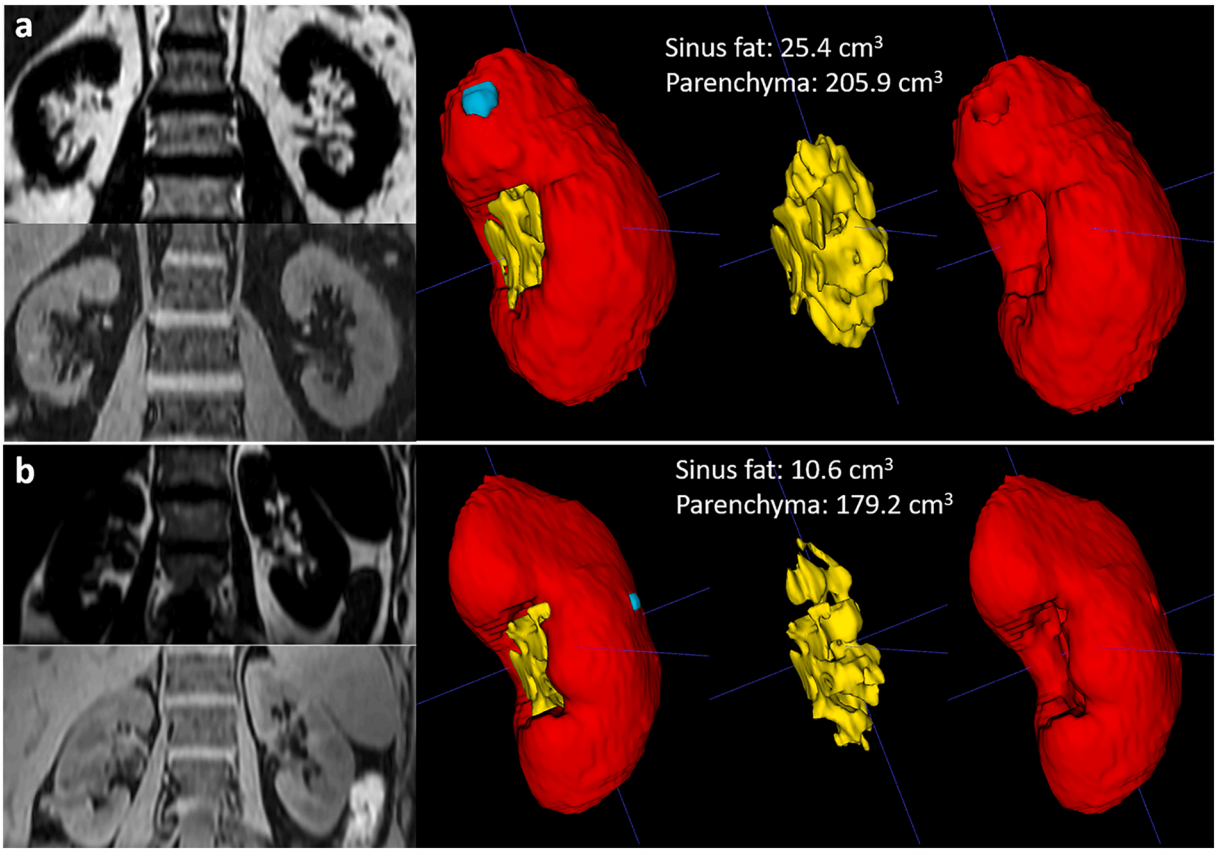

Fig. 4. Renal volumes of (A) a T2DM patient and (B) a healthy control, who are of similar body size. Renal volumes are obtained from fat-only and water-only DIXON images, where sinus fat is labeled yellow, and cysts (blue) are excluded from the calculation of parenchyma volume (red). (A) A 64-year European male T2DM patient whose height is 178.0 cm, weight is 86.9 kg, renal sinus fat volume is 25.4 cm^3, renal parenchyma volume is 205.9 cm^3. (B) A 61-year European male volunteer whose height is 178.5 cm, weight is 85.7 kg, renal sinus fat volume is 10.6 cm^3, renal parenchyma volume is 179.2 cm^3.

Table 3
Correlations among the clinical characteristics and renal parameters.

	Sinus fat	Parenchyma	Sinus fat-parenchyma ratio	age	BSA	Waist-hip ratio	HbA1c	Abdominal VAT	Triglycerides	Total cholesterol	eGFR
Sinus fat	1.00										
Parenchyma	0.54	1.00									
Sinus fat-parenchyma ratio	0.88	0.13	1.00								
age	0.36	0.06	0.41	1.00							
BSA	0.48	0.74	0.22	0.07	1.00						
Waist-hip ratio	0.51	0.53	0.38	0.36	0.59	1.00					
HbA1c	0.39	0.39	0.29	0.17	0.42	0.53	1.00				
Abdominal VAT	0.48	0.50	0.36	0.35	0.59	0.75	0.60	1.00			
Triglycerides	0.34	0.25	0.28	0.10	0.32	0.38	0.51	0.37	1.00		
Total cholesterol	0.11	−0.14	0.13	−0.09	−0.06	−0.23	−0.30	−0.33	0.18	1.00	
eGFR	−0.11	0.30	−0.29	−0.52	0.02	−0.11	0.04	−0.06	−0.08	−0.05	1.00

BSA, body surface area; HbA1c, Glycated hemoglobin A1c; VAT, visceral adipose tissue; eGFR, estimated glomerular filtration rate.

It is worth noting that the majority of T2DM patients (87 out of 95) in this study had UACR <30 mg/mmol. There has been evidence suggesting that even within "normal" range, there is a continuous relationship between albuminuria and risk of progression to overt nephropathy.[39] The progression of diabetic nephropathy can possibly be reversed or delayed at an early stage by tight metabolic control, inhibition of the renin-angiotensin-aldosterone system, and treatments of hypertension and lipidemia.[2] However, the residual risk of progression to end stage nephropathy remains high despite multifactorial treatment in diabetic patients.[40] Our findings shed light on the clinical value of renal sinus fat volume in early identification and treatment evaluation of diabetic nephropathy. As renal sinus fat is a body fat compartment, which is probably less variable than serum or urine parameters, it might reflect the overall renal implications over time.

Nevertheless, our study also shows that sinus fat volume is associated with age, parenchyma volume, body size and a number of clinical parameters (Table 3). Only 45% of the variance at most in renal sinus fat volume can be explained by the multivariable models (adjusted R^2 in Table 4). Therefore, the association of sinus fat-parenchyma ratio with HbA1c was also analyzed using multivariable models, in which the association with sex, ethnicity and BSA were attenuated. However, the variances of sinus fat-parenchyma ratio that could be explained by the regression models were lower than those of sinus fat volume. This could be due to the fact that parenchyma volume is affected by a number of

Table 4
Multiple linear regression results for renal sinus fat volume and sinus fat-parenchyma ratio.

Renal sinus fat volume						
	Model 1		Model 2		Model 3	
Characteristics	Standardized β (95% CI)	P value	Standardized β (95% CI)	P value	Standardized β (95% CI)	P value
HbA1c	0.47 (0.22, 0.72)	<0.001	0.36 (0.10, 0.62)	0.006	0.36 (0.10, 0.62)	0.006
Abdominal VAT	0.33 (0.14, 0.51)	0.001	0.32 (0.14, 0.50)	0.001	0.31 (0.10, 0.52)	0.004
Triglycerides	0.20 (0.05, 0.34)	0.008	0.003 (−0.16, 0.16)	0.974	0.003 (−0.16, 0.16)	0.975
Total cholesterol	0.24 (0.09, 0.39)	0.002	0.22 (0.06, 0.38)	0.007	0.22 (0.06, 0.38)	0.008
			Adjusted $R^2 = 0.454$		Adjusted $R^2 = 0.450$	
Sinus fat-parenchyma ratio						
HbA1c	0.47 (0.20, 0.75)	0.001	0.36 (0.07, 0.65)	0.015	0.36 (0.09, 0.67)	0.014
Abdominal VAT	0.25 (0.04, 0.46)	0.022	0.23 (0.03, 0.44)	0.026	0.29 (0.06, 0.53)	0.015
Triglycerides	0.21 (0.05, 0.37)	0.010	0.02 (−0.16, 0.20)	0.823	0.02 (−0.16, 0.20)	0.823
Total cholesterol	0.26 (0.10, 0.43)	0.002	0.23 (0.05, 0.40)	0.014	0.23 (0.05, 0.41)	0.011
			Adjusted $R^2 = 0.302$		Adjusted $R^2 = 0.303$	

Model 1 was built for each characteristic separately, adjusted for age, sex, ethnicity and T2DM.
Model 2 includes age, sex, ethnicity, T2DM, HbA1c, abdominal VAT, triglycerides and total cholesterol.
Model 3 was Model 2 + body surface area.
HbA1c, Glycated hemoglobin A1c; VAT, visceral adipose tissue; T2DM, type 2 diabetes mellitus.

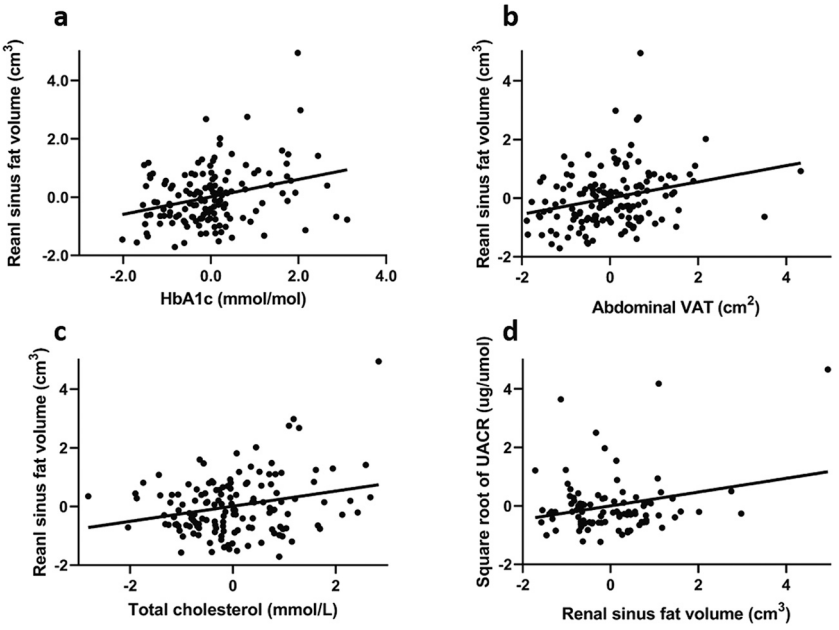

Fig. 5. Standardized residual scatter plots show that after adjustment for age, sex, ethnicity and T2DM, renal sinus fat volume was positively associated with HbA1c (A), abdominal VAT (B) and total cholesterol (C). In T2DM patients, the square root of UACR was positively associated with renal sinus fat after adjustment for age, sex and ethnicity (D).

clinical parameters that impact differently on sinus fat, making it not optimal for the correction of systemic bias of sinus fat volume. Further studies using serial MR scans to assess the alterations of renal sinus fat and parenchyma volumes during the clinical course of T2DM might provide more insights.

Strengths of this study are the volumetric analysis of renal sinus fat, the practical definition of the boundary and the meticulous segmentation. The application of high resolution 3D Dixon imaging enables accurate volumetric analysis, especially of sinus fat, which is of highly irregular shape and small volume. The boundary of renal sinus fat was defined as "a straight line between both dimples at the edge of renal sinus opening" on a single-slice CT or MR image in most previous studies,[10,11,13,14,17,18] which could be operator-dependent for 3D segmentation especially when the renal hilum is dilated due to excessive fat accumulation. Therefore, we defined the boundary on each transversal image by a straight line tangential to the margins of parenchyma around the hilum. Moreover, the non-fat structures in renal sinus were meticulously discarded, enabled by the combination of fat-only images and water-only images with higher resolution than those in previous volumetric studies based on MR.[23,37] As a result, the Bland-Altman plots (Fig. 3) of the repeated measurements of sinus fat and parenchyma volumes showed limited intra- and inter-observer differences with narrow ranges of variance.

Our study has several limitations. Firstly, the cross-sectional design does not allow an interpretation of causality regarding the associations between renal sinus fat accumulation and clinical characteristics. Secondly, potential reverse causation cannot be excluded in the multivariable analysis, and the number of adjustments are constrained by sample size. Finally, gold-standard GFR was not available in this study.

5. Conclusions

In this study, high resolution Dixon technique was used for 3D segmentation of the renal sinus fat and parenchyma on MRI. Our study

shows that excessive sinus fat accumulation is prominent in patients with type 2 diabetes compared with healthy controls accounting for age, sex and ethnicity. Larger renal sinus fat volume was associated with higher levels of glycated hemoglobin and metabolic risk factors, and with increased urinary albumin-to-creatinine ratio in patients with T2DM, indicating a potential role of sinus fat in the development of diabetic nephropathy. Future studies are needed to investigate whether sinus fat volume can serve as an early biomarker for diabetic nephropathy.

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CRediT authorship contribution statement

Ling Lin: Conceptualization, Methodology, Formal analysis, Visualization, Writing – Original Draft **Ilona A. Dekkers:** Conceptualization, Methodology, Investigation, Writing – Review & Editing **Lu Huang:** Formal analysis, Writing – Review & Editing **Qina Tao:** Visualization, Writing – Review & Editing **Elisabeth H. M. Paiman:** Investigation, Data Curation, Writing – Review & Editing **Maurice B. Bizino:** Investigation, Data Curation, Writing – Review & Editing **Ingrid M. Jazet:** Resources, Investigation, Data curation **Hildo J. Lamb:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no conflicts of interest.

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