Renal fat fraction is significantly associated with the risk of chronic kidney disease in patients with type 2 diabetes

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Backgrounds: Ectopic fat deposition is closely related to chronic kidney disease (CKD). Currently, there are few population studies that have been conducted to determine the relationship between renal parenchyma fat deposition and the risk of CKD among patients with type 2 diabetes mellitus (T2DM). Therefore, we employed magnetic resonance imaging (MRI) to detect renal parenchyma fat content in individuals with T2DM, expressed as renal fat fraction (FF), to explore whether renal FF is an important risk factor for CKD in patients with T2DM.

Methods: In this cross-sectional study, 189 subjects with T2DM were enrolled. CKD was defined as the estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m². Measurement of the renal FF was performed on a 3.0-T MRI (MAGNETOM Skyra, Siemens, Erlangen, Germany). Binary logistic regression was used to determine the association between tertiles of renal FF and the risk of renal FF in detecting CKD in T2DM patients.

Results: The patients were divided into three groups according to tertiles of the renal FF level (2.498 - 7.434). As renal FF increases, patients tend to be older, and more abdominally obese, with a decreased eGFR (p<0.05). After adjustment for potential confounders, patients in the highest tertile of renal FF had a significantly increased risk of CKD compared to those in the lowest tertile (odds ratio (OR) = 3.98, 95% confidence interval (CI) = 1.12 - 14.09, p = 0.032), and the area under the ROC curve for this model was 0.836 (0.765–0.907).

Conclusions: The renal FF is significantly independently associated with CKD in patients with T2DM.

KEYWORDS
renal fat fraction, chronic kidney disease, ectopic fat deposition, type 2 diabetes mellitus, magnetic resonance imaging
Introduction

Chronic kidney disease (CKD) is highly prevalent in patients with type 2 diabetes mellitus (T2DM), with approximately 30%-50% of patients with T2DM having CKD (1–4). CKD increases the risk of cardiovascular disease (5) and is the most common cause of end-stage renal disease (ESRD) worldwide (6), especially in patients with diabetes mellitus (DM) (7). The age-standardized 10-year cumulative all-cause mortality in patients with T2DM and CKD was increased by 24.4% (8). Due to severe complications and high mortality resulting from CKD, early identification of high-risk individuals with T2DM is a crucial strategy to prevent the development of CKD.

Patients with T2DM are often accompanied by lipid metabolism disorders (9), which are manifested in excess lipids that are ectopically deposited in non-adipose tissue such as the liver, heart, pancreas, and kidney (10, 11). In the kidney, ectopic fat often deposits in the peritubular space, renal sinus, and renal parenchyma (12). Previous studies (13–15) have confirmed that peritubular and renal sinus fat deposition is closely related to the increased risk of CKD, but the relationship between renal parenchymal fat deposition and CKD in patients with T2DM remains unclear.

Renal parenchymal fat deposition is a condition in which ectopic fat is deposited in the kidney’s cortex and medulla, which leads to renal cell injuries, such as podocytes, tubular cells, and mesangial cells (16–19). Numerous animal studies (20, 21) have shown that renal parenchymal lipid deposition causes kidney damage, such as glomerulosclerosis, renal interstitial fibrosis, and proteinuria. However, due to the limited methods of measuring renal parenchymal fat, which mainly rely on renal biopsy, invasive and complex, there have been few population studies of renal parenchymal fat deposition and renal impairment previously. Recently, Reeder SB et al. (22) used the proton-density fat fraction (FF) measured by magnetic resonance imaging (MRI) to evaluate the tissue fat deposition content, which is non-invasive, accurate, and convenient. With this method, Wang et al. (23) studied the relationship between renal parenchymal fat deposition and T2DM in 95 participants, and they found that the renal FF is significantly increased in diabetic patients, especially in patients with microalbuminuria. However, this research has not adjusted the other confounders, whether renal FF is independently associated with microalbuminuria is not clear. Besides, the impact of renal FF on renal function has not been reported.

In the current study, we measured fat deposition in renal parenchyma by MRI in patients with T2DM, to explore whether renal FF was an independent risk factor for CKD.

Research design and methods

Population

We recruited 213 patients with T2DM who attended the Department of Endocrinology at the First Affiliated Hospital of Chongqing Medical University from June 2021 to May 2022. T2DM was diagnosed based on the 1999 World Health Organization diagnostic criteria for T2DM (24). All patients signed informed consent forms and completed an abdominal MRI scan. The exclusion criteria are as follows: 1) age ≥75 years; 2) a previous history of chronic kidney disease caused by hypertension, kidney stones, IgA nephropathy, etc; 3) severe liver damage (transaminases exceeding the upper limit of normal values more than 3 times) and severe heart failure (New York Heart Association cardiac function grades II-IV); 4) combined with renal tumors, renal large cysts, abnormal renal location, congenital dysplasia of the kidneys, and other conditions that affect the renal fat measurement. In total, 189 participants were involved in the final analyses. This study was supported by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (Approval number: 2021-685). The research flowchart is shown in Figure 1.

Data collection and biochemical measurement

Those who participated answered questions (about smoking, drinking, and their history of serious illness), and had their blood pressure, height, weight, waist circumference (WC) and hip circumference (HIP) measured. BMI was calculated as weight in kilograms divided by the square of height in meters.

Glycosylated hemoglobin (HbA1c) was measured by a high-performance liquid chromatography analyzer. Fasting plasma glucose (FPG), serum lipid levels such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured enzymatically by an automatic analyzer (Model 7080; Hitachi, Tokyo, Japan) with reagents purchased from Leadman Biochemistry Co. Ltd. (Beijing, China). Serum creatinine, urinary creatinine, and albumin were measured with an automatic biochemical analyzer (Modular DDP; Roche). The urinary albumin-to-creatinine ratio (UACR) was calculated.

Definition of variables

Participants who self-reported having smoked or are currently smoking were defined as having a history of smoking. Drinking history was defined as patients who consumed ≥50 g of alcohol per day. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking antihypertensive medications. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (25). CKD was defined as eGFR < 60 mL/min/1.73m² (26).
Measurement of PDFF

All MRI examinations were performed on a 3.0-T MRI system (MAGNETOM Skyra, Siemens, Erlangen, Germany) with a sixteen-channel phased-array body coil. The sequences main including T1 VIBE two-point Dixon sequence and multi-echo Dixon VIBE sequence with two consecutive breath holds. The parameters of T1 VIBE two-point Dixon sequence was as follows: repetition time (TR), 4.66ms; echo times (TEs), 1.34 and 2.57ms; slice thickness, 3 mm; slice number, 64; matrix size, 210 × 320; number of excitations, 1; field of view (FOV), 400-450 mm × 87.5%; band-width, 820 Hz/pixel; acquisition time, 17 s. The multi-echo Dixon VIBE sequence as follows: TR, 9.46ms; TEs, 1.33, 2.64, 3.95, 5.26, 6.57, and 7.88ms; slice thickness, 4 mm; slice number, 64; matrix size, 137 × 224; number of excitations, 1; FOV, 360-450 mm × 87.5%; band-width, 1060 Hz/pixel; acquisition time, 20 s. FF and Fat only maps were generated automatically after the acquisition using Siemens built-in post-processing toolkit.

The measurements of the FF were performed in a software (syngo.via, Siemens Healthcare, Erlangen, Germany). The five levels centered on the renal hilum on each side of the kidney were chosen respectively. The free-hand region of interest (ROI) was placed in the entire renal parenchyma with the boundaries avoiding the perinephric and renal sinus fat (Figure 2). The unilateral renal FF was calculated by the arithmetic mean value of the five sections of measurements, and renal FF was obtained by the sum of bilateral renal FF in each individual.

Two radiologists from the radiology department (reader A, L.H.X., 3 years of experience, and reader B, P.Y., 2 years of experience) performed data measurements and were blinded to all clinical data under the supervision of an experienced abdominal radiologist (Y.M., 18 years of experience). The consistency between two readers was analyzed using the intraclass correlation coefficient (ICC). For the agreement analysis, the ICC values was interpreted as follows: less than 0.5, poor reliability; 0.5 and 0.75, moderate reliability; 0.75 and 0.9, good reliability; greater than 0.90, excellent reliability (27). There was good or excellent reliability for renal FF between the two readers (ICC = 0.822).

Statistical analyses

Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA). Continuous variables were described using mean ± standard deviation (SD) or median (25th and 75th percentiles), depending on whether the data distribution was normal (assessed by the Shapiro-Wilk test). As for Continuous variables, the Student t-test or Mann-Whitney U test was used to determine differences between two groups; ANOVA or the Kruskal-Wallis test was used to determine the differences among three groups. Categorical variables were expressed as frequencies (percentage), and χ² tests were used for group comparisons.

Binary logistic regression analysis was used to describe the relationship between renal FF and CKD while adjusting for potential confounding variables. Data were summarized as odds ratios and regression coefficients (OR, 95% CI). P < 0.05 was considered statistically significant.

Results

Clinical characteristics of the participants

A total of 189 patients with T2DM were included in the analysis. The clinical characteristics of participants grouped by
three tertiles of the renal FF were shown in Table 1. The average age of the total population included was 51 years, with 66.1% of men. There were 85 (45.0%) patients who reported a history of smoking, while 55 (29.1%) had a history of alcohol drinking. As the renal FF increases, patients tend to be older, and more abdominally obese, with a decreased eGFR (p<0.05). There was no difference in UACR between subjects in different tertiles. The proportion of CKD showed a significant difference among the three group (p<0.05).

Comparison of fat parameters between CKD and non-CKD

Of the 189 participants, 32 (16.9%) had CKD. Participants with CKD had a higher renal FF than patients without [ 4.69% (4.19%, 5.39%) vs. 4.08% (3.55%, 4.97%), p = 0.005]. No significant intergroup differences were detected with respect to BMI and WC. The results are shown in Table 2.

Relationship between renal FF and CKD

The binary logistic regression analysis was used to assess the correlation of the renal FF with CKD. In the crude model, with the low tertile of the renal FF set as the reference, the renal FF in the top tertile was associated with a higher OR for CKD (OR = 3.95, 95% CI = 1.35 - 11.57, p = 0.012). After adjustment for sex and age, renal FF located in the high-quartet still had a significantly increased risk of CKD relative to the low-quartet (OR = 3.52, 95% CI = 1.14 - 10.93, p = 0.029). After additional adjustment for BMI, WC, HbA1C, and TG (model 2), plus DM duration, history of hypertension, smoking and drinking history, insulin therapy, anti-hypertension drugs, and hypoglycemic therapy (model 3), this trend was retained (Figure 3). The area under the ROC curve was 0.836. Two experienced radiology doctors measured renal parenchymal fat by selecting 5 sections of each kidney, and renal FF was obtained by adding up the average of bilateral renal FF in each individual. The consistency within the group was good (ICC = 0.822). It is suggested that renal parenchymal fat is an independent risk factor for CKD.

Some studies (21, 31) have shown that there are abnormalities in kidney fat metabolism in diabetic patients, such as decreased β-oxidation of fatty acids, and increased intake of cholesterol and...
fatty acids, which is one of the main mechanisms of kidney fat deposition in patients with T2DM. The possible mechanism for kidney dysfunction caused by renal FF is lipotoxicity. Excessive lipids accumulate in the renal parenchyma, causing damage to various cells, including podocytes (16), mesangial cells (17), and proximal tubular epithelial cells (18, 19), being substantially detrimental to renal function in the long term. Besides, lipids accumulation within the renal parenchyma may cause oxidative stress, inflammation, and fibrosis (32, 33) and lead to renal damage.

Our study had some limitations. First, this was a cross-sectional study so that we could not establish a causal effect relationship between renal FF and CKD. Indeed, our study is the first to explore the relationship between renal fat and CKD in patients with T2DM, which is innovative. Second, the sample size of our study was relatively small because of the high expense of MRI. Nevertheless, our method of measuring renal parenchymal fat deposition is noninvasive and accurate compared to other methods, and our findings are credible. Further longitudinal and

| TABLE 1. Clinical features of the whole population stratified across tertiles of renal FF measured by the MRI |
|---------------------------------------------------------------|
| **All** | **Tertile 1 (2.498-3.778)** | **Tertile 2 (3.779 - 4.690)** | **Tertile 3 (4.691-7.434)** | **p-value** |
|---------|-----------------------------|-----------------------------|-----------------------------|-------------|
| n=189   | n=63 (2.498-3.778)          | n=63 (3.779 - 4.690)        | n=63 (4.691-7.434)          |             |
| Male, n (%) | 125 (66.1)                | 39 (61.9)                  | 46 (73.0)                  | 40 (63.5)   | 0.362 |
| Age (years) | 57 ± 11                    | 54 ± 12                    | 58 ± 10                    | 59 ± 10     | 0.041 |
| Duration of diabetes (years) | 10 ± 7                      | 9 ± 7                      | 11 ± 8                      | 11 ± 7      | 0.412 |
| Smoking | 85 (45.0)                   | 33 (52.4)                  | 28 (44.4)                  | 24 (38.1)   | 0.271 |
| History, n (%) | 55 (29.1)                 | 16 (25.4)                  | 19 (30.2)                  | 20 (31.7)   | 0.716 |
| Drinking history, n (%) | 92 (48.7)                 | 30 (47.6)                  | 29 (46.0)                  | 33 (52.4)   | 0.759 |
| History of hypertension, n (%) | 132 ± 17                   | 136 ± 19                   | 131 ± 17                   | 129 ± 14    | 0.061 |
| SBP (mmHg) | 81 ± 10                    | 83 ± 11                    | 79 ± 9                     | 81 ± 9      | 0.092 |
| DBP (mmHg) | 25.3 ± 3.0                 | 24.9 ± 3.1                 | 25.2 ± 2.7                 | 25.9 ± 3.3  | 0.157 |
| WC (cm) | 93.2 ± 8.1                  | 91.8 ± 8.6                 | 92.3 ± 6.6                 | 96.2 ± 8.1  | 0.001 |
| HC (cm) | 96.5 ± 6.2                  | 96.3 ± 6.0                 | 95.6 ± 5.8                 | 97.6 ± 6.7  | 0.171 |
| FPG (mmol/L) | 9.2 ± 3.9                  | 9.9 ± 4.7                  | 8.8 ± 3.3                  | 9.0 ± 3.4   | 0.271 |
| Hba1c (mmol/mol) | 8.5 ± 2.2                  | 8.9 ± 2.3                  | 8.3 ± 2.0                  | 8.4 ± 2.3   | 0.362 |
| TC (mmol/L) | 4.49 ± 1.35                | 4.59 ± 1.38                | 4.44 ± 1.29                | 4.43 ± 1.38 | 0.75 |
| TG (mmol/L) | 2.53 ± 2.82                | 2.40 ± 2.55                | 2.39 ± 2.46                | 2.81 ± 3.37 | 0.635 |
| HDL-C (mmol/L) | 1.10 ± 0.31                | 1.10 ± 0.30                | 1.09 ± 0.33                | 1.09 ± 0.31 | 0.959 |
| LDL-C (mmol/L) | 2.57 ± 1.01                | 2.72 ± 1.09                | 2.72 ± 1.09                | 2.48 ± 1.01 | 0.367 |
| UACR (mg/g) | 204.1 ± 669.5              | 158.9 ± 630.1              | 209.3 ± 621.7              | 244.2 ± 756.3 | 0.774 |
| eGFR (ml/min/1.73 m²) | 67.7 ± 23.0                | 97.2 ± 19.8                | 85.8 ± 23.5                | 80.1 ± 22.5 | 0 |
| CKD, n (%) | 32 (16.9)                   | 5 (7.9)                    | 11 (17.5)                  | 16 (25.4)   | 0.033 |
| Insulin, n (%) | 73 (39.7)                 | 19 (31.7)                  | 31 (50.0)                  | 23 (37.1)   | 0.103 |
| RX with ACE- I/ARBs, n (%) | 60 (31.7)                 | 18 (28.6)                  | 22 (34.9)                  | 20 (31.7)   | 0.746 |
| Hypolipidemic therapy, n (%) | 73 (38.6)                 | 20 (31.7)                  | 28 (44.4)                  | 25 (39.7)   | 0.335 |
| Renal FF (%) | 4.19 (3.59,5.03)            | 3.44 (3.12,3.59)           | 4.20 (4.04,4.52)           | 5.30 (5.01,5.9) | 0 |

| TABLE 2. The differences of BMI, WC and renal FF parameters between non-CKD group (eGFR ≥ 60ml/min/1.73m²) and CKD group (eGFR < 60ml/min/1.73m²). |
|---------------------------------------------------------------|
| **non-CKD** | **CKD** | **p-value** |
|---------|---------|-------------|
| n=157   | n=32    |             |
| BMI (kg/m²) | 25.3 ± 3.0 | 25.6 ± 3.1 | 0.539 |
| WC (cm) | 92.9 ± 8.1 | 94.7 ± 8.1 | 0.239 |
| Renal FF (%) | 4.08 (3.55,4.97) | 4.69 (4.19,5.39) | 0.005 |
| L-Renal FF (%) | 2.23 (1.89,2.73) | 2.49 (2.09,3.01) | 0.135 |
| R-Renal FF (%) | 1.87 (1.56,2.22) | 2.17 (2.03,2.61) | 0.000 |
FIGURE 3
Univariate (crude model) and multivariate analyses (Model 1 to 3) for logistic regression of CKD (eGFR < 60 ml/min/1.73 m²) risk according to the tertiles of the renal FF. Model 1 was adjusted for age and sex. Model 2 was adjusted for the BMI, WC, HbA1C, TG in addition to the variables in model 1. Model 3 was adjusted for duration of diabetes mellitus, history of hypertension, smoking history, drinking history, insulin therapy, RX with ACE-I/ARBs, hypolipidemic therapy in addition to the variables in model 2.

FIGURE 4
(A) Crude model was unadjusted. (B) Model 1 was adjusted for age and sex. (C) Model 2 was adjusted for the BMI, WC, HbA1C, TG, UACR in addition to the variables in model 1. (D) Model 3 was adjusted for duration of diabetes mellitus, history of hypertension, smoking history, drinking history, insulin therapy, RX with ACE-I/ARBs, hypolipidemic therapy in addition to the variables in model 2. AUC, area under the curve.
larger sample sizes studies are needed to ensure the association between the renal FF and CKD in diabetic patients.

Conclusions

The present study demonstrates that increased renal FF is significantly associated with CKD in patients with T2DM, independent of anthropometric, metabolic factors, and other fat indicators. Renal FF may be a reliable and valuable anthropometric measurement for the early identification of risk of CKD in patients with T2DM.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors made a significant contribution to the work reported by participating in some or all of the following processes: conception, design and execution of study; acquisition, analysis and interpretation of data; and drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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