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Original article

Perirenal fat and chronic kidney disease in type 2 diabetes: The mediation role of afferent arteriolar resistance

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ABSTRACT

Aim: Perirenal fat (PRF) is an independent predictor for chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM) patients. Previous studies speculated that PRF may promote renal dysfunction through affecting renal hemodynamics. To verify this hypothesis, we studied the relationship between PRF and renal hemodynamics in T2DM.

Methods: 91 T2DM patients were included. PRF thickness (PRFT) was measured by magnetic resonance imaging. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by renal dynamic imaging. Renal vascular resistance (RVR), glomerular hydrostatic pressure (P_{GLO}), afferent (R_A) and efferent (R_E) arteriolar resistance were calculated by Gomez equations. Multiple linear regression was used to determine the relationship between PRFT and renal hemodynamics. Mediation analysis was conducted to estimate the mediation effects of renal hemodynamics on the relationship between PRF and CKD.

Results: All patients were divided into three groups according to the tertiles of PRFT. Compared with patients in tertile 1, GFR and ERPF were significantly decreased in patients in tertile 3, while RVR and R_A were significantly increased. PRFT was negatively correlated with GFR, ERPF and P_{GLO}, and positively correlated with RVR and R_A after adjustment for sex, age, visceral adipose tissue and treatments with ACE inhibitors/angiotensin receptor blockers and sodium-glucose cotransporter protein-2 inhibitors. Moreover, RVR and R_A mediated the effect of PRF on GFR, with a mediated proportion of 29.1 % and 41.4 % respectively.

Conclusion: In T2DM patients, PRF was negatively correlated with GFR, and positively correlated with R_A. R_A mediated the relationship between PRF and CKD.

Introduction

Diabetic kidney disease (DKD) is highly prevalent in diabetes, influencing approximately 30–50 % of patients with type 2 diabetes mellitus (T2DM) [1–3]. As the leading cause of end-stage renal disease (ESRD) worldwide, DKD increases not only the risk of cardiovascular events but also all-cause mortality in T2DM [4–6]. Excessive fat deposition is closely associated with DKD and weight loss induced by bariatric surgery is associated with the reduced albuminuria excretion rate and improved kidney outcomes in obese patient with type 2 diabetes [7, 8]. Furthermore, previous studies have observed that fat deposited locally in the kidneys was closely associated with reduced glomerular filtration rate (GFR) and increased chronic kidney disease (CKD) risk in T2DM [9–11]. Our team further revealed that the predictive value of perirenal fat (PRF) for CKD in T2DM was significantly better than that of subcutaneous and visceral fat [11]. However, the mechanism of PRF impairing renal function remains not fully understood.

PRF is a fat pad that surrounds kidney [12], and is wrapped by Gerota fascia [13], which may restrict the expansion of adipose tissue when PRF is increased. Based on this, some researchers believed that the increased PRF has limited outward expansion, which in turn exerts physical pressure on renal blood vessels and renal parenchyma inward,

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thereby affecting renal hemodynamics such as renal blood flow resistance, and may be one of the mechanisms leading to renal dysfunction [14–16]. It was previously found that elevated intra-abdominal pressure would increase the renal vascular resistance (RVR) in rats and dogs, while reduce the GFR and renal blood flow (RBF) [17,18]. To our knowledge, few study has directly examined the hypothesis that excess PRF may affect renal hemodynamics via compressing renal blood vessels and parenchyma, ultimately leading to renal function decline. Lamacchia *et al.* [9] showed that ultrasound measured para- and perirenal fat thickness was positively correlated with renal resistance index (RRI) in T2DM patients. However, RRI is a sonographic index assessing the resistance to flow in intrarenal arcuate or interlobar arteries, which cannot reflect the resistance of more microscopic blood vessels such as the afferent and efferent arterioles, and other renal hemodynamics parameters, including RBF, effective renal plasma flow (ERPF), filtration fraction (FF), glomerular hydrostatic pressure (P_{GLO}) were not assessed comprehensively.

Hence, in the current study, we assessed the glomerular hemodynamic parameters comprehensively by renal dynamic imaging for 91 patients with T2DM, and analyzed whether PRF was associated with glomerular hemodynamic parameters, and investigated whether renal hemodynamic parameters mediated the effect of PRF on renal dysfunction in T2DM patients.

Methods

Study population

Patients with T2DM from Chongqing Diabetes Registry (CDR) cohort were enrolled in this study between June 2022 to August 2023. T2DM was diagnosed based on the 1999 World Health Organization diagnostic criteria for type 2 diabetes [19]. All patients signed informed consent and underwent abdominal magnetic resonance imaging (MRI) and renal dynamic imaging examinations. The criteria for exclusion were: 1) age ⟨ 18 years or ⟩ 75 years; 2) history of CKD caused by hypertension, IgA nephropathy, etc.; 3) severe liver damage (transaminases greater than 3 times the upper limit of normal) and severe heart failure (New York Heart Association cardiac function grades II-IV); 4) combined with renal tumors, large renal cysts, abnormal renal position, and other conditions affecting the measurement of PRF; and 5) combined with renal artery stenosis and moderate and severe hydronephrosis which affect renal hemodynamic function. This study was supported by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University [2018–042]. Flow chart of this research is shown in Fig. 1.

Anthropometric and biochemical measurements

The medical history and medication of all patients were reviewed. Anthropometric measurements, including height, weight, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained. BMI was calculated as weight in kilograms divided by the square of height in meters. Mean arterial pressure (MAP) was calculated as the sum of SBP and 2 times DBP divided by 3.

Glycosylated hemoglobin (HbA1c) was measured by a high-performance liquid chromatography analyzer. Fasting plasma glucose (FPG), serum lipid levels such as total cholesterol (TC), total 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 estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20]. CKD was defined as estimated glomerular filtration rate (eGFR) $<$ 60 ml/min/1.73 m^2. Abnormal albuminuria was defined as urinary albumin-to-creatinine ratio (UACR) $\geq$ 30 mg g^{-1} [21].

Measurement of PRF thickness (PRFT), subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)

Abdominal MRI examination was performed on a 3.0-T MRI system (MAGNETOM Syra, Siemens, Erlangen, Germany) with a sixteen-channel phased-array body coil. The sequences mainly consist of T1 VIBE two-point Dixon sequence and multi-echo Dixon VIBE sequence

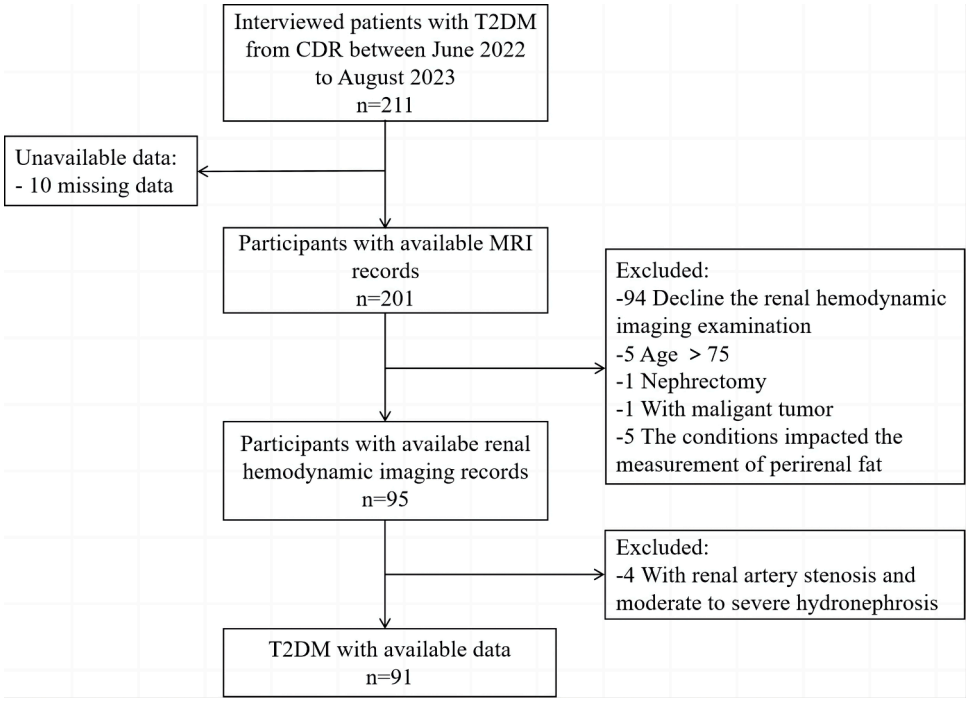

Fig. 1. Flow chart of study population in this study. T2DM, type 2 diabetes mellitus; CDR, Chongqing diabetes registry; MRI, magnetic resonance imaging.

with two consecutive breath holds, whose parameters as previously described [22].

The data were measured by a radiologist (L.H.X., 3 years of experience) who was masked to the clinical information under the supervision of an experienced abdominal radiologist (Y.M., 18 years of experience). PRFT was measured in the central slice of renal pelvis on T1-weighted images from the following three directions: 1): anterior, the vertical distance from top of anterior border of kidney to the anterior renal fascia or the closest visceral organ; 2) lateral, the vertical distance from top of lateral border of kidney to the lateral perirenal fascia or the closest visceral organ; and 3) posterior, the vertical distance from the top of posterior border of the kidney to the posterior renal fascia. All three measurements were taken on both sides of each patient. If the top border of the kidney was stuck closely to perirenal fascia or the closest visceral organ in any direction, the distance was recorded as zero. Moreover, SAT and VAT also were assessed. The external boundaries of the SAT and VAT regions were drawn, and then the entire SAT or VAT surface can be shaded and calculated automatically.

Measurement of renal hemodynamics

The renal dynamic imaging protocol was performed with injection of ^{99m}Tc-DTPA or ^{99m}Tc-EC to measure GFR and ERPF respectively, as described previously [23,24]. Notably, this method has a strong correlation with inulin and para-aminohippuric acid clearance methods [24]. In short, all patients were required to take a protein free breakfast and to drink 500 mL of water to stimulate diuresis 30 min before renal dynamic imaging. Besides, oral hypoglycemic agents were taken as usual. The height and weight were measured and routinely recorded. SPX-6 SPECT (General Electric Company, USA) was adopted to perform the examination with a low energy parallel-hole LEGP/LEHR collimator using 15–20 % window width, 140 keV energy peak and a 128×128 matrix. The ^{99m}Tc was purchased from China Atomic High Tech Co., Ltd. The DTPA and EC test kits were sourced from Xinkesida Pharmaceutical Technology Co., Ltd. in Beijing, China. The ^{99m}Tc-DTPA or ^{99m}Tc-EC were prepared by the Nuclear Medicine Department of the First Affiliated Hospital of Chongqing Medical University, with a radiochemical purity greater than 95 %. Patients were then placed in the supine position with the probe placed in the lower back to include the lung bases, kidneys, and bladder. The bolus of radiotracer, ^{99m}Tc-DTPA or ^{99m}Tc-EC, was injected into an elbow vein at a dosage of 2.96∼3.7 MBq/Kg and volume $\leq$ 1.0 mL, followed by computer acquisition immediately. Thereafter, 30 frames (2 s/frame) of blood perfusion phase and 60 frames (15 s/frame) of renal function phase were collected. The radioactive count inside the syringe was measured for 10–15 s before and after the injection to obtain residual radioactivity. At last, the double kidney GFR and ERPF were automatically calculated by an online computer after entering the patients' data of weight and height. FF was calculated as GFR/ERPF, RBF as ERPF/(1-hematocrit) and RVR as MAP/RBF.

Glomerular hemodynamic parameters, including P_{GLO}, R_A and R_E, were estimated according to Gomez equations. These equations were successfully used to evaluate patients with hypertension, endocrine disorders and diabetes [25]. Assumptions imposed by Gomez equations are as follows: 1) intrarenal vascular resistances are divided into afferent, postglomerular, and efferent; 2) hydrostatic pressures within the renal tubules, venules, Bowman's space, and interstitium (P_{Bow}) are in equilibrium of 10 mmHg; 3) glomerulus is in filtration disequilibrium; and 4) the gross filtration coefficient (K_{FG}) is 0.0867 ml/s/mmHg given a normal kidney. The Gomez equations were also used to calculate a second set of intraglomerular hemodynamic parameters assuming K_{FG} = 0.1012 ml/s/mmHg for patients with diabetes. MAP (mmHg), ERPF (ml/s), GFR (ml/s), and total protein (g/dl) were used to calculate R_A (dyne/s/cm^5) and R_E (dyne/s/cm^5), P_{GLO} (mmHg), filtration pressure across glomerular capillaries (ΔP_F; mmHg), and glomerular oncotic pressure (π_G; mmHg). Calculations are as follows:

$$\Delta P_F = GFR/K_{FG}$$

The π_G from the plasma protein mean concentration (C_M) within the capillaries: C_M = total protein (TP) / $FF \times \ln(1/1 - FF)$. $\pi_G = 5 \times (C_M - 2)$.

$$P_{GLO} = \Delta P_F + P_{Bow} + \pi_G$$

R_A and R_E were estimated using principles of Ohm's law, where 1328 is the conversion factor to dyne/s/cm^5:

$$R_A = [(MAP - P_{GLO})/RBF] \times 1328$$
$$R_E = [GFR/K_{FG} \times (RBF - GFR)] \times 1328$$

Statistical analyses

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 x2 tests were used for group comparisons. Multiple linear regression was conducted to describe the relationship between PRFT and renal hemodynamics. The mediation analysis were used to explore whether the relationship between PRF and CKD is mediated by renal hemodynamics, and quantify the mediation effect and mediated proportion. Statistical analyses were performed using SPSS 26.0 (IBM, Armonk, NY, USA) and R v4.3.2. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the participants

A total of 91 patients with T2DM were included in the analyses. 20 patients had eGFR < 60 ml/min/1.73m^2, 47 patients had UACR ≥ 30 mg g^{-1}. The clinical characteristics of participants grouped by tertiles of the PRFT is shown in Table 1. The average age and BMI of the total population were 58.00 (50.00, 67.00) years and 25.40 ± 2.93 kg/m^2, with 76.9 % of men. 48 (52.7 %) patients reported a history of hypertension, while 31 (34.1 %) patients had a treatment with ACE inhibitors/angiotensin receptor blockers (ACEi/ARBs) and 33 (36.3 %) patients had a treatment with sodium-glucose cotransporter protein-2 inhibitors (SGLT-2i). Compared with patients with lower PRFT, patients with higher PRFT were more likely to be male, to have longer diabetes duration, to use lipid lowering drugs, and to have CKD. The levels of WC and VAT were significantly increased in patients with higher PRFT, while eGFR was significantly decreased. There were no significant differences in SAT, UACR and other clinical variables among subjects in different PRFT tertiles.

Association of PRFT with CKD and albuminuria

Compared with non-CKD group, the right and bilateral PRFT of the CKD group were significantly increased ($P = 0.006$ and 0.012). Among the three thicknesses of PRF at the anterior, lateral, and posterior positions, lateral R-PRFT and posterior l-PRFT increased significantly in CKD group. Whereas, no distinct difference in PRFT was detected in albuminuria subgroups (Table S1; see supplementary materials associated with this article on line). After adjustment for sex, age, VAT, and treatment with SGLT-2i and ACEi/ARBs, PRFT was negatively correlated with eGFR ($\beta = -0.391$, $P = 0.003$), while was not significantly correlated with UACR (Table S2; see supplementary materials associated with this article on line).

Table 1
Clinical features of participants stratified across tertiles of PRFT.

	All	Tertile 1 (14.0 - 48.0)	Tertile 2 (48.1 - 68.0)	Tertile 3 (68.1 - 131.0)	P
	n = 91	*n* = 31	*n* = 31	*n* = 29	
Male, n (%)	70 (76.9 %)	23 (74.2 %)	20 (64.5 %)	27 (93.1 %)	0.029
Age (years)	58.00 (50.00, 67.00)	52.50 (45.75, 60.75)	61.00 (51.00, 68.00)	58.00 (52.00, 69.00)	0.069
Duration of diabetes (years)	12.75 ± 7.13	10.55 ± 6.14	15.18 ± 7.41	12.51 ± 7.23	0.035
Smoking, n (%)	46 (50.5 %)	18 (58.1 %)	14 (45.2 %)	14 (48.3 %)	0.571
Drinking, n (%)	31 (34.1 %)	12 (38.7 %)	8 (25.8 %)	11 (37.9 %)	0.489
History of hypertension, n (%)	48 (52.7 %)	12 (38.7 %)	18 (58.1 %)	18 (62.1 %)	0.149
SBP (mmHg)	131.40 ± 15.39	129.68 ± 17.27	133.87 ± 14.30	130.59 ± 14.53	0.535
DBP (mmHg)	79.60 ± 10.18	79.16 ± 11.07	79.06 ± 9.71	80.66 ± 9.95	0.800
MAP (mmHg)	96.87 ± 10.03	96.00 ± 11.44	97.33 ± 8.63	97.30 ± 10.11	0.841
BMI (kg/m^2)	25.40 ± 2.93	24.88 ± 3.14	24.92 ± 2.59	26.48 ± 2.83	0.055
WC (cm)	92.96 ± 7.89	89.90 ± 7.43	92.77 ± 6.57	96.41 ± 8.49	0.005
HC (cm)	96.12 ± 6.26	95.90 ± 6.22	95.61 ± 6.75	96.88 ± 5.89	0.721
SAT (cm^2)	135.56 (101.15, 165.39)	135.56 (87.98, 154.61)	137.26 (101.15, 178.27)	135.52 (113.56, 170.73)	0.381
VAT (cm^2)	163.26 (133.41, 212.64)	134.20 (98.23, 163.00)	165.25 (138.53, 196.86)	217.28 (165.08, 257.92)	<0.001
Hematocrit (%)	43.90 (40.30, 46.80)	43.00 (40.40, 45.60)	42.70 (38.20, 46.00)	46.40 (42.40, 47.25)	0.060
Total protein (g/l)	70.00 (66.00, 75.00)	69.00 (65.00, 74.00)	71.00 (68.00, 75.00)	72.00 (65.50, 75.00)	0.468
FPG (mmol/l)	7.90 (6.30, 10.80)	7.60 (6.25, 10.83)	8.80 (6.40, 11.80)	7.60 (6.35, 9.45)	0.675
HbA1c (%)	8.00 (6.75, 9.30)	7.80 (6.45, 10.15)	7.80 (6.60, 8.90)	8.30 (7.20, 9.50)	0.612
TC (mmol/l)	4.12 (3.44, 5.17)	4.27 (3.44, 5.53)	4.25 (3.48, 5.30)	3.84 (2.97, 4.65)	0.197
TG (mmol/l)	1.65 (1.10, 2.50)	1.58 (0.98, 2.28)	2.38 (1.13, 3.52)	1.61 (1.07, 2.23)	0.227
HDL-C (mmol/l)	1.01 (0.86, 1.24)	1.02 (0.91, 1.34)	0.98 (0.86, 1.33)	1.03 (0.85, 1.18)	0.744
LDL-C (mmol/l)	2.31 (1.68, 3.12)	2.40 (1.80, 3.36)	2.19 (1.65, 3.43)	2.34 (1.62, 3.06)	0.803
UACR (mg g^{-1})	33.65 (12.83, 141.02)	15.50 (9.25, 61.03)	48.20 (14.80, 396.30)	35.20 (16.60, 125.05)	0.054
eGFR (ml/min/1.73m^2)	82.97 ± 24.22	96.08 ± 18.78	77.14 ± 26.68	75.18 ± 21.34	0.001
CKD, n (%)	51 (56.0 %)	2 (6.5 %)	9 (29.0 %)	9 (31.0 %)	0.036
Treatments, n (%)					
SGLT-2i	33 (36.3 %)	10 (32.3 %)	11 (35.5 %)	12 (41.4 %)	0.759
ACEi/ARBs	31 (34.1 %)	8 (25.8 %)	13 (41.9 %)	10 (34.5 %)	0.407
Insulin	44 (48.4 %)	11 (35.5 %)	18 (58.1 %)	15 (51.7 %)	0.187
Lipid lowering drugs	41 (45.1 %)	7 (22.6 %)	15 (48.4 %)	19 (65.5 %)	0.003

Data are n (%), means ± SD or median (interquartile range) unless otherwise stated. Tertile limits were measured in mm. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BMI, body mass index; WC, waist circumference; HC, hip circumference; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; FPG, fast plasma glucose; TC, total cholesterol; TG, total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular rate; CKD, chronic kidney disease; SGLT-2i, sodium-glucose cotransporter protein-2 inhibitors; ACEi/ARBs, ACE inhibitors / angiotensin receptor antagonists.

Association of PRFT with renal hemodynamic parameters

As shown in Fig. 2, compared with patients in PRFT tertile 1, GFR (101.25 ± 22.32 vs 82.18 ± 18.80, $P = 0.001$), ERPF (335.65 ± 108.06 vs 238.27 ± 83.35, $P = 0.001$) and RBF (592.73 ± 195.29 vs 441.28 ± 171.89, $P = 0.003$) were significantly decreased, while RVR (0.18 ± 0.07 vs 0.26 ± 0.11, $P = 0.014$) and R_A (5847.02 ± 3400.53 vs 7969.67 ± 4051.8, $P = 0.039$) were significantly increased in patients in PRFT tertile 3. No significant differences of FF, P_{GLO} and R_E were found among PRFT tertiles.

After adjustment for sex, age, VAT, and treatment with SGLT-2i and ACEi/ARBs, PRFT was negatively correlated with GFR ($\beta = -0.527$, $P < 0.001$), ERPF ($\beta = -0.537$, $P < 0.001$), RBF ($\beta = -0.534$, $P < 0.001$), and P_{GLO} ($\beta = -0.304$, $P = 0.037$), while positively associated with RVR ($\beta = 0.302$, $P = 0.044$) and R_A ($\beta = 0.402$, $P = 0.007$) in whole group. The PRFT was not significantly correlated with FF, and R_E whether in above-multivariate adjusted models or not. Notably, similar associations were also observed in non-ACEi/ARBs and SGLT-2i group and non-hypertension group (Table 2). In age and sex subgroups, the results were consistent with the whole group substantially (Table S3; see supplementary materials associated with this article on line).

In order to more directly illustrate the role of local PRF in local renal hemodynamics, we analyzed the relationship between left PRF and left renal hemodynamics, and similarly on the right side. The left kidney had much more PRF (32.16 ± 14.67 vs 28.09 ± 12.11, $P = 0.043$) than the right kidney (Table S4; see supplementary materials associated with this article on line). In multiple linear regression analyses, the results showed that PRF on the left side was associated with lower measured GFR, ERPF, RBF, and higher RVR, R_A on the left side. The similar findings were observed on the right side (Table S5; see supplementary materials associated with this article on line).

In addition to PRF, another two types of fat deposited in the kidney, including renal sinus fat and renal fat fraction, were also analyzed in relation to renal hemodynamic parameters, and we did not observe any significant associations (Tables S6 and S7; see supplementary materials associated with this article on line), implying that only PRF influenced renal hemodynamics.

The mediation effect of renal hemodynamic parameters on the association between PRF and renal function

As mentioned above, we observed that the effect of PRFT on renal hemodynamic parameters was mainly to decrease ERPF, GFR and increase RVR, especially R_A. It is easy to assume that the close relationship between PRF and renal function is related to increased renal vascular resistance, especially R_A. So we conducted the mediation analyses of RVR and R_A on the association between PRF and renal function (Fig. 3A). It was found that RVR and R_A was negatively associated with GFR, after adjusting for age, sex, VAT, and treatment with SGLT-2i and ACEi/ARBs (RVR: $\beta = -0.579$, $P < 0.001$, R_A: $\beta = -0.605$, $P < 0.001$, Table S8; see supplementary materials associated with this article on line). And the mediating effect value of RVR and R_A between PRF and GFR was −0.147 and −0.208, with a mediated proportion of 29.1 % and 41.4 % respectively ($P = 0.044$ for RVR, $P = 0.002$ for R_A), after adjusting for age, sex, VAT, and treatment with SGLT-2i and ACEi/ARBs,

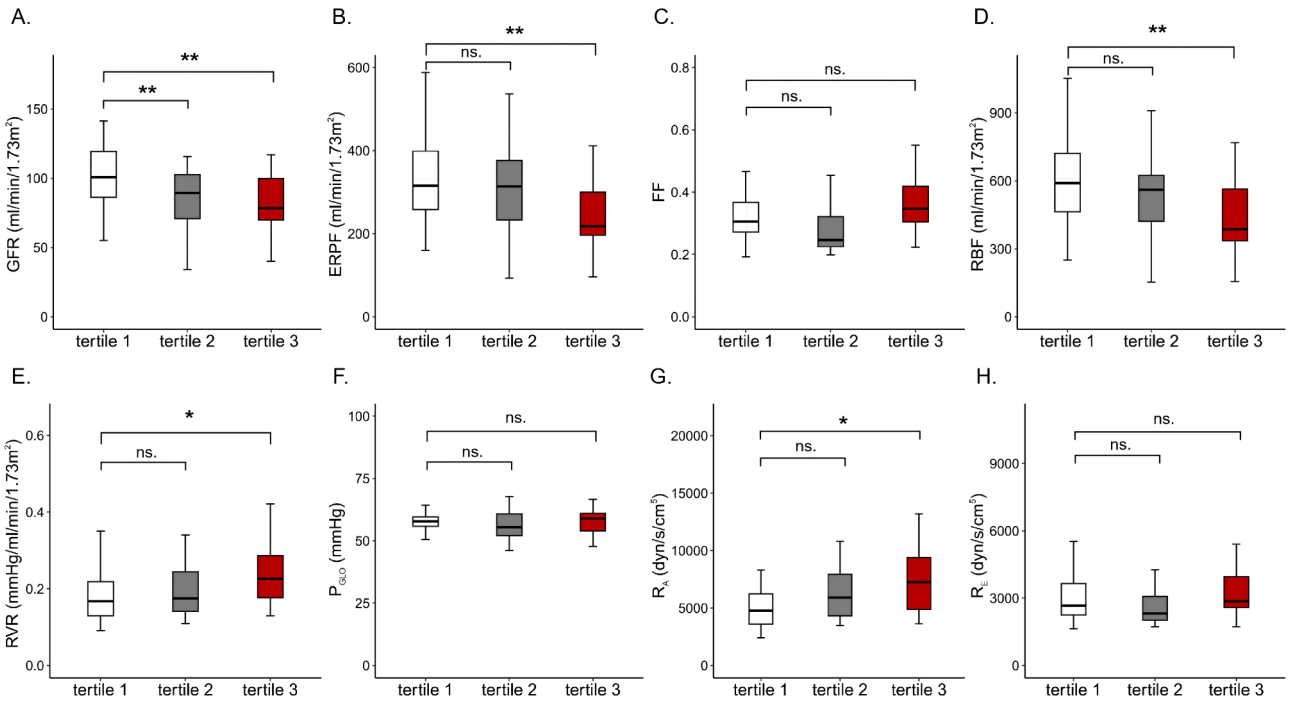

Fig. 2. Comparison of renal hemodynamic parameters among different PRFT tertiles. **A**. GFR, measured glomerular filtration rate. **B**. ERPF, effective renal plasma flow. **C**. FF, filtration fraction. **D**. RBF, renal blood flow. **E**. RVR, renal vascular resistance; **F**. P_{GLO}, glomerular hydrostatic pressure. **G**. R_A, afferent arteriolar resistance. **H**. R_E, efferent arteriolar resistance. * $P < 0.05$; ** $P < 0.01$; ns. no significance.

suggesting that RVR and R_A mediates the relationship between PRF and GFR partially (Fig. 3B-C and Table S9; see supplementary materials associated with this article on line).

Discussion

In this study, we used renal dynamic imaging to measure renal hemodynamic parameters, MRI to measure kidney related fat. Our study found that PRFT was independently associated with decreased GFR, ERPF, RBF, and increased RVR and R_A, whereas renal sinus fat and renal fat fraction had no significant association with renal hemodynamic parameters. In addition, RVR and R_A mediated the effect of PRF on GFR. These evidences suggested for the first time that the possible implications of PRF in the pathophysiology of T2DM-related kidney injury.

Several cross-sectional studies have revealed that PRF is associated with renal dysfunction[9,10], especially our longitudinal study reported that CT-measured PRFT is an independent predictor for CKD in T2DM patients [11]. Here, we confirmed that MRI-measured PRFT was negatively correlated with eGFR, while was not significantly correlated with UACR, which in line with prior studies. Owing to eGFR may be imprecise in clinical researches[26]. This study also considered measured GFR by ^{99m}Tc-DTPA, a more precise method to assess renal function, and the results showed that PRF was negatively correlated with GFR, even adjusted the confounding factors like VAT, treatment with SGLT-2i and ACEi/ARBs.

However, the mechanism by which PRF mediates renal injury remains unclear. Some researchers speculated that excess fat deposition around kidney may oppress renal vessels and parenchyma, increasing renal vascular resistance and renal interstitial hydrostatic pressure, then reducing renal blood flow and glomerular filtration rate [14–16]. Lamacchia and colleagues preliminarily investigated the relationship of ultrasound measured para- and perirenal fat with renal vascular resistance [9]. The results showed a positive correlation between para- and perirenal fat thickness and RRI, suggesting that PRF may correlate with renal hemodynamics. Nevertheless, the RRI only represents the resistance of renal interlobar arteries, which cannot reflect the resistance of more microscopic blood vessels such as the afferent and efferent arterioles [27,28], and other renal hemodynamics parameters, including RBF, ERPF, FF, P_{GLO} were not assessed comprehensively in Lamacchia's study. Moreover, treatment with SGLT-2i and ACEi/ARBs may have impacts on renal hemodynamics parameters, so further adjustment for treatment with SGLT-2i and ACEi/ARBs is necessary.

In this study, renal hemodynamic parameters were comprehensively assessed by renal dynamic imaging and estimated according to Gomez equations, and the results showed that in T2DM patients, MRI-measured PRFT was negatively correlated with RBF, ERPF and positively correlated with RVR and R_A after adjusting for age, sex, VAT, and treatment with SGLT-2i or ACEi/ARBs. In addition, considering that SGLT-2i and ACEi/ARBs will influence renal hemodynamics [29], we repeated the same analyses in the non SGLT-2i and ACEi/ARBs medications group and the non-hypertension group. Surprisingly, similar correlations still remained significant. We also conducted subgroup analyses on unilateral kidney, age, and sex. Compared with the right kidney, the left kidney has higher PRFT, RVR and R_A, and lower GFR and ERPF, which is consistent with the results of the overall analysis. Multiple linear regression results were consistent in the left, right and bilateral kidney. Those results made us speculate that the more PRF on one side, the lower GFR, ERPF and higher RVR and R_A on the same side. But these correlations were more pronounced in patients of age <60 years and males which may be due to small sample size. Interestingly, we explored the associations of renal sinus fat and renal fat fraction with renal hemodynamics additionally, and no any significant correlation was discovered, indicating that only excess PRF is indeed associated with increased RVR and R_A, and decreased RBF, ERPF,GFR in T2DM patients.

Furthermore, to verify whether increased RVR and R_A mediated the impact of PRF on renal function, we conducted the mediation analysis. As expected, we found that RVR and R_A was negatively associated with GFR, and mediated the relationship between PRF and GFR partially, with a mediated proportion of 29.1 % for RVR and 41.4 % for R_A respectively. The findings of our study suggested that increased R_A associated with PRF may be involved in renal dysfunction in T2DM, working in concert with previous hypothesis. Several potential

Table 2
Univariate and multivariate linear regression analyses of PRFT with renal hemodynamic parameters.

	Whole group		Subgroup							
	(n = 91)		Non-ACEi/ARBs		Non-SGLT-2i		Non-ACEi/ARBs and SGLT-2i		Non-hypertension	
			(n = 60)		(n = 58)		(n = 42)		(n = 43)	
	β	P	β	P	β	P	β	P	β	P
GFR (ml/min/1.73m^2)										
Crude	−0.391	<0.001	−0.476	<0.001	−0.359	0.006	−0.420	0.006	−0.503	0.001
Model 1	−0.506	<0.001	−0.628	<0.001	−0.691	<0.001	−0.696	0.002	−0.531	0.020
Model 2	−0.527	<0.001	−0.628	<0.001	−0.694	<0.001	—		−0.521	0.024
ERPF (ml/min/1.73m^2)										
Crude	−0.414	<0.001	−0.474	<0.001	−0.392	0.002	−0.322	0.038	−0.500	0.001
Model 1	−0.546	<0.001	−0.746	<0.001	−0.753	<0.001	−0.763	0.002	−0.628	0.006
Model 2	−0.537	<0.001	−0.746	<0.001	−0.753	<0.001	—		−0.612	0.009
FF										
Crude	0.182	0.084	0.244	0.060	0.235	0.076	0.016	0.920	0.091	0.564
Model 1	0.149	0.325	0.378	0.044	0.349	0.083	0.386	0.106	0.179	0.475
Model 2	0.101	0.494	0.378	0.045	0.345	0.083	—		0.134	0.577
RBF (ml/min/1.73m^2)										
Crude	−0.386	<0.001	−0.425	0.001	−0.342	0.009	−0.229	0.144	−0.453	0.002
Model 1	−0.544	<0.001	−0.718	<0.001	−0.704	<0.001	−0.695	0.004	−0.665	0.005
Model 2	−0.534	<0.001	−0.718	<0.001	−0.704	<0.001	—		−0.663	0.007
RVR (mmHg/ml/min/1.73m^2)										
Crude	0.298	0.004	0.435	0.001	0.360	0.006	0.339	0.028	0.370	0.015
Model 1	0.320	0.030	0.567	0.001	0.596	0.003	0.664	0.007	0.493	0.042
Model 2	0.302	0.044	0.567	0.002	0.596	0.003	—		0.450	0.059
P_{GLO} (mmHg)										
Crude	−0.074	0.488	−0.137	0.295	0.024	0.859	−0.038	0.813	−0.150	0.336
Model 1	−0.251	0.094	−0.252	0.177	−0.292	0.136	−0.217	0.374	−0.167	0.514
Model 2	−0.304	0.037	−0.252	0.180	−0.298	0.115	—		−0.218	0.348
R_A (dyn/s/cm^5)										
Crude	0.295	0.004	0.420	0.001	0.335	0.010	0.376	0.014	0.510	<0.001
Model 1	0.397	0.007	0.513	0.004	0.597	0.003	0.611	0.011	0.658	0.005
Model 2	0.402	0.007	0.513	0.004	0.599	0.003	—		0.646	0.007
R_E (dyn/s/cm^5)										
Crude	0.148	0.161	0.231	0.076	0.171	0.199	−0.066	0.677	0.057	0.718
Model 1	0.106	0.487	0.352	0.066	0.266	0.203	0.360	0.148	0.204	0.424
Model 2	0.065	0.665	0.352	0.068	0.262	0.206	—		0.162	0.505

Model 1: adjustment for sex, age, VAT. Model 2: adjustment for treatments with SGLT-2i and ACEi/ARBs in addition to the variables in model 1. When in non-ACEi/ARBs subgroup, Model 2 is adjustment for treatments with SGLT-2i.When in non-SGLT-2i subgroup, Model 2 is adjustment for treatments with ACEi/ARBs. GFR, measured glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; RBF, renal blood flow; RVR, renal vascular resistance; P_{GLO}, glomerular hydrostatic pressure; R_A, afferent arteriolar resistance; R_E, efferent arteriolar resistance.

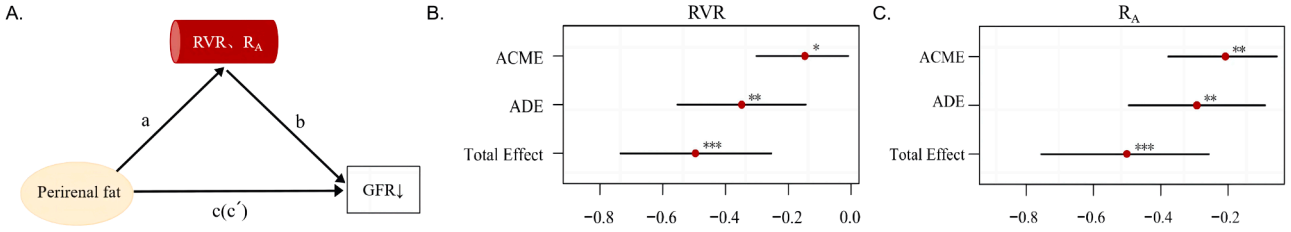

Fig. 3. The mediation analyses of RVR and R_A on the association between perirenal fat and GFR. **A.** The mediation effect model of RVR or R_A on the association between perirenal fat and GFR. In this mediation effect model, the indirect effect value of perirenal fat on GFR decline by affecting RVR or R_A is a*b, while the direct effect value is c' and the total effect is c. **B.** The mediation analysis of RVR on the association between perirenal fat and GFR after adjusting for age, sex, VAT, and treatment with SGLT-2i and ACEi/ARBs. **C.** The mediation analysis of R_A on the association between perirenal fat and GFR after adjusting for age, sex, VAT, and treatment with SGLT-2i and ACEi/ARBs. ACME, average causal mediation effects, indicates the value of the effect of perirenal fat on GFR through RVR or R_A; ADE, average direct effects, indicates the value of the direct effect of perirenal fat on GFR; Total Effect indicates the value of the total effect of perirenal fat on GFR. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

mechanisms may explain the impact of PRF on renal vascular resistance. Firstly, excess deposition of PRF will exert direct mechanical compression on renal vascular, on the other hand the parenchyma that may increase interstitial hydrostatic pressure, promote secretion of renin and activate intrarenal local renin-angotensin-aldosterone system, which has been reported to stimulate vasoconstriction predominantly afferent arterioles in diabetes patients [30,31]. Secondly, previous study confirmed the involvement of PRF afferent nerve reflex in hypertension and PRF ablation or denervation lowered blood pressure [32]. And afferent nerves reflex of PRF combined with mechanical compression would rise the sympathetic nerve system activity, which further exaggerate the aforementioned renal local RAAS and may also directly affect the afferent arterioles, causing myogenic contractions [33–35]. Lastly, PRF is an organ with active secretion of adipokines and cytokines. FFAs secreted by PRF could enter the kidney directly or indirectly, and damage vascular endothelial function via enhancing oxidation of tetrahydrobiopterin. This leads to the production of nitrogen superoxide from l-arginine via uncoupling of endothelial NO synthase, which attenuates the vasodilatory effect of NO [36]. More importantly, in obese patients with microalbuminuria, circulating FFAs level was significantly

and positively correlated with RRI [37]. And we can speculated that increased FFA secretion may be one of the reasons for PRF increasing R_A, which is consistent with our findings. Leptin secreted by PRF is also reported to prompt renal vascular remodeling and glomerular endothelial cell proliferation in rats with metabolic syndrome [38]. PRF may promote renal injury by affecting renal vascular function, although these adipokines may originate from other white adipose tissue [39]. At last, increased R_A is often accompanied by an augment of shear stress [40], and we speculated that increased R_A associated with PRF could exacerbate glomerular capillary endothelial cell and podocyte injury by elevating shear stress, and ultimately promotes the development of DKD.

Our study has advantages worth mentioning. Firstly, we directly measured GFR and ERPF by renal dynamic imaging for the first time to investigate the relationship between PRF and renal hemodynamics. Secondly, systematical analyses of relationships between kidney related fat and renal hemodynamics were performed in this study. Lastly, we also took into account the interference of drugs and blood pressure on the relationship between PRF and renal hemodynamics.

We acknowledge that this study has some limitations. First, the cross-sectional design of the study is incapable of explaining causal relationship between PRF and renal hemodynamic function. Second, the small sample size and the age, gender imbalance may make the conclusion not representative enough. Last, direct measurement of some glomerular hemodynamic parameters (e.g. P_{GLO}, R_A, R_E) is difficult, but we estimated those parameters according to Gomez formula. Further intervention studies are warranted to verify the effect of PRF on renal hemodynamic function.

Conclusions

Our findings showed that PRF was associated with decreased glomerular filtration rate, increased renal vascular resistance and afferent arteriolar resistance, suggesting the possible implications of PRF in the pathophysiology of T2DM-related kidney injury. It remains to be demonstrated whether weight loss induced by obesity surgery, GLP-1 agonist or GLP-1/GIP dual-agonist may reduce PRF and whether the weight loss benefits are related to decreased PRF. The mechanism needs further elucidation.

List of abbreviations

ACEi	Angiotension converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
BMI	Body mass index
CKD	Chronic kidney disease
CT	Computed tomography
DBP	Diastolic blood pressure
DKD	Diabetic kidney disease
eGFR	Estimated glomerular filtration rate
ERPF	Effective renal plasma flow
FPG	Fasting plasma glucose
FFAs	Free fatty acids
FF	Filtration fraction
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
GIP	Gastric inhibitory polypeptide
HbA1c	Glycated hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
PRFT	Perirenal fat thickness
P_{GLO}	Glomerular hydrostatic pressure
RAAS	Renin angiotensin aldosterone system
R_A	Afferent arteriolar resistance
R_E	Efferent arteriolar resistance
RBF	Renal blood flow
RVR	Renal vascular resistance
RRI	Renal resistance index
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SGLT-2i	Sodium-glucose cotransporter protein-2 inhibitors
SPECT	Single-photon emission computerized tomography
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TC	Total cholesterol
^{99m}Tc-DTPA	^{99m}Tc-Indiethylenetriaminepentaacetic acid
^{99m}Tc-EC	^{99m}Tc-Ethylenedicysteine
UACR	Urinary albumin-to-creatinine ratio
VAT	Visceral adipose tissue

CRediT authorship contribution statement

Xiangjun Chen: Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Yao Qin:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **Jinbo Hu:** Supervision, Software, Methodology. **Yan Shen:** Methodology, Investigation. **Yun Mao:** Validation, Methodology, Investigation. **Lianghua Xie:** Methodology, Investigation. **Jia Li:** Methodology, Investigation. **Jie Wang:** Methodology. **Shumin Yang:** Writing – review & editing, Funding acquisition. **Qifu Li:** Writing – review & editing, Funding acquisition. **John Cijiang He:** Writing – review & editing. **Zhihong Wang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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