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Role of perirenal adiposity in renal dysfunction among CKD individuals with or without diabetes: a Japanese cross-sectional study

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ABSTRACT

Introduction It remains unclear whether increased perirenal fat (PRF) accumulation is equally related to renal involvement in patients with and without diabetes mellitus (DM). We evaluated the association between PRF volume (PRFV) and low glomerular filtration rate (GFR) and proteinuria in people with or without type 2 diabetes mellitus (T2DM).

Research design and methods We performed a cross-sectional analysis of 473 individuals without T2DM (non-DM, n=202) and with T2DM (DM, n=271). PRFV (cm^3), obtained from non-contrast CT, was indexed as PRF index (PRFV/body surface area, cm^3/m^2). Multivariate-adjusted models were used to determine the ORs of PRFV and PRFV index for detecting estimated GFR (eGFR) decrease of <60 mL/min/1.73 m^2 proteinuria onset, or both.

Results Although body mass index (BMI), visceral fat area, and waist circumference were comparable between the non-DM and DM groups, kidney volume, PRFV, and PRFV index were higher in individuals with T2DM than in those without T2DM. In the multivariate analysis, after adjusting for age, sex, BMI, hypertension, smoking history, and visceral fat area ≥100 cm^2, the cut-off values of PRFV index were associated with an eGFR<60 in individuals with DM (OR 6.01, 95% CI 2.20 to 16.4, p<0.001) but not in those without DM.

Conclusions PRFV is associated with low eGFR in patients with T2DM but not in those without T2DM. This suggests that PRF accumulation is more closely related to the onset and progression of diabetic kidney disease (DKD) than non-DKD. Clarifying the mechanisms through which PRF influences DKD development could pave the way for novel prevention and treatment strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It has been reported that increased perirenal fat (PRF) accumulation is closely related to low estimated glomerular filtration rate (eGFR) and proteinuria in individuals with type 2 diabetes mellitus (T2DM).

⇒ It is unclear whether increased PRF accumulation is equally related to renal involvement in patients with and without diabetes mellitus.

WHAT THIS STUDY ADDS

⇒ This study found that PRF volume (PRFV) was higher in individuals with T2DM than in those without T2DM, although the other adiposity indices were comparable between two groups.

⇒ PRFV accumulation was also associated with low eGFR in individuals with T2DM but not in those without T2DM.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that PRF accumulation was independently and closely associated with onset of diabetic kidney disease (DKD) but not with that of non-DKD.

⇒ The study showed role of perirenal adiposity in DKD and affects research and practice on prevention and treatment of DKD.

INTRODUCTION

Diabetes-related kidney changes often lead to chronic kidney disease (CKD), also known as diabetic kidney disease (DKD).[1 2] DKD is typically characterized by persistent albuminuria and subsequent decline in the estimated glomerular filtration rate (eGFR). This trajectory is widely recognized as the classical phenotype of DKD and diabetic nephropathy. Non-classical phenotypes of DKD, such as reduced eGFR without albuminuria, have become increasingly common over the past decade.[2–4] The decline in kidney function is usually faster among people with diabetes than among those without diabetes.[5] Clarifying the clinical features of CKD with or without diabetes mellitus (DM), especially its modifiable risk factors such as obesity, is beneficial for the continued targeting of CKD prevention.[2–4]

Renal involvement owing to obesity is an increasingly common disorder, parallel to the current obesity epidemic. An increase in body mass index (BMI) is associated

with the development of proteinuria, lower eGFR, and a higher incidence of end-stage renal disease.[6] As obesity can exacerbate several primary kidney diseases and their prognoses,[7 8] it may be closely related to CKD progression, regardless of its etiology.[9] DKD develops more frequently in overweight and obese individuals (categorized using BMI) than in underweight or normal-weight individuals.[10 11] Furthermore, previous reports have indicated that increased perirenal fat (PRF) accumulation is closely related to low eGFR and proteinuria in individuals with type 2 diabetes mellitus (T2DM).[12–14] PRF[15–17] is regarded as one of the ectopic fat deposits in the liver, skeletal muscle, and cardiovascular system.[18–20] However, it has not been clarified whether increased PRF accumulation is equally related to renal involvement in patients with and without DM.

Herein, we evaluated the association between PRF volume (PRFV) and low GFR and proteinuria in people with or without T2DM.

METHODS

Study subjects and data evaluation

Japanese individuals who had undergone abdominal CT screening for suspected diseases at Tokushima University Hospital, Okinawa Tomishiro Central Hospital, or Fukushima Medical University Hospital between December 2009 and July 2015 were considered eligible to participate. The need for informed consent was waived by the ethics committee because the research did not use identifiable private information nor biospecimens and involved no more than minimal risk to the subjects. Instead, information about the study was made available within the hospital. Participants were given the option to decline the use of their personal information. Among the initially eligible 532 participants, 59 were excluded because of missing clinical parameters or inadequate abdominal CT images. Thus, a total of 473 participants were included in the study: 202 without T2DM (non-DM) and 271 with T2DM (DM). Their electronic medical records were carefully reviewed for details such as age, sex, diabetes duration, family and social history, medical check-up results, complications, medications, and laboratory data.

Biochemical measurements

Hypertension was defined as blood pressure ≥140/90 mmHg or the current use of antihypertensive medication(s). Diabetes was defined as HbA1c≥6.5%, fasting plasma glucose level >126 mg/dL, or the current use of antidiabetic medication. Dyslipidemia was defined as a total serum cholesterol level ≥220 mg/dL, low-density lipoprotein (LDL) cholesterol level ≥140 mg/dL, serum triglyceride level >150 mg/dL, and a serum high-density lipoprotein (HDL) cholesterol level of <40 mg/dL, in addition to current use of antihyperlipidemia medications. Smoking was defined as the patient being a past or current smoker, and non-smoking was defined as a patient who had never smoked. To measure renal function, we used the Japanese formula for GFR estimation: eGFR (mL/min/1.73 m^2)=194×serum creatinine (mg/dL)−1.094×age (years)$^{-0.287}$.[21] To detect proteinuria, dipstick urinalysis was performed using spontaneously voided fresh urine that was analyzed within a few minutes of collection. In this study, proteinuria was defined as (±) or greater. In both the non-DM and DM groups, the study subjects were categorized into subgroups based on the presence of proteinuria+ and proteinuria– or eGFR<60 and eGFR 60.

Adiposity evaluation by CT

BMI was calculated as weight (kg) divided by the square of height (m^2). All CT images were transferred to an offline workstation (Synaptic Vincent V.4.4, Fuji Film, Tokyo, Japan) at the Fukushima Medical University (Gulinu FE Paper). Using non-contrast CT, the subcutaneous adipose tissue (SAT) area, visceral adipose tissue (VAT) area, and waist circumference (WC) were measured at the umbilical level.[22 23] Kidney volume and PRFV were determined for the left kidney by using a three-dimensional medical image processing viewer (ZioCube V.1.0.2.0, Ziosoft, Tokyo, Japan). We chose the left but not right kidney for two reasons. First, it is recommended to assess the left-side renal fat for a reliable observation because the renal fat compartments distribute asymmetrically, with more fat accumulation in the left renal sinus than in the right.[24] Second, the right kidney lies posterior to the liver, with the colon lying anterior and the duodenum anteromedially and thus, with an enlarged liver sometimes observed in people with obesity, the right kidney was found rotated and displaced forward and downward.[25] The kidney size and PRF area surrounding the left kidney was determined on axial views by placing the region of interest on the renal fascia with modifications (figure 1).[26–28] Highlighted were the kidney parenchyma by a reddish brown color and the PRF by a green color using an attenuation range of –190 ~ –30 Hounsfield units. Kidney and PRF area of each slice was summed and then multiplied by the slice thickness and number of slices to calculate the kidney volume and the PRFV, respectively. The interobserver intraclass correlation coefficient was 0.977 (95% CI 0.854 to 0.993, n=24) and the intraobserver intraclass correlation coefficient was 0.930 (95% CI 0.811 to 0.976, n=15). The PRF index was calculated as follows: PRFV/body surface area (cm^3/m^2). Representative CT images of measurement for left kidney volume and PRFV in individuals with or without T2DM were shown in figure 1.

Statistical analysis

Continuous and parametric values are expressed as means (SDs), and non-parametric variables are expressed as medians (IQR). Two-tailed unpaired

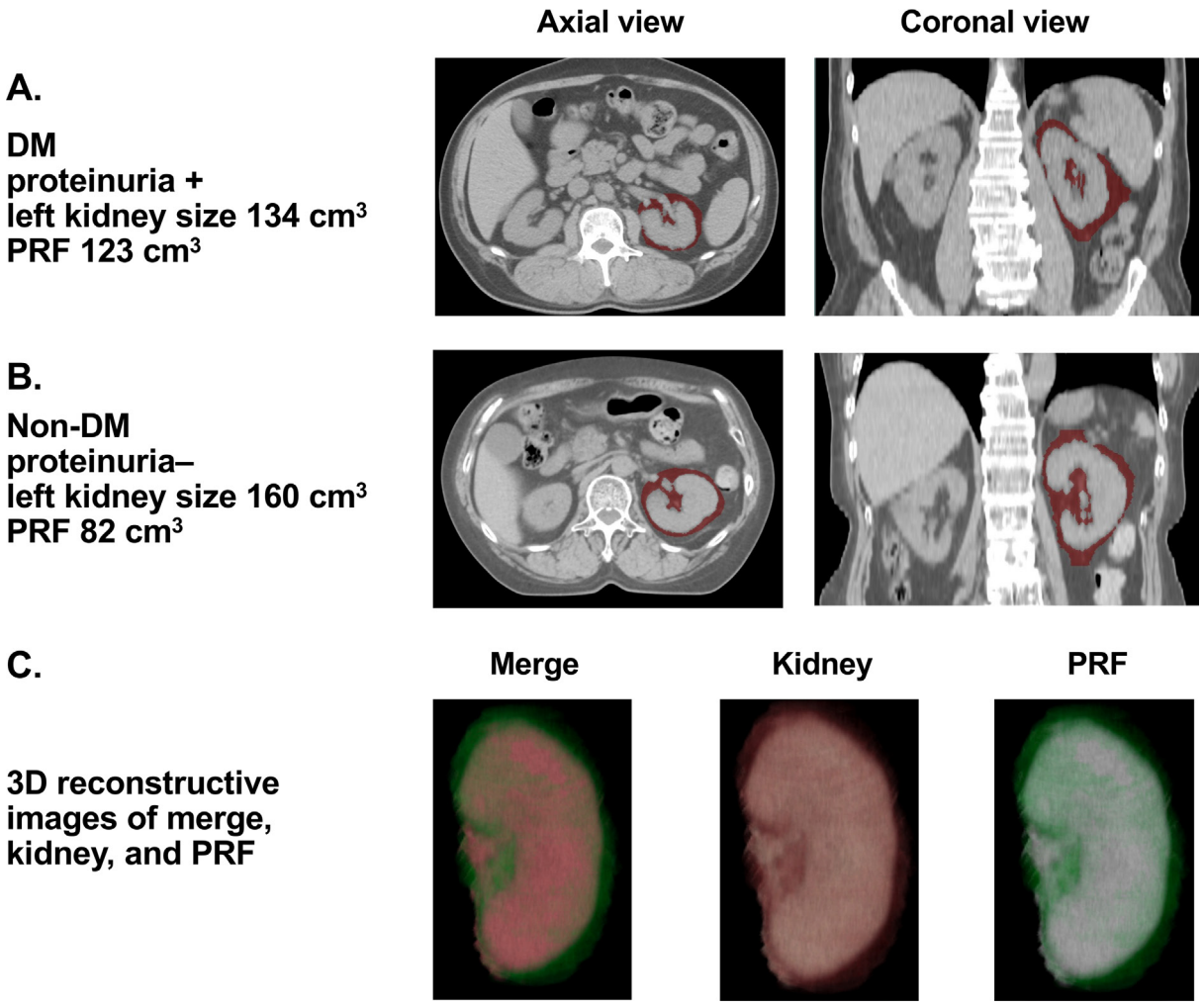

Figure 1 Representative CT images of measurement for left kidney volume and perirenal fat volume (PRFV) in individuals (A) with or (B) without type 2 diabetes mellitus and (C) three-dimensional (3D) reconstructive images of merge, kidney, and PRF in a case. The kidney and PRF area surrounding the left kidney was determined on axial views by placing the region of interest on the renal fascia with modifications.[26–28] Highlighted were the kidney parenchyma by a reddish brown color and the PRF by a green color using an attenuation range of –190 ~ –30 Hounsfield units. Kidney and PRF area of each slice was summed and then multiplied by the slice thickness and number of slices to calculate the kidney volume and the PRFV, respectively. DM, diabetes mellitus.

Student's t-tests and Mann-Whitney U tests were used to compare parametric and non-parametric data, respectively. Categorical variables are shown as percentages and were analyzed using the χ^2 test. Univariate survival analysis was performed using the Kaplan-Meier curve and analyzed using a log-rank test. Univariate and Cox proportional hazards analyses, along with 95% CI, were employed to determine the independent contributions of factors, either as continuous or dichotomous values, to proteinuria or eGFR<60 mL/min/1.73 m^2. These analyses were adjusted for age, sex, BMI, eGFR, hypertension, smoking history, and visceral fat area (VFA) ≥100 cm^2. Statistical significance was set at p<0.05. Statistical analyses were performed using SPSS V.25 (SPSS) or R V.3.6.3. The VIM package 5.1.1 and ggplot2 3.3 run on R V.3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

General characteristics: non-DM versus DM

The general characteristics of the overall participants (n=475), as well as those in the non-DM (n=203) and DM (n=272) groups, are presented in online supplemental table 1. Age and the percentage of males were comparable between the non-DM and DM groups. In the DM group, the mean fasting plasma glucose and HbA1c values were 131 mg/dL and 6.7%, respectively, whereas in the non-DM group, they were 116 mg/dL and 5.5%. Total and LDL cholesterol levels were lower in patients with T2DM. Regarding CKD risk parameters, the DM group showed a higher prevalence of smoking history, hypertension, dyslipidemia, eGFR<60, and proteinuria.

General characteristics: proteinuria– versus proteinuria+ and eGFR<60 versus eGFR≥60

For the *non-DM group*, as presented in the left panel of table 1, age and age ≥65 years were higher in the eGFR<60 group than in the eGFR≥60 group. HbA1c levels and hypertension prevalence were higher, whereas proteinuria prevalence exhibited a significant increase. Age and male sex distribution were comparable between the proteinuria– and proteinuria+ groups. Albumin levels were lower and gamma-glutamyl transferase and serum creatinine levels were higher in the proteinuria+ group, whereas other parameters were comparable between the two groups.

For the DM group, as shown in table 1, age and age ≥65 were higher in the eGFR<60 group. Fasting plasma glucose, HbA1c, and total, LDL and HDL cholesterol levels showed comparability between the groups, whereas triglycerides and dyslipidemia prevalence, as well as proteinuria prevalence, were higher in the eGFR<60 group. Age was comparable between the proteinuria– and proteinuria+ groups, but a higher percentage of males was observed in the proteinuria+ group. In the proteinuria+ group, fasting plasma glucose levels were elevated, whereas A1c levels remained unchanged. Furthermore, the proteinuria+ group exhibited lower eGFR and higher eGFR≤60. Although smoking history was more prevalent, the prevalence of hypertension, dyslipidemia, and a history of coronary heart disease did not exhibit an increase in the proteinuria+ group.

Adiposity and kidney-associated measures: non-DM versus DM

The adiposity and kidney-associated measures of the overall participants, as well as those in the non-DM and DM groups, are shown in figure 2 and online supplemental table 2. BMI, BMI≥25 kg/m^2, VFA, VFA≥100 cm^2, WC, and WC≥85 or ≥90 cm were all comparable between the non-DM and DM groups, with the exception of an increase in subcutaneous fat area in the DM group. Conversely, kidney volume, PRFV, and PRFV index were higher in patients with T2DM than in those without T2DM.

Adiposity and kidney-associated measures: proteinuria– versus proteinuria+ and eGFR<60 versus eGFR≥60

In the non-DM group (figure 2 and table 2, left panel), no differences were observed in adiposity-associated and kidney-associated measurements between the proteinuria– and proteinuria+ groups, as well as between the eGFR<60 and eGFR≥60 groups. For the DM group (table 2, right panel), BMI was lower in the proteinuria+ group, and left kidney volume was lower in the eGFR<60 group than in their respective counterparts. However, other adiposity-associated and kidney-associated measurements were comparable between the two groups (figure 2).

Factors associated with eGFR<60: non-DM

Online supplemental table 3 presents the univariate ORs. Age, HbA1c, low total cholesterol, low hematocrit, uric acid levels, and age ≥65, along with low diastolic pressure and hypertension, were associated with eGFR<60. In the multivariate analysis, the cut-off values of PRFV and PRFV index did not show an association with eGFR<60 before and after correcting for confounding factors (table 3, *models 1–3* A and B). Using continuous values in multivariate analysis, PRFV and PRFV index as well as VFA were also not associated with eGFR<60 (online supplemental table 4, *models 1–3*). In the multivariate analysis, eGFR in continuous values was not associated with the cut-off values of PRFV and PRFV index (online supplemental table 5).

Factors associated with eGFR<60: DM

Univariate analysis revealed that age, low hematocrit, uric acid, age ≥65, low diastolic pressure, dyslipidemia, and history of coronary artery disease were associated with eGFR<60 (online supplemental table 3). In the multivariate analysis, after adjusting for age, sex, BMI, hypertension, smoking history, and VFA≥100 cm^2, the cut-off values of PRFV and PRFV index were associated with an eGFR<60 (table 3, *model 3* C and D). Using continuous values in multivariate analysis, PRFV and PRFV index as well as VFA were not associated with an eGFR<60 (online supplemental table 4, *models 1–3*). In the multivariate analysis, eGFR in continuous values was also associated with the cut-off values of PRFV and PRFV index (online supplemental table 5).

Factors associated with proteinuria: non-DM

The univariate ORs for proteinuria are shown in online supplemental table 5. Low albumin, creatinine, low eGFR, and uric acid levels were associated with proteinuria. In terms of adiposity-associated and kidney-associated measures, VFA, PRFV cut-off (237 cm^3), and PRFV index cut-off (117 cm^3/m^2) showed an association with proteinuria. In multivariate analysis, the PRFV and PRFV index cut-off values were associated with proteinuria after adjusting for confounding factors (table 4, *model 4* A and B). As shown in the multivariate OR using continuous values (online supplemental table 6), PRFV and PRFV index were not associated with proteinuria (*models 1–4*).

Factors associated with proteinuria: DM

The univariate OR for eGFR<60 (online supplemental table 5) showed that male sex, low HDL cholesterol and creatinine levels, and low eGFR were associated with proteinuria. In terms of adiposity and kidney-associated measures, the PRFV cut-off (292 cm^3) and PRFV index cut-off (146 cm^3) were associated with proteinuria. The multivariate ORs for proteinuria using the cut-off values of PRFV and PRFV index are shown in table 4. In the multivariate analysis, after correcting for confounding factors, the PRFV and PRFV index cut-off values were associated with proteinuria (*model 4* C and D). However, in the multivariate analysis using continuous PRFV values (online supplemental table 4), the association between PRFV and proteinuria remained only when considering

Table 1 Clinical characteristics of the study participants: eGFR<60 versus eGFR≥60 and proteinuria– versus proteinuria+

	Non-DM						DM					
	eGFR<60	eGFR≥60		Proteinuria–	Proteinuria+		eGFR<60	eGFR≥60		Proteinuria–	Proteinuria+	
	n=56	n=146	P value	n=144	n=59	P value	n=118	n=153	P value	n=152	n=120	P value
Age (years)	71 (64, 79)	64 (53, 72)	<0.001	66 (56, 74)	66 (58, 73)	0.979	70 (63, 77)	67 (53, 72)	<0.001	68 (59, 74)	69 (60, 76)	0.224
Sex, male, n (%)	27 (48.2)	85 (58.2)	0.201	74 (51.4)	39 (66.1)	0.055	68 (57.6)	91 (59.5)	0.759	74 (48.7)	85 (70.8)	<0.001
Blood biochemistry												
Albumin (g/dL)	4.0 (3.8, 4.4)	4.2 (3.8, 4.4)	0.180	4.2 (4.0, 4.4)	3.9 (3.6, 4.4)	0.003	4.1 (3.8, 4.4)	4.2 (3.9, 4.4)	0.080	4.2 (3.9, 4.4)	4.1 (3.8, 4.4)	0.277
Fasting glucose (mg/dL)	101 (89, 112)	103 (96, 112)	0.287	103 (96, 112)	102±18	0.303	131 (113, 164)	132 (113, 155)	0.795	128 (109, 149)	140 (118, 164)	0.004
HbA1c (%)	5.7±0.4	5.5±0.4	0.025	5.5±0.4	5.5±0.5	0.740	6.7 (6.3, 7.5)	6.8 (6.1, 7.4)	0.381	6.7 (6.2, 7.4)	6.7 (6.3, 7.4)	0.639
Total cholesterol (mg/dL)	185±36	199±37	0.018	197±37	193±39	0.394	181 (159, 202)	186±35	0.382	186±35	183 (164, 203)	0.715
LDL cholesterol (mg/dL)	106 (86, 118)	114±30	0.081	111±30	110±32	0.988	99 (82, 119)	102±28	0.922	102±26	99 (80, 122)	0.887
HDL cholesterol (mg/dL)	57±15	55 (45, 70)	0.886	55 (45, 68)	57 (46, 71)	0.400	53 (43, 62)	53 (45, 63)	0.482	54 (46, 66)	51 (43, 60)	0.028
Triglycerides (mg/dL)	113 (91, 135)	125 (88, 185)	0.218	122 (91, 164)	114 (84, 148)	0.528	132 (83, 177)	106 (74, 154)	0.048	106 (75, 163)	126 (80, 175)	0.243
AST (IU/L)	22 (18, 26)	22 (18, 30)	0.301	22 (18, 28)	23 (19, 29)	0.417	21 (16, 30)	21 (17, 29)	0.650	21 (17, 29)	22 (17, 32)	0.881
ALT (IU/L)	17 (11, 24)	20 (15, 36)	0.017	19 (14, 30)	19 (11, 29)	0.518	17 (12, 28)	20 (15, 31)	0.030	19 (14, 29)	19 (12, 30)	0.471
GGT (IU/L)	27 (19, 44)	26 (18, 46)	0.958	24 (17, 44)	33 (20, 51)	0.038	26 (18, 46)	25 (18, 43)	0.605	24 (17, 37)	29 (19, 49)	0.057
Hematocrit (%)	38±5.3	40.7±4.4	<0.001	40.3 (37.7, 40.3)	39.7±5.4	0.459	39.1±6.0	40.4±4.5	0.046	40.4±4.5	39.2±6.0	0.068
Creatinine (mg/dL)	1.00 (0.83, 1.18)	0.72±0.15	<0.001	0.76 (0.64, 0.91)	0.85 (0.71, 0.96)	0.017	1.06 (0.93, 1.33)	0.71±0.15	<0.001	0.77 (0.64, 0.91)	0.95 (0.76, 1.23)	<0.001
eGFR (mL/min/1.73 m^2)	49.4 (42.3, 55.9)	74 (66.9, 84.0)	<0.001	70.3 (60.5, 80.8)	64.9 (52.5, 78.1)	0.098	48.5 (41.1, 54.9)	76.5 (67.6, 87.3)	<0.001	67.3 (56.0, 80.4)	58.3±22.9	<0.001
Proteinuria, n (%)												
–	34 (60.7)	109 (74.7)	0.033	144 (100)	0 (0)		51 (43.2)	100 (65.4)	<0.001	152 (100)	0 (0)	
±	12 (21.4)	21 (14.4)		0 (0)	33 (55.9)		25 (21.2)	37 (24.2)		0 (0)	62 (51.7)	
1+	4 (7.1)	7 (4.8)		0 (0)	11 (18.6)		21 (17.8)	10 (6.5)		0 (0)	31 (25.8)	
2+	6 (10.7)	4 (2.7)		0 (0)	10 (16.9)		17 (14.4)	5 (3.3)		0 (0)	22 (18.3)	

Continued

Table 1 Continued

	Non-DM						DM					
	eGFR<60	eGFR≥60		Proteinuria−	Proteinuria+		eGFR<60	eGFR≥60		Proteinuria−	Proteinuria+	
	n=56	n=146	P value	n=144	n=59	P value	n=118	n=153	P value	n=152	n=120	P value
3+	0 (0)	5 (3.4)		0 (0)	5 (8.5)		3 (2.5)	0 (0)		0 (0)	3 (2.5)	
4+	0 (0)			0 (0)	0 (0)		1 (0.8)	1 (0.7)		0 (0)	2 (1.7)	
Uric acid (mg/dL)	6.2±1.7	5.4±1.5	0.006	5.5±1.5	5.8 (5.0, 6.9)	0.049	5.9 (4.9, 6.8)	5.0 (4.0, 6.1)	<0.001	5.3 (4.3, 6.4)	5.4 (4.5, 6.8)	0.123
CKD risk parameters												
Age ≥65, n (%)	39 (69.6)	68 (46.6)	0.003	78 (54.2)	30 (50.8)	0.667	85 (72.0)	83 (54.2)	0.003	89 (58.6)	79 (65.8)	0.246
Systolic blood pressure (mm Hg)	129±22	132 (119, 145)	0.116	130 (114, 144)	137±21	0.054	133±20	136±19	0.272	132±19	137±20	0.052
Diastolic blood pressure (mm Hg)	73±12	79±13	0.005	76±13	79±13	0.112	73±13	77±13	0.012	73±13	76±13	0.158
Heart rate (beats per minute)	73±14	72 (66, 82)	0.340	71 (63, 82)	76±13	0.307	79±15	78 (66, 86)	0.454	77 (66, 88)	79±14	0.263
Smoking history, n (%)	19 (33.9)	57 (39.0)	0.691	50 (34.7)	26 (44.1)	0.310	61 (51.7)	77 (50.3)	0.909	68 (44.7)	71 (59.2)	0.024
Hypertension, n (%)	51 (91.1)	87 (59.6)	<0.001	94 (65.3)	45 (76.3)	0.142	97 (82.2)	118 (77.1)	0.304	116 (76.3)	100 (83.3)	0.155
Dyslipidemia, n (%)	33 (58.9)	84 (57.5)	0.857	82 (56.9)	35 (59.3)	0.756	93 (78.8)	104 (68.0)	0.045	111 (73.0)	87 (72.5)	0.923
History of coronary artery disease, n (%)	18 (32.1)	38 (26.0)	0.404	41 (28.5)	15 (25.4)	0.687	38 (32.2)	28 (18.3)	0.008	36 (23.7)	30 (25.0)	0.802
eGFR<60, n (%)				34 (23.6)	22 (37.3)	0.051				51 (33.6)	67 (55.8)	<0.001
Proteinuria ≥±, n (%)	22 (39.3)	37 (25.3)	0.055	0 (0)	59 (100)	<0.001	67 (56.8)	53 (34.6)	<0.001	0 (0)	120 (100)	<0.001

Values are presented as mean±SD, median (IQR) or percentage. P values were obtained by one-way analysis of variance (ANOVA), Kruskal-Wallis test or χ^2 test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

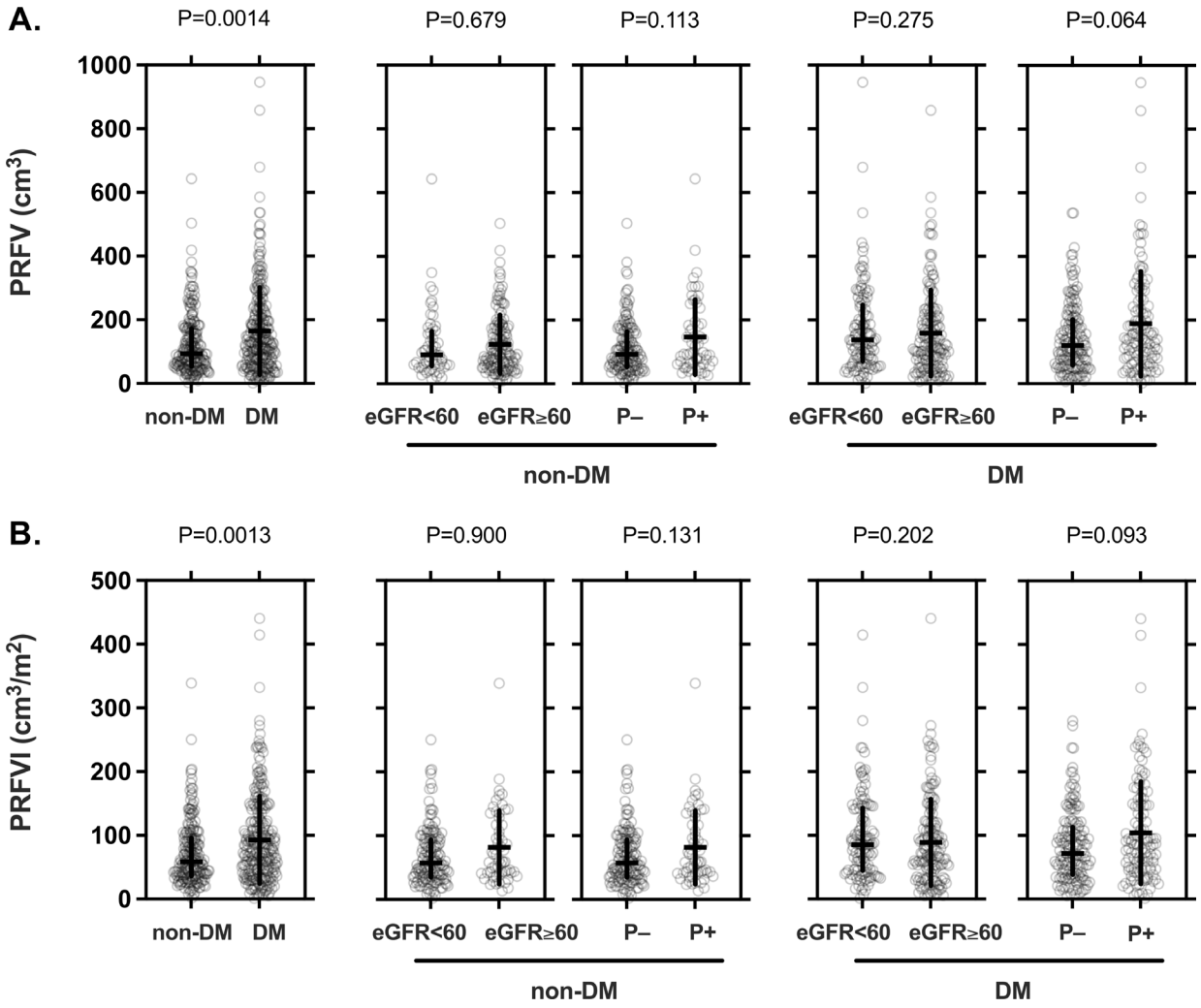

Figure 2 Scatter plot of perirenal fat volume (PRFV) (A) and perirenal fat volume index (PRFVI) (B) in individuals with or without type 2 diabetes mellitus (T2DM). Bars are medians (IQR). Individuals with or without T2DM were subdivided into eGFR<60 versus eGFR≥60 subgroups or into proteinuria– (P–) versus proteinuria+ (P+) subgroups. P values were obtained by Kruskal-Wallis test. Non-DM denotes without T2DM; DM denotes with T2DM. PRFV was determined in the left kidney as shown in figure 1 and PRFVI was calculated as PRFV/body surface area. eGFR, estimated glomerular filtration rate.

confounding factors (*models 1–3*), and it was lost after adjusting for VFA≥100 (*model 4*).

DISCUSSION

This study assessed the association between PRF accumulation, renal dysfunction, and proteinuria in individuals with and without T2DM. The study yielded two main findings. First, PRFV and PRFV index cut-off values were associated with an eGFR<60 in individuals with DM but not in those without DM. Even after adjusting for other CKD risk parameters, the association remained statistically significant, indicating that PRF accumulation was independently and closely associated with eGFR<60 in DKD. Second, the PRFV and PRFV index cut-off values were associated with proteinuria in patients with DM, as well as those without DM. To the best of our knowledge, this is the first study to simultaneously evaluate the relationship between PRFV and renal dysfunction in patients with and without DM. PRFV was found to be related to low eGFR in patients with DM but not in those without DM, suggesting that PRF accumulation is more closely associated with the onset and progression of DKD than in non-DKD (NDKD) patients.

Factors associated with eGFR<60

The major modifiable risk factors for CKD in the general population include obesity, elevated blood pressure, blood glucose levels, proteinuria, anemia, and dyslipidemia.[29 30] Non-modifiable risk factors include age, sex, race, and genetic predisposition.[29–32] Kidney function trajectories among people with diabetes are associated with modifiable (obesity, hyperglycemia, hypertension, dyslipidemia, smoking, unhealthy diet, and physical inactivity) and non-modifiable risk factors (older age, male sex, and ethnicity).[4 5 33] Obesity measures, BMI (per kg/m^2) and obesity (BMI≥30), are associated with low eGFR both in the non-DM[6 30] and DM[33] groups. Garofalo *et al* found that being overweight (BMI≥25) posed a risk

Table 2 Adiposity and kidney-associated measures: eGFR<60 versus eGFR≥60 and proteinuria– versus proteinuria+

	Non-DM						DM					
	eGFR<60	eGFR≥60		Proteinuria–	Proteinuria+		eGFR<60	eGFR≥60		Proteinuria–	Proteinuria+	
	n=56	n=146	P value	n=144	n=59	P value	n=118	n=153	P value	n=152	n=120	P value
Adiposity measures												
Body mass index (kg/m^2)	24.6±3.72	24.3 (21.7, 26.9)	0.911	24.4±3.6	23.8 (21.6, 27.6)	0.706	24.7 (21.9, 27.2)	24.6 (22.2, 28.3)	0.427	25.2 (22.6, 28.9)	24.0 (21.9, 26.8)	0.040
Body mass index ≥25, n (%)	21 (37.5)	63 (43.2)	0.420	62 (43.1)	22 (37.3)	0.404	54 (45.8)	72 (47.1)	0.793	77 (50.7)	49 (40.8)	0.086
Waist circumference (cm)	85.7±10.4	85.7 (78.3, 92.2)	0.966	85.0±8.9	87.5±13.9	0.422	87.4 (78.7, 95.6)	87.7 (79.3, 95.8)	0.529	88.0 (78.6, 95.5)	87.6 (79.4, 96.3)	0.965
Waist circumference ≥85 or 90 cm, n (%)	20 (35.7)	64 (43.8)	0.275	57 (39.6)	27 (45.8)	0.439	56 (47.5)	78 (51.0)	0.672	77 (50.7)	58 (48.3)	0.633
Subcutaneous fat area (cm^2)	112.2 (69.8, 149.7)	114.7 (77.7, 168.2)	0.518	111.9 (76.7, 166.9)	118.4 (78.3, 160.0)	0.598	134.0 (92.6, 198.6)	137.5 (95.7, 203.9)	0.782	147.4 (97.0, 214.4)	125.8 (89.9, 184.8)	0.074
Visceral fat area (cm^2)	125 (88.4, 178)	120.8 (91.9, 187.1)	0.934	119.4 (92.5, 171.0)	142.2 (81.4, 210.6)	0.170	138.9 (88.8, 206.7)	138.2 (97.8, 196.5)	0.958	135.1 (92.4, 190.8)	142.6 (97.2, 208.4)	0.364
Visceral fat area ≥100 cm^2, n (%)	38 (67.9)	99 (67.8)	0.955	99 (68.8)	39 (66.1)	0.664	78 (66.1)	113 (73.9)	0.244	105 (69.1)	87 (72.5)	0.634
Kidney-associated measures												
Kidney volume (cm^3)	132.7±29.9	168.3±65.9	0.198	141.7±36.6	156.2±66.7	0.610	160±48.3	178.6 (160.8, 217.7)	<0.001	170.3 (140.8, 196.9)	178.0±57.1	0.557
PRFV (cm^3)	90.7 (56.5, 165.1)	96.1 (53.4, 174.7)	0.679	91.5 (53.1, 162.8)	97.5 (61.2, 194.4)	0.113	137.7 (70.6, 246.9)	119.9 (60.4, 210.9)	0.275	119.8 (58.0, 202.0)	143.4 (77.8, 255.9)	0.064
PRFVI (cm^3/m^2)	55.0 (36.8, 98.8)	59.2 (35.4, 95.6)	0.900	57.2 (35.2, 94.0)	60.3 (41.6, 117.2)	0.131	85.2 (44.5, 143.0)	71.2 (36.2, 119.8)	0.202	71.7 (38.2, 112.9)	85.4 (46.6, 147.8)	0.093

Values are presented as mean±SD, median (IQR) or percentage. P values were obtained by one-way analysis of variance (ANOVA), Kruskal-Wallis test or χ^2 test.
Kidney volume and perirenal fat volume were determined in the left kidney.
DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PRFV, perirenal fat volume; PRFVI, perirenal fat volume index (PRFV/body surface area).

Table 3 Multivariate OR for eGFR<60 by using cut-off values of perirenal fat volume or perirenal fat volume index in non-DM and DM

	Univariate analysis		Multivariate analysis					
			Model 1		Model 2		Model 3	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
A. Non-DM, perirenal fat volume								
Age (per year)	1.06 (1.03, 1.10)	<0.001	1.06 (1.03, 1.10)	<0.001	1.05 (1.02, 1.09)	<0.001	1.06 (1.02, 1.10)	<0.001
Sex (male/female)	0.67 (0.36, 1.24)	0.201	0.95 (0.47, 1.94)	0.891	0.93 (0.42, 2.08)	0.862	0.95 (0.42, 2.16)	0.899
Body mass index (per kg/m^2)	0.99 (0.93, 1.07)	0.962	1.06 (0.96, 1.17)	0.226	1.06 (0.96, 1.17)	0.251	1.05 (0.94, 1.16)	0.402
Hypertension (yes/no)	6.80 (2.79, 20.4)	<0.001			6.27 (2.07, 19.0)	0.001	6.49 (2.13, 19.8)	0.001
Smoking history (yes/no)	0.88 (0.45, 1.68)	0.691			0.99 (0.45, 2.18)	0.971	1.10 (0.49, 2.46)	0.822
Visceral fat area ≥100 cm^2 (yes/no)	0.98 (0.51, 1.93)	0.955					1.49 (0.57, 3.86)	0.416
PRFV≥106 cm^3 (yes/no)	0.80 (0.42, 1.49)	0.481	0.63 (0.28, 1.46)	0.284	0.60 (0.23, 1.52)	0.280	0.50 (0.18, 1.37)	0.178
B. Non-DM, perirenal fat volume index								
Age (per year)	1.06 (1.03, 1.10)	<0.001	1.06 (1.03, 1.09)	<0.001	1.05 (1.02, 1.09)	0.002	1.05 (1.02, 1.09)	0.002
Sex (male/female)	0.67 (0.36, 1.24)	0.201	0.70 (0.34, 1.45)	0.341	0.63 (0.27, 1.48)	0.291	0.63 (0.27, 1.47)	0.282
Body mass index (per kg/m^2)	0.99 (0.93, 1.07)	0.962	1.01 (0.93, 1.11)	0.794	0.99 (0.91, 1.09)	0.944	0.99 (0.89, 1.10)	0.904
Hypertension (yes/no)	6.80 (2.79, 20.4)	<0.001			6.76 (2.20, 20.7)	<0.001	6.78 (2.21, 20.8)	<0.001
Smoking history (yes/no)	0.88 (0.45, 1.68)	0.691			0.86 (0.39, 1.87)	0.705	0.91 (0.41, 2.01)	0.818
Visceral fat area ≥100 cm^2 (yes/no)	0.98 (0.51, 1.93)	0.955					1.04 (0.42, 2.60)	0.927
PRFVI≥35 cm^3/m^2 (yes/no)	1.36 (0.65, 3.02)	0.416	1.65 (0.64, 4.24)	0.296	2.35 (0.81, 6.83)	0.118	2.18 (0.73, 6.47)	0.161
C. DM, perirenal fat volume								
Age (per year)	1.04 (1.02, 1.07)	<0.001	1.04 (1.02, 1.07)	<0.001	1.05 (1.02, 1.07)	<0.001	1.04 (1.02, 1.07)	<0.001
Sex (male/female)	0.93 (0.57, 1.51)	0.759	0.86 (0.51, 1.46)	0.581	0.75 (0.40, 1.43)	0.386	0.79 (0.42, 1.51)	0.479
Body mass index (per kg/m^2)	0.99 (0.95, 1.03)	0.642	1.00 (0.95, 1.06)	0.991	1.00 (0.94, 1.06)	0.982	1.02 (0.96, 1.08)	0.589
Hypertension (yes/no)	1.37 (0.75, 2.54)	0.304			1.04 (0.54, 2.02)	0.902	1.01 (0.52, 1.98)	0.969
Smoking history (yes/no)	1.03 (0.64, 1.67)	0.909			1.19 (0.64, 2.20)	0.576	1.15 (0.62, 2.15)	0.652
Visceral fat area ≥100 cm^2 (yes/no)	0.73 (0.43, 1.24)	0.244					0.50 (0.25, 0.99)	0.049

Continued

Table 3 Continued

	Univariate analysis		Multivariate analysis					
			Model 1		Model 2		Model 3	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
PRFV≥120 cm^3 (yes/no)	1.43 (0.88, 2.32)	0.149	1.63 (0.91, 2.92)	0.099	1.57 (0.88, 2.81)	0.130	2.01 (1.05, 3.87)	0.036
D. DM, perirenal fat volume index								
Age (per year)	1.04 (1.02, 1.07)	<0.001	1.05 (1.02, 1.07)	<0.001	1.05 (1.02, 1.07)	<0.001	1.05 (1.02, 1.08)	<0.001
Sex (male/female)	0.93 (0.57, 1.51)	0.759	0.89 (0.53, 1.49)	0.650	0.71 (0.37, 1.35)	0.300	0.75 (0.39, 1.44)	0.386
Body mass index (per kg/m^2)	0.99 (0.95, 1.03)	0.642	1.00 (0.95, 1.05)	0.997	0.99 (0.95, 1.05)	0.965	1.03 (0.97, 1.09)	0.358
Hypertension (yes/no)	1.37 (0.75, 2.54)	0.304			0.92 (0.47, 1.82)	0.821	0.82 (0.41, 1.64)	0.582
Smoking history (yes/no)	1.03 (0.64, 1.67)	0.909			1.33 (0.71, 2.47)	0.373	1.35 (0.72, 2.55)	0.349
Visceral fat area ≥100 cm^2 (yes/no)	0.73 (0.43, 1.24)	0.244					0.37 (0.18, 0.76)	0.007
PRFVI≥30 cm^3/m^2 (yes/no)	2.73 (1.28, 6.38)	0.009	3.16 (1.34, 7.45)	0.009	3.44 (1.43, 8.25)	0.006	6.01 (2.20, 16.4)	<0.001

Kidney volume and perirenal fat volume were determined by the left kidney.
DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PRFV, perirenal fat volume; PRFVI, perirenal fat volume index (PRFV/body surface area).

Table 4 Multivariate OR for proteinuria by using cut-off values of perirenal fat volume or perirenal fat volume index in non-DM and DM

	Univariate analysis		Multivariate analysis							
			Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
A. Non-DM, perirenal fat volume										
Age (per year)	0.99 (0.97, 1.02)	0.759	0.99 (0.97, 1.02)	0.942	0.99 (0.97, 1.02)	0.530	0.99 (0.96, 1.02)	0.513	0.99 (0.96, 1.02)	0.538
Sex (male/female)	1.84 (0.98, 3.46)	0.055	1.49 (0.76, 2.92)	0.241	1.54 (0.78, 3.04)	0.211	1.60 (0.76, 3.37)	0.212	1.53 (0.72, 3.23)	0.270
Body mass index (per kg/m^2)	1.03 (0.96, 1.10)	0.437	0.98 (0.90, 1.06)	0.609	0.99 (0.91, 1.08)	0.802	0.98 (0.90, 1.07)	0.595	0.99 (0.90, 1.09)	0.874
eGFR (per mL/min/1.73 m^2)	0.98 (0.97, 0.99)	0.042			0.98 (0.96, 0.99)	0.023	0.98 (0.96, 0.99)	0.026	0.98 (0.96, 0.99)	0.030
Hypertension (yes/no)	1.68 (0.84, 3.35)	0.142					1.44 (0.67, 3.12)	0.347	1.46 (0.67, 3.16)	0.333
Smoking history (yes/no)	1.38 (0.74, 2.58)	0.310					1.03 (0.51, 2.09)	0.932	1.05 (0.52, 2.15)	0.887
Visceral fat area ≥100 cm^2 (yes/no)	0.87 (0.45, 1.65)	0.664							0.71 (0.32, 1.61)	0.415
PRFV≥237 cm^3 (yes/no)	3.14 (1.37, 7.17)	0.005	3.47 (1.32, 9.12)	0.011	3.19 (1.20, 8.48)	0.020	2.98 (1.10, 8.09)	0.031	3.12 (1.14, 8.53)	0.026
B. Non-DM, perirenal fat volume index										
Age (per year)	0.99 (0.97, 1.02)	0.759	0.99 (0.97, 1.02)	0.933	0.99 (0.97, 1.02)	0.524	0.99 (0.96, 1.02)	0.511	0.99 (0.96, 1.02)	0.537
Sex (male/female)	1.84 (0.98, 3.46)	0.055	1.50 (0.77, 2.94)	0.235	1.55 (0.79, 3.06)	0.204	1.63 (0.78, 3.43)	0.193	1.55 (0.73, 3.27)	0.248
Body mass index (per kg/m^2)	1.03 (0.96, 1.10)	0.437	0.98 (0.90, 1.07)	0.602	0.99 (0.91, 1.08)	0.799	0.98 (0.90, 1.07)	0.597	0.99 (0.90, 1.09)	0.902
eGFR (per mL/min/1.73 m^2)	0.98 (0.97, 0.99)	0.042			0.98 (0.97, 0.99)	0.029	0.98 (0.97, 0.99)	0.028	0.98 (0.96, 0.99)	0.032
Hypertension (yes/no)	1.68 (0.84, 3.35)	0.142					1.44 (0.67, 3.12)	0.348	1.45 (0.67, 3.15)	0.338
Smoking history (yes/no)	1.38 (0.74, 2.58)	0.310					1.00 (0.50, 2.03)	0.993	1.02 (0.50, 2.08)	0.957
Visceral fat area ≥100 cm^2 (yes/no)	0.87 (0.45, 1.65)	0.664							0.68 (0.30, 1.55)	0.357
PRFVI≥116 cm^3 (yes/no)	2.93 (1.35, 6.36)	0.005	3.25 (1.33, 7.99)	0.010	2.98 (1.20, 7.38)	0.018	2.78 (1.10, 7.03)	0.030	3.00 (1.16, 7.64)	0.023
C. DM, perirenal fat volume										
Age (per year)	1.01 (0.98, 1.03)	0.610	0.99 (0.98, 1.02)	0.965	0.98 (0.96, 1.01)	0.164	0.98 (0.95, 1.00)	0.095	0.98 (0.95, 1.00)	0.071
Sex (male/female)	2.56 (1.54, 4.25)	<0.001	2.26 (1.34, 3.81)	0.002	2.36 (1.36, 4.08)	0.002	2.46 (1.26, 4.79)	0.008	2.28 (1.16, 4.46)	0.015
Body mass index (per kg/m^2)	0.97 (0.92, 1.01)	0.137	0.95 (0.90, 1.00)	0.056	0.94 (0.89, 0.99)	0.037	0.93 (0.88, 0.99)	0.015	0.92 (0.86, 0.98)	0.005

Continued

Table 4 Continued

	Univariate analysis		Multivariate analysis							
			Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
eGFR (per mL/min/1.73 m^2)	0.97 (0.96, 0.99)	<0.001			0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.98)	<0.001
Hypertension (yes/no)	1.55 (0.84, 2.85)	0.155					1.88 (0.93, 3.80)	0.074	1.94 (0.96, 3.93)	0.061
Smoking history (yes/no)	1.75 (1.08, 2.84)	0.024					0.94 (0.50, 1.78)	0.849	0.95 (0.50, 1.80)	0.870
Visceral fat area ≥100 cm^2 (yes/no)	1.13 (0.67, 1.95)	0.634							1.49 (0.77, 2.87)	0.236
PRFV≥292 cm^3 (yes/no)	2.53 (1.27, 5.02)	0.007	3.22 (1.46, 7.10)	0.003	3.32 (1.48, 7.44)	0.003	3.34 (1.48, 7.55)	0.003	3.16 (1.38, 7.24)	0.005
D. DM, perirenal fat volume index										
Age (per year)	1.01 (0.98, 1.03)	0.610	0.99 (0.97, 1.02)	0.712	0.98 (0.95, 1.00)	0.101	0.97 (0.95, 1.00)	0.053	0.97 (0.95, 0.99)	0.042
Sex (male/female)	2.56 (1.54, 4.25)	<0.001	2.31 (1.37, 3.90)	0.002	2.43 (1.41, 4.21)	0.001	2.61 (1.34, 5.09)	0.004	2.43 (1.24, 4.75)	0.009
Body mass index (per kg/m^2)	0.97 (0.92, 1.01)	0.137	0.94 (0.89, 0.99)	0.030	0.94 (0.88, 0.99)	0.022	0.92 (0.87, 0.98)	0.008	0.91 (0.85, 0.97)	0.004
eGFR (per mL/min/1.73 m^2)	0.97 (0.96, 0.99)	<0.001			0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.98)	<0.001	0.97 (0.96, 0.98)	<0.001
Hypertension (yes/no)	1.55 (0.84, 2.85)	0.155					1.94 (0.96, 3.91)	0.060	2.00 (0.99, 4.03)	0.051
Smoking history (yes/no)	1.75 (1.08, 2.84)	0.024					0.90 (0.47, 1.70)	0.736	0.90 (0.47, 1.72)	0.759
Visceral fat area ≥100 cm^2 (yes/no)	1.13 (0.67, 1.95)	0.634							1.41 (0.72, 2.73)	0.314
PRFVI≥146 cm^3 (yes/no)	2.33 (1.26, 4.29)	0.006	3.27 (1.59, 6.73)	<0.001	3.18 (1.52, 6.65)	0.002	3.30 (1.56, 6.98)	0.0013	3.08 (1.43, 6.62)	0.003

Kidney volume and perirenal fat volume were determined by the left kidney.
DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PRFV, perirenal fat volume; PRFVI, perirenal fat volume index (PRFV/body surface area).

(relative risk 1.18, 95% CI 1.07 to 1.31) for new-onset CKD in the general population of the Asian-Pacific regions, including Japan, Korea, China, and Thailand.[6] However, in our study, BMI (per kg/m^2) and overweight (BMI≥25), as well as the other measures of adiposity such as WC and subcutaneous fat area and VFA, were not associated with eGFR<60. The reason for the variance between our findings and those of prior reports[6 30 33] remains unclear. One possible explanation for the incongruity with Garofalo *et al*[6] could be that obesity does not confer an increased risk of low eGFR in patients with CKD[34] although it is a risk factor for de novo CKD.[6]

Although adiposity measures, such as BMI and VFA, were still unrelated to low eGFR, PRFV and PRFV index cut-off values were associated with an eGFR<60 in DM. Previous cross-sectional studies have shown that elevated PRF thickness (measured by ultrasound) is associated with low eGFR in patients with T2DM.[12] A longitudinal study further revealed that the association between PRF thickness measured using CT and low eGFR remained significant even after accounting for total body fat and SAT and VAT volume, suggesting that PRF mass possesses a higher predictive value for CKD than total and abdominal fat mass in T2DM.[14] For the first time, we have unveiled that PRFV was correlated with low eGFR exclusively in DM, implying that PRF accumulation is more intricately associated with the onset and progression of DKD than in NDKD patients.

Factors associated with proteinuria

A recent study reported that PRF thickness, measured using ultrasound, was positively associated with the urine albumin excretion rate in patients with T2DM.[13 35] This is the first study demonstrating the association of PRF accumulation with proteinuria in individuals without T2DM. Factors linked to proteinuria, apart from PRFV index, showed disparities between the non-DM and DM groups. Notably, low eGFR was linked to proteinuria in the non-DM group, whereas the DM group displayed associations with younger age, male sex, high BMI, and low eGFR (table 4). In a diabetes group extracted from the current Japanese database, we found that early-onset T2DM, occurring at age ≤40 years old, was linked to prospective proteinuria but not GFR decline (data submitted). Collectively, these findings suggest that the underlying pathophysiology connecting PRF accumulation and proteinuria differs between patients without DM and those with DM. Comprehensive large-scale prospective studies are needed to elucidate the relationship between PRFV accumulation and proteinuria, along with its underlying pathophysiology.

Clinical implication

PRF accumulation was independently and closely associated with an eGFR<60 in DKD cases but not in NDKD cases. However, PRF accumulation exhibited an association with proteinuria in both patients with DM and without DM. In classical DKD, proteinuria often precedes a decline in eGFR. Meanwhile, eGFR decline without albuminuria, a non-classical DKD phenotype, has become common in the past decades.[2–4] We further evaluated the relationship between PRFV or PRFV index and low eGFR in the proteinuria– and proteinuria+ subgroups (online supplemental table 7 and table 8). Notably, in individuals with DM, PRFV index was associated with eGFR<60 in proteinuria– and proteinuria+ subgroups, whereas this association was absent in individuals without DM. These results suggest that PRF accumulation is closely associated with DKD, independent of the presence of proteinuria.

At present, we are unable to fully elucidate the strong relationship between PRFV accumulation and renal dysfunction in patients with DM. Three possible underlying mechanisms are discussed below.

First, PRF levels may serve as an indicator of intrarenal fat accumulation. Currently, the best established mechanisms by which obesity may contribute to CKD include glomerular hyperfiltration, overactivation of the renin-angiotensin-aldosterone system, hyperinsulinemia, insulin resistance, increased release of proinflammatory cytokines, and intrarenal ectopic fat accumulation/lipotoxicity.[9 16 36] Given the strong correlation between PRFV and intrarenal fat mass,[37] PRFV may reflect the extent of intrarenal fat mass and not be a causal element. Second, PRF accumulation could potentially compromise renal function by directly interacting with the structural integrity of the renal parenchyma. Ectopic fat accumulation in the kidneys is associated with obesity-related glomerulopathy (ORG).[9 16] Ectopic fat is associated with structural and functional changes in mesangial cells, podocytes, and proximal tubular cells, which may contribute to the development of ORG and progression of CKD.[9 16] In a study using human kidney samples, we reported an inverse correlation between adiponectin expression and fat accumulation in the PRF region, but not in the subcutaneous fat area and VFA, suggesting that PRF may directly influence the local renal environment.[28] If this is true, future studies should clarify the mechanisms by which PRF accumulation affects the development of DKD. Third, PRFV accumulation first causes proteinuria, which gradually impairs glomerular and tubular function and may lead to a decrease in eGFR over several years. This trajectory is typical of classical DKD and diabetic nephropathy.[4] On the other hand, in non-DM, PRFV accumulation still causes proteinuria, but the time from proteinuria to eGFR decline may be longer than in DM. In fact, as shown in table 1, the median ages of individuals with and without proteinuria in DM and non-DM are all <70 years, but the median age of patients with eGFR<60 is clearly older than that of patients with eGFR≥60 (71 vs 64 years) in the non-DM group, which may support this possibility. This is a hypothesis and therefore this notion should be evaluated in the future studies. However, this is only a hypothesis, and future studies should explore why the effects of PRFV accumulation on proteinuria and low eGFR differ between the DM and non-DM groups.

Strengths and limitations

The volume measure for PRF accumulation was a strength of the current study compared with simple and relatively unreliable measures, such as the thickness of PRF measured by ultrasound[12 13 35] or CT[14] in previous reports. Another strength was the use of the PRFV index, which is indexed by body surface area, to standardize PRFV by whole-body size. Third, another strength of this study was that it compared the relationship between PRFV and renal complications simultaneously in the DM and non-DM groups. Simultaneous comparisons enabled us to identify differences in PRFV connections between the DM and non-DM groups.

The limitations of our study are as follows. First, the cross-sectional design of our study restricts our ability to explain the cause–effect relationship between kidney fat accumulation and renal dysfunction. A prospective design and a larger sample size are required to elucidate the role of kidney fat in the trajectories of low eGFR and proteinuria. Furthermore, to establish proof of concept of PRFV as a pathophysiological condition, it is essential to demonstrate a connection between the protection of kidney function and potential interventions to reduce PRFV, such as lifestyle modifications, medications, and metabolic surgery.[9] Second, proteinuria was determined using a single semiquantitative dipstick urinalysis measurement. This could introduce random measurement errors and regression dilution biases, both of which might lead to an underestimation of the actual association. Third, we excluded patients with primary kidney disease based on clinical signs or urine abnormalities in electronic medical records. However, distinguishing NDKD, such as glomerulonephritis and nephrosclerosis, without kidney biopsy is not entirely reliable.[38] Fourth, medication use data were unavailable in the current study. Information about prescription medications, especially angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, could have enriched our results. Fifth, this study solely focused on the Japanese population. Therefore, these results may not be generalizable to other ethnic groups. Lastly, PRFV is a relatively novel parameter, and its clinical characteristics and pathophysiological futures remain unclear. The associations of PRFV on the different adiposity parameters, that is, BMI, VFA, and liver fat in terms of coincidental low eGFR and proteinuria, should be evaluated in future studies.

CONCLUSION

In this study, we observed that PRFV is associated with low eGFR in patients with T2DM but not in those without T2DM. This suggests that PRF accumulation is more closely related to the onset and progression of DKD than NDKD. Clarifying the mechanisms through which PRF influences DKD development could pave the way for novel prevention and treatment strategies.

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