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Para- and perirenal fat thickness is an independent predictor of chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients

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Abstract

Background. Many interfering factors may reduce the reliability of waist circumference (WC) measurement in estimating the risk for chronic kidney disease (CKD) associated

with obesity. Therefore, we determined the independent associations of para- and perirenal ultrasonographic fat thickness with the main markers of kidney function.

Methods. A cross-sectional study was performed in 151 type-2 diabetic subjects. Para- and perirenal fat thickness was measured from the inner side of the abdominal musculature to the surface of the kidneys. CKD was defined as $\text{eGFR} < 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$.

Results. Using both univariate and multivariate regression analyses, eGFR , renal resistance index and uricaemia were best predicted by para- and perirenal fat thickness even when BMI and waist circumference were further added in the statistical model (r^2 : 0.366, $P = 0.001$; r^2 : 0.529, $P = 0.005$; r^2 : 0.310, $P = 0.026$, respectively), whereas waist circumference and BMI did not contribute independently of para- and perirenal fat thickness. Albuminuria was predicted by waist circumference but not by para- and perirenal fat thickness. In subjects with waist circumference above the diagnostic values of metabolic syndrome (48M/59F), eGFR significantly and progressively declined across tertiles of para- and perirenal fat thickness (87.0 ± 27.9 vs 83.5 ± 26.0 vs $62.3 \pm 30.6 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$, adjusted $P < 0.0001$) despite comparable waist circumference, and an increasing frequency of CKD was observed across tertiles of subjects with waist circumference both below and above the metabolic syndrome diagnostic values ($P < 0.05$).

Conclusions. Para- and perirenal fat thickness is an independent predictor of kidney dysfunction in type-2 diabetes explaining an important proportion of the variance of eGFR , renal resistance index and uricaemia.

Keywords: diabetes mellitus; kidney dysfunction; perirenal fat; uricaemia; visceral obesity

Introduction

Obesity is an independent risk factor for the development and progression of chronic kidney disease (CKD), and multiple mechanisms by which obesity may initiate and exacerbate CKD have indeed been established [1–5]. However, most studies aimed at exploring the association between obesity and kidney dysfunction have commonly used body mass index (BMI) [6,7] or waist circumference (WC) [8] as markers of adiposity. However, the increasingly evident differences among various fat tissue deposits make BMI a less than ideal marker [9], abdominal fat accumulation being the major determinant of the increased risk for cardiorenal and metabolic diseases associated with obesity and the metabolic syndrome [10]. On the other hand, in a given patient, many interfering factors may also reduce the reliability of WC in estimating abdominal fat deposition, as well as the associated risk for CKD. WC is indeed a global measurement of both subcutaneous adipose tissue and abdominal content, and unlike visceral fat, subcutaneous adipose tissue is more abundant in female than in male subjects; moreover, it commonly diminishes during ageing [11]. On the basis of these considerations, we presume that para- and perirenal ultrasonographic fat thickness (PUFT) measurement may better reflect the risks commonly associated with increased visceral fat accumulation and particularly those related to renal function im-

pairment. It should be noted indeed that PUFT represents a direct measurement of an important component of abdominal fat content [12], and in addition, it may give further information on the potential influence of visceral fat on kidney function, since an increase in para- and perirenal adipose tissue has been shown to compress renal vessels and renal parenchyma, causing elevated renal interstitial hydrostatic fluid, and reductions in both renal blood and tubular flow rates [13]. Obesity-related glomerulopathy may indeed not be the only histopathologic feature of obesity-related renal disease, particularly in non-proteinuric obese patients with renal dysfunction [13,14].

However, to the best of our knowledge, the association of para- and perirenal fat thickness with the degree of kidney dysfunction has not yet been investigated in diabetics, even though the underlying mechanisms linking kidney dysfunction and fatness are well documented [15–17].

Therefore, the aim of the present study was to determine the independent associations of PUFT as measured directly by ultrasonography in a cohort of 151 type-2 diabetes mellitus (T2DM) patients with the main markers of kidney function, such as estimated glomerular filtration rate (eGFR), renal resistance index (RI) and albuminuria as well as with serum urate values.

Materials and methods

This study was conducted in Caucasian patients with T2DM, resident in Apulia, southeastern Italy. A total of 151 consecutive patients were recruited at the Unit of Endocrinology and Diabetology of the University of Foggia, Italy. All patients were interviewed regarding the duration of type-2 diabetes, diagnosis, and ongoing antidiabetic, hypolipidaemic and antihypertensive treatments. The duration of diabetes was calculated from the calendar year of data collection minus the calendar year of diabetes diagnosis. All subjects enrolled in the study underwent physical examination including measurements of height, weight, waist circumference and blood pressure (i.e. two measurements rounded to the nearest 2 mmHg in the sitting position after at least a 5-min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V). BMI was calculated as body weight divided by squared height (kilogram per square metre). WC was measured at the umbilicus level at the end of expiration using a flexible plastic tape measure while subjects were standing with their weight equally distributed on both feet and with their head facing straight forward. Blood samples were drawn after an overnight fast of at least 12-h, and serum creatinine [automated colorimetric method (Jaffé reaction)], total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, and uric acid were determined by routine biochemical methods. eGFR was calculated both with the abbreviated Modification of Diet in Renal Disease (MDRD) formula [$\text{GFR} = 186 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$] and with the EPI-CKD formula [$141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$] [18,19]. The mean absolute eGFR value normalized to BSA using the DuBois and DuBois formula [$\text{BSA} 0.007184 \times \text{weight (kg)}^{0.425} \times \text{height (m)}^{0.725}$] was also calculated. CKD was defined as $\text{eGFR} < 60 \text{ mL min}^{-1} 1.73 \text{ m}^{-2}$ [20]. Urinary albumin and creatinine concentrations were determined on the morning of the clinical examination using an early-morning first void sterile urine sample with the immunoturbidimetric and the Jaffé reaction-rate methods, respectively. The urinary albumin-to-creatinine ratio (ACR) was then calculated. Microalbuminuria was diagnosed if the ACR was $\geq 2.5 \text{ mg/mmol}$ but $< 30 \text{ mg/mmol}$. Macroalbuminuria was defined as an ACR $\geq 30 \text{ mg/mmol}$, a level that approximates an albumin excretion of 300 mg/24-h , considered as the upper limit of microalbuminuria [21]. Ultrasound examinations by a duplex Doppler apparatus (Model SSA-550A; Toshiba) were performed to measure resistive index as previously reported [22]. PUFT was measured with the patient in the supine position. The probe was kept perpendicular to the skin on the lateral aspect of the abdomen. Longitu-

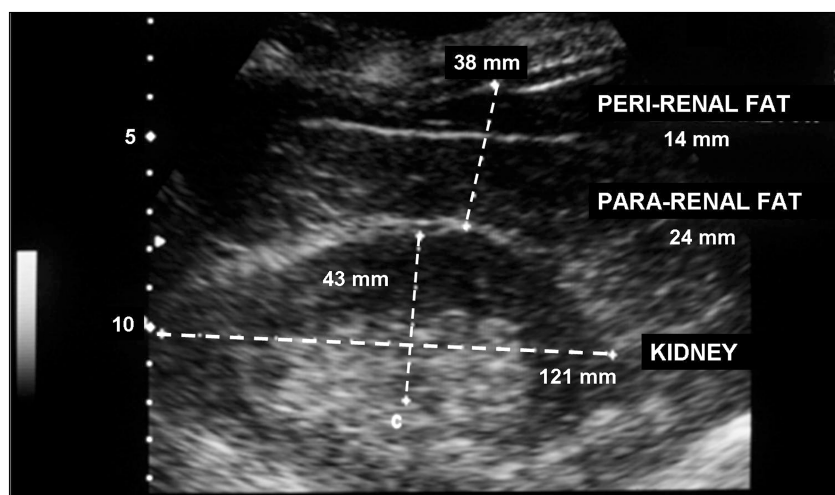


Fig. 1. A typical longitudinal sonographic measurement of combined para-perirenal fat ultrasound fat thickness (PUFT) in an obese male T2DM subject (age: 71 yrs, WC: 121 cm, BMI: 32.1 kg/m²).

dinal scanning was performed, and the probe was slowly moved laterally until the optimal position was found, at which the surface of the kidney was almost parallel to the skin. The pressure exerted on the probe was as minimal as possible so that the fat layers were not compressed. Then, the thickness of fat (consisting of **para- and perirenal** fat) was measured from the inner side of the abdominal musculature to the surface of the kidney and designated ultrasound measure (Figure 1). The average of the ultrasound measurement of the maximal thickness values on both sides was defined as the PUFT. The correlation between PUFT values measured on both sides was 0.745 ($P < 0.0001$). PUFT was measured three times. The intraoperator coefficient of variation was 4.7%. Sonographer (V.N.) was blinded to any other aspect of the study. Validation of the PUFT measurement technique was performed by comparison with computed tomography (CT) measurements in 13/151 subjects, obtaining a good grade of correlation ($r = 0.760$; $P = 0.003$). The PUFT measured in 10 normal subjects (M/F 5/5; age 26 ± 2 years; BMI 23 ± 1 kg/m²) was 8 ± 2 and 5 ± 2 mm ($P < 0.05$) in men and women, respectively. The study was performed according to the Helsinki Declaration, and the protocol was approved by the local ethics committee. All subjects provided written informed consent.

Statistical analysis

Data are expressed as mean \pm SD for normally distributed variables and median and range for skewed variables. Mean differences were compared by unpaired Student's *t*-test or one-way ANOVA *F*-test, as appropriate. Differences between categorical variables were tested by Pearson's χ^2 . Clinical variables were tested as linear trends according to the tertiles of PUFT. Univariate and multivariate analyses were performed to correlate independent variables, with ACR, eGFR, RI and serum urate values as dependent variables. Three separate linear regression models were used to determine the relationships between PUFT, WC, BMI and ACR, eGFR, RI, and serum urate values—Model 1, controlled for age and gender; Model 2, controlled for age, gender, HbA1c, SBP and LDL cholesterol; and Model 3, controlled for age, gender, HbA1c, SBP, ACR, LDL cholesterol and anthropometric parameters. Skewed variables or non-linear related variables were log-transformed. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered to be significant.

Results

Clinical features of the population as a whole as well as stratified by tertiles of PUFT are reported in Table 1.

No significant differences were found in BMI (29.7 ± 4.9 vs 31.1 ± 7.7 kg/m², $P = 0.209$), WC (105.5 ± 14.9 vs 109.1 ± 17.0 cm, $P = 0.176$) and PUFT (30.3 ± 9.5

vs 31.5 ± 10.9 mm, $P = 0.511$) by gender (in men and in women, respectively). Forty-eight (57.1%) male subjects had WC values > 102 cm, and 59 (88.1%) females > 88 cm which are the cut-off values for metabolic syndrome (MS) diagnosis [23]. Waist circumference measurements of 102 cm in men and 88 cm in women were equivalent to PUFT values of 29.56 and 26.09 mm, respectively.

A significant correlation between PUFT and WC ($r = 0.513$, $P < 0.0001$) and between PUFT and BMI ($r = 0.574$, $P < 0.0001$) was found.

Using both univariate and multivariate regression analyses (Table 2), eGFR, RI, and serum urate levels were best predicted by PUFT even when BMI and WC were further added in the statistical analysis (Model 3, r^2 : 0.366, $P = 0.001$; r^2 : 0.529, $P = 0.005$; r^2 : 0.310, $P = 0.026$, respectively), whereas WC and BMI did not contribute independently of PUFT. Similar results were obtained when the EPI-CKD formula was used for the same statistical analyses (see Table 2). BSA-normalized eGFR values were also predicted by PUFT in all statistical models (Model 1, r^2 : 0.388, $P = 0.02$; Model 2, r^2 : 0.386, $P = 0.05$; Model 3, r^2 : 0.449, $P = 0.004$, respectively), but not by WC and BMI. On the other hand, albuminuria was predicted in all statistical models by WC but not by PUFT (Table 2).

Then, we stratified the population investigated by the tertiles of PUFT (Table 1). A significant progressive decline in serum HDL cholesterol values ($P < 0.05$) with a concomitant increase in those of triglycerides ($P < 0.0001$) and SBP ($P < 0.05$) across the tertiles of PUFT was found. Moreover, a significant gradual increase across the tertiles of pulse pressure (PP) values was also observed ($P < 0.05$).

To further explore the relationship between WC and PUFT in affecting eGFR, we stratified the population according to the WC values recommended for MS diagnosis (i.e. > 88 cm in women and > 102 cm in men) and further to tertiles of PUFT values (Table 3). In subjects with higher WC values (48M/59F), eGFR values significantly and progressively declined across the tertiles of PUFT (87.0 ± 27.9 vs 83.5 ± 26.0 vs 62.3 ± 30.6 mL min⁻¹ 1.73 m⁻²,

Table 1. Clinical features of the whole population stratified across tertiles of **para- and perirenal** ultrasonographic fat thickness

	Whole population <i>n</i> = 151	Tertile 1 <i>n</i> = 49	Tertile 2 <i>n</i> = 51	Tertile 3 <i>n</i> = 51
Sex (M/F)	84/67	26/24	29/22	29/21
Age (years)	61.4 ± 12.0	60.9 ± 12.9	60.4 ± 11.4	62.1 ± 12.1
Duration of diabetes (years)	14.8 ± 9.8	14.6 ± 11.8	15.6 ± 10.1	14.5 ± 8.8
BMI (kg/m ²)	30.3 ± 6.3	25.4 ± 3.3	30.9 ± 4.2	34.1 ± 7.2*
Waist circumference (cm)	107.1 ± 15.9	95.9 ± 12.4	110.5 ± 13.2	114.0 ± 16.3*
PUFT (mm)	30.8 ± 10.1	19.5 ± 3.9	31.0 ± 3.1	41.8 ± 6.0*
SBP (mmHg)	125.5 ± 12.6	121.9 ± 11.7	125.2 ± 12.5	130.3 ± 12.3**
DBP (mmHg)	74.6 ± 7.7	73.5 ± 7.4	75.8 ± 8.2	75.2 ± 7.2
Pulse pressure	50.8 ± 11.1	48.4 ± 11.9	49.3 ± 8.8	55.1 ± 11.7**
Glycated haemoglobin (%)	9.4 ± 2.2	9.9 ± 2.3	9.2 ± 2.1	9.3 ± 2.1
Total cholesterol (mg/dL)	175.0 ± 53.5	171.7 ± 39.7	168.1 ± 43.3	183.2 ± 73.3
HDL cholesterol	44.8 ± 13.0	49.2 ± 14.0	43.1 ± 13.1	42.6 ± 10.9**
LDL cholesterol	91.7 ± 35.0	94.1 ± 35.4	89.1 ± 32.8	90.0 ± 38.4
Triglycerides ^a	154 (42–1624)	110 (45–558)	181 (42–355)	178 (68–1624)*
Uric acid (mg/dL)	5.5 ± 1.9	4.6 ± 1.5	5.6 ± 1.7	6.0 ± 2.1**
ACR (mg/mmol) ^a	2.5 (0.25–1005)	2.2 (0.25–128)	2.4 (0.35–1005)	3.1 (0.38–671)
MA, <i>n</i> (%)	68 (45.0)	21 (42.8)	24 (47.0)	23 (45.0)
eGFR (mL min ⁻¹ 1.73 m ⁻²) MDRD formula	81.8 ± 30.6	94.5 ± 27.5	82.5 ± 25.2	71.2 ± 33.8*
eGFR (mL min ⁻¹ 1.73 m ⁻²) EPI-CKD formula	77.7 ± 26.7	89.0 ± 20.5	79.1 ± 23.7	67.7 ± 30.0*
eGFR (mL min ⁻¹ ·BSA)	89.2 ± 34.9	94.8 ± 31.5	91.4 ± 29.8	84.9 ± 41.5
RI	0.69 ± 0.08	0.66 ± 0.08	0.70 ± 0.07	0.72 ± 0.07*
CKD, <i>n</i> (%)	36 (23.8)	5 (10.2)	12 (23.5)	19 (37.2)**
Normoalbuminuric CKD (%)	13 (8.6)	2 (4.0)	4 (7.8)	7 (13.7)**
Antidiabetic Rx				
Diet alone, <i>n</i> (%)	14 (9.2)	5 (10.2)	5 (9.8)	4 (7.8)
OHA, <i>n</i> (%)	64 (42.3)	17 (34.6)	20 (39.2)	27 (52.9)
Insulin ± OHA, <i>n</i> (%)	73 (48.3)	27 (55.1)	26 (50.9)	20 (39.2)
Arterial hypertension, <i>n</i> (%)	117 (77.4)	32 (65.3)	41 (80.3)	44 (86.2)**
RX with ACE-I/ARBs, <i>n</i> (%)	100 (66.2)	27 (55.1)	35 (68.6)	38 (74.5)**
Dyslipidaemia, <i>n</i> (%)	126 (83.4)	40 (81.6)	43 (84.3)	43 (84.3)
Treatment with hypolipidaemic therapy, <i>n</i> (%)	99 (65.5)	28 (57.1)	38 (74.5)	33 (64.7)
Retinopathy, <i>n</i> (%)	73 (48.3)	27 (55.1)	23 (45.0)	23 (45.0)

Data are number (*n*) and percentage (%), mean ± standard deviation (SD), or median with range in parentheses. P-values are for trend among tertiles. ACE-I, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARBs, angiotensin II receptor blockers; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MA, micro-macroalbuminuria; OHA, oral hypoglycaemic agent; PUFT, para- and perirenal ultrasonographic fat thickness; RI, renal resistance index; SBP, systolic blood pressure.

^aMedian with range in parentheses.

**P* < 0.0001, adjusted for age and gender.

***P* < 0.05, adjusted for age and gender.

P < 0.0001, after adjustment for age and gender), and an increasing frequency of CKD was also observed [7 (20.0%) vs 8 (21.6%) vs 18 (51.4%), *P* < 0.05 after adjustment for age and gender] despite comparable WC values among tertiles. On the other hand, no significant differences (most likely due to the restricted number of subjects) were observed across the tertiles of PUFT in subjects with lower WC values (36M/8F) and in eGFR values (96.7 ± 23.4 vs 99.5 ± 27.1 vs 86.2 ± 34.16 mL min⁻¹ 1.73 m⁻², *P* = 0.428 across tertiles), although an increasing frequency of CKD [0 (0%) vs 0 (0%) vs 3 (20.0%), *P* < 0.05 after adjustment for age and gender] was observed.

Discussion

In humans and most animal models, the development of obesity also leads to significant lipid deposition within and around other tissues (ectopic fat storage) [24,25]. There is growing evidence that a marked increase in ectopic fat around the organs may eventually impair their functions [24].

In the present study on T2DM patients, we confirm the association of increased adiposity and impaired kidney function [1–5]. Indeed, in a sample of 151 T2DM subjects, we described a strongly negative correlation between eGFR and PUFT, WC, and BMI. However, after adjusting for several confounders, PUFT maintained a significant correlation with GFR values even when WC and BMI values were added to the statistical model, whereas correlations of WC and BMI with eGFR and RI were lost after corrections for PUFT. Therefore, perirenal fat expansion, irrespective of general adiposity and WC, seems an independent determinant of kidney dysfunction in T2DM. These findings can be explained in several ways.

First, visceral fat has been hypothesized to be a portal vein-circulating fat tissue such as that found in the greater omentum, lesser omentum and subperitoneum [26,27]. In contrast, PUFT is an index for fat in the non-portal system, which may produce different metabolic and haemodynamic effects [13]. Indeed, PUFT and WC in our study have different correlations with the parameters investigated. This is probably also due to the fact that the subjects were

Table 2. Standardized β -coefficients for associations between para- and perirenal ultrasonographic fat thickness and anthropometric parameters with eGFR (MDRD formula), eGFR (EPI-CKD formula), ACR, renal resistance index and serum urate levels

	eGFR (MDRD formula)	eGFR (EPI-CKD formula)	ACR	RI	Serum urate levels
Univariate analysis					
PUFT	-0.399*	-0.414*	0.124	0.344*	0.355*
WC	-0.201**	-0.205**	0.199**	0.173**	0.341*
BMI	-0.209**	-0.223**	0.172**	0.188**	0.221**
Multivariate analysis					
Model 1					
PUFT	-0.361*	-0.368*	0.115	0.303*	0.362*
WC	-0.174**	-0.180**	0.196**	0.147**	0.358*
BMI	-0.214**	-0.240*	0.178**	0.209**	0.264**
Model 2					
PUFT	-0.331*	-0.338*	0.115	0.271*	0.303**
WC	-0.130	-0.133	0.184**	0.119	0.299**
BMI	-0.158**	-0.184**	0.172	0.162**	0.175
Model 3					
PUFT ^a	-0.342**	-0.327**	-0.072	0.256**	0.299**
WC ^b	0.069	0.092	0.239**	-0.086	0.218
BMI ^c	0.036	-0.018	0.085	0.025	-0.172

Model 1 was controlled for age and gender; Model 2 was controlled for age, gender, HbA1c, LDL cholesterol and SBP; and Model 3 was controlled for age, gender, HbA1c, SBP, LDL cholesterol, ACR and for the other anthropometric parameters. ACR, albumin-to-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; PUFT, para- and perirenal ultrasonographic fat thickness; RI, renal resistance index; WC, waist circumference.

^aBMI and WC.

^bBMI and PUFT.

^cPUFT and WC.

*P < 0.0001.

**P < 0.05.

diabetic patients taking, among others, drugs for hypertension and dyslipidaemia. Additionally, although PUFT and WC have been shown to have a significant positive correlation, the *r*-square values in female and male were 0.161 and 0.391, respectively, suggesting a certain degree of non-

coincidence between PUFT and WC as surrogated markers of visceral fat deposition.

Furthermore, it is well known that the size of fat pads around key organs may increase substantially in obese patients. This, together with an increase in the intra-abdom-

Table 3. Clinical features of the study population stratified by the WC values recommended for the metabolic syndrome diagnosis and across the tertiles of para- and perirenal ultrasonographic fat thickness

Parameters	WC <88 cm in F WC <102 cm in M			WC >88 cm in F WC >102 cm in M		
	Tertile 1 <i>n</i> = 14	Tertile 2 <i>n</i> = 15	Tertile 3 <i>n</i> = 15	Tertile 1 <i>n</i> = 35	Tertile 2 <i>n</i> = 37	Tertile 3 <i>n</i> = 35
Sex (M/F)	10/4	13/2	13/2	12/23	18/19	18/17
Age (years)	62.7 ± 11.8	54.6 ± 12.2	58.0 ± 12.4	62.3 ± 12.9	59.9 ± 11.7	64.9 ± 10.4
BMI (kg/m ²)	23.7 ± 2.2	24.8 ± 2.3	28.2 ± 2.5*	28.2 ± 3.9	34.3 ± 7.6	33.7 ± 5.0*
WC (cm)	85.6 ± 7.0	90.8 ± 6.7	92.0 ± 7.7	111.0 ± 11.9	113.8 ± 11.3	118.3 ± 13.7
PUFT (mm)	15.1 ± 1.8	21.7 ± 2.1	32.5 ± 5.9*	24.4 ± 4.7	34.3 ± 1.8	43.8 ± 6.0*
HbA1c (%)	10.2 ± 3.1	10.1 ± 2.1	9.2 ± 2.7	8.9 ± 1.7	9.4 ± 1.8	9.6 ± 2.3
Uric acid (mg/dL)	4.4 ± 1.6	5.1 ± 1.5	5.5 ± 1.5	5.1 ± 1.6	5.4 ± 1.9	6.2 ± 2.2
ACR (mg/mmol) ^a	1.2 (0.25–97)	2.0 (0.40–54)	2.6 (0.59–536)	2.9 (0.37–128)	2.0 (0.35–1005)	3.2 (0.38–379)
eGFR (mL min ⁻¹ 1.73 m ⁻²)	96.7 ± 23.4	99.5 ± 27.1	86.2 ± 34.1	87.0 ± 27.9	83.5 ± 26.0	62.3 ± 30.6*
MDRD formula						
eGFR (mL min ⁻¹ 1.73 m ⁻²)	89.9 ± 12.8	94.0 ± 19.2	79.8 ± 27.7	83.0 ± 24.6	80.5 ± 22.8	59.7 ± 29.2*
EPI-CKD formula						
eGFR (mL min ⁻¹ · BSA)	94.6 ± 26.7	105.0 ± 32.5	96.5 ± 42.0	89.4 ± 30.8	97.2 ± 33.8	73.1 ± 35.8**
RI	0.67 ± 0.08	0.64 ± 0.08	0.69 ± 0.06	0.67 ± 0.08	0.71 ± 0.07	0.73 ± 0.07**
CKD, <i>n</i> (%)	0 (0)	0 (0)	3 (20.0)**	7 (20.0)	8 (21.6)	18 (51.4)**

Data are number (*n*) and percentage (%), mean ± standard deviation (SD), or median with range in parentheses. P-values are for trends across tertiles. ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PUFT, para- and perirenal ultrasonographic fat thickness; RI, renal resistance index; WC, waist circumference.

^aMedian with range in parentheses.

*P < 0.0001, adjusted for age and gender.

**P < 0.05, adjusted for age and gender.

inal pressure of visceral obesity, could modify organ function either by simple physical compression or because peri-organ fat cells may secrete various locally acting substances [28,29]. As fat deposition grows within the renal sinus, compression of various renal structures may indeed occur, especially of the inner medulla that, unlike the entire kidney, is not protected by the fibrous capsule. As a consequence, a large increase in renal interstitial fluid hydrostatic pressure tends to compress the medullary vasa recta and tubules, reducing blood and tubular flow through the distensible loop of Henle [30]. The resulting decrease in tubular transit velocity combined with that in medullary blood flow may likely promote fluid, sodium and urate reabsorption [30]. These findings may likely provide an explanation for the increasing frequency we found across PUFT tertiles of CKD and hypertension as well as for the gradual increase in serum urate levels. It should indeed be noted that, in contrast with WC and BMI, PUFT was not correlated with albuminuria which mainly accounts for other pathogenetic mechanisms leading to glomerular endothelial damage [31]. Moreover, much evidence suggests that advanced arteriosclerosis and arterial stiffness may increase renal RI values [32,33]. The significant increase in pulse pressure by PUFT tertiles seems in line with the above suggestions and provides further explanations about similar findings reported by our group in a different cohort of normoalbuminuric T2DM [22].

It is noteworthy that in the group of patients having WC above diagnostic values of MS, the frequency of CKD gradually and significantly increased ($P = 0.010$) across the tertiles of PUFT even though WC values across tertiles were comparable.

There have been several reports on the use of abdominal sonography for evaluation of visceral fat volume (VFA) [34–37]. In the study by Kawasaki S *et al.* [12], abdominal fat index (AFI), as described by Suzuki *et al.* [37], was measured, but the surface morphology of the liver varied and pre-peritoneal fat was difficult to determine, and as a result, AFI and VFA were not correlated in men or women [37]. We therefore excluded the AFI from our investigation, since in the above-cited study, PUFT was indeed the best predictor of visceral fat as measured by computed tomography [12].

Our data indicating PUFT as an independent anthropometric risk factor for CKD in T2DM suggest that the previously documented association between obesity and CKD may also in part be explained by excess para- and perirenal fat deposition [1,2,4,15]. To the best of our knowledge, this is the first evidence demonstrating that perirenal fat is a powerful predictor of CKD independently of several confounders, including BMI, WC and albuminuria. It is plausible that expansion of perirenal fat deposition may explain a significant proportion of type-2 diabetic patients who progress to chronic renal failure while remaining normoalbuminuric, accounting in our study for 36.1% of CKD subjects [38–40].

The limitations of this study warrant mention. The cross-sectional design in the present study helps to generate hypotheses, but does not allow us to define the cause–effect relationship between PUFT expansion and renal dysfunctional profile in T2DM patients, even though it seems un-

likely that GFR reduction as well as an increase in RI may promote perirenal fat deposition. Thus, the study design may limit the generalizability of the results but should not affect the internal validity. However, it should be underscored that the study sample consisted of deeply characterized patients who underwent the common management strategy adopted for the vast majority of type-2 diabetes patients.

Much evidence suggests that kidney dysfunction is an important risk factor for cardiovascular mortality in patients with type-2 diabetes [41,42]. Thus, prompt recognition of risk factors for CKD in diabetic patients is strongly recommended. Although longitudinal studies are needed to better clarify the role of PUFT in determining the impairment of renal function in T2DM patients, para- and perirenal ultrasonographic fat measurement should be implemented in clinical practice in order to improve our estimates in T2DM patients of the risk of kidney dysfunction linked to adiposity.

Conflict of interest statement. None declared.

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