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Para-perirenal distribution of body fat is associated with reduced glomerular filtration rate regardless of other indices of adiposity in hypertensive patients

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Obesity is a well-known risk factor for the development and progression of chronic kidney disease. Recently, para-perirenal ultrasonographic fat thickness (PUFT) has shown to correlate with both total and visceral fat better than body mass index (BMI), waist circumference (WC), and other indices of obesity. Moreover, a local paracrine and mechanical action of the PUFT on kidney has been described in recent studies. Aim of our study was to assess the relationship between glomerular filtration rate (GFR) and PUFT in comparison with other anthropometric and ultrasonographic indices of adiposity. Two hundred and ninety-six hypertensive patients were enrolled. PUFT, cutis-rectis thickness and rectis-aorta thickness were obtained by ultrasonography. Anthropometric measures of adiposity were also measured. Estimated GFR was calculated using the CKD-EPI equation. Higher PUFT values were observed in patients with impaired renal function ($P < 0.001$), whereas no differences in BMI and WC were shown between groups divided by GFR. PUFT significantly correlated with GFR in all patients ($r = -0.284$; $P < 0.001$), with no differences in groups divided by sex, diabetes, or BMI. This association held in multivariate analyses also after correction for confounding factors, including other adiposity indices ($P < 0.001$). When receiver operating characteristic curves were built to detect a eGFR < 60 mL/minutes per 1.73 m^2, a PUFT value ≤3.725 cm showed a negative predictive value of 94.0%, with the largest area under the curve (AUC: 0.700) among the variables considered. In conclusion, the relationship between PUFT and GFR seems to be more accurate and less influenced by the bias affecting traditional indices of adiposity.

1 | INTRODUCTION

Obesity has been traditionally considered as an independent risk factor for the development and progression of chronic kidney disease (CKD), and numerous mechanisms by which adipose tissue negatively could affect renal function have been clarified.[1-4] The most commonly used indices of obesity, such as body mass index (BMI) and waist circumference (WC), have shown an independent association with renal damage and a prognostic impact on the development of CKD in different subsets of patients.[5-9]

However, some limitations significantly prevent their extensive and uncritical use as adiposity indices. First, BMI does not differentiate the muscle tissue from the fat mass,[10-12] which is the only one associated with an increased risk of death[13] and worsening renal function.[14,15] Furthermore, BMI does not provide information about the regional distribution of body fat: visceral adiposity, rather than overall fat, is associated with CKD progression and cardiovascular events.[5,6,16-19] More reliable indexes of visceral fat, such as WC and waist circumference-to-height ratio (WC/H), are also not without limitations in predicting renal dysfunction, and

they do not seem to improve the prognostic classification of obesity-related overall risk compared to BMI.[6,20-23]

Recently, new anthropometric and imaging indices have been proposed for a more reliable evaluation of visceral adiposity to better predict the cardiometabolic and renal risk than other traditional measures of obesity. Para-perirenal ultrasonographic fat thickness (PUFT) provides a direct measurement of abdominal fat content,[24] and in many studies, it has been shown to correlate with visceral fat (assessed by computed tomography[24,25]) and with total adiposity[24] better than anthropometric parameters of obesity. Like BMI or WC, PUFT has shown a close relationship with microalbuminuria and reduced glomerular filtration rate in animal models.[26,27] A few studies on diabetic or obese patients would seem to confirm this finding even in humans.[28-31] No data are available about nondiabetic patients or in hypertensive patients.

PUFT might relate to renal function not only due to its relationship with visceral adiposity: some data exist about a potential paracrine action of the PUFT on kidney,[32] and a mechanical interference on the intrarenal vascular and interstitial compartment has been described together with perirenal fat expansion.[29,33]

The aim of our study was to assess, in hypertensive patients regardless of their metabolic status, the relationship between glomerular filtration rate and PUFT in comparison with traditional anthropometric indices of adiposity or other direct measurement of abdominal fat content,[34] for which no local mechanical or paracrine action on the kidney has yet been demonstrated.

2 | MATERIALS AND METHODS

2.1 | Patients

This cross-sectional study includes a total of 296 hypertensive outpatients selected from Caucasian essential hypertensive patients consecutively attending our unit of Nephrology and Hypertension for specialist advice. In agreement with more recent European Society of Hypertension (ESH) guidelines, hypertension was defined as a blood pressure ≥140/90 mmHg or treatment with antihypertensive drugs.[35]

The exclusion criteria were as follows:

- Age <30 years and >85 years.
- Severe obesity, defined as a body mass index (BMI) ≥ 40 kg/m^2.
- Renovascular, malignant, endocrine hypertension, or hypertension associated with obstructive sleep apnea syndrome, as described in detail in previous studies.[36,37]
- Rapid deterioration of renal function, defined as a reduction in estimated glomerular filtration rate (eGFR) >25% or an increased serum creatinine >1.5 times baseline.[38]
- Renal replacement therapy (transplanted or dialyzed patients).
- Abnormal renal morphology (difference in renal length >1.5 cm between the two kidneys, the presence of solitary or supernumerary kidneys, congenital renal abnormalities, polycystic kidney disease, hydronephrosis ≥ grade 2)
- Low-quality renal sonographic recordings.
- Major noncardiovascular diseases (liver cirrhosis, chronic obstructive lung disease, and anamnestic presence of neoplasms).

Written informed consent was obtained from each subject. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local review board.

2.2 | Clinical and laboratory evaluation

In all patients, careful clinical history and physical examination were performed. Patients who reported smoking cigarettes regularly during the past year were considered current smokers. Clinic blood pressure was recorded by a doctor, following the recommendations of the 2013 European Society of Hypertension/European Society of Cardiology guidelines.[35] Routine biochemical parameter determination was performed with standard techniques using an autoanalyzer (Boehringer Mannheim for Hitachi system 911, Mannheim, Germany). Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation.[39]

2.3 | Anthropometric evaluation

Body weight and height were measured by a nurse, and BMI was calculated as body weight divided by squared height (kg/m^2). WC was measured in orthostatic position at the umbilicus level at the end of expiration, and the WC/H ratio was obtained as a further measure of body fat distribution. Body surface area (BSA) was calculated with the DuBois formula ($0.20247 \times \text{height [m]}^{0.725} \times \text{weight [kg]}^{0.425}$).

2.4 | Ultrasonographic evaluation

Ultrasound examinations were performed by a single well-trained operator, unaware of the patient's clinical data, through a GE Logiq P5-PRO instrument (General Electric Company, Milan, Italy). All measurements were obtained in the supine position, with the probe perpendicular to the skin of patients.

PUFT was measured by a 3.5- to 5-MHz transducer on the lateral aspects of the abdomen, through optimal longitudinal scans with the surface of the kidney almost parallel to the skin. The thickness from the inner side of the abdominal musculature to the surface of the kidney was calculated three times for each side, and the average of six measurements was defined as the PUFT.[29] Our laboratory intraobserver coefficient of variation for PUFT was 4.5%.

The cutis-rectis thickness (CR) and the rectis-aorta thickness (RA) were also obtained, as measures of respectively subcutaneous or visceral abdominal fat, with transverse scans obtained 5 cm above the umbilicus along the xipho-umbilical line. CR was measured as the distance between the cutis and the conjunction of rectus muscles at

TABLE 1 Characteristics of the overall study population and of the population divided into tertiles based on para-perirenal ultrasonographic fat thickness (PUFT)

	Overall population (n = 296)	PUFT I (<3.16 cm)	PUFT II (3.16–3.98 cm)	PUFT III (>3.98 cm)	*P*-value
Age (y)	61 ± 12	58 ± 13^{NS}	61 ± 10^{NS}	65 ± 11***	<0.001
Male sex, n (%)	201 (67.9)	50 (51.0)	69 (69.7)	82 (82.8)	<0.001
Smoke, n (%)	95 (32.1)	28 (28.6)	32 (32.3)	35 (35.4)	*NS*
Diabetes, n (%)	105 (35.5)	25 (25.5)	36 (36.4)	44 (44.4)	0.020
BMI ≥30 Kg/m^2, n (%)	72 (24.3)	5 (5.1)	20 (20.2)	47 (47.5)	<0.001
eGFR <60 mL/min per 1.73 m^2, n (%)	39 (13.2)	4 (4.1)	11 (11.1)	24 (24.2)	<0.001
Hypolipidemic therapy, n (%)	136 (45.9)	34 (34.7)	48 (48.5)	54 (54.5)	0.016
Antihypertensive therapy, n (%)	250 (84.5)	84 (85.7)	80 (80.8)	86 (86.9)	*NS*
Clinic systolic BP (mmHg)	131 ± 17	130 ± 16	129 ± 17	134 ± 18	*NS*
Clinic diastolic BP (mmHg)	77 ± 10	79 ± 10	76 ± 9	78 ± 10	*NS*
Clinic mean BP (mmHg)	95 ± 11	96 ± 11	94 ± 11	96 ± 11	*NS*
Clinic pulse pressure (mmHg)	53 ± 14	51 ± 12^{NS}	53 ± 13^{NS}	56 ± 15*	0.018
Clinic heart rate (beats)	72 ± 14	72 ± 14$^{\#}$	67 ± 13$^{\Delta\Delta\Delta}$	77 ± 14^{NS}	<0.001
Biochemical parameters					
Serum glucose (mg/dL)	116.8 ± 37.1	107.3 ± 24.7^{NS}	112.8 ± 25.4$^{\Delta\Delta}$	129.8 ± 50.9***	<0.001
Serum uric acid (mg/dL)	6.03 ± 1.45	5.82 ± 1.47	6.05 ± 1.26	6.20 ± 1.60	*NS*
Serum total cholesterol (mg/dL)	178 ± 43	183 ± 43	179 ± 46	172 ± 41	*NS*
LDL-C (mg/dL)	108 ± 39	117 ± 39^{NS}	108 ± 41^{NS}	98 ± 36**	0.004
HDL-C (mg/dL)	49 ± 14	55 ± 14$^{\#\#}$	48 ± 13^{NS}	44 ± 12***	<0.001
Serum tryglicerides (mg/dL)	117 (86–150)	107 (78–140)$^{\#}$	115 (88–164)^{NS}	123 (96–155)**	0.001
Serum creatinine (mg/dL)	0.99 ± 0.38	0.85 ± 0.22^{NS}	0.98 ± 0.28$^{\Delta\Delta}$	1.13 ± 0.53***	<0.001
eGFR (mL/min per 1.73 m^2)	87.1 ± 26.5	96.2 ± 25.5$^{\#}$	85.7 ± 22.6^{NS}	79.5 ± 28.6***	<0.001
Serum sodium (mEq/L)	140 ± 3	140 ± 3	140 ± 3	140 ± 3	*NS*
Serum potassium (mEq/L)	4.45 ± 0.41	4.36 ± 0.35^{NS}	4.39 ± 0.41	4.61 ± 0.43***	<0.001
Anthropometric measurements					
Body height (cm)	168 ± 8	166 ± 9^{NS}	168 ± 8^{NS}	169 ± 7*	0.016
Body weight (Kg)	79.2 ± 14.3	70.7 ± 9.4$^{\#\#\#}$	79.9 ± 12.5$^{\Delta\Delta\Delta}$	87.1 ± 15.4***	<0.001
Waist circumference (cm)	95 ± 11	89 ± 9$^{\#\#}$	94 ± 9$^{\Delta\Delta\Delta}$	101 ± 12***	<0.001
WC/H	0.57 ± 0.07	0.54 ± 0.07^{NS}	0.56 ± 0.07$^{\Delta\Delta}$	0.60 ± 0.07***	<0.001
BMI (Kg/m^2)	28.1 ± 4.0	25.7 ± 2.82$^{\#\#\#}$	28.2 ± 3.55$^{\Delta\Delta\Delta}$	30.3 ± 4.06***	<0.001
BSA (m^2)	1.89 ± 0.18	1.82 ± 0.16$^{\#}$	1.90 ± 0.17$^{\Delta\Delta}$	1.95 ± 0.18***	<0.001
Ultrasonographic parameters					
PUFT (cm)	3.57 ± 0.92	2.57 ± 0.46$^{\#\#\#}$	3.55 ± 0.23$^{\Delta\Delta\Delta}$	4.57 ± 0.53***	<0.001
CR (cm)	1.84 ± 0.87	1.80 ± 0.50	1.81 ± 0.41	1.91 ± 0.49	*NS*
RA (cm)	5.67 ± 1.92	4.96 ± 1.88^{NS}	5.43 ± 1.69$^{\Delta\Delta\Delta}$	6.63 ± 1.81***	<0.001
RA/CR	3.14 ± 1.03	2.76 ± 0.79^{NS}	3.06 ± 1.00$^{\Delta\Delta\Delta}$	3.59 ± 1.11***	<0.001

BMI: body mass index; BP: blood pressure; BSA: body surface area; CR: cutis-rectis thickness; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PUFT: para-perirenal ultrasonographic fat thickness; RA: rectis-aorta thickness; WC/H: waist circumference/body height.

PUFT I vs PUFT II:

PUFT I vs PUFT III: $^{NS}P > 0.05$.

PUFT II vs PUFT III: $^{NS}P > 0.05$.

^{NS}p>0.05.

$^{\#}P \le 0.05$.

$^{\#\#}P \le 0.01$.

$^{\#\#\#}P \le 0.001$.

$^{*}P \le 0.05$.

$^{**}P \le 0.01$.

$^{***}P \le 0.001$.

$^{\Delta}P \le 0.05$.

$^{\Delta\Delta}P \le 0.01$.

$^{\Delta\Delta\Delta}P \le 0.001$.

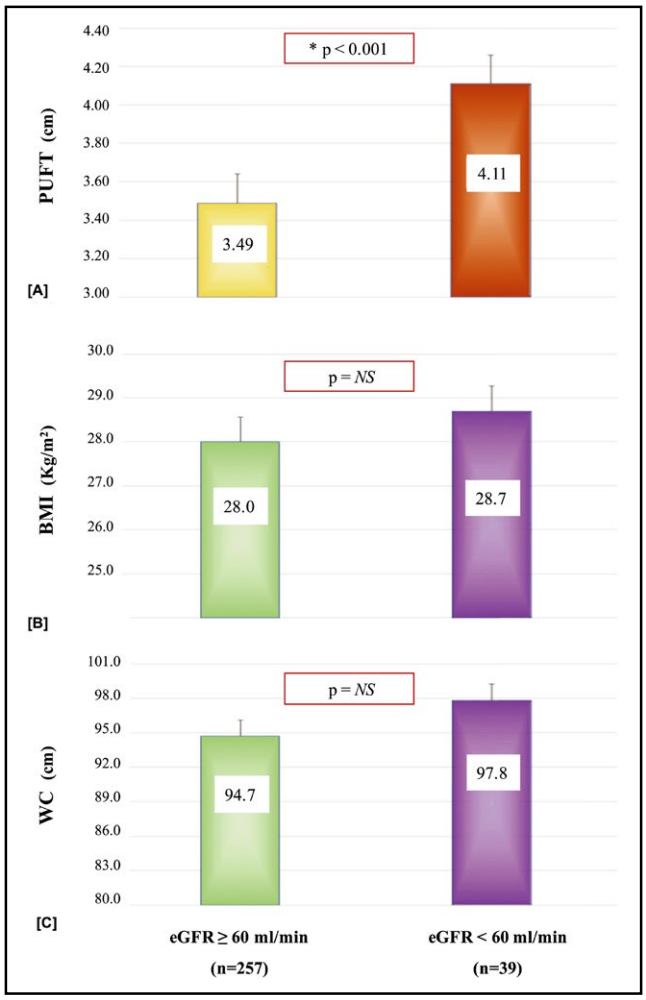

FIGURE 1 PUFT and anthropometric indices of adiposity in the population divided by eGFR. Values of para-perirenal ultrasonographic fat thickness (PUFT) [A], body mass index (BMI) [B], and waist circumference (WC) [C] in the two groups divided by estimated glomerular filtration rate (eGFR) (≥ or <60 mL/min per 1.73 m^2)

the linea alba through a 10-MHz linear probe, whereas a 3.5-MHz convex probe was used to assess RA as the distance between the linea alba and the anterior wall of the abdominal aorta. The RA-to-CR ratio (RA/CR) was also calculated and considered an indirect measure of body fat distribution.[34] The intraoperator coefficients of variation for CR and RA were 2.0% and 4.4%, respectively. For all measurements, special care was taken not to compress the kidney and not to have the patient perform a Valsalva maneuver, due to possible errors in the evaluation.

2.5 | Statistical analysis

Statistical analysis was initially performed in the whole study population, and it was subsequently carried out in the population divided either into tertiles based on PUFT (PUFT I: <3.16 cm; PUFT II: 3.16-3.98 cm; PUFT III: >3.98 cm) or in two groups divided by eGFR (≥60 mL/minutes per 1.73 m^2, n = 257; <60 mL/minutes per 1.73 m^2, n = 39).

Continuous variables were given as mean ± SD. Triglycerides (expressed as median and interquartile range because of its skewed distribution) were log-transformed to better satisfy distributional assumptions before parametric tests were used. Categorical variables were expressed as percentage values.

Differences between groups were evaluated using analysis of variance (ANOVA) with Holm-Sidak test for multiple comparisons, Student's *t* test for unpaired data, and chi-square test, as appropriate. Adjustment for potential confounders was performed by analysis of covariance (ANCOVA).

The univariate and multivariate relationships were tested by simple and multiple linear regression analyses. The strength of the associations between the variables was expressed respectively by the Pearson correlation coefficients (*r*) and the standardized (β) multiple regression coefficients. Fisher's *r*-to-*z* transformation was used to compare different correlation coefficients.

The stepwise multiple regression models were carried out considering PUFT as outcome variable, and including into the models as potential explanatory parameters: age, sex (0 = females; 1 = males), smoking habit (0 = nonsmokers; 1 = smokers), BMI (or WC or WC/H or BSA), eGFR, serum glucose levels (or diabetes as dichotomous variable), LDL-c, HDL-c, triglycerides (log-transformed), RA, serum uric acid, clinic systolic BP, clinic diastolic BP, clinic heart rate, and hypolipidemic therapy (0 = no treatment, 1 = treatment). Further stepwise multivariate models were built on the overall study population considering eGFR as outcome variable, and including, as confounders, PUFT, BMI (or WC or WC/H or BSA), and those variables regarded as regressors in the previous multivariate models.

In all multiple regression analyses, a backward stepwise procedure was used, with α = 0.15 as the cutoff for entry or removal of variables. Collinearity was assessed by calculating the variance inflation factor (VIF): Variables with VIF ≥ 2 were excluded from the models. The null hypothesis was rejected at a two-tailed $P \leq 0.05$.

To assess the global accuracy of PUFT as well as of other measures of adiposity in the detection of eGFR < 60 mL/minutes per 1.73 m^2, receiver operating characteristic (ROC) curves were built. The area under the ROC curves (AUC) were compared statistically by means of a two-tailed univariate z test of the difference between the areas under two performance curves.

The statistical analyses were performed using the IBM SPSS Statistics software package, version 22 for Macintosh (SPSS, Chicago, IL).

3 | RESULTS

Table 1 summarizes the characteristics of the overall study population and of the population divided into tertiles based on PUFT. All anthropometric and ultrasonographic indices of adiposity, as well as eGFR, were not different in smokers compared to nonsmokers, whereas significant differences were found in the population divided by diabetes (absence or presence) or BMI (<or ≥30 kg/m^2; Supplementary Table S1).

TABLE 2 Main correlations of anthropometric and ultrasonographic parameters in the entire study population

	PUFT	CR	RA	RA/CR	BMI	WC	WC/H	BSA
	r	*r*	*r*	*r*	*r*	*r*	*r*	*r*
PUFT (cm)	1	0.267***	0.471***	0.311***	0.484***	0.461***	0.353***	0.420***
CR (cm)	0.267***	1	0.443***	−0.213***	0.193**	0.196**	0.161**	0.155**
RA (cm)	0.471***	0.443***	1	0.758***	0.433***	0.359***	0.317***	0.287***
RA/CR	0.311***	−0.213***	0.758***	1	0.350***	0.253***	0.221***	0.235^{NS}
BMI (Kg/m^2)	0.484***	0.193**	0.433***	0.350***	1	0.846***	0.788***	0.603***
WC (cm)	0.461***	0.196**	0.359***	0.253***	0.846***	1	0.913***	0.527***
WC/H	0.353***	0.161**	0.317***	0.221***	0.788***	0.913***	1	0.221***
BSA (m^2)	0.420***	0.155**	0.287***	0.235***	0.603***	0.527***	0.221***	1
Age (y)	0.231***	−0.029^{NS}	0.117*	0.149*	0.052^{NS}	0.078^{NS}	0.155**	−0.132*
Height (cm)	0.183**	0.058^{NS}	0.045^{NS}	0.034^{NS}	−0.001^{NS}	0.035^{NS}	−0.370***	0.656***
Weight (Kg)	0.487***	0.175**	0.369***	0.310***	0.824***	0.707***	0.429***	0.868***
Serum glucose (mg/dL)	0.287***	0.145*	0.306***	0.193**	0.283***	0.224***	0.222***	0.129*
Serum uric acid (mg/dL)	0.299***	0.054^{NS}	0.152**	0.137*	0.297***	0.294***	0.298***	0.147*
Serum total cholesterol (mg/dL)	−0.138*	−0.016^{NS}	−0.083^{NS}	−0.094^{NS}	−0.041^{NS}	0.022^{NS}	0.013^{NS}	−0.030^{NS}
LDL-C (mg/dL)	−0.216***	0.033^{NS}	−0.094^{NS}	−0.121*	−0.100^{NS}	−0.025^{NS}	−0.011^{NS}	−0.048^{NS}
HDL-C (mg/dL)	−0.324***	−0.074^{NS}	−0.143*	−0.105^{NS}	−0.243***	−0.181**	−0.087^{NS}	−0.291***
Serum tryglicerides (mg/dL)	0.200**	0.053^{NS}	0.059^{NS}	0.035^{NS}	0.273***	0.203***	0.160**	0.245***
Serum creatinine (mg/dL)	0.324***	0.033^{NS}	0.137*	0.127*	0.112^{NS}	0.144*	0.085^{NS}	0.110^{NS}
eGFR (mL/min per 1.73 m^2)	−0.284***	0.013^{NS}	−0.086^{NS}	−0.091^{NS}	−0.109^{NS}	−0.127*	−0.122*	0.010^{NS}
Serum sodium (mEq/L)	−0.049^{NS}	−0.005^{NS}	−0.067^{NS}	−0.068^{NS}	−0.087^{NS}	0.044^{NS}	0.006^{NS}	0.031^{NS}
Serum potassium (mEq/L)	0.216***	0.088^{NS}	0.225***	0.180**	0.209***	0.128*	0.088^{NS}	0.181**
Systolic BP (mmHg)	0.001^{NS}	−0.062^{NS}	0.021^{NS}	0.077^{NS}	0.008^{NS}	−0.019^{NS}	−0.015^{NS}	−0.013^{NS}
Diastolic BP (mmHg)	−0.119*	0.001^{NS}	−0.102^{NS}	−0.111^{NS}	−0.010^{NS}	0.084^{NS}	0.064^{NS}	0.037^{NS}
Mean BP (mmHg)	−0.070^{NS}	−0.032^{NS}	−0.050^{NS}	−0.026^{NS}	−0.002^{NS}	0.040^{NS}	0.031^{NS}	0.016^{NS}
Pulse pressure (mmHg)	0.087^{NS}	−0.078^{NS}	0.099^{NS}	0.177**	0.018^{NS}	−0.084^{NS}	−0.064^{NS}	−0.043^{NS}
Heart rate (beats)	0.122*	0.043^{NS}	0.089^{NS}	0.037^{NS}	0.091^{NS}	0.174**	0.173**	0.002^{NS}

BMI, body mass index; BP, blood pressure.; BSA, body surface area; CR, cutis-rectis thickness; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PUFT, Para-perirenal ultrasonographic fat thickness (PUFT); RA, rectis-aorta thickness; WC, waist circumference; WC/H, waist circumference/body height.

^{NS}p>0.05.

*$P \leq 0.05$.

**$P \leq 0.01$.

***$P \leq 0.001$.

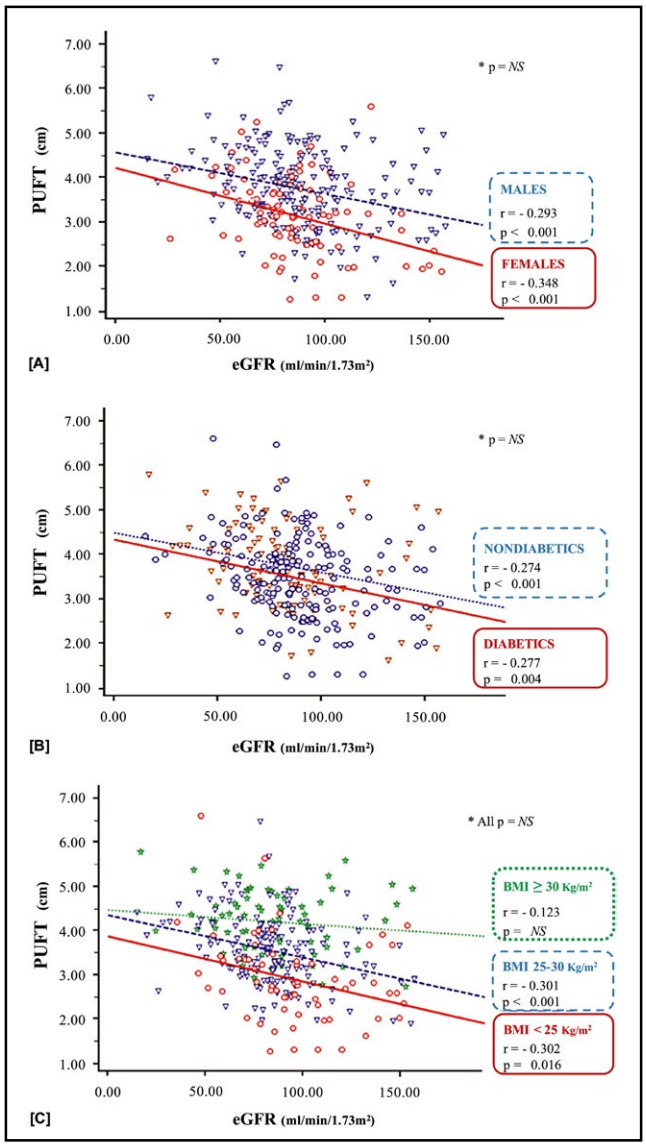

FIGURE 2 Correlations between PUFT and eGFR in different subsets of population. Correlations between para-perirenal ultrasonographic fat thickness (PUFT) and estimated glomerular filtration rate (eGFR) in the population divided by sex [A], diabetes [B], or body mass index (BMI) [C]

Patients belonging to the uppermost tertile of PUFT had lower eGFR compared to those in the lowest ones ($P < 0.001$), and this difference among tertiles also remained statistically significant after adjustment for age ($P < 0.001$). Similarly, higher PUFT values were observed in patients with eGFR < 60 mL/minutes per 1.73 m^2 rather than in patients with normal renal function (Figure 1A). It is interesting to note that no statistically significant differences in BMI and WC were observed between the groups divided by eGFR (Figure 1B,C), also after age-adjustment performed by ANCOVA.

The univariate correlations of adiposity measures with other variables in the entire study population are shown in Table 2. PUFT significantly correlated with eGFR in all patients, whereas other ultrasonographic indices of abdominal fat did not correlate with eGFR. Similarly, BMI was not significantly associate with eGFR, and WC and WC/H were the only anthropometric parameters related with eGFR, even if less than PUFT ($P = 0.048$ and $P = 0.041$, respectively).

TABLE 3 Independent multivariate correlates of PUFT [A] and eGFR [B] in the overall study population. The other variables included in the models are described in the text (*statistical section*)

	Regression coefficients	
	Standardized	
Outcome variable	***β***	***P***
PUFT[a]		
[A] Model ($R^2 = 0.466$)		
BMI (Kg/m^2)	0.289	<0.001
RA (cm)	0.279	<0.001
Sex	0.241	<0.001
eGFR (mL/min per 1.73 m^2)	−0.179	<0.001
Age (y)	0.141	0.002
HDL-c (mg/dL)	−0.115	0.014
eGFR[a]		
[B] Model ($R^2 = 0.140$)		
Age (y)	−0.249	<0.001
PUFT (cm)	−0.227	<0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PUFT, Para-perirenal ultrasonographic fat thickness (PUFT); RA, rectis-aorta thickness; WC, waist circumference.
[a]In these models were tested alternatively BMI, WC, WC/H, or BSA along with all the other covariates, with similar results (see text).

When we separately analyzed the relationship between PUFT and eGFR in women and men, no significant difference was observed (Figure 2A). Similarly, no differences were found when we separately compared this relationship in the groups divided by diabetes (Figure 2B) or BMI (Figure 2C). In the overall study population, the association between PUFT and eGFR held also after correction for various confounding factors in multiple linear regression analyses, including both RA and BMI (Table 3A). Similar results were obtained by replacing BMI alternatively with WC (*eGFR* $\beta = -0.173$; $P < 0.001$), WC/H (*eGFR* $\beta = -0.183$; $P < 0.001$), or BSA (*eGFR* $\beta = -0.181$; $P < 0.001$).

When we built further multivariate model considering eGFR as outcome variable and including PUFT, RA, and BMI (or alternatively WC or WC/H or BSA) along with other confounding factors, only age and PUFT were independently associated with eGFR (Table 3B), and similar results were obtained when serum creatinine was forced into this model among the covariates (*PUFT* $\beta = -0.227$; $P < 0.001$). Consistent with this finding, when we excluded PUFT by the confounding factors, the resulting overall determination coefficient (R^2) was lower (0.091) than the abovementioned model (0.140), even if the difference did not reach statistical significance.

The ROC curves built to assess the global accuracy of PUFT and other adiposity measures in the detection of eGFR < 60 mL/minutes per 1.73 m^2 are shown in Figure 3. The PUFT best cutoff able to better distinguish patients with low eGFR from those with normal renal function was 3.725 cm (Figure 3), and the sensitivity and specificity

were 71.8% and 63.0%, respectively (AUC: 0.700). Thus, patients with a PUFT value ≤3.725 cm showed a probability of 94% to have a normal renal function (negative predictive value = 94.0%). When we compared the different ROC curves of all considered variables, PUFT had AUC significantly higher than anthropometric indices, whereas the difference did not reach significance when PUFT was compared with RA (Figure 3).

4 | DISCUSSION

The most important finding of our study is that para-perirenal fat expansion is negatively associated with renal function in hypertensive patients. Thus, we have demonstrated that higher PUFT values correlate with lower eGFR, and this association holds significance at multivariate analysis after adjustment for many confounding factors including both RA and BMI (or alternatively other anthropometric measures of adiposity).

Several studies have shown that the traditional measures of obesity, such as BMI and WC, have significant limitations as adiposity indices because of their low accuracy both in differentiating the muscle tissue from the fat mass[10-12] and in detecting the regional distribution of body fat, which is the anthropometric feature most associated with CKD progression and cardiovascular events.[5,6,16-19] This could explain some inconsistencies in literature data. Although BMI and WC have shown an independent association with renal damage in different studies,[5-9] the Framingham Offspring Study demonstrated that obesity was not associated per se with an independent risk to develop stage 3 CKD, after adjustment for known risk factors of cardiovascular disease.[40] Similarly, in 1856 hypertensive patients of the cross-sectional REDHY study, Cerasola et al observed an unexpected inverse association between WC and stages 3-5 CKD, probably due to the characteristics of enrolled patients or the poor nutritional status of CKD patients with low eGFR.[23]

In recent studies, PUFT has demonstrated a close association with several cardiovascular and metabolic risk factors such as fasting plasma glucose, uric acid, HDL-C, or tryglicerides,[29,30] and our data seem to confirm these results (see Table 2). Moreover, PUFT has been shown to correlate with visceral fat and with total adiposity[24,25] better than anthropometric parameters of obesity, so the relationship between PUFT and eGFR could be more accurate and less affected by the abovementioned bias.

No study currently exists that analyzes this relationship in hypertensive patients, and the few previous data of literature involving only diabetic or obese patients provide conflicting results. In 151 type-2 diabetic patients, Lamacchia et al described a strongly negative correlation between eGFR and PUFT, independently by BMI or WC,[29] whereas no relationship between the variables was found by Sun et al[31] in nonhypertensive nondiabetic obese patients, probably due to the exiguity of simple size or the young age of enrolled patients. In both reported studies, however, PUFT was compared and adjusted only for traditional anthropometric indexes of adiposity (BMI or WC), and no study compared PUFT with direct measurements of adiposity assessed by ultrasonography such as RA or CR (and RA/CR). In our study, the close association between PUFT and eGFR was documented not only by correlation analyses, as in previous studies, but also through C statistics. Indeed, PUFT had AUC significantly higher than anthropometric indices, even if the accuracy of the ROC curve of PUFT was moderate.

The evidence of a strong relationship between PUFT and eGFR independently of all other adiposity indices in our study population could have different possible explanations.

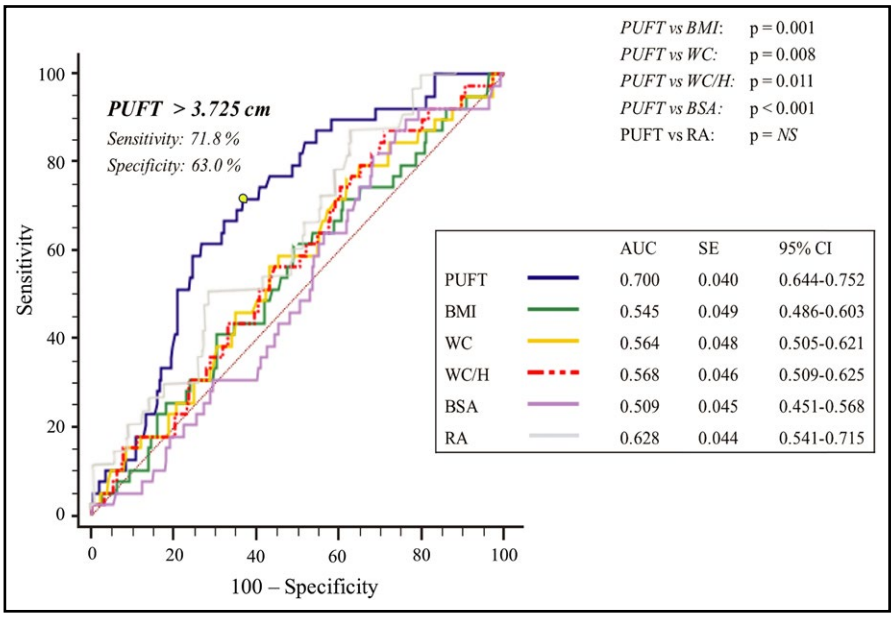

FIGURE 3 ROC curves for detection of impaired renal function. Receiver operating characteristic (ROC) curves of para-perirenal ultrasonographic fat thickness (PUFT) and other adiposity measures for detection of estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2. AUC, area under curve; CI, confidence interval; SE, standard error

PUFT provides a direct measurement of abdominal fat content, and it has been shown to correlate with visceral fat better than anthropometric parameters of obesity.[24,25] In 1956, Vague[41] already identified abdominal fat as predictor of obesity-related comorbidity, and several authors subsequently confirmed that visceral distribution of body fat, more than obesity per se, was related to kidney damage and cardiometabolic outcomes.[40,42,43] In line with this, PUFT previously demonstrated to correlate with metabolic risk factors,[30] fatty liver infiltration,[44] and hypertension,[45] and similarly, it might also reflect glomerular filtration better than other indices of adiposity due to the better accuracy in the identification of visceral fat and its pathological implications.

The ectopic fat around the kidneys could influence their function also through local mechanisms.[29,31] First, PUFT secretes paracrine substances with functional or metabolic renal action that could play a key role in the development of nephropathy. In a previous study, Li et al[32] found that perirenal adipose tissue exacerbated renal vascular remodeling in rats through the production of leptin, a well-known adipocytokine with an adverse effect on kidney, and different paracrine substances were observed by other authors to have a similar action.[27,32] In addition, excessive free fatty acids released from PUFT could escape into the kidney and lead to renal lipotoxicity by increasing intracellular fatty acids metabolites.[31,46,47] PUFT might also reflect renal function better than other indices of visceral fat due to the different venous drainage of perirenal adipose tissue: In fact, it drains into the caval system, whereas the venous circulation of the visceral fat around omentum (detected by RA) is part of the portal axis, and this might produce different systemic effects.[48] Furthermore, PUFT could exert a direct mechanical compression on the kidney, particularly on renal vessels and parenchyma, causing kidney damage through increased interstitial hydrostatic pressure and reduced renal blood flow.[29,31]

It is also conceivable that para-perirenal distribution of body fat is secondary to a reduction in the kidney sizes related to eGFR.[49] In this way, the adipose tissue could fill the free space left by kidneys, and therefore, PUFT could be the epiphenomenon of an impaired renal function. However, it is not possible to establish a causal relationship between PUFT and eGFR due to the cross-sectional design of our research, and further studies are needed to verify these hypotheses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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