REFERENCES

1. Gorostidi M, Sanchez-Martinez M, Ruilope LM, Graciani A, de la Cruz JJ, Santamaria R, et al. Chronic kidney disease in Spain: prevalence and impact of accumulation of cardiovascular risk factors. Nefrologia (Engl Ed). 2018;38:606–15, http://dx.doi.org/10.1016/j.nefro.2018.04.004.
2. Kuma A, Kato A. Lifestyle-related risk factors for the incidence and progression of chronic kidney disease in the healthy young and middle-aged population. Nutrients. 2022:14, http://dx.doi.org/10.3390/nu14183787.
3. Prieto-Velasco M, Del Pino YPMD, Buades Fuster JM, Craver Hospital L, Pons Prades R, Ruiz San Millan JC, et al. Advanced Chronic Kidney Disease Units in Spain: a national survey on standards of structure, resources, results and patient safety. Nefrologia (Engl Ed). 2020;40:608–22, http://dx.doi.org/10.1016/j.nefro.2020.06.006.
4. Airg E, Ekpf, Alcer, Friat, Redinren, Ricors, Senefro, Set, ONT. CKD: the burden of disease invisible to research funders. Nefrologia (Engl Ed). 2022;42:65–84. doi:10.1016/j.nefroe.2021.09.005.
5. Nefrología SEd. La Enfermedad Renal Crónica en España; 2022.
6. Documento Marco sobre Enfermedad Renal Crónica (ERC) dentro de la Estrategia de Abordaje a la Cronicidad en el SNS; 2015. Available from: https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Enfermedad_Renal_Cronica_2015.pdf.
7. Aiyegbusi OL, Kyte D, Cockwell P, Anderson N, Calvert M. A patient-centred approach to measuring quality in kidney care: patient-reported outcome measures and patient-reported experience measures. Curr Opin Nephrol Hypertens. 2017;26:442–9, http://dx.doi.org/10.1097/mnh.0000000000000357.
8. Nimmo A, Bell S, Brunton C, Campbell J, Doyle A, MacKinnon B, et al. Collection and determinants of patient reported outcome measures in haemodialysis patients in Scotland. QJM. 2017;111:15–21, http://dx.doi.org/10.1093/qjmed/hcx180.
9. Tang E, Bansal A, Novak M, Mucsi I. Patient-reported outcomes in patients with chronic kidney disease and kidney transplant – Part 1. Front Med (Lausanne). 2017;4:254, http://dx.doi.org/10.3389/fmed.2017.00254.
10. Escalada J, Carretero Gómez J, Anguita M, de Sequera P, García-Río F, Dávila I, et al. Enhancing the management of chronic diseases in clinical practices: the CARABELA methodology. J Healthc Qual Res. 2024, http://dx.doi.org/10.1016/j.jhqr.2024.06.001 [in press].

Borja Quiroga[a,1], Juan José Gorgojo[b,1], Jesús Ignacio Diago[c], Pedro Ruiz[d,*], CARABELA-CKD Scientific Committee[2]

[a] *Departamento de Nefrología, Hospital Universitario de La Princesa, RICORS 2040, Madrid, Spain*
[b] *Hospital Universitario Fundación Alcorcón, Madrid, Spain*
[c] *Departamento Médico, AstraZeneca Farmacéutica Spain, Madrid, Spain*
[d] *Sociedad Española de Calidad Asistencial, Oviedo, Spain*

[*] *Corresponding author.*
E-mail address: pedromruizl@gmail.com (P. Ruiz).
[1] Both authors contributed equally to this manuscript.
[2] List and affiliation of the CARABELA-CKD Scientific Committee members are shown in Appendix A.

https://doi.org/10.1016/j.nefro.2024.07.003

Is it useful to measure peri-parenal fat thickness by ultrasonography as a marker of cardiovascular risk in obese patients with chronic kidney disease?

¿Es útil medir el grosor de la grasa peri-pararrenal mediante ultrasonografía como marcador de riesgo cardiovascular en pacientes obesos con enfermedad renal crónica?

Dear Editor,

Obesity has become a global pandemic[1] and is considered an independent cardiovascular risk factor (CVRF) for the development and progression of chronic kidney disease (CKD).[2] Furthermore, visceral adipose tissue itself is also a CVRF. Recent studies have found that the accumulation of ectopic renal fat (ERF) in non-adipose tissue, called "fatty kidney", is related to obesity-associated kidney disease, and has a better correlation with total and visceral fat than measurements such as waist circumference or body mass index.[2,3]

The anatomical distribution of ERF is divided into: a) renal sinus fat (RSF), adipose tissue located on the medial surface of the kidney, which shares space with vascular, nervous and lymphatic structures, major and minor calyces, renal pelvis and proximal ureter; b) perirenal fat (PeRF), which is located between the renal capsule and Gerota's fascia (GF); c) pararenal fat (PaRF), which surrounds the kidney outside the GF; and d) renal parenchymal fat (RPF), which is the adipose tissue within the renal cortex and medulla. The impact of lipid tox-

DOI of original article:
https://doi.org/10.1016/j.nefro.2024.08.001.

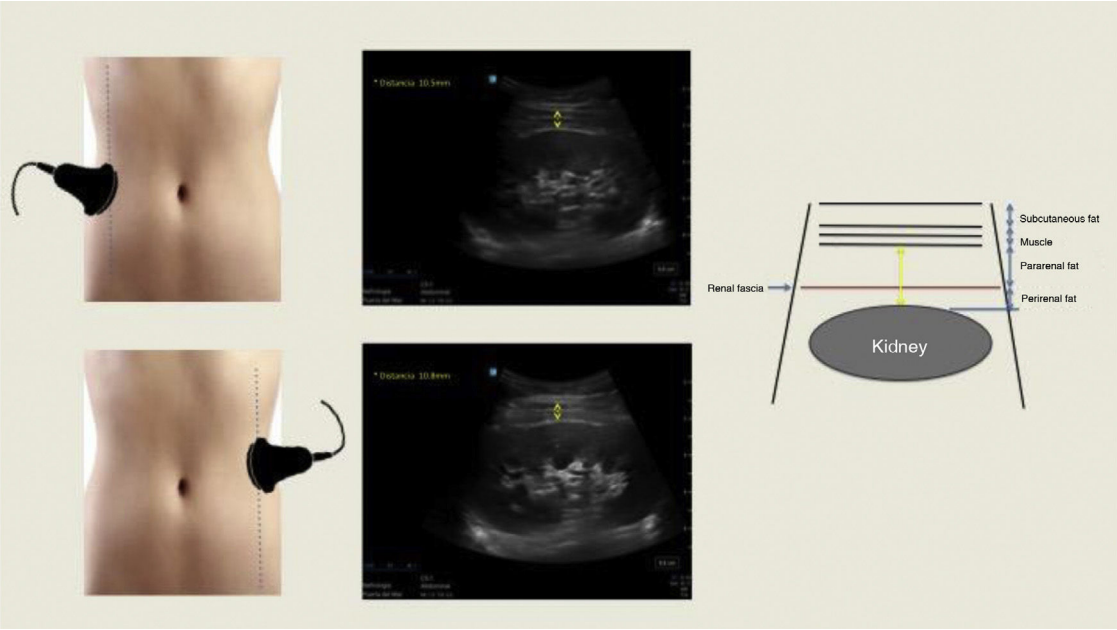

Fig. 1 – Ultrasound measurement of right and left para-perirenal fat thickness. Longitudinal kidney ultrasound shows the distance between the abdominal wall musculature and the kidney surface (yellow arrow). The ultrasound diagram is shown on the right. Authors' own image.

icity on the kidneys arises from an accumulation of lipid droplets in the renal parenchyma (podocytes, mesangium and proximal tubular cells), contributing to kidney dysfunction through chronic inflammation mechanisms via the release of adipokines and cytokines that can exacerbate atherosclerosis and other cardiovascular pathological processes, oxidative stress, mitochondrial dysfunction and autophagy, in addition to direct mechanical compression by fat deposition resulting in hypoperfusion.[4,5]

Multiple imaging techniques such as ultrasonography (US), computerised axial tomography (CT) and magnetic resonance imaging (MRI) have been used to quantify peri-pararenal fat thickness (PPRFT), RSF and RPF, respectively.[4] These measurements provide a direct insight into the ectopic distribution of visceral fat. However, MRI and CT are expensive, and the latter also uses ionising radiation, making it difficult to be used on a large scale. US-measured abdominal fat thickness is a non-invasive, accessible, cost-effective and reliable imaging technique that correlates significantly with CT.[6] Kawasaki et al.[7] were pioneers in measuring PPRFT by US, demonstrating that the examination was simple and technically reproducible, and that satisfactory images were obtained without interference from intestinal gas. The examination is performed with the subject in the supine position, with the convex probe placed perpendicular to the skin on the lateral surface of the abdomen. A longitudinal scan is performed and the probe is slowly moved laterally until the optimal position is found, in which the surface of the kidney is almost parallel to the skin. As little pressure as possible is exerted on the probe to avoid compression of the fat layers. PPRFT measurement is performed from the inner surface of the abdominal muscles to the surface of the kidney and the mean US measurement of the maximum thickness values in both kidneys is recorded (Fig. 1). The technique was validated by performing comparisons with CT measurements, obtaining a good degree of correlation ($r = 0.760$; $p = 0.003$).[7]

Several studies have shown a significant positive correlation between PPRFT separately and together (PaRF, PeRF) with traditional cardiovascular risk (CVR) markers, such as arterial hypertension (HTN),[8–10] insulin resistance,[9] albuminuria,[10,11] metabolic syndrome[9,12–15] and endothelial damage[12,13] (Table 1). Furthermore, in patients with and without obesity, diabetes and different stages of CKD, US PPRFT[16] and perirenal fat thickness (PeRFT)[17] measurements show a negative correlation with decreased glomerular filtration rate estimated with the Chronic Kidney Disease Epidemiology Collaboration, creatinine equation-2009 (CKD-EPI) and Modification of Diet in Renal Disease-4 (MDRD-4) equations. This association is particularly relevant, since chronic inflammation and metabolic dysfunction are prominent factors that contribute to the progression of CKD and the development of CV complications.[2,14] Even in obese patients without HTN or diabetes, the PPRFT shows a positive correlation with the albumin-creatinine ratio (ACR), which makes it to be considered a predictive factor of early renal injury.[10] Although there are no established cut-off values for normality in US-measured PPRFT, some studies have observed values in healthy controls ranging from 4.3 ± 2.3 to 7.95 ± 1.57 mm.[9,10]

In conclusion, the use of US to measure PPRFT is a promising tool to identify obese patients with risk of developing CKD secondary to lipotoxicity, and can be easily incorporated into daily clinical practice. However it is important, to mention that further research is needed to establish standardised clinical protocols and population cut-off points, and to fully understand the biological mechanisms underlying this association.

Table 1 – Studies demonstrating the association between ectopic renal fat thickness and cardiovascular risk factors.

Studies	Marker	Type of ultrasound measurement	Primary objective	Type of study	Study population	Results	Conclusions
Kawasaki et al.,[7] 2008	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To compare PPRFT measurements by US and CT	Cross-sectional	57 overweight type 2 diabetic patients (Japan)	The mean PPRFTs of both kidneys measured by US and CT were 1.26 ± 7.1 cm and 1.16 ± -6.5 cm, respectively US-measured PPRFT was significantly correlated with CT-measured VFA and WC ($p < 0.0001$). A 100-cm^2 VFA was equivalent to 1 cm of US-measured PPRFT	A US-measured PPRFT > 1 cm reflects an increase in visceral fat deposits
Grima et al.,[12] 2010	PeRFT	Longitudinal scan along the right MCL, from the edge of the right hepatic lobe to the edge of the right lower renal pole	To evaluate the association between PeRFT and CIMT as a metabolic risk factor	Cross-sectional	70 HIV-1-positive patients receiving antiretroviral therapy for more than 12 months (Italy)	The means of the right PeRFT and the CIMT were 0.5 ± 0.25 cm and 0.06 ± 0.02 cm, respectively The mean PeRFT and CIMT in HIV-1 patients with visceral obesity was significantly higher than in patients without visceral obesity ($p < 0.0001$ and $p < 0.01$, respectively)	A PeRFT of 0.65 cm was the most discriminatory value to predict a CIMT of 0.09 cm (S: 83.3%, Sp: 83.9%) PeRFT measurement can be used as an early predictor of increased CIMT in HIV-1 patients receiving antiretroviral therapy
Grima et al.,[13] 2010	PeRFT	Longitudinal scan along the right MCL, from the edge of the right hepatic lobe to the edge of the right lower renal pole	To evaluate the association between PeRFT and RI-OA as an index of carotid artery occlusion and metabolic risk factor	Cross-sectional	88 HIV-1-positive patients receiving antiretroviral therapy for more than 12 months (Italy)	The right PeRFT and RI-OA means were 0.81 ± 0.23 cm and 0.32 ± 0.9 cm, respectively The PeRFT and RI-OA means in HIV-1 patients with visceral obesity were higher than in patients without it ($p < 0.0001$ and $p < 0.001$, respectively)	US evaluation of PeRFT may have potential as a marker of increased endothelial damage with specific involvement of the ocular vascular region in HIV-1-infected patients
Lamacchia et al.[16], 2011	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To evaluate the association between PPRFT by US and eGFR and RRI	Cross-sectional	151 Caucasian type 2 diabetic patients with overweight and obesity (Italy)	The mean US-measured PPRFT of both kidneys was 3.8 ± 1.01 cm. PPRFT is an independent predictor of kidney dysfunction in diabetic patients (eGFR measured by MDRD-4 and CKD-EPI-r^2 0.366, $p = 0.001$ and RRI-r^2 0.529, $p = 0.005$)	US-measured PPRFT is an independent predictor of kidney dysfunction in patients with T2DM and obesity PPRFT was negatively correlated with eGFR, regardless of BMI or WC

– Table 1 (*Continued*)

Studies	Marker	Type of ultrasound measurement	Primary objective	Type of study	Study population	Results	Conclusions
						Albuminuria was a predictor of WC, but not for PPRFT	
Sun et al.,[10] 2013	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To evaluate association between US-measured PPRFT and MAU	Cross-sectional	67 obese patients without diabetes and hypertension and sex-matched healthy controls (China)	The mean US-measured PPRFT of both kidneys was significantly higher in obese subjects than in healthy controls (24 ± 4.9 mm vs 7.9 ± 1.57, $p < 0.05$). In obese patients, PPRFT was higher in patients with MAU than in those with NAU (29 ± 4.9 vs 24 ± 4.9 mm, $p < 0.05$)	PPRFT may be an independent predictor of early kidney injury in non-hypertensive and non-diabetic obese patients, and could be a useful tool for assessing visceral fat and early kidney injury in obese subjects.
Sahin et al.,[9] 2015	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To compare US-measured PPRFT with SAF	Cross-sectional	68 PCOS patients and 40 age- and BMI-matched healthy controls (Turkey)	The mean PPRFT value was $0.61 \text{ cm} \pm 0.29 \text{ cm}$ in PCOS patients and $0.43 \text{ cm} \pm 0.23 \text{ cm}$ in healthy controls, ($p = 0.002$). The PPRFT was positively correlated with BMI/$r = 0.368$), WC ($r = 0.441$), SBP ($r = 0.213$) and DBP ($r = 0.215$)	A significant positive correlation was observed between PPRFT and SBP and DBP. PPRFT was higher in non-obese PCOS subjects than in healthy non-obese controls
From Pergola et al.,[8] 2015	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To evaluate association with hypertension measured with 24-h ABPM	Cross-sectional	42 overweight and obese patients with no other apparent diseases (Italy)	The mean PPRFT value of both kidneys was 2.50 ± 0.81 cm. PPRFT was significantly and positively correlated with WC levels ($p < 0.01$), insulin ($p < 0.01$) and mean DBP levels measured with ABPM ($p < 0.05$)	The PPRFT was positively correlated with the mean DBP by ABPM
Geraci et al.,[15] 2018	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To evaluate the association between eGFR and PPRFT independent of metabolic status	Cross-sectional	296 Caucasian patients with essential hypertension (Italy)	PPRFT is negatively correlated with eGFR measured by CKD-EPI ($r = -0.284$, $p < 0.001$). 94% NPV of PPRFT to better distinguish patients with low eGFR was 3.7 cm (S: 71.8%, Sp: 63.0%, respectively, AUC: 0.70).	The relationship between PPRFT and eGFR appears to be more accurate and less influenced by the bias affecting traditional adiposity indices

– Table 1 (*Continued*)

Studies	Marker	Type of ultrasound measurement	Primary objective	Type of study	Study population	Results	Conclusions
D'Marco et al.,[14] 2019	PeRFT	Renal distal 1/3 between the cortex and the hepatic and/or splenic margin	To evaluate the association between CKD grades and metabolic risk factors	Cross-sectional	103 patients with various stages of CKD (1–5) (Venezuela)	Right PeRFT was higher in patients with CKD and impaired glucose vs normal glucose levels (1.10 ± 0.40 cm vs 0.85 ± 0.39 cm, $p < 0.021$)	In patients with CKD, PeRFT was significantly correlated with metabolic risk factors that could affect kidney function
Fang et al.,[17] 2020	PeRFT	From the inner side of the abdominal musculature to the renal surface, difference between peri- and pararenal fat separated by GF	To evaluate the association between PeRFT and eGFR in patients with T2DM	Cross-sectional	171 patients with T2DM (China)	The mean PeRFT was 0.97 ± 0.50 cm. Patients were divided into tertiles according to PeRFT (<0.6 cm, 0.6–1.33 cm and >1.33 cm) PeRFT was negatively correlated with eGFR measured by MDRD-4 ($r = -0.181$, $p < 0.05$)	PeRFT was independently and negatively correlated with eGFR, especially in men, suggesting a possible role in kidney dysfunction in patients with T2DM
Shen et al.,[11] 2020	PPRFT	From the inner side of the abdominal musculature to the kidney surface	To evaluate association between US-measured PPRFT and MAU	Cross-sectional	89 patients with T2DM (66 with MAU and 23 without MAU) (Taiwan)	T2DM patients with MAU have a higher PPRFT than patients without MAU (2.52 ± 0.38 cm vs 2.28 ± 0.45 cm, respectively) PPRFT was positively associated with MAU grade in linear regression analysis ($r = 0.233$, $p = 0.03$)	Increased PPRFT was positively associated with MAU in T2DM patients. These findings suggest that PPRFT measurement may represent a useful tool to assess the risk of developing MAU in patients with T2DM.

ABPM: Ambulatory Blood Pressure Monitoring; AUC: area under the curve; BMI: body mass index; CIMT: carotid intima-media thickness; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CT: computerised axial tomography; CVRF: cardiovascular risk factor; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GF: Gerota's fascia; HIV-1: human immunodeficiency virus type 1; HTN: arterial hypertension; MAU: microalbuminuria; MCL: midclavicular line; MDRD-4: Modification of Diet in Renal Disease; NAU: normal albuminuria; NPV: negative predictive value; PCOS: polycystic ovary syndrome; PPRFT: para-perirenal fat thickness; PeRFT: perirenal fat thickness; RI-OA: resistive index of ophthalmic artery; RRI: renal resistive index; S: sensitivity; SAF: subcutaneous abdominal fat; SBP: systolic blood pressure; Sp: specificity; T2DM: diabetes mellitus type 2; US: ultrasonography; VFA: visceral fat area; WC: waist circumference.

Ethical responsibilities

The study complied with the principles set out in the Declaration of Helsinki. No experiments were performed on humans or animals for this study.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that they have not used AI or AI-assisted technologies to write this manuscript.

Funding

No funding was received for this paper.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Prevalence of overweight among adults, BMI ≥ 25 (age-standardized estimate) (%). [Accessed 15 July 2024]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-overweight-among-adults-bmi-=-25-(age-standardized-estimate)-(-).
2. De Vries APJ, Ruggenenti P, Ruan XZ, Praga M, Cruzado JM, Bajema IM, et al. Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease. Lancet Diabetes Endocrinol. 2014;2:417–26.
3. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int. 2017;91:1224–35.
4. Hti Lar Seng NS, Lohana P, Chandra S, Jim B. The fatty kidney and beyond: a silent epidemic. Am J Med. 2023;136:965–74.
5. Mende C, Einhorn D. Fatty kidney disease: the importance of ectopic fat deposition and the potential value of imaging. J Diabetes. 2022;14:73–8.
6. Armellini F, Zamboni M, Castelli S, Micciolo R, Mino A, Turcato E, et al. Measured and predicted total and visceral adipose tissue in women. Correlations with metabolic parameters. Int J Obes Relat Metab Disord. 1994;18:641–7.
7. Kawasaki S, Aoki K, Hasegawa O, Numata K, Tanaka K, Shibata N, et al. Sonographic evaluation of visceral fat by measuring para- and perirenal fat. J Clin Ultrasound. 2008;36:129–33.
8. De Pergola G, Campobasso N, Nardecchia A, Triggiani V, Caccavo D, Gesualdo L, et al. Para- and perirenal ultrasonographic fat thickness is associated with 24-hours mean diastolic blood pressure levels in overweight and obese subjects. BMC Cardiovasc Disord. 2015;15:108.
9. Sahin SB, Durakoglugil T, Ayaz T, Sahin OZ, Durakoglugil E, Sumer F, et al. Evaluation of para- and perirenal fat thickness and its association with metabolic disorders in polycystic ovary syndrome. Endocr Pract. 2015;21:878–86.
10. Sun X, Han F, Miao W, Hou N, Cao Z, Zhang G. Sonographic evaluation of para- and perirenal fat thickness is an independent predictor of early kidney damage in obese patients. Int Urol Nephrol. 2013;45:1589–95.
11. Shen FC, Cheng BC, Chen JF. Peri-renal fat thickness is positively associated with the urine albumin excretion rate in patients with type 2 diabetes. Obes Res Clin Pract. 2020;14:345–9.
12. Grima P, Guido M, Chiavaroli R, Zizza A. Ultrasound-assessed perirenal fat is related to increased ophthalmic artery resistance index in HIV-1 patients. Cardiovasc Ultrasound. 2010;8:24.
13. Grima P, Guido M, Zizza A, Chiavaroli R. Sonographically measured perirenal fat thickness: an early predictor of atherosclerosis in HIV-1-infected patients receiving highly active antiretroviral therapy? J Clin Ultrasound. 2010;38:190–5.
14. D'Marco L, Salazar J, Cortez M, Salazar M, Wettel M, Lima-Martínez M, et al. Perirenal fat thickness is associated with metabolic risk factors in patients with chronic kidney disease. Kidney Res Clin Pract. 2019;38:365–72.
15. Geraci G, Zammuto MM, Mattina A, Zanoli L, Geraci C, Granata A, et al. Para-perirenal distribution of body fat is associated with reduced glomerular filtration rate regardless of other indices of adiposity in hypertensive patients. J Clin Hypertens (Greenwich). 2018;20:1438–46.
16. Lamacchia O, Nicastro V, Camarchio D, Valente U, Grisorio R, Gesualdo L, et al. Para- and perirenal fat thickness is an independent predictor of chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients. Nephrol Dial Transplant. 2011;26:892–8.
17. Fang Y, Xu Y, Yang Y, Liu C, Zhao D, Ke J. The relationship between perirenal fat thickness and reduced glomerular filtration rate in patients with type 2 diabetes. J Diabetes Res. 2020;2020:6076145.

José Carlos De La Flor Merino [a,b,*], Carlos Narváez Mejía [c], Adriana Puente García [d], Jonay Pantoja Pérez [e], Michael Cieza Terrones [f], Maite Rivera Gorrín [b,g]

[a] *Servicio de Nefrología, Hospital Central de la Defensa Gómez Ulla, Madrid, Spain*
[b] *Facultad de Medicina, Universidad de Alcalá de Henares, Madrid, Spain*
[c] *Servicio de Nefrología, Hospital Universitario Puerta del Mar, Cádiz, Spain*
[d] *Servicio de Nefrología, Hospital Universitario de Fuenlabrada, Madrid, Spain*
[e] *Servicio de Nefrología, Hospital Universitario Doctor Peset, Valencia, Spain*
[f] *Facultad de Medicina, Universidad Peruana Cayetano Heredia, Lima, Peru*
[g] *Servicio de Nefrología, Hospital Universitario Ramón y Cajal, Madrid, Spain*

[*] *Corresponding author.*
E-mail address: jflomer@mde.es (J.C. De La Flor Merino).

https://doi.org/10.1016/j.nefroe.2024.11.023