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Perirenal fat differs in patients with chronic kidney disease receiving different vitamin D-based treatments: a preliminary study

Ana Checa-Ros[1,2], Antonella Locascio[3], Owahabanun-Joshua Okojie[1], Pablo Abellán-Galiana[1] and Luis D'Marco[1*]

Abstract

Introduction Chronic kidney disease (CKD) patients show high rates of cardiovascular disease (CVD) and mortality. In the general population, obesity, hypertension, and diabetes are known as the classical CVD risk factors. However, CKD patients have other predisposing CVD factors more associated with bone and mineral metabolism disorders (BMD). BMD originates from reduced 1,25-dihydroxy vitamin D and hypocalcemia, which lead to secondary hyperparathyroidism, with increased parathyroid hormone (PTH) levels and hyperphosphatemia as the progression of renal damage. Due to their pleiotropic effects, vitamin D and its analogs, such as cholecalciferol, calcitriol, or paricalcitol, have proven effective in controlling BMD and CVD. On the other hand, visceral adiposity has been shown to increase the risk for CVD in both the general and CKD populations via complex autocrine and paracrine hormonal mechanisms. This seems to be the case with fat surrounding the epicardium. Although it has not been widely evaluated, the fat surrounding the kidneys, or the perirenal adipose tissue (PAT), could also share similarities with the epicardial in terms of its potential contribution to the CVD risk observed in these patients. We conducted a preliminary study to assess differences in PAT on a sample of patients with CKD presenting diverse CVD history and who were receiving different vitamin D-receptor activators.

Methods/Results An observational study was performed at UNIRENAL Center (Venezuela), from January to November 2015. Analytical and clinical parameters were evaluated. The PAT thickness was measured in centimeters through a B-mode ultrasound. Thus, we included 83 CKD patients treated with vitamin D or analogs (mean age 58.3 ± 16y); 57.83% were females. Nearly half of the sample was classified as CKD-G3 ($n=40$). Prior history of CVD was present in 55.4% ($N=46$) of participants. Must of the patients ($n=46$;55.42%) receiving oral cholecalciferol (1000 IU/day) as part of the treatment for lower levels of vitamin D or BMD related to CKD (mainly elevated PTH), followed by those under calcitriol at 0.5 mcg/day ($n=27$;32.53%), and around 12% ($n=10$;12.05%) on paricalcitol (1 mcg/day). The mean treatment vintage was 20 ± 6 months for cholecalciferol, 18 ± 4 months for calcitriol, and 16 ± 2 months for paricalcitol. Those with a history of CVD ($n=46$) showed higher levels of urea (mean 62.0vs45.2 mg/dl, $p<0.05$), uric acid (mean 5.5vs4.3 mg/dl; $p<0.03$), and iPTH (mean 186.2vs65.2pcg/dl; $p<0.05$) than patients free of CVD events ($n=37$). These findings were also in parallel with decreased renal function in the group with previous CVD history, as evidenced by a significantly lower eGFR (mean 53.55vs89.00 ml/min/1.73 m^2,$p<0.001$). Similarly,

*Correspondence:
Luis D'Marco
luis.dmarcogascon@uchceu.es

Full list of author information is available at the end of the article

the mean PAT thickness was elevated in the group with a history of CVD in relation to those with no previous CVD events (0.99vs0.80 cm; SD ± 0.30;$p \sim 0.05$). The comparative analysis for the patients with prior cardiovascular events between the three treatments revealed that those on paricalcitol had lesser PAT accumulation than those treated with cholecalciferol or calcitriol ($p < 0.05$). In conclusion, our study shows that PAT thickness in CKD may be influenced by vitamin D analog-based treatment. Further research is needed to better understand the mechanistic links between PAT, BMD, and CVD in this population.

Keywords Vitamin D, Analogs, Cardiovascular disease, Chronic kidney disease, Inflammation

Introduction

Patients with chronic kidney disease (CKD) show high cardiovascular complication rates [1–3], being cardiovascular disease (CVD) their main cause of morbidity and mortality [4]. Obesity, dyslipidemia, hypertension, and diabetes are known as the classical cardiovascular risk factors. However, other risk factors predisposing to CVD that appear in CKD are associated with the bone and mineral metabolism disorders (BMD) frequently present in these patients [5, 6]. BMD originates from reduced 1,25-dihydroxy vitamin D and hypocalcemia, which lead to secondary hyperparathyroidism, with increased parathyroid hormone (PTH) levels [7] and hyperphosphatemia as the kidney damage progresses [8].

Diverse therapeutic strategies are used to address BMD in CKD. Due to their pleiotropic effects, vitamin D and its analogs, such as cholecalciferol, calcitriol, or paricalcitol, have proven effective in controlling BMD secondary to CKD and cardiovascular pathologies [9, 10]. They bind to the vitamin D receptor in the parathyroid gland, thereby reducing PTH synthesis, increasing calcium absorption and the release of phosphorus from the bone [11]. As a result, they may induce hypercalcemia and hyperphosphatemia, with the consequent risk of vascular calcifications. This adverse effect is often reported with the use of calcitriol, but rarely with paricalcitol [12, 13]. On the contrary, calcimimetic agents, such as cinacalcet and etelcalcetide, which increase the sensitivity of the calcium-sensing receptor to extracellular calcium and decrease PTH secretion [14], may cause hypocalcemia [15, 16], leading to an increased risk of arrhythmia and heart failure [17].

On the other hand, visceral adiposity has been shown to increase the risk for CVD in both the general population and patients with CKD via complex autocrine and paracrine hormonal mechanisms [18]. This seems to be the case with the adipose tissue surrounding the epicardium, also known as the epicardial adipose tissue (EAT) [19]. Although it has not been widely evaluated, the adipose tissue surrounding the kidneys, or the perirenal adipose tissue (PAT), could also share similarities with the EAT in terms of its potential contribution to cardiovascular risk [20, 21].

PAT, which comprises both white and brown adipose tissue, is anatomically located in the retroperitoneal space around the kidneys. It is richly vascularized by branches of the abdominal aorta, including the inferior adrenal, dorsal, and gonadal arteries [22, 23]. As a perivisceral fat, PAT is metabolically active. The specific cells from this tissue, or adipocytes, secrete several adipokines, such as adiponectin and leptin, which are cytokines involved in energy metabolism that also influence vascular function, inflammation and macrophage polarization to an anti-inflammatory or pro-inflammatory phenotype [24, 25]. Therefore, the proximity to major vascular structures and in a dysfunctional environment suggests that PAT may contribute to cardiovascular disease through various systemic and/or local mechanisms, including hormone secretion, inflammation, and lipid metabolism alterations [26, 27] (Fig. 1).

Another potential contribution of PAT to cardiovascular physiopathology is the link with the vitamin D-fibroblast growth factor 23 (FGF-23) axis. Adipocytes are capable of storing vitamin D, and vitamin D receptor activation has been shown to influence the expression of the FGF-23, a key regulator of phosphate metabolism, that has been implicated in CVD among CKD patients [28]. The dysregulation of this axis via an imbalance in the concentrations of adiponectin and leptin, which modulate FGF-23 production, may be responsible for the cardiovascular load in CKD-affected patients [29, 30].

Given the immune-regulatory properties of vitamin D and its link with cardiovascular risk factors, diverse studies focused on the morphometric and biochemical effects of vitamin D deficiency on EAT. Increased EAT thickness, in parallel with higher levels of pro-inflammatory interleukins at the EAT level, was observed in animal and clinical populations with vitamin D deficiency [31–34]. Consequently, supplementation with cholecalciferol was reported to decrease EAT thickness [35] and switch the EAT macrophage phenotype to the anti-inflammatory M2 state [36]. However, the potential association between vitamin D supplementation and PAT is scarcely explored. To date, only one study conducted on murine models revealed that those with diabetic kidney disease showed hypertrophic PAT in comparison with the controls and that vitamin D supplementation induced PAT 'browning´, with a structural change in adipocyte mitochondria [37]. On the other hand, the differential effects

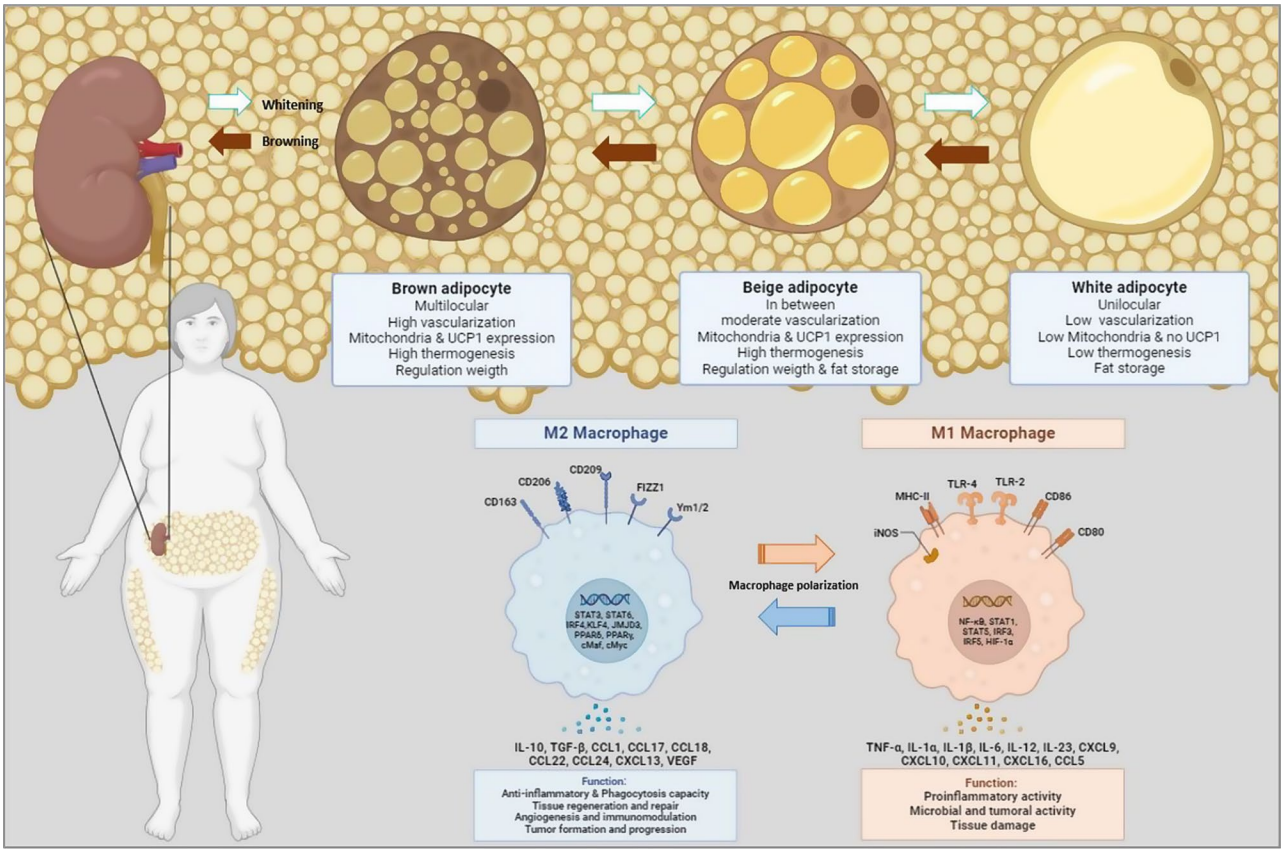

Fig. 1 Morphological and biochemical changes of adipocytes in response to inflammatory/anti-inflammatory stimuli. The process of 'whitening' consists of the gradual conversion of brown adipocytes, which contain many mitochondria expressing uncoupled protein-1 (UCP-1) and are responsible for thermoregulation, into white adipocytes, whose main function is fat storage. Beige adipocytes represent an intermediate state between brown and white adipocytes. The 'whitening' process generally occurs in response to a pro-inflammatory environment, in which the predominant adipokine is leptin, which triggers the polarization of macrophages to an M1 phenotype. The opposite process or 'browning', in which the white adipocyte becomes brown, is also possible in response to anti-inflammatory stimuli: the predominant adipokine at this point is adiponectin, which prompts the macrophage polarization to an M2 phenotype

induced by the diverse vitamin D analogs in either EAT or PAT are yet to be reported.

Based on the aforementioned, we hypothesized that PAT characteristics in patients with CKD could not only vary depending on their cardiovascular risk factors, but also concerning the treatment received for BMD, particularly vitamin D and analogs. Under this hypothesis, we conducted a preliminary study to assess differences in PAT thickness on a sample of patients with CKD presenting diverse CVD history and who were receiving different vitamin D-receptor activators.

Methods

Design

An observational study was performed at the UNIRENAL Clinical Center, Puerto Ordaz City in Venezuela, from January to November 2015. The study protocol was detailed in a prior study by our group [21], and here it is briefly summarized.

Patient recruitment

Patients diagnosed with CKD and receiving treatment with vitamin D and analogs were the target population for this study. They needed to meet the following inclusion criteria to be invited to participate: (1) age ≥ 18 years; (2) diagnosis of CKD as per the Kidney Disease Improving Global Outcomes (KDIGO) 2012 definition (*abnormality of kidney structure or function*, *present for more than 3 months*, *with health implications*), classified as grades (G) G1 to G4 (not on dialysis); (3) treatment with vitamin D or analogs (cholecalciferol, calcitriol, paricalcitol), not in combination, initiated one year before and following the current guidelines at that moment [38] depending of 25(OH)D3 and intact (iPTH) levels (mainly iPTH levels); (4) life expectancy > 1 year. The CKD Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR). Also, we used the CKD classification guidelines modified by KDIGO, which define an: eGFR (in mL/min/1.73

m^2) > 90 as CKD G1; from 60 to 89 as CKD G2; between 30 and 59 as CKD G3; and from 15 to 29 as CKD G4.

Patients excluded from this study were those suffering from an acute inflammatory process, such as infection, active cancer, or other inflammatory states beyond the ones mentioned in inclusion, as well as subjects with acute kidney injury, polycystic kidney disease, CKD G5 (eGFR < 15 ml/min/1.73m^2) and/or requiring renal replacement therapy.

Clinical data collection

Electronic medical records from patients were assessed to collect the following clinical information: age; sex; eGFR and CKD grade; weight and height at recruitment onset; prior history of cardiovascular events (understood as coronary artery disease, stroke, or peripheral vascular disease); vitamin D-based treatment (cholecalciferol, calcitriol, paricalcitol), dosage and treatment duration.

Blood pressure (BP) was measured in the office at recruitment onset with a digital monitor placed on the upper arm, while the patient was sitting down with the arm on a table at the same height as the heart and after 3 min of resting (mean value of three measures).

Analytical data collection

Blood samples to measure mineral metabolism, renal function, and inflammation markers were collected after 8 to 12 h of fasting and a 15-minute resting period, and stored at a temperature between 4 °C and 15 °C. The samples were later centrifuged in cold for 15 min and processed by absorbent photometry and turbidometry on an automatized analyzer (MINDRAY® model: BS-240 China; Mindray Medical International Limited, Shenzhen, China).

Imaging data collection

PAT thickness was measured in centimeters (cm) through a B-mode ultrasound with a 3.5-MHz convex transductor (Alpinion® E-CUBE 9; Alpinion Medical Systems, Seoul, Korea). Patients underwent a bilateral renal ultrasound, and the kidneys were measured anteroposteriorly, transversally, and longitudinally. PAT was measured in the distal third between the cortex and the hepatic border and/or spleen (Fig. 2). The imaging studies were performed by one of the authors (LDM) and stored in DICOM format. Then, in the radiology department of the hospital, the imaging were processed by an expert radiologist blind to patient data.

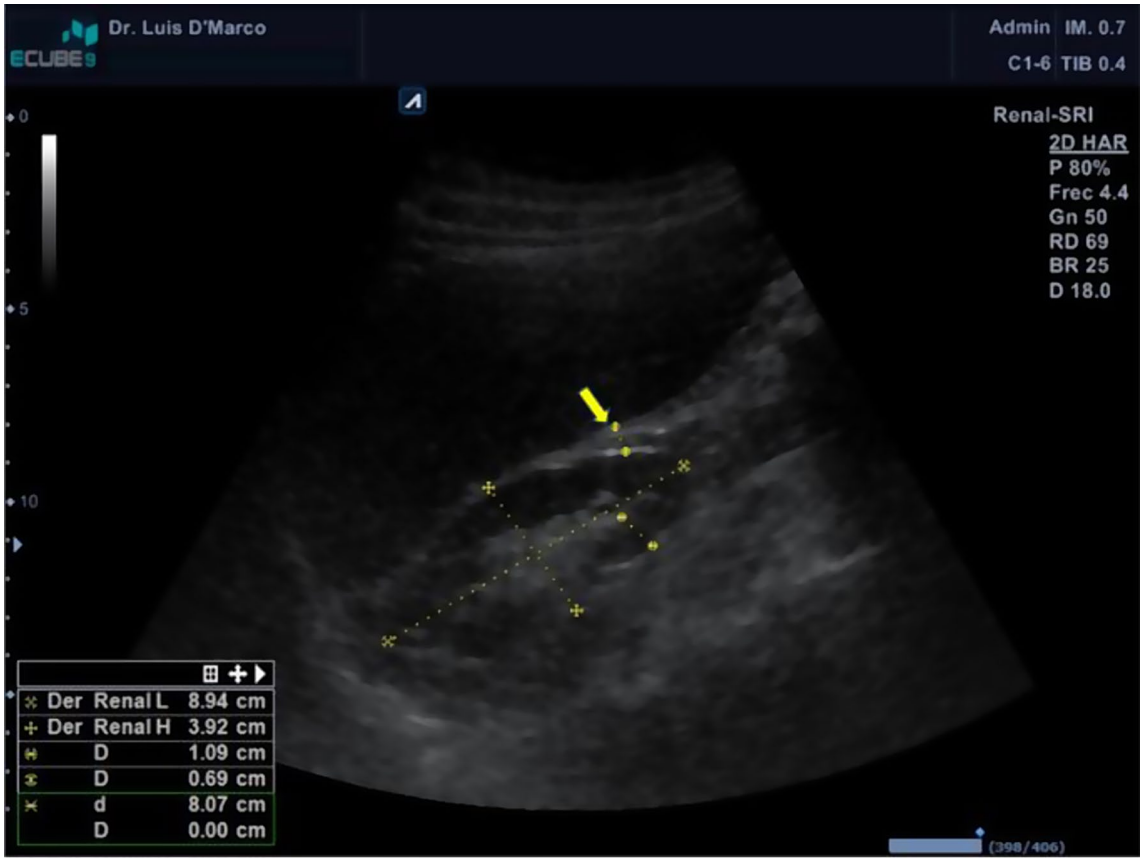

Fig. 2 Imaging of the perirenal adipose tissue measurement by ultrasound. The arrow shows the adipose tissue thickness in the right kidney [21]

Ethical aspects

The research was conducted following the Declaration of Helsinki as revised in 2013. The Ethics Committee of Biomedical Research approved the study protocol. The informed consent was obtained from all patients before being included in the study.

Statistics

The Kolmogorov-Smirnov test was used to test if the data followed a normal distribution. Descriptive data were presented as mean ± standard deviation (SD). Comparative analyses were performed through Student's t-tests after log transformation. Comparisons of clinical, analytical, and imaging data were made between patients divided according to their prior history of cardiovascular events (history of cardiovascular disease: yes/no). PAT thickness in patients with previous CVD was later compared between the three treatment groups (cholecalciferol, calcitriol, and paricalcitol). The alpha value was set at 0.05. Calculations were performed with the SPSS 17® software.

Results

Demographic and clinical characteristics of our sample

Our sample was composed of 83 patients with CKD under treatment with vitamin D and analogs, with a mean age of 58.3 ± 16 years, all of them of Hispanic ethnicity. Forty-eight of our patients (57.83%) were females.

Table 1 General characteristics of patients according to the history of cardiovascular disease

History of cardiovascular disease					
	Yes ($n=46$)		No ($n=37$)		
	Mean	SD	Mean	SD	*p*
Body mass index (kg/m^2)	26.0	± 7.0	27.7	± 7.8	--
eGFR (mL/min/1.73 m^2)	53.5	± 30.6	89.0	± 39.2	*< 0.001*
BP Mean (mmHg)	101.3	± 23.4	96.4	± 15.4	--
Hemoglobin (gr/dL)	12.4	± 1.3	12.5	± 1.9	--
Glucose (mg/dL)	104.5	± 19.6	102.8	± 31.3	--
Creatinine (mg/dL)	1.5	± 1.1	1.2	± 1.0	--
Urea	62.0	± 33.4	45.2	± 32.7	*< 0.05*
LDL-C (mg/dL)	106.5	± 28.9	107.9	± 31.6	--
Triglycerides (mg/dL)	131.0	± 57.4	132.3	± 73.3	--
Uric acid (mg/dL)	5.5	± 1.9	4.3	± 2.0	*< 0.03*
Albumin (gr/L)	3.7	± 0.6	4.0	± 0.5	--
Calcium (mg/dL)	9.4	± 0.6	9.4	± 0.7	--
Phosphate (mg/dL)	3.8	± 0.9	3.4	± 0.8	--
Phosphatase Alkaline (IU/L)	139.0	± 80.0	189.0	± 45.2	--
iPTH (pg/mL)	186.2	± 194.3	65.2	± 31.0	*< 0.05*
CRP (mg/dL)	7.07	± 10.5	1.29	± 1.26	*< 0.005*
PAT thickness (cm)	0.99	± 0.3	0.80	± 0.3	~ 0.05

Data are presented as mean ± standard deviation (SD). Comparisons between groups were made via the Student's t-test after log transformation. Abbreviations: eGFR, estimated glomerular filtration rate; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; iPTH, intact parathyroid hormone; CRP, C-Reactive protein; PAT, perirenal adipose tissue

According to the eGFR, nearly half of our sample was classified as CKD-G3 ($n=40$), followed by G2 ($n=22$) and G1 ($n=15$), with only a few patients considered as CKD-G4 ($n=6$). Prior history of CVD was present in 46 participants (55.42%).

The majority of the patients ($n=46$; 55.42%) were receiving oral cholecalciferol (1000 IU/day) as part of the treatment for lower levels of vitamin D or BMD related to CKD (mainly elevated iPTH), followed by those under calcitriol at 0.5 mcg/day ($n=27$; 32.53%), and around 12% patients ($n=10$; 12.05%) on paricalcitol (1 mcg/day). No combination of these drugs was used in any of the patients. The mean treatment duration was 20 ± 6 months for cholecalciferol, 18 ± 4 months for calcitriol, and 16 ± 2 months for paricalcitol.

Comparisons of clinical, analytical and imaging parameters based on CVD history

Mean values of clinical, analytical, and PAT thickness are shown in Table 1, comparing patients with and without previous cardiovascular disease history. Those with a cardiovascular disease history ($n=46$) showed significantly higher serum levels of urea (mean 62.0 vs. 45.2 mg/dl, $p<0.05$), uric acid (mean 5.5 vs. 4.3 mg/dl; $p<0.03$), and iPTH (mean 186.2 vs. 65.2 pcg/dl; $p<0.05$) than the patients free of cardiovascular events ($n=37$). These findings were also in parallel with a more decreased renal function in the group with previous CVD history, as evidenced by a significantly lower eGFR (mean 53.55 vs. 89.00 ml/min/1.73 m^2 [CKD-EPI], $p<0.001$). Regarding the inflammatory status, patients with prior CVD history also showed significantly higher levels of C-reactive protein (CRP) (7.1 vs. 1.2 mg/dL; $p<0.005$). No significant differences were observed for the other analytical parameters between patients with and without CVD history.

The mean PAT thickness was observed to be elevated in the group of patients with a history of CVD in relation to those with no previous cardiovascular events, although this difference did not reach statistical significance (0.99 vs. 0.80 cm; SD ± 0.30; $p \sim 0.05$) (Fig. 3).

When distinguishing between groups of treatment, 28 of the patients on cholecalciferol (60.87%) referred prior CVD history, whereas this occurred with 16 of the patients (59.26%) receiving calcitriol and in 2 of the patients on paricalcitol (20%). The comparative analysis for the patients with prior cardiovascular events between the three treatments revealed that those on paricalcitol had significantly lesser PAT accumulation than those treated with cholecalciferol or calcitriol ($p<0.05$) (Fig. 4). These results were not adjusted for confounding factors such as weight, height, body mass index (BMI), and/or any other treatments.

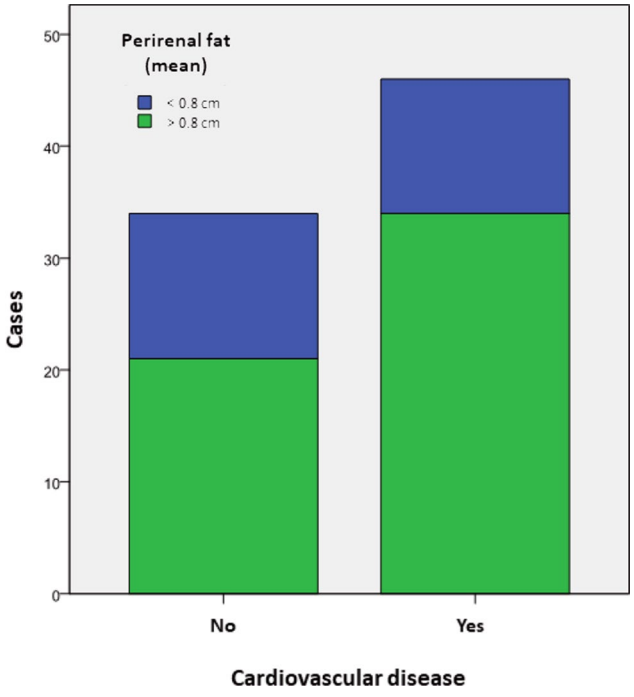

Fig. 3 Distribution of the patients according to the history of cardiovascular disease and perirenal fat thickness

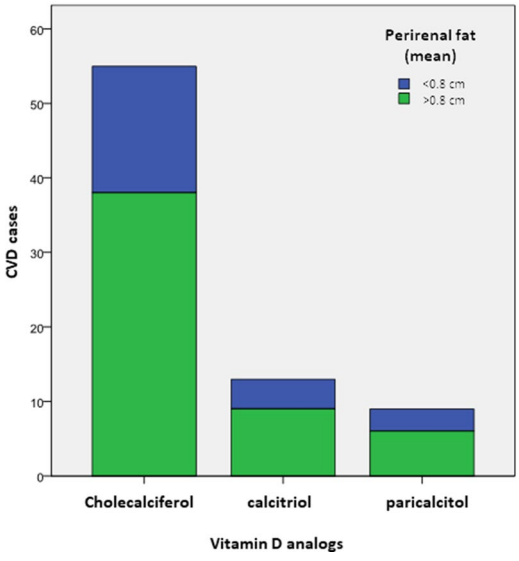

Fig. 4 Distribution of patients according to vitamin D analogs treatments and perirenal fat thickness

Discussion

The results from our study suggest a potential association between PAT thickness and the presence of cardiovascular events in patients with CKD, highlighting that the role of PAT as a potential marker of cardiovascular risk needs in-depth assessment. Furthermore, the percentage of patients with prior CVD history in the paricalcitol group, which was relatively lower than with the other treatments, showed significantly decreased PAT thickness, suggesting a potential protective effect associated with this therapeutic regimen.

The finding of a thicker average PAT in patients with prior cardiovascular history raises the question about the potential role of region-specific fat storages as independent risk factors for cardiovascular damage. Although this phenomenon has been widely explored with the EAT [20, 39], the mechanisms underlying this association remain incompletely understood. As aforementioned, the adipose tissue behaves as a paracrine and endocrine organ able to influence vascular dysfunction and the inflammation status, both locally and systemically, via the secretion of different factors (adipokines) depending on the predominant adipocyte phenotype (brown/beige/white) (Fig. 1) [40].

Vitamin D deficit has been related to a greater prevalence of cancer and cardiovascular diseases [41–43]. The administration of cholecalciferol or vitamin D agonists has pleiotropic effects beyond controlling BMD, such as the regulation of immunological pathways that may be beneficial in patients with low-grade chronic inflammatory states [44, 45]. Paricalcitol is a selective vitamin D receptor agonist associated with higher efficacy, higher survival rates, and a more adequate tolerability profile than cholecalciferol or calcitriol [46–48]. Several studies have reported anti-inflammatory and antioxidant actions induced by paricalcitol that may be independent of its effects on hemodynamics and PTH suppression [49–51]. In murine models, the administration of paricalcitol was associated with reduced macrophage infiltration in the glomerular and tubular tissues after inducing renal tubular injury. On a molecular level, this occurred in parallel with decreased renal IL-6 and tumor necrosis factor-alpha (TNF-α) levels, as well as lower NADPH activity, probably via inhibition of the NLRP3 inflammasome pathway [52–54]. Although this is the first study exploring the actions of paricalcitol on PAT, the anti-inflammatory properties attributed to this drug could serve to support the hypothesized morphological and molecular actions at the PAT level.

As expected, our results show that those patients with a CVD history were more prone to higher levels of iPTH (mean 186.2 ± 194.3 vs. 65.2 ± 31.0 pg/mL; p 0.05) and CRP (mean 7.07 ± 10.5 vs. 1.29 ± 1.26 mg/dL; $p < 0.005$) than those free of events. Besides, those patients who have suffered prior cardiovascular events had increased uric acid serum levels (mean 5.5 ± 1.9 4.3 ± 2.0 mg/dL; $p < 0.03$). These findings are in line with the notion that altered bone and mineral metabolism are intimately related to chronic inflammatory status in renal-affected patients. Thus, careful control of these altered parameters may help to improve these conditions and avoid vascular as well as non-vascular complications.

Despite the insights provided by our study, several limitations should be acknowledged. The observational nature of our study design precludes causal inference, and the relatively small sample size limits the generalizability of our findings. Additionally, we lacked comprehensive data on more inflammatory markers and bone and mineral metabolism parameters, which may have provided further insights into the mechanisms linking PAT with cardiovascular risk in CKD patients. Regarding vitamin D serum levels, there were many missing values, and despite many patients showing higher or duplicate levels of iPTH, no vitamin D serum levels were ordered since they received direct treatment with paricalcitol depending on their iPTH serum levels.

Conclusion

In conclusion, our study highlights that PAT thickness in CKD may be influenced by the specific vitamin D analog-based treatment used for BMD. In this regard, the use of paricalcitol could be linked to a diminishing effect on PAT thickness, which may be associated with a more favorable cardiovascular prognosis. Further research and large prospective cohort studies are needed to better understand the mechanistic links between PAT, adipokines, bone and mineral metabolism, and cardiovascular health in this population of patients. Ultimately, a deeper understanding of these pathways may open new avenues for the development of novel therapeutic strategies, such as those related to the bone-mineral, metabolic, and renal axis, to mitigate cardiovascular risk and improve outcomes in CKD patients.

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Author contributions
All authors participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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This research received no external funding.
Data availability Raw data is not publicly available to preserve individuals' privacy under the European General Data Protection Regulation.

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Biomedical Research from Puerto Ordaz Hospital (Venezuela). All procedures were performed in accordance with the Declaration of Helsinki as revised in 2013. Verbal and written informed consent was obtained from all subjects involved.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Grupo de Investigación en Enfermedades Cardiorrenales y Metabólicas, Departamento de Medicina y Cirugía, Facultad de Ciencias de la Salud, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia 46115, Spain
[2]Aston Institute of Health & Neurodevelopment (AIHN), School of Life & Health Sciences, The Aston Triangle, Aston University, Birmingham B4 7ET, UK
[3]Departamento de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia 46115, Spain

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