NUTRITIONAL OR ACTIVE VITAMIN D FOR THE CORRECTION OF MINERAL METABOLISM ABNORMALITIES IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS?

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Abstract

Context. Benefits of vitamin D therapies in chronic kidney disease (CKD) are debated.

Objective. To compare the effects of medium-term native (VitD) and active (VDRA) vitamin D on parameters of mineral metabolism and arterial function in non-dialysis CKD.

Design. Open-label, active comparator, randomized study.

Subjects and Methods. Forty-eight adult patients, vitamin D naïve, CKD stage 3 to 5 with increased parathyroid hormone (iPTH) were randomized to receive either oral cholecalciferol 1000UI/day (n=24) or paricalcitol 1mcg/day (n=24) for 6 months. Median changes at end of study vs. baseline in serum calcidiol, iPTH, total alkaline phosphatase (ALP), and cardio-ankle vascular index (CAVI) were the efficacy parameters.

Results. Higher increase in calcidiol (15.5 [95%CI 13.3; 17.2] vs. 0.4 [95%CI -6.1; 3.7]ng/mL, p<0.001) were found in VitD group. Conversely, the decline of iPTH (-35.2 [95%CI -83; 9] vs. 13.3 [95%CI -8.1; 35]pg/mL, p=0.008) and ALP (-34 [95%CI -58; -11] vs. -10 [95%CI -23; -2] U/L, p=0.02) were greater after paricalcitol. More subjects experienced iPTH decrease in VDRA group (71% vs. 39%, p=0.03). The variation in CAVI and the incidence of hypercalcemia and hyperphosphatemia were similar.

Conclusions. It seems that secondary hyperparathyroidism was more efficiently treated by VDRA, whereas cholecalciferol better corrected the calcidiol deficiency in non-dialysis CKD.

Key words: chronic kidney disease, native vitamin D, vitamin D receptor activators, secondary hyperparathyroidism, arterial stiffness.

INTRODUCTION

Chronic kidney disease associated mineral and bone disorder (CKD-MBD) includes biochemical and

bone abnormalities as well as vascular calcifications (1). Such abnormalities, related to the loss of kidney function, arise as early as the onset of the glomerular filtration rate decline and aggravate with its progression (1, 2).

Secondary hyperparathyroidism (SHPT), a major feature of CKD-MBD, is the consequence of multiple mineral metabolism dysregulations, mainly the fall off biologically active form of vitamin D [i.e. calcitriol - 1,25(OH)₂D] (3). Vitamin D deficiency contributes to SHPT through loss of its endocrine actions at intestinal, renal and parathyroid levels, resulting in hypocalcaemia (3,4), increased synthesis of parathyroid hormone (PTH) and proliferation of the parathyroid cells (4).

Several mechanisms account for the low calcitriol levels in chronic kidney disease (CKD) patients: (i) the decrease in the functional renal mass impairs the synthesis of calcitriol by proximal tubular cells; (ii) and the increase in fibroblast growth factor 23 (FGF23), due to the phosphate retention, inhibits renal hydroxylation of the calcidiol and, also, accelerates vitamin D catabolism (5). Additionally, a poorer synthesis of cholecalciferol in the skin, because of an inadequate sun exposure and restricted diet, reduces the availability of calcidiol [25(OH)D] for the second hydroxylation and, consequently, the calcitriol formation (5, 6).

Selective and non-selective vitamin D receptor activators (VDRA) have a dose-dependent, direct inhibitor effect on PTH synthesis (7), and thus are established therapies of the severe and progressive SHPT in advanced CKD stages (8). Because of their specific actions on various cell types (i.e. more pronounced in the parathyroid than in the intestine and bone), selective VDRA were assumed to have some advantages over non-selective vitamin D receptor activators.

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However, the correction of the nutritional vitamin D deficiency by supplementation with native vitamin D compounds (cholecalciferol or ergocalciferol), through the restoration of the 25(OH)D levels, could provide enough substrate to the 1- α -hydroxylase action in kidney. Consequently, it could contribute to the calcitriol increase and, thus, even to the suppression of PTH synthesis (9-11). Such a strategy could also improve the local tissue production of calcitriol, required for auto-/paracrine actions.

Although observational and randomized controlled studies have shown some degree of PTH suppression after nutritional vitamin D supplementation both in non-dialysis and dialysis CKD subjects (11-14), the endocrine modulation conferred by this approach remains uncertain, as the severity of renal dysfunction seems to dictate the therapeutic response (7,15). Moreover, the medium-long term clinical significance of native vitamin D supplementation or VDRA therapy with respect to CKD-MBD manifestations in non-dialysis CKD subjects is still debated.

The present study aims to compare the effects of a native vitamin D (i.e. cholecalciferol) with those of a selective VDRA (i.e. paricalcitol), on biochemical parameters of mineral metabolism and vascular function markers, in non-dialysis CKD subjects.

MATERIALS AND METHODS

An open label, multicentric, randomized, active comparator, controlled study, which enrolled

subjects with CKD stages G3 to G5 (non-dialysis) and SHPT was performed over a period of 18 months (between March 2010 - September 2011) divided in a screening phase (12 months) and an intervention phase (6 months).

Two tertiary care Nephrology departments from the south-east part of the country were involved. The study protocol was approved by the local Ethics Committees.

Patients

Subjects were selected from patients admitted in the two participant Nephrology centers, based on a set of selection criteria (Table 1). Adults with diagnosis criteria for CKD, persistent on two distinct occasions in a 3-month period according to current guidelines (1,2), were considered eligible and entered the screening phase after signing an informed consent form.

Of 195 patients initially screened, 157 met CKD criteria for inclusion, and of these, 76 agreed to participate (Fig. 1). Only 48 subjects who had persistently elevated serum intact PTH (iPTH) values (on two consecutive measurements at least 2 months apart) and lower serum 25(OH)D were enrolled in the intervention phase. One subject from the cholecalciferol group dropped out due to inconvenience to adhere to the study visits. The final analysis included 47 subjects, 23 in the cholecalciferol group (VitD) and 24 in the paricalcitol group (VDRA) (Fig.1).

Table 1. Selection criteria

Inclusion criteria	Exclusion criteria
1. Age > 18 years old	1. Acute kidney injury
2. Chronic kidney disease defined as: eGFR <60mL/min 1.73m ² (MDRD4) and/or ACR >30mg/g, persistent for > 3 Mo	2. Ongoing RRT or RRT predictable in the next 12 months (Mo)
3. Serum iPTH > 75pg/mL	3. Presence of an arterio-venous fistula
4. Serum 25(OH)D <30ng/mL	4. Immunosuppressive therapy in the prior 6 Mo
	5. Bisphosphonates therapy in the prior 6 Mo
	6. VDRA treatment in the prior 6 Mo
	7. Active cancers or cancers in the prior 6 Mo
	8. Malabsorption-maldigestion syndrome
	9. Active hepatopathies (ALT or AST levels more than 3 times higher than the reference range of laboratory)
	10. Hepatic insufficiency (at least Child B Class)
	11. Active infections
	12. Known allergy or intolerance for a vitamin D compound
	13. Serum calcium >10.5mg/dL at inclusion
	14. Serum phosphate >5mg/dL at inclusion

eGFR - estimated glomerular filtration rate; ACR - urinary albumin to creatinine ratio; iPTH - intact parathormone; 25(OH)D - calcidiol; RRT - renal replacement therapy; VDRA - vitamin D receptor activator; ALT - alanine aminotransferase; AST - aspartate aminotransferase; Mo - months.

Figure 1. Study outline.

Intervention

At the end of the screening phase, subjects who fulfilled the selection criteria were randomized 1:1 after stratification by CKD stages, to receive either cholecalciferol (vitD) 1000IU daily, with no further dose adjustment, or paricalcitol (Zemplar®) 1mcg once daily if iPTH was <500pg/mL and 2mcg once daily if iPTH was >500pg/mL at enrolment. The dosage of paricalcitol was adjusted if hypercalcemia (serum calcium >10.5mg/dL), severe hyperphosphatemia (serum phosphorus >6mg/dL), and/or abrupt changes in iPTH, persistent at two consecutive measurements, occurred.

The duration of therapeutic intervention was 6 months. Study medication was provided by medical prescriptions and adherence to treatment was evaluated by counting the remaining pills at each study visit. Subjects who omitted 5% or more of the total monthly dose were considered non-compliant and were excluded from the study.

Study assessments

After treatment allocation, subjects were

assessed every 2 weeks during the first month and monthly afterwards, until the study completion.

Clinical assessment and adverse events recording were performed at each visit. Biochemical parameters were measured, as follows: serum total calcium (tCa) and phosphate (PO₄) at each visit, iPTH monthly during the first two months and bi-monthly thereafter, 25(OH)D and alkaline phosphatase (ALP) at baseline, 2 and 6 months, respectively. Serum creatinine (SCr) for eGFR calculation and urinary biochemical parameters (urinary protein, albumin, creatinine, calcium and phosphorus) from 24-Hour urine collections were measured monthly.

Serum iPTH was assessed using a second generation commercial chemiluminometric kit (LIAISON® N-TACT® PTH gen II, DiaSorin), with the normal reference range between 17.2 and 73.9pg/mL. SHPT was considered at iPTH values greater than 75pg/mL. Serum calcidiol was measured with a chemiluminometric commercial kit (LIAISON® 25OH vitamin D TOTAL, DiaSorin). The reference interval of this method is 30-100ng/mL. Values

below 10ng/mL and between 10-30ng/mL defined the deficiency and insufficiency status, respectively. Standard spectrophotometric methods on automatic multi-parameter analyzer were used to measure the routine serum and urinary biochemical parameters. The laboratory reference values for ALP were 42-140IU/L, for tCa: 8.5-10.5mg/dL and for PO4: 2-5mg/dL.

Arterial stiffness was evaluated at baseline and at 6 months, by cardio-ankle vascular index (CAVI), using VaSera VS-1500, an automated waves analyzer, as described by the manufacturer (Fukuda Denshi Co

LTD, Tokyo). A CAVI ≥ 9 was indicative for arterial stiffness (16).

Study end-points

The median differences in serum concentrations of iPTH, 25(OH)D and alkaline phosphatase at the end of study (EOS) as compared to baseline were assessed as primary efficacy end-points.

The percentages of subjects who had (i) a 30% decrease in serum iPTH, (ii) any reduction in

Table 2. General characteristics of the subjects

Parameter	VitD (n=23)*	VDRA (n=24)*	p
Age	61 (55; 66)	63 (54; 67)	0.87
Male (%)	48%	67%	0.19
BMI (kg/m ²)	27.1 (25.5; 29.0)	26.4 (24.6; 27.0)	0.36
Smokers (%)	13%	21%	0.47
Co-morbidities (%)			
Diabetes mellitus	30%	17%	0.26
HBP	92%	96%	0.97
ATS	42%	58%	0.31
ACR (mg/g)	47 (101; 582)	286 (322; 1452)	0.02
eGFR (mL/min/1.73m ²)	30.0 (25.4; 37.2)	24.6 (21.9; 33.9)	0.38
CKD stage (%)			
G3a	26%	17%	0.67
G3b	26%	29%	0.81
G4	39%	37%	0.91
G5	9%	17%	0.70
Primary renal disease (%)			
Vascular nephropathies	44%	46%	0.87
Glomerulonephritis	27%	29%	0.79
Interstitial nephropathies	25%	25%	0.38
Hereditary nephropathies	4%	17%	0.37

*Data are presented as median/mean (95% confidence interval) or percentage.

VitD - native vitamin D (Cholecalciferol) group; VDRA - Vitamin D receptor activators (Paricalcitol) group.

BMI - body mass index; HBP - arterial hypertension; ATS - atherosclerosis; ACR - urinary albumin-to-creatinine ratio; eGFR - estimated glomerular filtration rate; CKD - chronic kidney disease.

Table 3. The changes of the main study parameters after the two therapeutic interventions

Parameter	Group	Baseline	End of Study	Difference (EOS - Bs)	p#
iPTH (pg/mL)	VitD	80.8* (78.2; 123)	110 (64.5; 170)	13.3 (-8.1; 35.0)	0.008
	VDRA	161 (102; 327)	137.5 (85.4; 217)	-35.2 (-83.0; 9.0)	
25(OH)D (ng/mL)	VitD	11.4 (7.73; 15.7)	25.8* (22.9; 34.2)	15.5 (13.3; 17.2)	<0.001
	VDRA	14.7 (11.5; 19.7)	15.3 (9.0; 20.5)	0.4 (-6.1; 3.7)	
ALP (IU/L)	VitD	66* (59; 101)	59 (49; 75)	-10 (-23; -2)	0.02
	VDRA	101 (78; 128)	68 (47; 81)	-34 (-58; -11)	
CAVI	VitD	9.7 (9.1; 11.1)	9.7 (9.0; 10.3)	-0.10 (-0.84; 0.58)	0.9
	VDRA	11.1 (9.6; 12.5)	10.3 (9.5; 12.0)	-0.15 (-0.72; 0.24)	
eGFR (mL/min)	VitD	30 (23; 38)	29 (18; 41)	-2 (-5; 0)	0.3
	VDRA	25 (18; 35)	22 (14; 32)	-4 (-6; -2)	
ACR (mg/g)	VitD	47 (14; 182)*	38 (24; 198)	-5 (-39; 20)	0.6
	VDRA	286 (65; 965)	207 (32; 550)	-19 (-202; 30)	

Data are presented as median (95%CI); * p <0.05 between groups at Bs or EOS; # p value for the comparison of median changes (EOS - Bs) in study parameters between groups.

EOS - End of study; Bs - Baseline; VitD - native vitamin D (Cholecalciferol) group (n=23); VDRA - Vitamin D receptor activator (Paricalcitol) group (n=24); iPTH - Serum intact parathyroid hormone; 25(OH)D - Serum calcidiol; ALP - Serum total alkaline phosphatase; CAVI - cardio-ankle vascular index; eGFR - estimated glomerular filtration; ACR - Urinary albumin-to-creatinine ratio (mg/g).

absolute values of iPTH, (iii) who reached normal vitamin D status (serum calcidiol $>30\text{ng/mL}$), or (iv) had an increase in $25(\text{OH})\text{D}$ serum concentrations at the end of study, served as secondary efficacy end-points. Another secondary end-point was the median change at EOS from baseline in CAVI, as marker of arterial function.

The primary safety parameters were the rate of incidence of hypercalcemia ($>10.5\text{mg/dL}$) and hyperphosphatemia ($>5.0\text{mg/dL}$).

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA) and Analyse-it software.

All investigated variables were tested for normality. Continuous variables were evaluated for normality with the Shapiro-Wilk test and are presented as mean or median and 95% confidence interval (95%CI). Student's *t* test, Wilcoxon and Mann-Whitney tests were used to compare parametric and non-parametric variables, as appropriate. The effect size was estimated with Hodges Lehman location shift in means/medians. Nominal variables were described using frequencies (percentages) and Chi2 test was used for analysis.

A *p* value <0.05 was considered statistically significant for all the tests applied.

RESULTS

The demographic characteristics, primary kidney disease and kidney function at baseline were similar in both groups, but proteinuria was higher in the VitD group (Table 2). Subjects had a median age over 60 years. Arterial hypertension was similarly highly prevalent. Almost one in two patients had at least one clinical manifestation of atherosclerosis, but less than one third had diabetes mellitus.

The CKD-MBD related parameters at baseline were comparable in both groups, with the notable exceptions of higher serum concentrations of iPTH and alkaline phosphatase in the VDRA group. Arterial stiffness was also similar, and the median CAVI over 9 suggested advanced arteriosclerosis in both groups (Table 3).

After the therapeutic intervention, there was an increasing trend in serum iPTH in the VitD group and a decreasing one in the VDRA group (Table 3). The differences between groups in the median change of iPTH from baseline to EOS (Fig. 2A), and in the proportion of patients with a decrease of iPTH from

Table 4. The effects of therapeutic interventions on the secondary study end-points

Parameter	VitD (n=23)	VDRA (n=24)	Difference between groups (VitD-VDRA)*	<i>p</i>
Patients with $>30\%$ reduction in serum iPTH at EOS (%)	13	25	-12 (-17; 27)	0.6
Patients with lower iPTH at EOS than at baseline (%)	39	71	-32 (-3; -56)	0.03
Patients with serum calcidiol $\geq 30\text{ng/mL}$ at EOS (%)	39	8	31 (7; 53)	0.01
Patients with higher serum calcidiol at EOS than at baseline (%)	100	54	46 (28; 65)	<0.001
Incidence of hypercalcemia ($>10.5\text{mg/dL}$) [†] (%)	0.6	1.8	1 (-1.7; 3.7)	0.5
Incidence of hyperphosphatemia ($>5\text{mg/dL}$) [†] (%)	0.6	0.6	0 (-6; 6)	1

* Expressed as median (95%CI); † per 100 measurements

VitD - native vitamin D (Cholecalciferol) group; VDRA - Vitamin D receptor activator (Paricalcitol) group; EOS - End of study; iPTH - Serum intact parathyroid hormone; ALP - Serum total alkaline phosphatase.

Figure 2. Median changes in serum concentrations of: A) intact parathyroid hormone (iPTH), B) alkaline phosphatase (ALP), and C) calcidiol [$25(\text{OH})\text{D}$], at 2 and 6 months from baseline, in cholecalciferol (VitD) and paricalcitol (VDRA) groups. Mo - months

baseline to EOS (Table 4) were significantly higher in the VDRA group. However, the iPTH serum concentration and the proportion of subjects with more than 30% decrease in iPTH were similar in the two groups (Table 3, 4).

In contrast, the median increase from baseline in 25(OH)D levels was higher in the VitD group at any study moment than in the VDRA group (Fig. 2C). Treatment with cholecalciferol normalised the vitamin D levels (serum calcidiol >30ng/mL) in a higher proportion of subjects, and the improvement in 25(OH)D status was observed in all subjects who received cholecalciferol as compared to only half of those treated with paricalcitol (Table 4). Moreover, at the end of study, serum calcidiol was significantly

higher in subjects receiving native vitamin D (Table 3).

Although the serum concentrations of ALP were initially lower in the VitD group, the median decrease at EOS compared to baseline was higher in the VDRA group (Table 3, Fig. 2B).

Furthermore, the absolute differences between groups (VitD-VDRA) as regards the median changes in the primary efficacy parameters at the end of therapeutic intervention *versus* baseline were statistically significant: a higher decrease of serum iPTH and ALP was found after active vitamin D, while serum calcidiol increased more in cholecalciferol-treated group (Figure 3).

The variation in CAVI was minimal in both groups, and the median variation (EOS - baseline) was not significant (Table 3). The intervention did not induce variations either in ACR or in eGFR in any group (Table 3).

As for the safety parameters, median serum calcium and phosphate varied only in the accepted range (Fig. 4). Moreover, the incidence of hypercalcemia and hyperphosphatemia was small and alike in both groups (Table 4).

DISCUSSION

In the present multicentre randomized controlled-trial, comparing effects of a native vitamin D and a selective VDRA on biochemical and vascular parameters of CKD-MBD in non-dialysis subjects with SHPT, the VDRA was effective in ameliorating serum iPTH and ALP, whereas the native vitamin D corrected only the nutritional vitamin D deficiency. Neither intervention influenced the arterial stiffness.

More than 85% of circulating calcidiol is bioactivated in peripheral tissues, achieving auto- and paracrine functions, whereas only approximately 5% is hydroxylated by the kidney, to accomplish

Figure 3. The absolute differences in median changes of the primary efficacy parameters at end of study vs. baseline between groups (VitD-VDRA). Data expressed as median and 95%CI. VitD - native vitamin D (Cholecalciferol) group; VDRA - Vitamin D receptor activator (Paricalcitol) group; iPTH - Serum intact parathyroid hormone; ALP - Serum total alkaline phosphatase; 25(OH)D - Serum calcidiol.

Figure 4. Serum A) calcium and B) phosphate at study moments in cholecalciferol (VitD) and paricalcitol (VDRA) groups. EOS - end of study; Mo - months.

endocrine functions (17). The discovery of 1- α -hydroxylase in extrarenal sites and the possibility of extrarenal calcitriol synthesis (18) made native vitamin D supplementation a potential therapeutic weapon for vitamin D deficiency and SHPT in CKD patients. Some studies have shown improved 25(OH)D and 1,25(OH)₂D concentrations and a reduction in SHPT after supplementation with native vitamin D alone, even in patients undergoing dialysis, which can be explained by an increased extrarenal production of calcitriol (6,13). A degree of PTH suppression consecutive to nutritional vitamin D supplementation was reported in observational and randomized controlled studies with variable statistical power (15,19), but the effects seemed to be limited (10). On the other hand, the role of VDRA, selective or not, regarding efficient SHPT reduction has been clearly documented (17,20). A better safety profile (21) and a stronger association with survival benefit (15) made selective VDRA the preferred choice in clinical practice, at least in dialysis patients.

There are few prospective studies which directly compared the efficacy of two vitamin D compounds that are fundamentally different regarding their mechanism of action. One of them compared the effects of 3-month therapy with cholecalciferol and doxercalciferol on biochemical CKD-MBD parameters in stage 3-4 CKD patients (22). The results were concordant to those of the current study: serum iPTH was significantly suppressed only in subjects receiving the active vitamin D, but no difference in iPTH concentrations was documented at the end of study between the two investigated arms. Furthermore, only supplementation with native vitamin D had efficiently corrected vitamin D nutritional deficiency, as reflected by improved serum calcidiol (22). Similarly, Kovesdy *et al.* (23) compared the effects of a 4-month therapy with paricalcitol to ergocalciferol in a randomized controlled study which included 3-4 CKD patients with SHPT and vitamin D insufficiency. A significant reduction of iPTH was obtained only after active vitamin D treatment and a significant improvement in vitamin D status was reached only with native vitamin D therapy. However, serum iPTH concentrations at the end of treatment period differed significantly between the two groups, in favour of paricalcitol. Moreover, in line with the present study, serum ALP was reduced only by active vitamin D therapy. The incidence of hypercalcemia and hyperphosphatemia were not a problem (23).

In line with the aforementioned studies, in our

data, cholecalciferol better replenished the 25(OH)D stores, correcting the vitamin D nutritional deficiency, while paricalcitol better suppressed PTH. It can therefore be speculated that the association of both compounds could have cumulative beneficial effects in patients with a moderate-severe decline in kidney function, but randomized controlled studies are needed in order to verify this hypothesis. Nevertheless, the rather low doses of cholecalciferol (1000UI/day) and the duration of only six months in the current study had probably influenced the results. One might speculate that higher doses would be required to reveal beneficial systemic effects of native vitamin D.

Serum alkaline phosphatase, especially the bone isoenzyme, is expressed by osteoblasts and is considered by some a marker of high bone turnover and even a better predictor of outcome in CKD patients than iPTH (24). Persistently increased serum ALP have been associated with cardiovascular and all-cause mortality, and also with accelerated progression towards renal replacement therapy (RRT), independently of iPTH concentrations (25, 26). All these associations may be explained by the increased PTH-related activity of ALP, which result in higher local concentration of inorganic phosphate in bone, where it favours mineralization (26), and in vascular muscle cells, where it induces phenotypic changes and initiates calcification (24, 27). As reported by others (7), in the present study, iPTH and ALP decreased only in VDRA group, which suggests not only a benefit of paricalcitol in the treatment of high-turnover bone disease, but also a possible improvement in CKD patients' outcome.

Arterial stiffness is a component of CKD-MBD. Experimental data support a beneficial effect of VDRA on arterial stiffness, by modulating the blood vessels calcification (28). However, the clinical results were conflicting, suggesting that this effect is dependent on the biochemical milieu, on dosage and treatment duration (28-31). In our data, CAVI - a measure of arterial stiffness, independent of blood pressure - was not influenced by any of the interventions. It is possible that the short study duration and the low used doses hampered the result. Also, as the investigated patients had advanced arteriosclerosis (median CAVI at baseline >9), it is conceivable that these pre-existing arterial lesions were difficult to be influenced by any intervention.

The serum calcium and phosphate remained in the accepted range along the study, irrespective of the type of vitamin D therapy. The incidence of

hypercalcemia and hyperphosphatemia was low, as reported in other studies (23, 32, 33).

Vitamin D receptor activators are also modulators of the renin-angiotensin-aldosterone axis (32,34). Accordingly, a degree of reduction in eGFR and proteinuria are to be expected with such therapies, as described in other reports (32,35,36). However, neither eGFR nor proteinuria varied in our patients. Possible explanations are the use of a low paricalcitol dosage and the mild depressing effect exerted by vitamin D compounds on angiotensin, as stated in the literature (37).

To our knowledge, this study is the only one conducted in our country to compare two essentially different vitamin D compounds, with a randomized multicentre design. However, some limits of this study should be highlighted: the relatively small sample size, which reduces the statistical power, and the open label design, which could have influenced adherence to intervention. Moreover, the doses of cholecalciferol were small and the study duration was too short, probably insufficient to reveal the full potential of the therapy.

In conclusion, in non-dialysis CKD patients, it seems that secondary hyperparathyroidism is more efficiently treated by active vitamin D, whereas the native compound better corrected the nutritional deficiency of vitamin D. None of the compounds modified arterial stiffness parameters.

Conflict of interest

The authors declare that they have no conflict of interest.

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