

Benefits of selective vitamin D receptor activators in kidney transplanted patients

Benefícios dos ativadores seletivos dos recetores de vitamina D em doentes transplantados renais

Aníbal Ferreira^{1, 2}, Inês Aires^{1,2}, Fernando Nolasco^{1,2}, Domingos Machado^{3,4}, Fernando Macário⁵, Pedro L. Neves^{6,7}, António G. Costa⁸, António M. N. Cabrita^{9,10}, Rui Castro¹¹, João B. Pereira¹²

¹ Nephrology Unit, Centro Hospitalar Lisboa Central EPE, Hospital Curry Cabral, Lisbon, Portugal

² Nova Medical School, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal

³ Transplantation Unit, Centro Hospitalar de Lisboa Ocidental EPE, Hospital de Santa Cruz, Carnaxide, Portugal

⁴ Portuguese Society of Diabetology, Lisbon, Portugal

⁵ Nephrology Unit, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal

⁶ Nephrology Unit, Centro Hospitalar do Algarve EPE, Faro, Portugal

⁷ Department of Biomedical Sciences and Medicine, Universidade do Algarve, Faro, Portugal

⁸ Nephrology Unit, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte EPE, Lisbon, Portugal

⁹ Nephrology Unit, Centro Hospitalar do Porto EPE, Porto, Portugal

¹⁰ Uninefro Matosinhos, Matosinhos, Portugal

¹¹ Nephrology Unit, Centro Hospitalar de Trás-os-Montes e Alto Douro EPE, Vila Real, Portugal

¹² Scientific ToolBox Consulting, Lisbon, Portugal.

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■ ABSTRACT

Severe chronic kidney disease may lead to disturbances, such as hyperphosphatemia, increased secretion of fibroblast growth factor-23 (FGF-23) and vitamin D deficiency. These may increase plasmatic levels of parathyroid hormone, and decrease plasmatic levels of calcium. Altogether, these may contribute to the development of secondary hyperparathyroidism, and to abnormalities in mineral metabolism. Kidney transplantation is the best option to improve longevity and quality of life in end-stage chronic kidney disease patients. Vitamin D deficiency has been associated with cardiovascular disease, which is the leading cause of death in chronic kidney disease. Therefore, diagnosing this deficiency may be pivotal for minimizing mortality in chronic kidney disease, because pharmacological treatments for this deficiency may be prescribed. Calcitriol is indicated for the treatment of vitamin D deficiency, both in chronic kidney disease and in kidney transplanted patients. However, calcitriol may increase the plasmatic levels of calcium and phosphorous, which can lead to vascular calcifications, that have been associated with cardiovascular mortality. Selective vitamin D receptor activators are indicated for the treatment of vitamin D deficiency in chronic kidney disease. These have the advantage of being associated with lower increases of plasmatic levels of calcium and phosphorous. These drugs also seem to have additional effects that may minimise patient morbidity and mortality, especially due to potentially reducing cardiovascular events. Unfortunately, there are few studies about the use of these drugs in kidney transplanted patients. Here we present a review

about the physiology of vitamin D, the consequences of its deficiency in chronic kidney disease and in kidney transplanted patients, and about the diagnosis and treatment of this deficiency. Finally, we discuss the new line of research about the efficacy and safety of selective vitamin D receptor activators in kidney transplanted patients.

Key-Words: Calcitriol; cholecalciferol; CRF-chronic renal failure; paricalcitol; renal Insufficiency, chronic; review; vitamin D.

■ RESUMO

A doença renal crônica pode conduzir a distúrbios metabólicos como hiperfosfatemia, aumento da secreção do “fibroblast growth factor- 23”, e deficiência de vitamina D, que por sua vez, podem conduzir a um aumento dos níveis plasmáticos da paratormona, e a uma diminuição dos níveis plasmáticos de cálcio. Consequentemente, a doença renal crônica pode contribuir para o desenvolvimento de hiperparatiroidismo secundário, e de anomalias no metabolismo mineral ósseo. A transplantação renal é a opção que proporciona a maior longevidade e qualidade de vida, a doentes com doença renal crônica terminal. A deficiência de vitamina D tem sido associada a doença cardiovascular, que é a causa principal de mortalidade nos transplantados renais. Logo, o diagnóstico desta deficiência poderá ser crucial para tentar minimizar esta mortalidade, uma vez que esta deficiência de vitamina D pode ser corrigida terapêuticamente. O calcitriol tem como indicação terapêutica o tratamento da deficiência de vitamina D, tanto em doentes com doença renal crônica, como em doentes transplantados renais. No entanto, este fármaco pode aumentar os níveis plasmáticos de cálcio e de fósforo, conduzindo a potenciais calcificações vasculares, que têm sido associadas a mortalidade cardiovascular. Os ativadores seletivos dos recetores da vitamina D têm como indicação terapêutica o tratamento da deficiência de vitamina D na doença renal crônica. A vantagem destes fármacos é que têm sido associados a aumentos inferiores dos níveis plasmáticos de cálcio e fósforo. Estes fármacos têm ainda efeitos adicionais que podem minimizar a morbidade e a mortalidade, principalmente devido ao seu potencial para reduzir eventos cardiovasculares. Neste artigo apresentamos uma revisão de literatura sobre a fisiologia da vitamina D, sobre as consequências da sua deficiência na doença renal crônica e em doentes transplantados renais, e sobre o diagnóstico e tratamento desta deficiência. Finalmente, discutimos os resultados de estudos recentes, sobre a segurança e eficácia dos ativadores seletivos dos recetores da vitamina D em doentes transplantados renais.

Palavras-Chave: Calcitriol; colecalciferol; insuficiência renal, crônica; paricalcitol; revisão; vitaminaD.

■ INTRODUCTION

Disturbances in bone and mineral metabolism may be observed since early stages of chronic kidney disease (CKD). For example, mild CKD (or stage 2 CKD), is characterised by an estimated glomerular filtration rate (GFR) between 60 and 90 ml/min/1.73 m², as well as by disturbances in bone and mineral metabolism, such as increased levels of fibroblast growth factor- 23 (FGF-23), and decreased levels of calcidiol and calcitriol. Usually, at these stages of CKD,

serum phosphate levels are either normal or reduced, due to the effects of the phosphaturic hormones (FGF-23 and parathyroid hormone [PTH]) on the kidney tissue that still responds to these, and also due to the decrease in intestinal phosphate absorption (consequence of the vitamin D deficiency)

More severe CKD, such as stage 5 CKD, is characterized by a GFR < 15 mL/min/1.73 m² and, if untreated, by severe disturbances in bone and mineral metabolism, such as hyperphosphatemia,

increase in FGF-23, and active vitamin D deficiency, due to a decreased activity of the 1α -hydroxylase (an enzyme mainly present on the tubular cells of the kidney, that hydroxylates 25-OH-vitamin D)¹. This leads to the rise of the plasmatic levels of PTH and eventually to hypocalcaemia. Altogether, these contribute to the development of secondary hyperparathyroidism (SHPT) and to abnormalities in mineral metabolism.

Kidney transplantation is the treatment option that offers the best longevity and quality of life for end-stage CKD patients. However, although successful kidney transplantation may improve GFR, kidney transplanted patients may still have CKD, which may lead to severe mineral bone metabolic disease. Furthermore, despite a better 1α -hydroxylase activity, kidney transplanted patients may still have vitamin D deficiency for several reasons, such as: inadequately high FGF-23 serum levels, regular use of corticosteroids (part of the normal post-transplant immunosuppressive therapy), low exposure to sun light (normally recommended to prevent cutaneous tumours), diet restrictions, and mild to moderately decreased kidney function always present after kidney transplant.

Vitamin D deficiency has been associated with cardiovascular disease (CVD), which is the leading cause of death in CKD². There is no clear evidence from randomised controlled trials that vitamin D supplementation may be associated with a reduction of mortality in CKD patients. However, according to a meta-analysis by Duranton *et al.*³ that included 14 observational studies (observing altogether more than 35,155 deaths, in a total population of 194,932 patients with CKD or undergoing dialysis), supplementation with vitamin D derivatives is significantly associated with a 27% relative risk reduction of all-cause mortality (relative risk 0.73, 95% CI 0.65–0.82) and with 37% relative reduction of cardiovascular mortality risk (relative risk 0.63, 95% CI 0.44–0.92). Therefore, diagnosing vitamin D deficiency in CKD may be pivotal for minimizing mortality of CKD patients, because appropriate pharmacological treatments may be prescribed for this deficiency.

Calcitriol has been prescribed to treat vitamin D deficiency both in CKD and in kidney transplanted patients⁴. Although calcitriol may treat this deficiency, undesirably it also may increase the plasmatic levels

of calcium and phosphorous, which can lead to vascular calcifications that have been associated with mortality⁵⁻⁷.

Alternatively, selective vitamin D receptor activators (VDRA) may also be used to treat vitamin D deficiency in CKD, with the advantage of being associated with a lower incidence of hypercalcaemia and hyperphosphatemia⁸⁻¹⁰. Furthermore, these drugs also seem to have non-inflammatory (including immunomodulatory) and anti-inflammatory effects, which may minimise patient morbidity and mortality, especially due to potentially reducing cardiovascular events¹¹⁻¹³.

Given the benefits of paricalcitol in CKD (the only selective VDRA drug currently licensed in Europe and USA), it is possible to hypothesise that this drug may also benefit kidney transplanted patients. Unfortunately, there are few studies investigating this.

In this review we present an overview about the physiology of vitamin D, the consequences of its deficiency in CKD, especially after kidney transplantation. Furthermore, we discuss the state of the art about the treatment of vitamin D deficiency in CKD, including the non-inflammatory (including immunomodulatory) and anti-inflammatory benefits of selective VDRA therapy. Finally, we discuss the current line of research about the efficacy and safety of selective VDRA in kidney transplanted patients.

■ THE PHYSIOLOGY OF VITAMIN D

Vitamin D is a steroid-derived hormone whose activation requires several enzymatic steps. Briefly, 7-dehydrocholesterol is photo-activated in the skin into cholecalciferol, which is then converted in the liver into calcidiol (25[OH]D), which is finally converted in the kidney (by the 1α -hydroxylase) into calcitriol (1,25[OH]₂D₃) that is the most active form of vitamin D. Then calcitriol binds to nuclear vitamin D receptors (VDRs), regulating the expression of more than 200 genes, such as those encoding the FGF-23 and its co-receptor klotho. These play a major role in the regulation of plasmatic calcium and phosphorous

Vitamin D deficiency has been associated with opportunistic infections after kidney transplantation¹⁴,

and cancer¹⁵, and it is not yet clear whether vitamin D supplementation may prevent these^{16, 17}. Furthermore, as presented below, this deficiency may also lead to SHPT, CVD, and to poor outcomes after kidney transplantation.

■ VITAMIN D DEFICIENCY AND SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism is a common metabolic disorder that may occur due to vitamin D deficiency, both in CKD¹⁸ and in post-kidney transplantation patients¹⁹. This disorder is characterized by an increased synthesis of PTH by the parathyroid gland, contributing to bone mass loss²⁰ and hypercalcaemia²¹. Therefore, the reduction of the plasmatic levels of PTH toward normal levels is a strategy for preventing or treating SHPT. As it will be presented in detail later in this review, this can be done using drug classes such calcimimetics, non-selective VDRAs, and selective VDRAs. Treating SHPT is important because this disease has been associated with CVD, due to ventricular hypertrophy and coronary heart disease²².

■ VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Vitamin D deficiency has been associated with CVD morbidity and mortality. A recent cohort study²³ investigated the association between pre-operative plasmatic levels of calcidiol (a precursor of vitamin D) and major cardiac and cerebral vascular events in a sample of 4,418 cardiac surgical patients. For 38.0% of patients these levels were deficient (i.e., < 30 nmol/L), for 32.3% insufficient (i.e., between 30 and 49.9 nmol/L), and for 3.1% high (i.e., > 100 nmol/L). The odds ratio for major cardiac and cerebrovascular events was 2.23 (95% CI, 1.31-3.79) for deficient levels, 1.73 (95% CI 1.01-2.96) for insufficient levels, and 2.34 (95% CI, 1.12-4.89) for high levels, when compared to calcidiol levels between 75-100 nmol/L. Therefore, it was concluded that vitamin D deficiency is prevalent in pre-operative cardiac surgical patients, and that it is an independent risk factor for major cardiac

and cerebral vascular events. Further research is still needed to investigate whether native vitamin D supplementation may reduce the risk of CVD in CKD patients²⁴.

■ THE ROLE OF VITAMIN D DEFICIENCY IN THE OUTCOME OF KIDNEY TRANSPLANTATION

Vitamin D deficiency has been associated with a poor outcome of renal transplantation, but it is unclear whether this may be improved by correcting this deficiency. For example, a retrospective study²⁵ suggested that vitamin D supplementation, between 3 and 12 months post-transplantation, did not confer structural and functional nephroprotection in a sample of 64 patients. However, a recent study²⁶ suggested that vitamin D supplementation, within the first 90 days post-transplantation, was associated with fewer cases of acute cellular rejection. Further research is still needed to investigate whether vitamin D supplementation may improve the outcome of kidney transplantation.

For all the above, the diagnosis of vitamin D deficiency in CKD, and in post-kidney transplantation, may be pivotal for deciding on the appropriateness of prescribing a treatment for it. This may potentially prevent not only SHPT and CVD, but also poor kidney transplantation outcomes, reducing morbidity and mortality of CKD patients.

■ DIAGNOSIS OF VITAMIN D DEFICIENCY

Vitamin D deficiency is diagnosed by dosing deficient plasmatic levels of calcidiol. However, there is no consensus regarding its normal and pathological plasmatic levels. Generally, plasmatic levels of calcidiol between 30 and 150 ng/ml (75-375 nmol/l) are indicative of normal vitamin D levels, above 150 ng/ml (375 nmol/l) are indicative of excessive vitamin D levels, between 20 and 30 ng/ml (50-75 nmol/l) are indicative of deficient vitamin D levels, and below 20 ng/ml (50 nmol/l) are indicative of severely deficient vitamin D levels^{2, 27}.

■ TREATMENT OF VITAMIN D DEFICIENCY IN SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism may be treated with calcimimetic drugs (e.g., cinacalcet), and/or with vitamin D receptor activators (VDRAs), which may be non-selective (e.g., alfacalcidol, calcitriol) or selective (e.g., paricalcitol)^{10, 28}. Cinacalcet can induce hypocalcaemia and, therefore, it requires frequent monitoring of the plasmatic levels of calcium. Calcitriol has been used to treat SHPT in CKD patients, because it binds to VDRs in the parathyroid glands reducing PTH production²⁹. It also acts in the intestines increasing calcium absorption, and in the bones balancing their reabsorption and formation. Unfortunately, this treatment has important side effects such as hypercalcaemia and hyperphosphatemia, which may increase the risk of extraosseous calcifications that have been associated with increased cardiovascular mortality⁶.

Unlike with non-selective VDRAs, selective VDRAs are more specific to VDRs located in the parathyroid, rather than those located in the intestines and bone. Therefore, the action of selective VDRAs results in lower increases of the plasmatic levels of calcium and phosphate^{8, 9}. Paricalcitol is the only commercially available selective VDRA in Europe and USA, and it is licensed for the prevention and treatment of SHPT in CKD patients (stages 3, 4, and 5), both in pre-dialysis and during dialysis.

Paricalcitol reduces PTH levels, with fewer cases of hypercalcaemia and hyperphosphatemia, and prevents deleterious bone reabsorption. According to an early double blind randomised controlled trial⁹, paricalcitol decreased PTH plasmatic levels in CKD patients with SHPT, by approximately 60% over 12 weeks of study, and it led neither to hypercalcaemia, nor to significant increases in plasmatic phosphate levels. Furthermore, a recent prospective observational study⁸ investigated the safety and efficacy of intravenous paricalcitol in the treatment of SHPT in 1,313 dialysed patients. After 6 months of treatment, a PTH reduction of $\geq 30\%$ was observed in 63.0% of the patients, and a PTH reduction of $\geq 60\%$ was observed in 35.9% of patients. Furthermore, calcium and phosphorous levels remained stable over time in the majority of patients, and alkaline phosphatase (i.e., a bone

turn-over marker) plasmatic levels improved significantly ($p < 0.0001$) from baseline (median = 98U/L) to study end (median = 83 U/L).

Further research is still needed to compare all-cause mortality, CVD morbidity, and CVD mortality, for SHPT patients treated with paricalcitol versus cinacalcet²⁴. In a recent RCT³⁰, the use of paricalcitol was associated with beneficial effects on bone turn-over markers (alkaline phosphatase and bone specific alkaline phosphatase) when compared to cinacalcet. However, levels of FGF-23 were increased with paricalcitol, and this could suggest that paricalcitol was associated with a higher risk of death than cinacalcet. This result may be explained by the different mechanisms of action of these drugs. Cinacalcet reduces PTH plasmatic levels by antagonizing calcium-sensing receptors, whereas paricalcitol does this by activating VDRs, which may also promote the production of FGF-23. The authors of this study suggested that it is necessary to further investigate the association between FGF-23 and death, because paricalcitol has been consistently associated with decreased mortality in numerous studies³¹⁻³⁷.

Observational studies suggest that the risk of death (from all causes) in CKD patients is significantly reduced with paricalcitol versus calcitriol, or no treatment. For example, a cohort study³⁷ investigated survival in 67,399 patients on haemodialysis, taking either paricalcitol ($n = 29,021$) or calcitriol ($n = 38,378$). It suggested that patients taking paricalcitol had 16% (95% CI; 10-21) superior 3-year survival rate than those taking calcitriol. Increased survival rates were also identified for patients taking paricalcitol versus no treatment³¹⁻³⁵, but survival rates for paricalcitol (15.3 [95% CI; 13.6-16.9] deaths/100 patient-years) versus doxercalciferol (15.4 [95% CI; 13.6-17.1] deaths/100 patient-years) were not found to be significantly different³³.

Studies have also reported that paricalcitol is associated with lower CVD mortality, when compared to calcitriol. Indeed, it was reported that the CVD death rates for patients taking paricalcitol were 0.106 per person-year, whereas for those taking calcitriol were 0.128 per person-year³⁷. Similarly, lower death rates due to CVD were also identified for treatment with alfacalcidol when compared to no treatment³⁶. These results are encouraging, because it is known that CVD is a major cause of death in CKD patients.

Curiously, studies report that CKD patients taking paricalcitol have lower mortality rates, independently of the plasmatic levels of calcium, phosphorous, or PTH at the end of study^{35, 37}. This suggests that the benefits of paricalcitol may not be limited to its effects on mineral and PTH metabolism. In fact, as presented below, several studies proposed different potential non-inflammatory (including immunomodulatory) and anti-inflammatory effects for paricalcitol (or selective VDRA) that may explain its improved survival rates in CKD patients⁵.

■ NON-INFLAMMATORY AND ANTI-INFLAMMATORY EFFECTS OF SELECTIVE VITAMIN D RECEPTOR ACTIVATORS

Four non-inflammatory effects have been identified for selective VDRA. Firstly, selective VDRA regulate the plasmatic levels of PTH, with a low incidence of hypercalcaemia and hyperphosphatemia³⁸. This is important because increased levels of phosphate and calcium may contribute to vascular calcifications⁶. Secondly, studies in animals showed that treatment with paricalcitol may also prevent these vascular calcifications, by interactions with vascular smooth muscle cells⁶. Thirdly, studies in animals showed that paricalcitol improves left ventricular function¹³. Finally, studies in animals also showed that paricalcitol treatment suppresses the renin-angiotensin system (RAS), which may potentially decrease the risk of hypertension, myocardial infarction and stroke¹¹. However, further research is still needed to further investigate the last 3 effects in humans.

Recently, in the PENNY study⁵, a positive role of paricalcitol in conditioning endothelium-dependent vasodilatation was described. In fact, a significant endothelium-dependent vasodilatation and change in low-mediated dilation in paricalcitol treated patients was observed. Furthermore, the post-hoc analysis of PRIMO study⁷ showed that CKD patients randomized to the paricalcitol arm developed less atrial volume.

Chronic kidney disease is characterized by chronic inflammation³⁹, which is strongly correlated with increased morbidity and mortality⁴⁰. Such as

calcitriol, selective VDRA also have anti-inflammatory effects. In fact, an *in vitro* study¹² demonstrated that calcitriol and paricalcitol have immunomodulatory effects, by inhibiting the maturation of dendritic cells, and consequently decreasing the production of bioactive IL-2. Furthermore, in a randomised placebo-controlled trial⁴¹ with CKD patients (stages 2 and 3), it was observed that treatment with paricalcitol for a month reduced inflammation status, by decreasing reactive C protein levels. As similar results were obtained in other studies⁴²⁻⁴⁴, it is possible to raise the hypothesis that paricalcitol treatment may reduce inflammation status, decreasing the risk of atherosclerosis in CKD patients.

Kidney transplantation is the best option for decreasing mortality in end-stage CKD patients. Despite this, nearly all renal transplanted patients have a decreased GFR (lower than 60 mL/min per 1.73 m²), when compared with normal native kidney function. Furthermore, vitamin D deficiency may remain in renal transplanted patients due to several reasons (e.g., corticosteroid therapy, decreased exposure to sun light). As it will be presented below, there are few studies investigating whether the benefits of paricalcitol identified for CKD patients can also be identified in kidney transplanted patients.

■ EFFICACY AND SAFETY OF SELECTIVE VITAMIN D RECEPTOR ACTIVATORS IN KIDNEY TRANSPLANTED PATIENTS

To our knowledge, there are only 6 published studies investigating the efficacy and safety of paricalcitol in the treatment of SHPT in kidney transplanted patients (see Table I). Four⁴⁵⁻⁴⁸ of these were reported in original articles, and 2 in conference abstracts^{49, 50}. Among these studies, 4 were interventional (i.e., 3 randomised, open-label, parallel two-arm studies^{46, 48, 50}, and 1 randomised, open-label, crossover, two-arm study⁴⁵), 2 were observational (1 prospective cohort study⁴⁷, and 1 retrospective cohort study⁴⁹), 4 included a control group^{45, 46, 48, 50} and 2 did not^{47, 49}. The number of patients included varied between 12⁴⁸ and 100⁵⁰. The prescribed doses of oral paricalcitol were:

Table 1

Studies investigating the efficacy and safety of paricalcitol in the treatment of secondary hyperparathyroidism in kidney transplanted patients

Authors	Patients, study design, and follow-up	Interventions	PTH levels
Trillini M. <i>et al.</i> 2014 ⁴⁵	Patients (N = 43): >18-year-old kidney transplanted patients with secondary hyperparathyroidism ^a Study design: Randomized, open-label, crossover two-arm study (6 months treatment with oral paricalcitol, followed by 6 months of treatment without paricalcitol, or vice-versa) Follow-up: 12 months	Treatment: 1 µg/day of paricalcitol. If this dose was tolerated (calcium ≤ 10.2 and phosphate ≤ 5.1 mg/dL) for 3 months, it was increased to 2µg/day Control: Treatment without paricalcitol	After 3 months of paricalcitol: Significant reduction ($p < 0.001$) for treatment with paricalcitol 1µg/day (median = 77.90 [60.50-106.50] pg/mL) vs. control at the same time point (median = 116.45 [84.50-158.10] pg/mL) After 6 months of paricalcitol: Significant reduction ($p < 0.001$) for treatment with paricalcitol 2µg/day (median = 63.25 [52.00-79.70] pg/mL) vs. control at the same time point (median = 128.00 [94.00-166.40] pg/mL)
Amer H. <i>et al.</i> 2013 ⁴⁸	Patients (N = 100): > 18 year-old patients receiving first or second kidney transplant, and eligible for the corticosteroid avoidance immunosuppression protocol offered at Mayo Clinic ^b Study design: Randomized, open-label, parallel, two-arm study Follow-up: 1 year	Treatment (n = 51): Calcium carbonate supplement (500 mg of elemental calcium) twice a day, in combination with: – Paricalcitol 1 µg/day orally (between days 3 to 15 post-transplant) – Paricalcitol 2 µg/day orally (from day 15 post-transplant onwards), only if no hypercalcaemia Control (n = 49): Calcium carbonate supplement (500 mg of elemental calcium) twice a day	Transplant day (day 0): No significant ($p \geq 0.05$) differences between treatment (median = 198 pg/mL) and control (median = 236 pg/mL) 21 days post-transplant: Significantly ($p = 0.005$) lower for treatment (median = 50 pg/mL) vs. control (median = 69 pg/mL) 90 days post-transplant: Significantly ($p < 0.0001$) lower for treatment (median = 42 pg/mL) vs. control (median = 70 pg/mL) 365 days post-transplant: Significantly ($p = 0.0004$) lower for treatment (median = 42 pg/mL) vs. control (median = 85 pg/mL)
Gonzalez E. <i>et al.</i> 2013 ⁴⁷	Patients (N = 58): Post-kidney transplantation patients taking paricalcitol ^c Study design: Prospective Cohort study Follow-up: 2 years	Treatment (N = 58): Oral paricalcitol (1 µg on alternate days)	Reduction of baseline PTH ≥ 30%: 55% of patients (n = 32) at month 3; 65% of patients (n = 38) at month 6; 69% of patients (n = 40) at month 9; 72% of patients (n = 42) at month 12; 75% of patients (n = 44) at month 18; 75% of patients (n = 44) at month 24
Perez V. <i>et al.</i> 2013 ⁴⁶	Patients (N = 52): Stable post-kidney transplantation patients ^d Study design: Randomized, parallel, two-arm study Follow-up: 12 months	Treatment (n = 31): Oral paricalcitol 1 µg/day orally Control (n = 21): No paricalcitol	Treatment: Significant reduction from baseline (median = 110.00 [74.80-140.30]pg/mL) to month 3 (median = 74.25 [47.35-93.88]pg/mL; $p < 0.001$), and to month 12 (median = 59.70 [40.30-90.60]pg/mL; $p < 0.001$) Control: Non-significant change ($p \geq 0.05$) from baseline (median = 92.80 [71.13-118.65] pg/mL) to month 3 (median = 89.20 [70.13-120.85] pg/mL), and to month 12 (median = 79.15 [63.78-134.05] pg/mL)
Oliden C. <i>et al.</i> 2012 ⁵⁰	Patients (N = 12): Post-kidney transplantation patients ^e Study design: Randomized, open-label, parallel, two-arm study Follow-up: 24 weeks	Treatment (N = 6) Oral paricalcitol (no dose reported) Control (N = 6) Oral calcitriol 0.25 mg/day	Reduction of baseline PTH ≥ 30%: 6/6 patients in the treatment group vs. 3/6 patients in the control group (OR: 2; 95% CI 1.1 to 4.4; $p = 0.046$)
Valga E. F. <i>et al.</i> 2012 ⁴⁹	Patients (N = 66): Post-kidney transplantation outpatients ^f Study design: Retrospective cohort study Follow-up: 3 months	Treatment (N = 66) Paricalcitol 1 µg 3 times a week	Significant ($p = 0.006$) decrease from baseline (median = 175 [120-175]pg/mL) to month 3 (median = 157 [98-227]pg/mL)

Note: ^aInclusion criteria: serum intact parathyroid hormone levels >80 pg/mL (after a natural vitamin D or analogues washout period of at least 1-month), serum calcium ≤ 10.2 mg/dL, serum creatinine < 2 mg/dL, maintenance immunosuppressive therapy with calcineurin inhibitors and mycophenolate mofetil or azathioprine, no ongoing therapy with vitamin D analogues, and no evidence of active hepatitis C or B virus; or HIV infection or drug or alcohol abuse; Exclusion criteria: Patients with previous history of hypersensitivity, allergy, or intolerance to paricalcitol, changes in serum creatinine > 30% or acute rejection episodes over the last 6 months, or chronic clinical conditions expected to affect completion of the study or jeopardize data interpretation as well as pregnant, lactating, or fertile women without adequate contraception; ^bInclusion criteria: ≥ 18-year-old patients, receiving their first or second compatible kidney transplant and eligible for the corticosteroid avoidance immunosuppression. Exclusion criteria: prior hypercalcaemia, total 25-hydroxyvitamin D <10 ng/mL, recipients of multiple organs, or receiv-

Plasmatic levels of calcium and phosphorous	Glomerular filtration rate, creatinine clearance or serum creatinine	Proteinuria	Adverse events
<p>Calcium (after 3 months of paricalcitol): No significant differences ($p \geq 0.05$) between treatment with paricalcitol 1µg/day (mean = 9.59 [0.44] mg/dL) and control (mean = 9.53 [0.50] mg/dL)</p> <p>Calcium (after 6 months of paricalcitol): No significant differences ($p > 0.05$) between treatment with paricalcitol 2µg/day (mean = 9.61 [1.14] mg/dL) and control (mean = 9.56 [0.47] mg/dL)</p> <p>Phosphate (after 3 months of paricalcitol): Significantly higher ($p < 0.05$) for treatment with paricalcitol 1µg/day (mean = 3.34 [0.62] mg/dL) vs. control (mean = 3.20 [0.62] mg/dL)</p> <p>Phosphate (after 6 months of paricalcitol): No significant differences ($p \geq 0.05$) between treatment with paricalcitol 2µg/day (mean = 3.42 [0.71] mg/dL) and control (mean = 3.23 [0.62] mg/dL)</p>	<p>Creatinine clearance (mL/min./1.73 m²) after 3 months of paricalcitol: No significant differences ($p \geq 0.05$) between treatment with paricalcitol 1µg/day (median = 65.07 [47.79-81.09]) and control (median = 65.71 [50.90-87.76])</p> <p>Creatinine clearance (mL/min./1.73 m²) after 6 months of paricalcitol: Significantly lower ($p < 0.01$) for treatment with paricalcitol 2µg/day (median = 60.38 [44.10-79.24]) vs. control at the same time point (median = 68.11 [52.75-87.04])</p>	<p>Proteinuria after 3 months of paricalcitol: No significant differences ($p \geq 0.05$) between treatment with paricalcitol 1µg/day (median = 0.20 [0.13-0.48] g/24h) and control (median = 0.22 [0.14-0.74] g/24h)</p> <p>Proteinuria after 6 months of paricalcitol: No significant differences ($p \geq 0.05$) between treatment with paricalcitol 2µg/day (median = 0.14 [0.10-0.41] g/24h) and control (median = 0.23 [0.10-0.54] g/24h)</p>	<p>No serious adverse events were considered to be treatment-related</p> <p>Hypercalcaemia was observed at one single occasion in two patients taking paricalcitol 2 µg/day. Both events recovered with dose reduction to 1 µg/day. No hyperphosphatemia cases were reported</p>
<p>Calcium 365 days post-transplant: Significantly ($p < 0.001$) higher for treatment (mean = 9.9 [0.5] mg/dL) vs. control (mean = 9.7 [0.5] mg/dL)</p> <p>Phosphorous: 365 days post-transplant: No significant differences ($p = 0.11$) between treatment (mean = 3.2 [0.6] mg/dL) and control (mean = 3.5 [0.6])</p>	<p>Estimated glomerular filtration rates (mL/min./1.73 m²) 356 days post-transplant: No significant ($p = 0.66$) differences between treatment (mean = 51.2 [15.4]) and control (mean = 52.7 [14.1])</p>	<p>Proteinuria 356 days post-transplant: No significant ($p = 0.21$) differences between treatment (median = 91 [51-177] mg/24h) and control [median = 118 (66-242) mg/24h]</p>	<p>No serious adverse events were attributed to the study medication; only mild, reversible hypercalcaemia and hypercalciuria were attributed to paricalcitol (reversed by stopping calcium supplement and, in some cases, discontinuation of paricalcitol)</p>
<p>Calcium: Significant ($p < 0.01$) increase from baseline (mean = 9.3 [0.5] mg/dL) to month 24 (9.6 [0.4] mg/dL)</p> <p>Phosphorous: Significant ($p < 0.01$) increase from baseline (mean = 3.4 [0.5] mg/dL) to month 24 (mean = 3.5 [0.5] mg/dL)</p>	<p>Glomerular filtration rates (mL/min./1.73 m²): No significant ($p \geq 0.05$) differences between baseline (mean = 34.9 [14.1]) and month 24 (33.9 [14.0])</p>	<p>Proteinuria: Significant ($p < 0.01$) reduction from baseline (mean = 1.1 [0.7] g/24h) to month 24 (mean = 0.7 [0.7] g/24h)</p>	<p>Mild hypercalcaemia and mild hyperphosphatemia (responded to paricalcitol dose reduction)</p>
<p>Calcium (treatment): Significant increase ($p < 0.001$) from baseline (median = 9.34 [9.06-9.57] mg/dL) to month 12 (median = 9.64 [9.28-9.96] mg/dL)</p> <p>Calcium (control): Non-significant changes ($p = 0.027$) from baseline (median = 9.60 [9.35-9.87] mg/dL) to month 12 (median = 9.85 [9.55-10.18] mg/dL)</p> <p>Phosphorous (treatment): Non-significant changes ($p = 2.223$) from baseline (median = 3.10 [2.79-3.44] mg/dL) to month 12 (median = 3.13 [2.71-3.47] mg/dL);</p> <p>Phosphorous (control): Non-significant changes ($p = 1.764$) from baseline (median: 2.94 [2.52-3.39] mg/dL) to month 12 (median: 2.87 [2.50-3.33] mg/dL)</p>	<p>Serum creatinine (treatment): No significant change ($p = 0.189$) from baseline (median = 1.51 [1.22-1.93] mg/dL) to month 12 (1.47 [1.19-1.80] mg/dL)</p> <p>Serum creatinine (control): No significant ($p = 0.651$) change from baseline (median = 1.40 [1.10-1.70] mg/dL) to month 12 (median 1.24 [1.12-1.52] mg/dL)</p>	<p>Proteinuria (treatment): No significant change ($p = 1.884$) from baseline (median = 0.18 [0.13-0.35] g/24h) to month 12 (median = 0.21 [0.13-0.39] g/24h)</p> <p>Proteinuria (control): No significant change ($p = 2.925$) from baseline (median = 0.20 [0.13-0.41] g/24h) to month 12 (median = 0.16 [0.12-0.50] g/24h)</p>	<p>Incidence of hypercalcaemia and hyperphosphatemia were not significantly different between treatment vs. control; serum levels of calcium increased in both groups, but remained within normal range</p>
<p>Not reported</p>	<p>Not reported</p>	<p>Only the treatment group had a significant ($p = 0.02$) proteinuria reduction from baseline (mean = 481.6 [126.5] mg/L) to week 24 (mean = 203 [284] mg/L)</p>	<p>Episodes of hyperphosphatemia and hypercalcaemia were not significantly different between the 2 groups</p>
<p>Calcium (after 3 months of treatment): No significant ($p = 0.719$) changes from baseline (mean = 9.63 [0.81] mg/dL) to month 3 (mean = 9.57 [1.14] mg/dL)</p> <p>Phosphate (after 3 months of treatment): No significant changes ($p = 0.957$) from baseline (mean = 3.41 [0.82] mg/dL) to month 3 (mean = 3.40 [0.86] mg/dL)</p>	<p>Estimated glomerular filtration rates: No significant ($p = 0.784$) changes from baseline (mean = 35.5 [15.4] mL/min) to month 3 (mean = 36.21 [15.5] mL/min)</p>	<p>No significant ($p = 0.571$) changes from baseline (median = 436 [177-772] mg/L) to month 3 (median = 360 [177-789] mg/L)</p>	<p>7 patients developed hypercalcaemia</p>

ing a calcimimetic agent prior to transplant; ³Inclusion criteria: serum intact parathyroid hormone ≥ 150 pg/mL, serum calcium ≤ 10 mg/dL, and serum phosphorus ≤ 4.5 mg/dL; ⁴Inclusion criteria: patients who were receiving a triple immunosuppressive regime consisting of prednisone, calcineurin inhibitor (cyclosporine or tacrolimus) and mycophenolate mofetil. ⁵Inclusion criteria: glomerular filtrate rate < 60 mL/min and secondary hyperparathyroidism; Exclusion criteria: glomerular filtration rate > 60 mL/min, intact parathyroid hormone levels < 110 pg/mL, corrected $Ca^{2+} > 10.5$ mg/dL, Phosphorus > 5.5 mg/dL; ⁶Treated with paricalcitol 1 µg 3 times a week, for a minimum of 3 months.

1 µg/day for 3 months which, if tolerated, was then increased to 2 µg/day⁴⁵; 1 µg/day for 15 days which, if tolerated, was then increased to 2 µg/day⁴⁸; 1 µg on alternate days⁴⁷; 1 µg/day⁴⁶; 1 µg 3 times a week⁴⁹. Only in one of the studies⁵⁰ the dose of paricalcitol was not reported. To our knowledge, there are no randomised, double blind, controlled studies about the use of paricalcitol in kidney transplanted patients.

All studies demonstrated the efficacy of paricalcitol in reducing the plasmatic levels of PTH in kidney transplanted patients⁴⁵⁻⁵⁰. The randomized, open-label, parallel two-arm study by Amer *et al.*⁴⁸ was the largest study (100 patients) investigating the efficacy and safety of oral paricalcitol in the treatment of SHPT in kidney transplanted patients. The treatment group (51 patients) received 500 mg of elemental calcium twice a day, in combination with oral paricalcitol 1 µg/day (between days 3 and 15 post-transplant) which, in the absence of hypercalcaemia, was then increased to oral paricalcitol 2 µg/day from day 15 post-transplant onwards, until the end of study (follow-up: 1 year). The control group (49 patients) was only treated with 500 mg of elemental calcium twice a day. One year after kidney transplantation, 15 patients (29%) in the treatment group had hyperparathyroidism when compared to 31 patients (63%) in the control group ($p = 0.0005$). Furthermore, median plasmatic PTH concentrations identified in the treatment group (42 pg/mL) were half of those identified in the control group (85 pg/mL).

All studies also demonstrated the safety of paricalcitol in kidney transplanted patients⁴⁵⁻⁵⁰. For example, in the study by Amer *et al.*⁴⁸ the levels of plasmatic calcium at the end of the study were significantly higher ($p < 0.001$) for the treatment group (mean = 9.9 [0.5] mg/dL) versus the control (mean = 9.7 [0.5] mg/dL). Despite this, no patients developed severe hypercalcaemia (total plasmatic calcium > 11 mg/dL with symptoms). All hypercalcaemia events were reversible by stopping calcium supplement and, in some cases, discontinuation of paricalcitol. Furthermore, in the study by Prerez *et al.*⁴⁶ the incidence of hypercalcaemia and hyperphosphatemia was not significantly different between oral paricalcitol and no treatment. Despite the increased plasmatic

calcium levels in both groups, these remained within normal ranges. Similarly, in the study by Trillini *et al.*⁴⁵ hypercalcaemia was only observed in 2 patients taking paricalcitol 2 µg/day, and this was resolved reducing this dose to 1 µg/day. Hyperphosphatemia was never observed. Finally, in the study by Oriden *et al.*⁵⁰, episodes of hyperphosphatemia and hypercalcaemia were not significantly different between patients taking oral paricalcitol and oral calcitriol.

Most studies also demonstrated that patients taking paricalcitol had a stable kidney function at the end of the study⁴⁶⁻⁵⁰. Only in the study by Trillini *et al.*⁴⁵, the creatinine clearance at the end of the study was significantly lower in patients taking paricalcitol (median 60.38 [44.10–79.24 mL/min./1.73 m²]) than in those in the control group (median 68.11 [52.75–87.04] mL/min./1.73 m²). However, this was probably a consequence of decreased creatinine tubular secretion, increased creatinine generation, or both, because paricalcitol is not nephrotoxic, as demonstrated by studies both in animals and in humans⁴⁶⁻⁵¹.

Furthermore, most studies did not identify significant changes in proteinuria in patients taking paricalcitol^{45, 46, 48, 49}. Indeed, as presented in Table I, this was only identified in the studies by Gonzalez *et al.*⁴⁷ (mean proteinuria reduction in patients taking paricalcitol from 1.1 [0.7] g/24h to 0.7 [0.7] g/24h at month 24) and by Oriden *et al.*⁵⁰ (patients taking paricalcitol had a significant [$p = 0.02$] mean proteinuria reduction from 481.6 [126.5]mg/L to 203 [284] mg/L).

In addition to the above, there is an ongoing study investigating whether the association between paricalcitol and dietary sodium restriction provides further proteinuria (albuminuria) reduction in non-diabetic CKD patients, on top of renin-angiotensin-aldosterone system (RAAS) blockade (ViRTUE study: vitamin D receptor activator and dietary sodium restriction to reduce residual urinary albumin excretion in chronic kidney disease)⁵². This study is important because albuminuria reduction is a cornerstone of CKD treatment, as albuminuria is a major contributor for CKD progression towards end-stage CKD⁵³, and a predictor of CVD outcomes⁵⁴. The first results of this study are expected starting from the 3rd quarter of 2015.

PILOT STUDIES INVESTIGATING THE TREATMENT OF VITAMIN D DEFICIENCY IN KIDNEY TRANSPLANTED PATIENTS

We undertook 2 prospective interventional pilot studies, investigating the efficacy and safety of the vitamin D deficiency treatment in kidney transplanted patients (see acknowledgements). In the first pilot study, kidney transplanted patients (naïve to vitamin D deficiency treatment, and on a stable dose of ACE inhibitors/ARAs) were treated with cholecalciferol for 6 months, according to calcidiol levels (i.e., deficiency [< 15 ng/ml]; insufficiency [15 to 30 ng/ml]; normal [> 30 ng/ml]).

The baseline characteristics of these patients are presented in Table II. Only 6.9% of the patients had normal calcidiol levels at baseline, whereas after treatment this number increased to 46.6% (see Table III). Mean serum PTH levels decreased significantly ($p = 0.005$) from 139.9 ± 95 to 114 ± 94 pg/ml, and mean proteinuria levels decreased significantly ($p < 0.0001$) from 0.89 ± 1.2 g/day to 0.64 ± 0.9 g/day. Proteinuria was the highest in patients taking sirolimus, and it was on these patients that it reduced the most (see Table IV). Finally, no significant ($p > 0.05$) differences between baseline and study end were identified for plasmatic creatinine,

Table II

Baseline characteristics of the patients

Population (N = 131)	Mean
Age	54±13 years
Sex	
Male	62%
Female	38%
Post-treatment follow-up	79 ± 13 months
Diabetes*	25%
Immunosuppressive drugs	
Sirolimus	26%
Tacrolimus	67%
Other	7%
Kidney disease aetiology	
Chronic glomerulonephritis	25.6%
Hypertension	22.1%
Unknown	19%
Other	16.7%
Autosomal dominant polycystic kidney	10.6%
Diabetes mellitus	6%

Note: *19% of the patients developed NODAT

Table III

Percentage of patients, per stratum of calcidiol levels, before and after 6 months treatment with cholecalciferol

Stratification according to calcidiol levels	Baseline (% patients)	After 6 months treatment with cholecalciferol (% patients)
Deficiency (< 15 ng/mL)	54.9	3.8
Insufficiency (15 to 30 ng/mL)	38.2	48.6
Normal (> 30 ng/mL)	6.9	46.6

Table IV

Proteinuria levels according to immunosuppressive treatment, before and after 6 months treatment with cholecalciferol

Stratification according to calcidiol levels	Mean proteinuria levels at baseline (g/day)	Mean proteinuria levels after 6 months treatment with cholecalciferol (g/day)
Sirolimus	1.23	0.79
Tacrolimus	0.78	0.60
Other regimen	0.7	0.35

Table V

Creatinine, haemoglobin, calcium, and phosphorous levels, between baseline and after six months treatment with cholecalciferol

	Baseline	After 6 months treatment with cholecalciferol	P-value*
Creatinine (mg/dL)	1.43 ± 0.6	1.46 ± 0.60	> 0.05
Haemoglobin (g/dL)	13.0 ± 1.5	12.9 ± 2.1	> 0.05
Calcium (mg/dL)	9.8 ± 1.2	9.8 ± 0.7	> 0.05
Phosphorous (mg/dL)	3.3 ± 0.8	3.4 ± 0.7	> 0.05

Note: *Wilcoxon test

haemoglobin, and phosphorous levels (see Table V). Therefore, our pilot study seemed to show that 6 months treatment with cholecalciferol is an effective and safe treatment for vitamin D deficiency in kidney transplanted patients.

Our second pilot study included the first 36 patients that concluded the pilot study described above. For the first 6 months, all patients ($n = 36$) were treated with cholecalciferol (mean dose: 2664 IU) plus calcitriol (mean dose: 0.24 ± 0.02 µg). Then, for the following 6 months, 18 out of these patients remained on the same treatment, and 17 switched to therapy with cholecalciferol (mean dose: 2664 IU) plus paricalcitol (only one patients was lost to follow-up).

Table VI

Results of pilot study about treatment of kidney transplanted patients with cholecalciferol plus calcitriol, and cholecalciferol plus paricalcitol

	T-6, mean (sd) (n = 36)	To, mean (sd) (n = 35)	T+6, mean (sd) (n = 17)	P-value*
Plasmatic calcium (mg/dl)	9.9 (0.8)	10.0 (0.9)	10.0 (0.9)	NS
Plasmatic phosphorous (mg/dl)	3.3 (0.8)	3.5 (0.9)	3.6 (1.3)	NS
Plasmatic PTH (pg/ml)	152.2 (99.0)	181.6 (105.6)	190.6 (± 142.3)	NS
Proteinuria (g/24h)	1.5 (2.0)	1.3 (1.9)	0.9 (1.3)	P < 0.05

Abbreviations: T-6, baseline (only calcitriol therapy); To, after 6 months of cholecalciferol + calcitriol; T+6, after 6 months of switching calcitriol for paricalcitol; sd = standard deviation; * To vs. T+6 (Wilcoxon test)

Mean stable dose prescription during the 12 months (SD): Calcitriol 0.24 (0.02)µg; Cholecalciferol 2664 IU; Paricalcitol 0.94 (0.44) µg

The results of this second pilot study seemed to show that 6 months treatment with cholecalciferol plus calcitriol did not significantly amplify the reduction of proteinuria, in kidney transplanted patients (see Table VI). However, replacing calcitriol by paricalcitol lead to a significant intensification of the reduction in proteinuria, after 6 months of treatment (see Fig. 1).

Both pilot studies were only exploratory, as they included small sample sizes and no control groups. Despite this, these pilot studies provided valuable data to inform the larger and more robust studies that we are currently undertaking.

Three factors underline the clinical significance of undertaking such studies. Firstly, to our knowledge

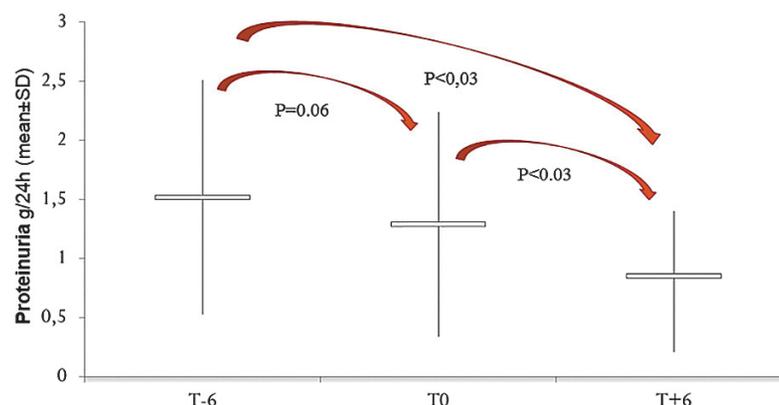
there are no published studies about the association of cholecalciferol plus paricalcitol. Secondly, this association successfully reduced proteinuria, in patients whose proteinuria did not reduce after 6 months of treatment with cholecalciferol plus calcitriol. Finally, the doses of paricalcitol prescribed in association with cholecalciferol were lower, than those prescribed in single therapy. This may be a strategy for reducing the costs of paricalcitol therapy.

CONCLUSION

Vitamin D deficiency has been associated with CVD, which is the leading cause of death in CKD.

Figure 1

Cholecalciferol supplementation plus paricalcitol after kidney transplantation.



Abbreviations: T-6, baseline (only calcitriol therapy); To, after 6 months of cholecalciferol + calcitriol; T+6, after 6 months of switching calcitriol for paricalcitol; * Wilcoxon test; ** Anova test

Mean stable dose prescription during the 12 months (SD): Calcitriol 0.24 (0.02) µg; Cholecalciferol 2664 IU; Paricalcitol 0.94 (0.44) µg

Therefore, to diagnose this deficiency, and to prescribe an appropriate treatment, may potentially reduce morbidity and mortality in CKD patients. Vitamin D deficiency may be treated with native vitamin D, non-selective and selective VDRAs. However, selective VDRAs seem to be associated with improved survival rates, potentially due to non-inflammatory (including immunomodulatory) and anti-inflammatory effects, which were not described with other treatments.

Published studies suggest that paricalcitol is an effective and safe approach to reducing PTH levels in kidney transplanted patients. The use of calcimimetics in this population has not been approved, even though being frequently prescribed as an “off label” use. More research is still needed to investigate the efficacy and safety of the combination of paricalcitol plus cholecalciferol in kidney transplanted patients, but our preliminary data suggests that it may be a cost-effective approach to reduce proteinuria levels. An ongoing study will provide important evidence on the role of the association between paricalcitol and sodium restriction, on top of RAAS blockade, on proteinuria reduction.

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Correspondence to:

Prof. Doutor Aníbal Ferreira
Nova Medical School – Faculdade de Ciências Médicas
Universidade Nova de Lisboa
Serviço de Nefrologia, Hospital Curry Cabral
Centro Hospitalar de Lisboa Central
Rua da Beneficência 8, 1069-166 Lisboa
E-mail:anibalferreira@netcabo.pt
anibalferreira@netcabo.pt