REVIEW ARTICLE

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# 25-hydroxyvitamin D and chronic kidney disease

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## ABSTRACT

In chronic kidney disease, abnormalities in vitamin D metabolism contribute to the development of bone and mineral disorders, systemic inflammation, hypertension and renal and cardiovascular damage. Chronic kidney disease induces a progressive loss of the capacity of the kidney not only to convert 25-hydroxyvitamin D to circulating calcitriol, the vitamin D hormone, but also to maintain serum 25-hydroxyvitamin D levels for non-renal calcitriol synthesis. The resulting calcitriol and 25-hydroxyvitamin D deficiency associates directly with accelerated disease progression and death.

In this article, we review the association between 25-hydroxyvitamin D deficiency, inflammation, cardiovascular disease and mortality. The potential role of native vitamin D in both chronic kidney disease and renal transplant patients is also reviewed.

**Key-Words:**
Cholecalciferol; chronic kidney disease; 25-hydroxyvitamin D; vitamin D deficiency.

## INTRODUCTION

Patients with chronic kidney disease (CKD) frequently have low serum 25-hydroxyvitamin D [25(OH)D] or calcidiol, which is the substrate of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol[1-3]. There are several reasons for this 25(OH)D deficiency or insufficiency in these patients: they are inactive and have decreased exposure to sunlight, have reduced ingestion of foods that are natural sources of vitamin D, and endogenous synthesis of vitamin D in the skin is also compromised in uraemic patients[1,2]. There is also an increased urinary loss of protein-bound vitamin D metabolites in proteinuric patients[3]. As CKD progresses, this tendency to vitamin D substrate insufficiency, coupled with the demonstrated loss of the renal 1α-hydroxylase activity, leads to progressive calcitriol deficiency[4,5].

An additional factor that contributes to a reduction of the levels of 1,25$(OH)_2$D in the course of kidney disease is the progressive increase in the levels of fibroblast growth factor 23 (FGF-23)[6,7]. FGF-23 has been shown to directly suppress the activity and expression of 1α-hydroxylase[7] and thus can be an important factor which limits the ability of the failing kidney to maintain 1,25$(OH)_2$D production during the course of kidney disease. FGF-23 also induces the expression of 24-hydroxylase[6], the enzyme responsible for the degradation of 1,25$(OH)_2$D. Thus, increases in FGF-23 in the course of CKD may be a major mechanism contributing to the decreased net production of 1,25$(OH)_2$D.

Levels of 25(OH)D have been shown to be the best indicator of vitamin D status[8]. The importance of measuring 25(OH)D levels is also supported by the newly emerging concept that an extra-renal 1α-hydroxylase is expressed in many sites outside the kidney. The extra renal pool of 1α-hydroxylase

(unlike its renal pool) seems to remain intact in kidney disease. This locally produced $1,25(OH)_2D$ seems to have autocrine or paracrine effects and to promote additional roles for vitamin D, beyond its classical functions in mineral metabolism. Indeed, recent studies have demonstrated that $1,25(OH)_2D$ acts as a cell differentiating factor and anti-proliferative agent on a variety of tissues[9,10]. By influencing gene expression in multiple tissues, including the immune system, skin, muscle, pancreas, kidney and brain, it is believed that vitamin D is involved in the pathogenesis of autoimmune, infectious and cardiovascular (CV) diseases, as well as in certain types of cancer[11].

## DEFICIENCY OF 25(OH)D AND INFLAMMATION

Recent studies have shown an association between 25(OH)D deficiency and inflammation markers[12-14]. In the Third National Health and Nutrition Examination Survey (NHANES III), with 16,301 participants, an inverse relationship between 25(OH)D levels and C-reactive protein (CRP) was clearly evident[12].

In our study, based on an evaluation of 223 prevalent haemodialysis (HD) patients, serum 25(OH)D correlated negatively ($r = -0.25$, $p<0.001$) with CRP levels[13]. The potential role of 25(OH)D as an anti-inflammatory mediator (or at least as a marker) was reinforced by a coexistent positive correlation with albumin ($r = 0.27$, $p<0.0001$)[13].

More recently, Pecoits-Filho *et al.*[14] confirmed our results in a population of 384 HD patients. These authors also found that patients with 25(OH)D insufficiency or deficiency had higher CRP and lower albumin concentrations[14].

Finally, it should be noted that in both our population[13] and in the Brazilian population[14] described above (in total over 600 HD patients) the correlations between CRP and $1,25(OH)_2D$ were not significant.

Potential mechanisms for this anti-inflammatory action of vitamin D, such as reduction of the inflammation marker tumor necrosis factor-α (TNF-α) and increases of the anti-inflammatory cytokine interleukin-10 (IL-10), have already been documented[15-17].

## DEFICIENCY OF 25(OH)D AND CARDIOVASCULAR DISEASE

Various epidemiological studies have reported reduced 25(OH)D concentrations in patients with previous and prevalent CV or cerebrovascular diseases[18-21]. Moreover, population-based studies have partially documented that poor vitamin D status is associated with an increased risk of CV events and CV mortality[20-23]. Significant associations of low 25(OH)D levels and increased risk of fatal CV events, in particular, sudden cardiac death, were also observed in patients referred for coronary angiography, as well as in diabetic dialysis patients[24,25].

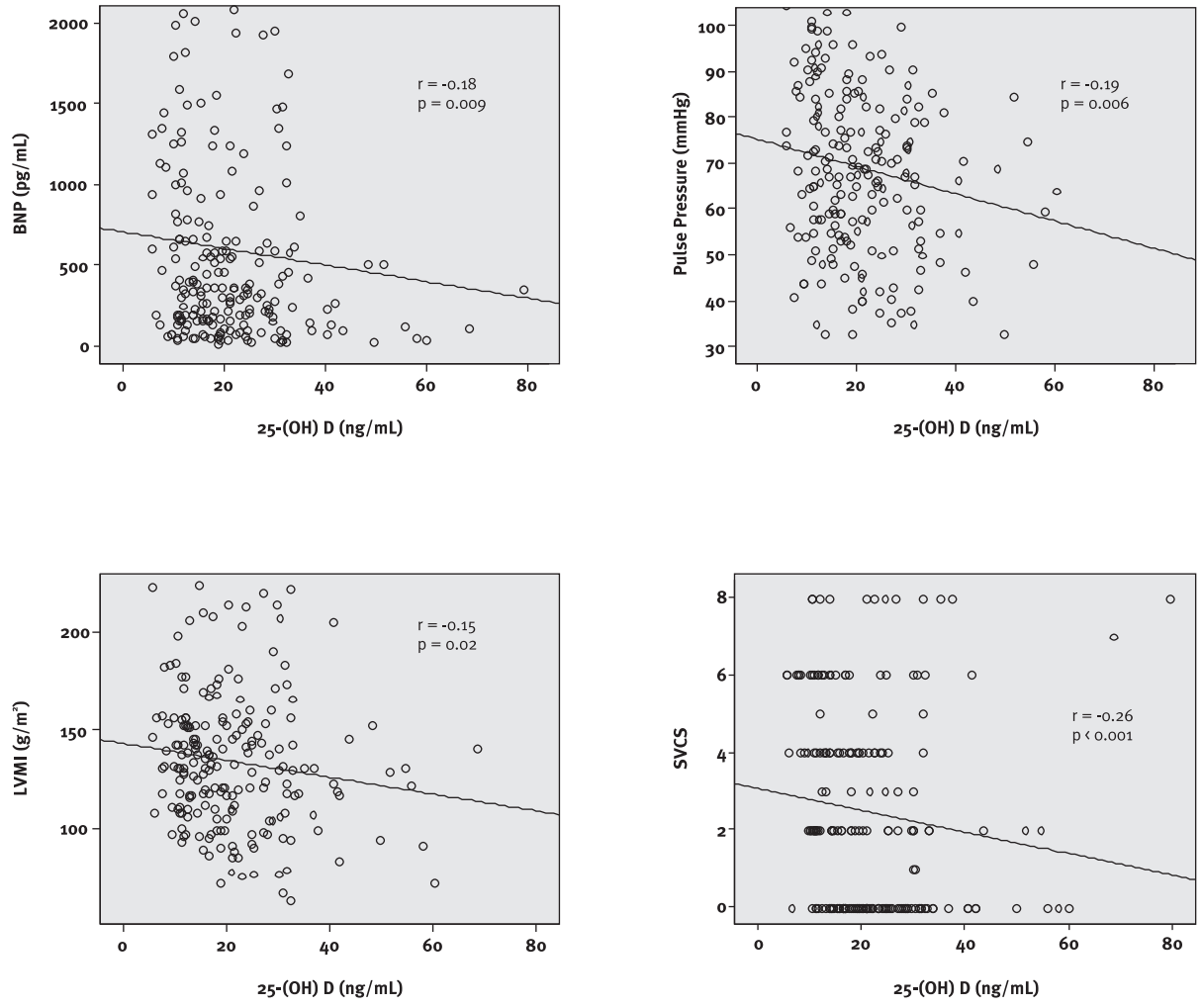
We performed a cross-sectional study in 223 chronic HD patients to evaluate the relationship between vascular calcifications, traditional CV risk factors [including the brain natriuretic peptide (BNP), pulse pressure (PP) and left ventricular mass index (LVMI)] and 25(OH)D and $1,25(OH)_2D$ serum levels, taken at two different time points, after summer and winter[26]. Vascular calcifications were evaluated using a simple vascular calcification score (SVCS) based on plain X-rays of pelvis and hands[27].

In this population, 25(OH)D serum levels were low (21.6±12.2 ng/mL) and correlated negatively with age ($r = -0.31$, $p< 0.001$), time on HD ($r = -0.14$, $p=0.04$), diabetes mellitus ($r = -0.20$, $p=0.004$), CRP ($r = -0.25$, $p<0.001$), BNP ($r = -0.18$, $p=0.009$), PP ($r = -0.19$, $p=0.006$), LVMI ($r = -0.15$, $p=0.02$) and SVCS ($r = -0.26$, $p<0.001$) (Fig. 1). In multivariate analysis, 25(OH)D deficiency (<15 ng/mL) was independently associated with higher BNP values (>800 pg/mL) ($p=0.03$), PP >65 mmHg ($p=0.01$), LVMI >140 g/m² ($p=0.02$) and higher SVCS (≥3) ($p=0.004$). Levels of $1,25(OH)_2D$ were only positively correlated with 25(OH)D ($r = 0.25$, $p<0.001$). These results suggest that 25(OH)D deficiency is a CV risk marker in HD patients, since it is strongly associated with higher BNP levels, increased PP and LVMI and with the presence of vascular calcifications.

The effects of vitamin D in the CV system can be divided into direct effects, on heart and blood vessels, and indirect effects, on CV risk factors.

### a) Vitamin D effects on heart and blood vessels

Evidence is accumulating that vitamin D may exert various direct effects on the CV system. Vitamin D




BNP, brain natriuretic peptide; LVMI, left ventricular mass índex; SVCS, simple vascular calcification score

**Figure 1**

Inverse correlations between 25-hydroxivitamin D levels and BNP, pulse pressure, left ventricular mass index and simple vascular calcification score.

receptors (VDR) have been identified on cardiomyocytes, endothelium and vascular smooth muscle cells (VSMC)[15,28], which suggests an involvement of vitamin D in the pathophysiology of CV disease.

VDR and 1α-hydroxylase knockout mice develop impaired cardiac relaxation and contractility, myocardial hypertrophy and cardiac failure, despite normalised calcium levels[15,29-31]. Increased activation of the renin-angiotensin-aldosterone system (RAAS) seems to be the mediating pathway because RAAS blockade reverses cardiac abnormalities in these mouse models[29-31].

Increased VDR expression in myocardial hypertrophy suggests a direct effect of vitamin D in the regulation of cardiomyocyte differentiation[18,28]. Experimental studies have documented anti-hypertrophic and anti-proliferative actions of vitamin D metabolites which downregulate several genes, such as cyclins and cyclin-dependent kinases, involved in the development of myocardial hypertrophy[18,32]. VDR

activation modulates cardiac calcium flux and thereby induces an accelerated relaxation of cardiomyocytes, which may improve diastolic function[18,33]. Vitamin D-mediated regulation of cardiac extracellular matrix turnover may also be important to maintain cardiac health[18,34].

Vitamin D may also protect against atherosclerosis, vascular calcification and endothelial dysfunction[19]. Anti-atherosclerotic vitamin D effects may include (i) inhibition of macrophage cholesterol uptake and foam cell formation, (ii) downregulation of VSMC proliferation and migration, and (iii) suppression of inflammation-triggered endothelial activation and expression of endothelial adhesion molecules[19,35,36]. Vitamin D effects may also protect against endothelial dysfunction, for example by anti-oxidative actions and by inhibiting lipid peroxidation[19,37].

Finally, the role of vitamin D in vascular calcification has remained controversial[19,38]. High doses of active vitamin D, due to their potential impact of increasing serum phosphorus and calcium, may cause vascular calcifications[39]. On the other hand, recent findings demonstrate an inhibitory role of more physiological doses of vitamin D in vascular calcifications[40]. VDRs are present in VSMCs, and treatment with active vitamin D inhibits the synthesis of type I collagen[19]. More importantly, vitamin D treatment reduces core binding alpha-I (cbfa-I) synthesis, stimulates the synthesis of matrix gla protein (MGP) and inhibits bone morphogenetic protein-2 (BMP-2) production in cultured osteoblastic cells[19,41].

### b) Vitamin D and cardiovascular risk factors

Accumulating evidence suggests that low 25(OH)D levels strongly correlate with increased prevalence of classical CV risk factors.

PTH levels are inversely correlated with 25(OH)D concentrations and epidemiological studies demonstrated that elevated and high-normal PTH levels are associated with an increased risk of CV events and mortality[42]. PTH increases blood pressure and exerts various effects on the heart, including myocardial hypertrophy and pro-arrhythmic actions[43]. PTH suppression by vitamin D supplementation might therefore reduce CV risk.

Low 25(OH)D levels are an independent risk factor for prevalent and incident hypertension[44]. Proposed antihypertensive effects of vitamin D include PTH suppression, reno- and vasculo-protective properties and anti-inflammatory and anti-diabetic actions. In addition, $1,25(OH)_2D$ has been shown to suppress renin transcription[15,45]. VDR and 1α-hydroxylase-knockout mice also demonstrates increased activity of the RAAS[15,45].

A poor vitamin D status is associated with a higher prevalence and incidence of diabetes mellitus[46]. Possible mechanisms by which vitamin D deficiency could promote diabetes mellitus include impaired insulin secretion via pancreatic β-cell dysfunction, alteration of plasma calcium levels, decreased peripheral tissue sensitivity to insulin and chronic inflammation[15,47]. Vitamin D-binding protein has been localised to pancreatic tissue and pancreatic islet cells have been shown to express VDRs as well as locally produce 1α-hydroxylase, suggesting an autocrine link between 25(OH)D level and pancreatic function[47].

Vitamin D may also affect blood lipids and coagulation parameters, but currently available data are insufficient to draw final conclusions[48,49].

Vitamin D insufficiency or deficiency is not only common among CKD patients but is also a risk factor for decline in renal function[50]. This may be explained by several reno-protective effects of vitamin D such as anti-proteinuric (e.g. vitamin D might increase megalin-mediated tubular protein reabsorption, decrease slit membrane permeability and stabilise actin from the podocyte cytoscheletum) and antihypertensive properties, suppression of the RAAS, and anti-inflammatory and anti-autoimmunological actions[50,51].

Anti-infectious and anti-inflammatory actions of vitamin D may also play a role in CV disease[15-17].

## DEFICIENCY OF 25(OH)D AND MORTALITY

Deficient levels of 25(OH)D have been associated with all-cause and CV mortality in CKD patients[52-55]. In a recent meta-analysis[56], 10 prospective studies were selected, with a total of 6853 patients. In this

evaluation, which included patients with different CKD stages (2 to 5D), higher levels of 25(OH)D were associated with a significant increase in survival, secondary to a very significant reduction in overall mortality[56].

We performed a prospective study to evaluate the relationship between 25(OH)D and $1,25(OH)_2D$ and morbidity and mortality, in 223 HD patients[57]. With this purpose, we measured 25(OH)D and $1,25(OH)_2D$ serum levels twice (at the end of winter and summer)

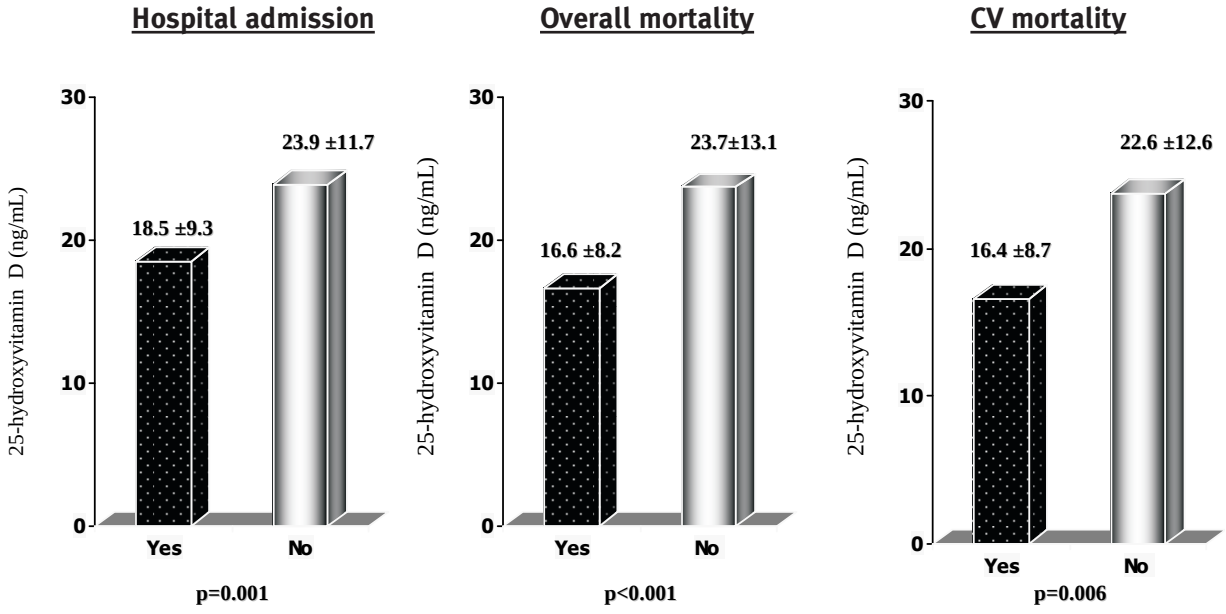



**Figure 2**

Levels of 25-hydroxivitamin D according to hospital admission, overall and cardiovascular mortality.

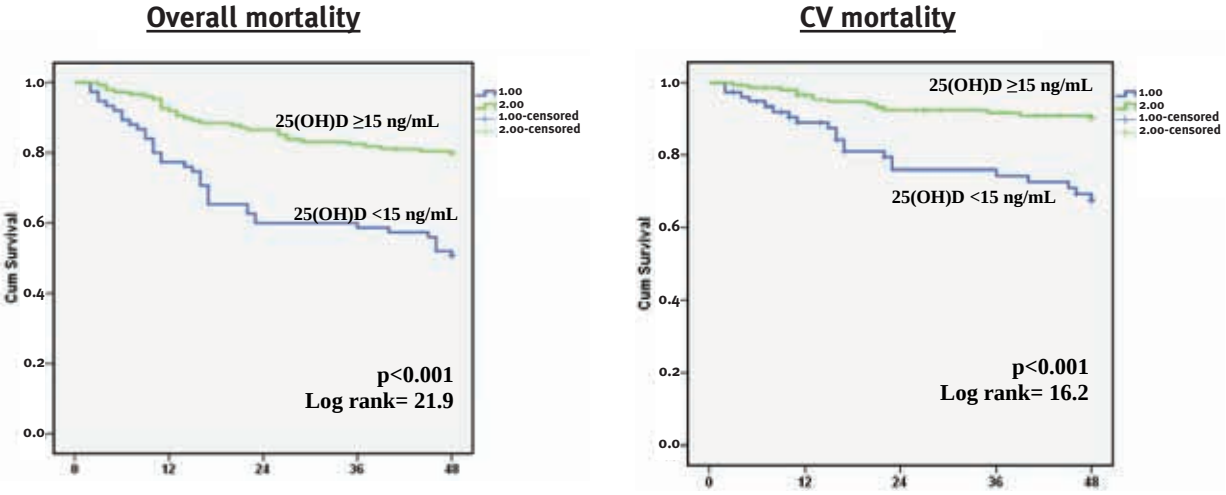



**Figure 3**

Lower survival in relation to overall and cardiovascular mortality in patients with 25-hydroxyvitamin D <15 ng/mL (Kaplan-Meier analysis).

and correlated them with hospital stays and overall and CV mortality for the following 48-month period. All patients were submitted to oral cholecalciferol supplementation according to baseline calcidiol levels during the studied period. During the study, 44% of the patients were admitted to hospital at least once and 29% of the patients died (mainly from CV causes). Levels of 25(OH)D were significantly lower in the patients that died from all causes (16.6±8.2 *vs.* 23.7±13.1 ng/mL, p<0.001) and in patients that died from CV causes (16.4±8.7 *vs.* 22.6±12.6 ng/mL, p=0.006). 25(OH)D levels were also lower in patients admitted to hospital during the study (18.5±9.3 *vs.* 23.9±11.7 ng/mL, p=0.001) (Fig. 2). $1,25(OH)_2D$ levels were similar in all groups.

In multivariate analysis, lower levels of 25(OH)D were predictors of hospitalisation (p=0.01), death from all causes (p=0.001) and death from CV causes (p=0.02). Patients with 25(OH)D deficiency (<15 ng/mL) had a significantly lower survival at the end of the 48-month period studied (p<0.001) (Fig. 3).

## THE ROLE OF NATIVE VITAMIN D SUPPLEMENTATION

The evaluation of calcidiol serum levels in CKD patients with an estimated glomerular glomerular filtration rate (eGFR) <60 mL/min/1.73m² is suggested by the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) recommendations and the proposed strategy for correction of 25(OH)D deficiency/insufficiency is similar to that used in general population[58]. This recommendation is based on a low evidence level, but impaired vitamin D metabolism may have deleterious consequences on renal function, proteinuria, and outcome in CKD patients[25,50,59,60].

### a) Cholecalciferol supplementation in CKD patients

In the general population, a meta-analysis of randomised trials showed a non-significant trend toward CV disease risk reduction with vitamin D supplementation[61]. There are, however, no data on the effect of vitamin D supplementation on CV events or mortality in CKD patients. A few interventional studies among CKD patients showed that vitamin D intake improves bone and mineral metabolism, including reductions in PTH levels, decreases inflammatory parameters, and improves glucose metabolism[62-66].

We performed a 1-year prospective study[67], including 158 prevalent HD patients, to evaluate the effects of oral cholecalciferol supplementation on mineral metabolism, inflammation and cardiac dimension parameters. There was a significant increase in 25(OH)D (22.3±12.0 *vs.* 42.0±12.1 ng/mL; p<0.001) and $1,25(OH)_2D$ (4.6 *vs.* 5.9 pg/mL; p=0.001) levels after supplementation. In 136 (86%) of the patients 25(OH)D levels became normal (>30 ng/mL) at the end of the study, in comparison with only 32 (20%) at baseline. Patients whose 25(OH)D levels did not increase were mostly diabetics (p<0.001). None of the patients achieved a toxic level – 25(OH)D >100 ng/mL.

Serum calcium (p=0.014), phosphorus (p=0.011) and iPTH (p=0.01) showed a significant reduction with supplementation. A significant reduction in the number of treated patients as well as in active vitamin D dose was also observed (p<0.001). Darbepoietin use also decreased (p=0.013), with no modification of haemoglobin and ferritin values. Serum albumin increased (p<0.001) and CRP decreased (p=0.004) with supplementation.

BNP plasma levels showed a significant reduction during the study (p=0.008). LVMI also had a significant decrease after supplementation (p=0.01). There was a significant negative correlation between the percentage of change in 25(OH)D *versus* the percentage of change in BNP levels (r= – 0.21, p=0.009) and LVMI (r= – 0.24, p=0.003). The percentage of change in BNP was also positively correlated with the percentage of change in LVMI (r=0.19, p=0.02).

In our study, oral cholecalciferol supplementation allowed a reduction of vitamin D deficiency, better control of mineral metabolism with less use of active vitamin D, attenuation of inflammation, reduced dosing of erythropoiesis stimulating agents, and improvement of cardiac dysfunction.

### b) Cholecalciferol supplementation in renal transplant patients

Similarly, after renal transplantation, 25(OH)D insufficiency or deficiency is a very common condition[68]. In this population, 25(OH)D levels showed a significant negative correlation with circulating levels of iPTH[68].

We started a protocol of cholecalciferol supplementation in 124 renal transplant patients, aiming to maintain 25(OH)D in sufficiency values (›30 ng/mL)[69]. After 6 months of supplementation, 25(OH)D serum levels increased from 14.6±7.8 to 30.5±12.3 ng/mL (p‹0.001). Fifty-nine percent of the patients had calcidiol deficiency at the beginning of the study and, after 6 months of cholecalciferol supplementation, only 6% remained 25(OH)D deficient. iPTH, serum calcium and phosphorus did not change significantly with the supplementation.

More important was the reduction of proteinuria from 0.931±1.48 to 0.685±0.66 g/day (p=0.03) after 6 months cholecalciferol supplementation (Fig. 4). A negative correlation between the severity of proteinuria and 25(OH)D serum levels (r= – 0.31, p=0.01) after supplementation was also observed.

The reduction of proteinuria in CKD stage 3 and 4 diabetic patients, treated with paricalcitol (an analog of active vitamin D) was first described in observational studies[70,71], gained consistency in animal models[72] and was recently confirmed in the VITAL study[73], a randomised double-blind controlled trial.

Our results indicate that the correction of native vitamin D deficiency was also associated with a significant reduction of proteinuria in a population of renal transplant patients[69].

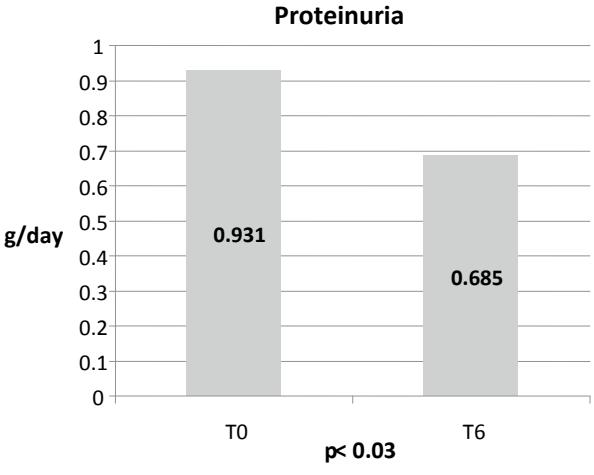



**Figure 4**

Proteinuria before and after 6-month cholecalciferol supplementation in renal transplant patients.

## CONCLUSIONS

In summary, native vitamin D supplementation is an easy and cost-effective therapeutic measure. Recently, some groups have decided to suggest a 25(OH)D target level of ›30 ng/mL[58,74]. A daily intake of 1,000 IU raises 25(OH)D levels about 10 ng/mL[75]. Adverse effects, mainly related to hypercalcemia, are not observed at daily doses of up to 10,000 IU vitamin D or at 25(OH)D levels up to 150 ng/mL[76,77]. These data were mainly derived from general populations, but studies among CKD patients showed similar results on the safety of vitamin D[62-67,77].

It should also be stressed that native vitamin D supplementation can slightly increase circulating $1,25(OH)_2D$ levels[65,78]. There are, however, no adequate data on possible interactions or additive effects of native and active vitamin D treatment.

Based on the results reviewed above and on our own data we suggest that all CKD patients (including pre-dialysis, dialysis and transplanted populations) should be evaluated and supplemented with native vitamin D in order to obtain stable serum levels above 30 ng/mL. In our opinion, this should be the first step to optimise the treatment of vitamin D insufficiency/deficiency so frequently observed in CKD patients.

***Conflict of interest statement.***

P.M. None declared.

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