Vitamin D and the vasculature: can we teach an old drug new tricks?

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**Background**: Vitamin D is a steroid hormone known for its role in regulating levels of calcium and phosphorus. Vitamin D has important autocrine/paracrine roles and it is involved in vascular biology. Clinical studies have shown a relationship between vitamin D levels and cardiovascular health, and low levels of vitamin D metabolites have been associated with higher incidence of congestive heart failure and increases in mortality. **Objective**: To summarise the effect of vitamin D on cardiovascular pathology, the leading cause of death in chronic kidney disease patients. **Conclusions**: All results indicate a potential effect of vitamin D on cardiovascular health. Therefore, maintaining optimum levels of circulating vitamin D is critical for a healthy cardiovascular system. In patients with low vitamin D status, like renal patients, supplementation with vitamin D metabolites has shown beneficial cardiovascular effects.

**Keywords**: arterial calcification, atherosclerosis, cardiovascular disease, hypertension, paricalcitol, vitamin D


1. **Introduction and physiology of vitamin D**

Vitamin D is a steroid hormone that has long been known to have an important role in regulating body levels of calcium and phosphorus, and in mineralisation of bone. Vitamin D3, derived from the diet or by bioactivation of 7-dehydrocholesterol, is inert and must be activated to exert its biological activity. Vitamin D3 (cholecalciferol) is produced in the skin by ultraviolet-light-induced photolytic conversion of 7-dehydrocholesterol to previtamin D3 (1,2) followed by thermal isomerisation to vitamin D3 or cholecalciferol (3,4). Thus, sun exposure is the principal source of circulating vitamin D stores and skin pigmentation is a main regulator of circulating vitamin D levels. In fact, migration activity in the 20th century (leading to dark-skinned individuals living in latitudes with low sunlight hours), together with cultural habits like dress codes and the widespread use of sunscreens have led to what some experts consider a hypovitaminosis D pandemic (5).

Cholecalciferol, however, is not yet the active metabolite and needs to undergo two additional steps. The first step in the metabolic activation of vitamin D is hydroxylation of carbon 25. This reaction occurs primarily in the liver, although other tissues including skin, intestine, and kidney have been reported to catalyse 25-hydroxylation of vitamin D. 25(OH)D3 (calcidiol) is the main metabolite found in blood and it is used to determine the vitamin D status of a population. The levels of calcidiol in blood considered normal are changing almost yearly. Although some experts believe the lower limit of adequate calcidiol levels to be around 30 ng/ml (6,7), others recommend up to 40 ng/ml (8). Nonetheless, levels
found in humans who live or work in the sun, are considerably higher (50 – 70 ng/ml) [9].

The second and more important step in vitamin D bioactivation, the formation of calcitriol from calcidiol, occurs under physiological conditions mainly in the kidney [4]. The renal enzyme responsible for producing calcitriol, 25(OH)D-1α-hydroxylase (CYP27B1), is located in the inner mitochondrial membrane and is a cytochrome P-450 monooxygenase requiring molecular oxygen and reduced ferredoxin [10]. In this step, the active metabolite is synthesised and circulating calcitriol levels are directly related to renal 1-alpha hydroxylase activity. In recent years, many reports have demonstrated that the kidney is not unique in its ability to convert calcidiol to calcitriol. Numerous cells and tissues express CYP27B1 in vitro; however, in humans, these extrarenal sources of calcitriol only contribute significantly to circulating calcitriol levels during pregnancy, in chronic renal failure and in pathological conditions such as sarcoidosis, tuberculosis, granulomatous disorders and rheumatoid arthritis. Nevertheless, local production of calcitriol could be important as a paracrine regulator of certain cell functions. For instance, both endothelial [11] and vascular smooth muscle cells (VSMC) [12,13] show CYP27B1 activity together with the vitamin D receptor (VDR), pointing to the vitamin D endocrine system as a regulator of vascular function.

Most of the biological activities of calcitriol are mediated by a high-affinity receptor that acts as a ligand-activated transcription factor. The major steps involved in the control of gene transcription by VDR include ligand binding to the receptor, heterodimerisation with retinoid X receptor (RXR), binding of the heterodimer to vitamin D response elements (VDREs) in the promoter of target genes, and recruitment of other nuclear proteins into the transcriptional preinitiation complex. Then, the complex modulates the transcription of the target genes, either upregulating or downregulating, depending on the nature of the VDRE. Among the genes that present positive VDREs (which increase transcription) we can find the VDR, p27 and osteopontin; genes with negative VDREs include CYP27B1, c-myc, parathyroid hormone (PTH) and collagen type 1. Several single-nucleotide polymorphisms in VDR gene have been described, and related to the susceptibility to suffer from cardiovascular diseases. This is not, however, the scope of this review, and for further information we refer the reader to a more detailed manuscript [14].

The vitamin D endocrine system is critical in the control of bone and calcium homeostasis. Furthermore, it has also been shown that vitamin D plays an important role in other metabolic pathways, such as those involved in the immune response and cancer [15]. The involvement of vitamin D in cardiovascular health has been known for years. Since the first report in 1928 showing that high doses of vitamin D cause vascular calcification [16] lots of papers have studied the role of the hormone in cardiovascular physiology and pathophysiology. In the present review we will try to summarise the latest findings on the involvement of the vitamin D endocrine system in cardiovascular physiology, focusing on the role of the hormone in the vascular bed.

2. Clinical studies relating vitamin D to cardiovascular diseases

As we indicated before, the prevalence of hypovitaminosis D is common worldwide. However, and due to the UVB-dependent synthesis of the hormone, several geographic and cultural factors are involved in the phenomenon. For instance, populations from northern latitudes, receiving lower sun exposure, are expected to have lower vitamin D levels. Indeed, the closer we go to the equator, the higher levels of calcidiol we find in the population. Interestingly enough, the correlation is also clear with cardiovascular disease, showing an increase in deaths from ischemic heart disease in countries with lower sunlight exposure [17]. The same findings are true with altitude. As we climb higher UVB radiation exposure increases exponentially, and it has been demonstrated that increases in UVB cause increases in blood vitamin D levels [18]. A number of papers have looked at the relationship of ischaemic heart disease (IHD) deaths with altitude and found the same results. The higher the population lives, the lower the number of deaths from IHD we find [19]. Another factor involved in regulating vitamin D levels in blood is seasonality. It has been demonstrated that vitamin D levels have seasonal variations, reaching a peak in summer and a nadir in winter [20,21]. The results in the literature looking at the variations of IHD also found seasonality, with higher number of deaths in winter, in the months when blood vitamin D levels are lower [22-25]. Finally, urbanisation is associated with an increase in deaths from IHD [26], together with decreases in vitamin D levels due to pollution [27,28]. In fact, the number of IHD deaths in 2020 is predicted to increase 120 – 137% with respect to 1990 in parallel with a doubling of the urban population [29-31]. Supporting data have been recently published by Giovannucci et al. They examined, in a nested case-control design study, the relationship between calcidiol and myocardial infarction in 18,225 men recruited in a population-based study. They found a significant and inverse relationship between calcidiol concentration and the risk of suffering from a myocardial infarction, even after adjustment for classical cardiovascular risk factors. Interestingly, those participants in the lowest calcidiol quartile presented lower HDL cholesterol concentrations [31]. Furthermore, Dobnig et al. [32] published the results of vitamin D measurement in a cohort of 3258 patients scheduled for coronary angiography, and they found that low calcidiol and calcitriol levels are independently associated with all-cause and cardiovascular mortality. These results have been also supported by recent studies based on the Framingham cohort [33], showing that vitamin D deficiency is associated with incidence of cardiovascular disease.
2.1 Vitamin D deficiency and chronic kidney disease

Outside the general population, vitamin D deficiency is frequently found in any of the stages of chronic kidney disease (CKD). These patients have impairment in the homeostasis of calcitriol and are not able to adjust its levels to normal range concentrations. Wolf et al. [34] examined the effects of the deficit in calcidiol on mortality, and concluded that any vitamin D metabolite was significantly related to a higher mortality rate, but that this association was especially relevant concerning deficits in calcidiol. These results are in accordance with the fact that those patients with the lowest calcidiol concentrations were those in whom treatment with vitamin D was most beneficial. Most patients with End Stage Renal Disease (ESRD) are being treated with active metabolites of the vitamin D, with the aim of stopping secondary hyperparathyroidism. Furthermore, some studies have demonstrated a link between treatment with active vitamin D compounds and survival in a dialysis population. In a study by our group we showed that patients in dialysis receiving vitamin D therapy showed a better survival than those that did not [35]. A study in a historic cohort of 51,037 incident dialysis patients, who were under vitamin D therapy showed that, after adjusting for several confounders, those patients under treatment experienced a 20% higher survival rate in comparison with those untreated [36]. It is relevant to highlight that these results remained stable after adjusting for several variables, such as calcium, phosphorus and intact PTH (iPTH). In another study by the same group, the significant superiority of using a selective vitamin D analogue (paricalcitol) versus calcitriol, in the survival of a large cohort of patients under dialysis was shown [37]. These studies, however, have been largely debated due to methodological issues, that is: selection bias and retrospective nature. We should acknowledge, however, that many of these studies are historic cohorts, and consequently they are not strictly retrospective. Posterior studies have also confirmed these results. Tentori et al. [38] analysed the mortality risk of patients under haemodialysis who were receiving different vitamin D analogues (calcitriol, paricalcitol or doxercalciferol). Use of any of these compounds resulted in significantly higher survival, but again, paricalcitol and doxercalciferol were significantly superior to calcitriol. Two recently published studies have analysed the effect of mineral-metabolism-related variables in the survival of patients on dialysis. Whether patients received either paricalcitol or calcitriol was included in the analyses, and again one of the results was that those therapies have a beneficial effect on survival [39,40]. A recent meta-analysis [41], has questioned the beneficial role of administering vitamin D analogues on mortality of renal patients. However, we have to keep in mind that the results of this meta-analysis are quite confusing, since the doses of vitamin D are not homogeneous in the trials analysed. Furthermore, of the five studies in the meta-analysis, none seemed to titrate vitamin D to achieve PTH level suppression or to have PTH level suppression as a primary goal. These results aroused several critical opinions and deserved editorials and correspondence in the same journal, arguing about the generalisation of its conclusions.

The leading cause of death among CKD-affected patients is cardiovascular disease and vitamin D is actively involved in its pathophysiology. In the following sections, we summarise the main findings relating vitamin D and vascular conditions.

2.2 Vitamin D and hypertension

It has been known for years that there is an association between vitamin D levels and blood pressure (BP) in men. Thus, low levels of calcidiol in blood have been related to higher levels of BP in both in normotensive [42-45] and hypertensive humans [46,47] in cross-sectional studies. Furthermore, two recent papers show that individuals with lower levels of calcidiol are at higher risk of developing hypertension [33,48]. However the data about supplementation of vitamin D in the diet and risk of developing hypertension reveals conflicting results, with some authors reporting a benefit [49] and others showing no differences [50].

The possible rationale behind the relationship between vitamin D and BP was uncovered in 2002 by Li et al. [51], when they published their results pointing to a regulation of the renin-angiotensin system by vitamin D. In that paper, renin expression and plasma angiotensin II production were increased several fold in VDR-null mice, leading to hyper-tension. However, the salt- and volume-sensing mechanisms that control renin synthesis were still intact in the mutant mice. Furthermore, the administration of calcitriol in wild-type animals led to a decrease in renin expression. Thus, it is logical to think that administration of active vitamin D compounds could reduce BP in some hypertensive patients. However, the beneficial effects of active vitamin D in reducing renin expression could be hindered by the fact that VSMC acutely respond to calcitriol, increasing resistance artery force and thus, contractility [52].

The administration of calcitriol to spontaneously hypertensive rats has given consistent results, showing decreases in BP [53-55]. However, high doses of calcitriol also increased BP in normal animals [56-59]. The apparent discrepancy can be explained by the effect of high doses of calcitriol on the arterial wall. It has been shown that high doses of calcitriol can modify the arterial wall properties, increasing proliferation [60-63] and calcification [59,64] of VSMC. Thus, blood levels of calcitriol in relation with toxicity show a U-shaped curve, with low and high levels being equally deleterious. Human therapy with vitamin D to decrease BP reported also contradictory results. Exposure of humans to UVB light showed decreases in BP together with increases in calcidiol levels in blood [18]. Some papers showed decreases in BP in patients treated with VDR activators [65-67]. However, another study showed a transient increase in BP, probably due to a direct effect of calcitriol on the contractility of VSMC [68] or even no effect at all [69]. The multifactorial nature of hypertension can explain the lack of effect of
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vitamin D treatment in some cases. For instance, Park et al. [70] showed that patients with secondary hyperparathyroidism treated with calcitriol display a decrease in renin and angiotensin II but no changes in BP. Furthermore, Resnick et al. [71] showed that calcitriol levels were elevated in hypertensive patients with low renin activity, demonstrating a negative correlation between renin and calcitriol levels.

2.3 Vitamin D and arterial dysfunction
Arterial dysfunction is characterised by a decrease in arterial compliance to accommodate changes in BP. This decrease in compliance is an early marker of atherosclerosis and could be related to both endothelial and VSMC dysfunction. On the one hand, endothelial dysfunction leads to decreased endothelium-dependent vasodilatation, mainly endothelium-derived nitric oxide (NO). On the other hand, excessive proliferation and calcification of VSMC increase the stiffness of the artery and, therefore, its ability to relax. As we indicated before, both endothelial and VSMC, have the capacity to produce and respond to calcitriol. In the following section we will summarise the findings related to the effects of vitamin D on endothelial and VSMC biology in relation to arterial dysfunction.

Unfortunately there is little information on the effect of activation of VDR on synthesis of endothelial-derived NO. The information available is restricted to a single paper showing that, in diabetic individuals, administration of ergocalciferol increased endothelial function (measured as flow-mediated brachial artery dilatation) [72] and to a very recent paper showing that calcitriol improves the activity of endothelial NO synthase in advanced glycation end product-treated cells [73]. In addition, a few papers studied the role of vitamin D regulating endothelial cell proliferation. Those papers showed that, in endothelial cells derived from tumours, calcitriol treatment induced a decrease in proliferation which was not seen in endothelial cells derived from matrigel plugs (considered by the authors as ‘normal’ cells) [74,75]. The authors concluded that the different effect was explained by the fact that, unlike cells derived from tumours, cells derived from matrigel plugs responded to calcitriol treatment, increasing the expression of CYP24, the enzyme responsible for calcitriol metabolism [76].

The role of calcitriol on VSMC proliferation is still a matter of debate. Whereas most papers, including results from our laboratory, show that calcitriol increases VSMC proliferation [60-63,77] some others report the opposite results [78,79]. The discrepancy however is only present in the in vitro studies, where different culture conditions can affect the final outcome. Administration of high doses of calcitriol to experimental animals increases VSMC proliferation [60,80] and it has been used (alone or in combination with cholesterol or nicotine) as a model of atherosclerosis in rats. Furthermore a recent paper from Razzaque et al. [81] shows that ablation of vitamin D activity in fibroblast growth factor (FGF)-23-null mice led to the elimination of atherosclerosis, again indicating a role for vitamin D in increasing VSMC proliferation.

The role of vitamin D in VSMC calcification has been widely studied. As mentioned before, the first known report showing that high doses of vitamin D increase VSMC calcification is dated to 1928. Since then, a number of papers have also shown that supraphysiological levels of calcitriol increase vascular calcification both in vitro and in vivo [59,64,83-84]. Vascular calcification can be roughly divided in two main types. Medial calcification, typical of ESRD patients, is characterised by concentric calcium deposition in the VSMC layer. In contrast, atherosclerotic calcification is located in the intimal layer, and is associated with inflammatory cell infiltration and macrophage activation. Administration of large doses of calcitriol provokes medial calcification, probably mediated by a calcitriol-induced phenotypic change in VSMC, which start expressing osteoblastic markers [59]. Interestingly enough, calcitriol-induced vascular calcification in animals with intact renal function has been proved to be a reversible phenomenon, with total remission within 9 weeks after stopping the treatment [85].

Most of the clinical data regarding vitamin D levels and vascular calcification are related to CKD patients. In those patients we also find a bimodal curve. Paediatric dialysis patients showed that both low and high calcitriol levels are associated with increases in vascular calcification, whereas calcidiol levels did not correlate with calcification [86]. There are also several studies showing an inverse relationship between calcitriol levels and vascular calcification [87,88], whereas some others report no association at all [89,90]. Thus, the role of endogenously produced calcitriol in vascular calcification is still unclear. However, we should point out that plasma levels of calcitriol may not be a reflection of vascular levels, since both arterial cell types have the ability to synthesise it. In addition, low levels of circulating calcitriol might be a stimulus to arterial CYP27B1 because of the presence of a negative VDRE in its promoter. Therefore, arterial levels of calcitriol could be much higher than circulating levels, due to an activation of the local synthesis. At the present time, however, the measurement of local levels is still technically impossible, so this theory will remain unproven for some time.

2.4 Vitamin D and atherosclerosis
All these molecular process and risk factors (high BP, hypercholesterolemia) lead to the development of atherosclerosis, the anatomic lesion which causes most of the vascular events. The role of vitamin D in its development has been extensively reported since the 1960s [91]. The first experimental studies were based on the relationship between vitamin D supplements and the development of atherosclerosis, and reported a dose–effect response, that is the higher the calcidiol concentration, the bigger the atherosclerotic plaque [92,93]. Since then it is known that atherosclerotic plaque may be induced easily in coronary arteries of animal models fed a cholesterol-free diet, by feeding
excessive amounts of vitamin D for short periods in early life. Atherosclerosis is a systemic, immunoinflammatory disease of medium-sized and large arteries. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease, which eventually may originate a cardiovascular event through plaque rupture and thrombosis [94]. Vitamin D exerts influence in many of these active players in the development of atherosclerosis. In fact, calcitriol influences the gene expression of VEGF, matrix metalloproteinase type 9, myosin and structural proteins, such as elastin and type I collagen, which are specially involved in the first steps of atherosclerosis development [95,96]. Furthermore, vitamin D largely influences changes in the VSMC by different mechanisms, that are not within the scope of this review, but essentially it promotes VSMC proliferation [60] and migration to the subendothelial layer [97].

However, all these results were obtained using very high doses of vitamin D. Again, it seems that both an excess and a deficit in vitamin D levels may have deleterious consequences in the formation of the atherosclerotic plaque. In the plaque the inflammatory content is directly related to plaque vulnerability, and it is known that highly inflamed plaques are more prone to rupture and to provoking atherothrombotic events. Vitamin D also modulates the inflammatory response, since the expression of inflammatory markers by monocytes from patients with Type 2 diabetes mellitus was attenuated by calcitriol [98]. Further studies have demonstrated the potential ameliorative effects of VDR activation on the pathogenesis of atherosclerosis by enriching the T helper type 2 (Th2) cell population of lymphocytes. Calcitriol treatment of cells results in marked inhibition of IFN-γ [99] and upregulation of IL-10 [100]. In addition, IL-1β and IL-6 are inhibited by calcitriol [101], which would also mitigate or inhibit macrophage activation and prevent plaque instability.

An additional mechanism by which VDR activation may maintain plaque stability is by preventing thrombosis, as demonstrated in VDR-null mice that develop arterial thromboses in association with downregulation of antithrombin and thrombomodulin and upregulation of tissue factor [102]. Moreover, calcitriol and paricalcitol suppress plasminogen activator inhibitor-1 (PAI-1), a mediator of thrombosis and one of the risk markers for coronary heart disease [103].

Another critical step in both the development of atherosclerosis and in the destabilisation of the atherosclerotic plaque is the degree of neovascularisation of the artery wall. The increase in the vasa vasorum density is related, in animal models of atherosclerosis, to the inflammatory content of the plaque and the risk of rupture [104], and therefore, its assessment has been proposed as a potential diagnostic and therapeutic target [105]. Several studies have explored the role of the vitamin D in neovascularisation with promising and interesting results. Most of them are based on cancer models and demonstrate that vitamin D is a powerful suppressant of angiogenesis [106,107]. Although there are no studies so far exploring the effect of vitamin D on vasa vasorum, results have recently been published showing that calcitriol inhibits retinal neovascularisation [108], and this data opens up new and promising research topics in the near future concerning atherosclerosis and vitamin D.

In summary, cardiovascular disease is complex, with more than 200 risk factors involved. Vitamin D has a role in its development and this is both supported by epidemiological and basic research studies. However, further analyses of the molecular steps of inflammation and angiogenesis are needed to clearly elucidate the implications of targeting vitamin D to stop atherosclerosis and its cardiovascular consequences.

3. Expert opinion

After the extensive review, we focus in this section on the potential role of vitamin D treatment in both kidney and cardiovascular diseases, and also raise unanswered questions of clinical relevance.

There are several molecules, metabolites and vitamin D analogues, with different biological actions. This is in part due to the different response of the target organ to vitamin-D-related molecules. Prescription of such drugs was primarily aimed at mineral and bone abnormality reconstruction, and consequently the first epidemiological data relating vitamin D deficiency to cardiovascular disease was interpreted with scepticism by the scientific community. However, in recent years several basic research manuscripts have been published, showing a causal relationship between vitamin D and cardiovascular diseases (atherosclerosis, hypertension, arterial dysfunction, left ventricular hypertrophy). Nephrologists are especially interested in this field, since CKD-affected patients suffer from a significant deficit of both calcidiol and calcitriol. This metabolic impairment might be in part one of the factors contributing to the higher cardiovascular disease incidence of CKD patients when compared with the general population.

For all these reasons, cardiovascular diseases and atherosclerosis constitute a hot topic of debate in nephrology. Simultaneously, the development of new vitamin D analogues exerting less vascular calcification, has led pharmaceutical industries to include these issues in their portfolio, and consequently financial interests have been followed by the promotion and implementation of research protocols and their publication. All these efforts have largely influenced the appearance of cardiovascular diseases in international meetings and nephrologists focus of discussion. However, clinical trials assessing the theoretically beneficial influence of either calcitriol or calcidiol supplementation, on cardiovascular disease incidence is lacking. In observational studies, those haemodialysis patients under calcitriol treatment with a deficit in both calcidiol and calcitriol presented a longer life expectancy than those without therapy. However, we should acknowledge the lack of information based on randomised clinical trials with calcidiol, calcitriol or vitamin D analogues. This lack of evidence does not allow physicians to prescribe...
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these drugs to further improve the cardiovascular prognosis of either CKD-affected patients or the general population. Having this in mind, and according to the whole body of scientific data, it would not be advisable to ignore all these studies, and therefore we recommend being cautious and avoiding significant deficits of calcidiol or calcitriol.

In order to set specific therapeutic recommendations, it is relevant to differentiate two scenarios:

1. CKD-affected patients.
   a. The synthesis of calcitriol is impaired along with calcium and phosphorus imbalance as kidney function progressively becomes impaired. Consequently, it is reasonable to support the correction of calcidiol as a first step, as recommended in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Eventually, we should also correct the deficiency of the active metabolite (either with calcitriol or vitamin D analogues) according to PTHi concentration as referenced in the KDOQI guidelines. Under these circumstances it is of paramount importance to monitor calcium and phosphorus metabolism thoroughly. Clinical studies demonstrated so far the superiority of paricalcitol in terms of life expectancy and its minimum effect on calcium and phosphorus intestinal absorption. Furthermore, basic research studies revealed that paricalcitol exerts less detrimental influence in the calcification of the artery wall.
   b. The use of cinacalcet in CKD-stage 5D patients controls secondary hyperparathyroidism without hypercalcaemia or hyperphosphoremia, allows the simultaneous use of vitamin D aimed at a boosting effect for controlling secondary hyperparathyroidism and pleiotropic effects. There is no data yet available on the effects of these new drugs on cardiovascular incidence, although the EVAluation Of Cinacalcet HCI Therapy to Lower CardioVascular Events (EVLOLVE) trial is running. However, the beneficial effects on calcium and phosphorus homeostasis may be interpreted as very promising for the future control of vascular events. Furthermore, new phosphorus binders (calcium free) may constitute also a useful group of drugs in supporting treatment with vitamin D analogues.

2. General population.
   a. There is no data from randomised controlled clinical trials supporting the use of vitamin D in the general population, in terms of improving cardiovascular status. However, we should encourage healthy strategies and therapeutic lifestyle changes to maintain calcidiol concentrations above 30 ng/ml. In those individuals at risk of suffering from a deficit, calcidiol concentration should be measured.

In both groups several questions remain to be answered:

1. When should be the measurement of vitamin D concentration performed?
   - Vitamin D concentration measurement is not an easy, readily available technique, and it is not well established its cost-efficiency. Furthermore, there are also different methods and there is not a consensus concerning cardiovascular protective levels.

2. Which doses and what is the follow up to be applied?
   Should we correct simultaneously the deficit of calcidiol in CKD-affected patients under active-metabolite therapy?

3. Should we prescribe active metabolites to CKD-affected patients with controlled secondary hyperparathyroidism and 'in range' mineral metabolism variables, in the search for cardiovascular outcomes?

In summary, the main message of this manuscript is to keep in mind the double edge of vitamin D and its effects on the cardiovascular system. We must control the deficit of any metabolite, but being very careful with the dosage in order to avoid vitamin D intoxication.

Declaration of interest

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