VITAMIN D
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The use of vitamin D in chronic kidney disease

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INTRODUCTION

The term "vitamin D" denotes a group of steroid, fat-soluble compounds that are essential for the regulation of calcium and phosphorous metabolism, mediated mainly through intestinal absorption.[1]

The two most important isoforms, referred to cumulatively as "native vitamin D", are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol, which is only synthesised by plants and fungi, is introduced through the diet, whereas cholecalciferol, on the other hand, is both exogenously and endogenously synthesised and is derived from the photolysis of 7-dehydrocholesterol, mediated by UVB radiation affecting the skin [15].

Ergocalciferol and cholecalciferol represent the two inactive forms of vitamin D. Their transformation into the biologically active form, calcitriol [1,25(OH)$_2$D], requires a hydroxylation process that takes place in two consecutive steps. The first step takes place in the liver, where, vitamins D_2 and D_3 are hydroxylated at the C25 position by vitamin D 25-hydroxylase and converted to 25-hydroxy-vitamin D [25(OH)D or calcifediol], which is the quantifiable form primarily used to determine serum vitamin D levels. The second step takes place at the level of the proximal tubule of the kidney by way of 1-alpha-hydroxylase, where, 25(OH)D is hydroxylated at C1 to form 1,25-dihydroxyvitamin D, also known as 1,25(OH)$_2$D or calcitriol [1]. Nevertheless, it is also known that 1-alpha-hydroxylase activity (which represents the ability to produce 1,25-dihydroxyvitamin D) can also be found in activated macrophages, osteoblasts, and keratinocytes, whilst its presence has also been documented in the prostate, colon and breast. Furthermore, 1-alpha-hydroxylase is capable of activating nutritional and prohormonal forms of vitamin D.

1,25(OH)$_2$D is the "active" form of vitamin D. Its serum quantification, although important in some diseases, provides little information on vitamin D status, which can usually be normal or even elevated when hyperparathyroidism is associated with vitamin D deficiency [1].

Upon reaching its target organs, 1,25(OH)$_2$D, which is delivered into the bloodstream by a circulating vitamin D binding protein (VDBP), binds with the vitamin D receptor (VDR). The VDR, which can boast an almost ubiquitous and tissue-dependent expression in nucleated cells, belongs to a large group of ligand-activated nuclear transcription factors. This explains how vitamin D, in addition to regulating intestinal absorption and the mobilisation of calcium and phosphorous, also exerts several functions pertaining to mineral metabolism, aside from its osteogenic effects. Vitamin D responsive elements (VDRE) mediate the effects of vitamin D and lead to changes in the expression of several genes [2] (Fig. 1).

The morphological and functional integrity of bone tissue reflects the regulation and maintenance of bone remodelling. This latter is the expression of the activity of osteoblasts, which control bone neoformation, and osteoclasts, which have the ability to resorb mineralised bone, an activity that is modulated by osteoblasts through the RANK-RANKL-OPG system. The RANK ligand, which is secreted by osteoblasts, and binds to a receptor (RANK) present on the surface of pre-osteoclasts, stimulates their differentiation into active (mature) osteoclasts, whilst OPG, which is also secreted by osteoblasts, prevents RANK ligand binding to its receptor, thus inhibiting osteoclastic activation.

These complex interactions are regulated by local and systemic hormones such as PTH, Wnt signalling pathways, FGF23 and precisely 1,25(OH)$_2$D, which plays a key role in the regulation of bone remodelling [3].

The primary "endocrine" effect that follows vitamin D receptor (VDR) activation is the regulation of mineral and bone homoeostasis. VDR activation controls calcium and phosphate ab-

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Conflict of interest
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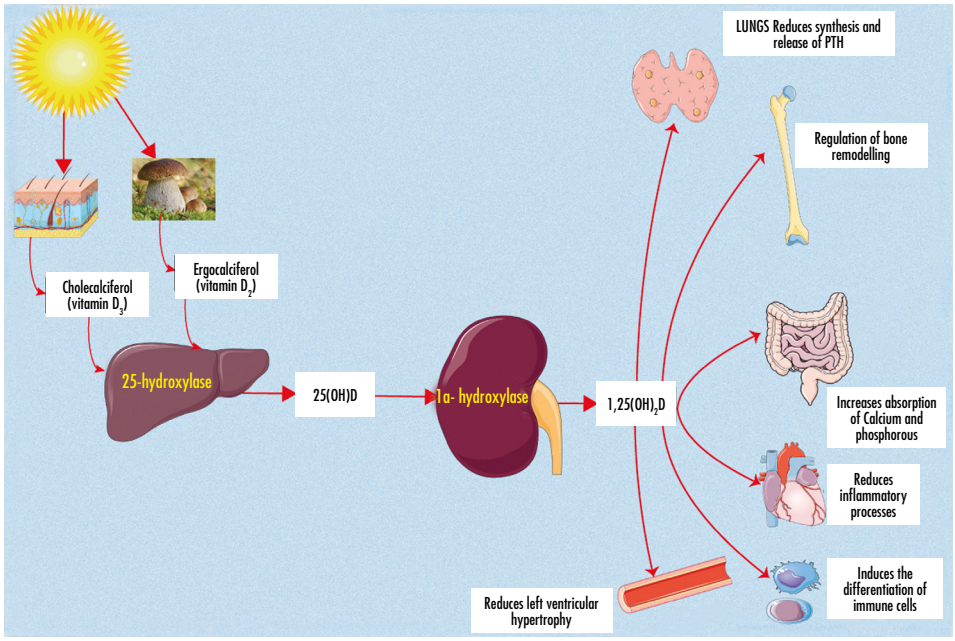

FIGURE 1.
Vitamin D metabolism and its effects.

sorption in the intestine, tubular calcium reabsorption in the kidney and the activity and vitality of bone cells. At the level of osteoblasts, 1,25$(OH)_2$D is able to increase the expression of the Runt-related transcription factor (RUNX2) [2], of osterix (OSX) and of alkaline phosphatase, which are molecules involved in osteoblastic differentiation and mineralisation in several ways. Furthermore, the expression of the Wingless-type (Wnt beta catenin pathway), an important regulator of osteoblast differentiation and function, is increased by 1,25$(OH)_2$D [4].
In addition to stimulating bone formation, calcitriol also promotes bone resorption by increasing the number and activity of osteoclasts. The effects may be mediated by VDRs and alpha-hydroxylase, which are also expressed in osteoclasts, macrophage colony-stimulating factor (m-CSF) and by the receptor activator of nuclear factor kappa-B ligand (RANKL) [5].

VITAMIN D IN CHRONIC KIDNEY DISEASE

Native vitamin D deficiency, which is extremely common in patients with chronic kidney disease (CKD), is attributable to several conditions, such as reduced nutritional intake secondary to dietary restrictions to which kidney patients are frequently subjected (low-protein and low-phosphate diet), reduced appetite and gastrointestinal symptoms, diminished UVB exposure related to reduced mobility and frequent hospitalisations [6]. Then, progressive decline in eGFR has been associated with an increase in the prevalence of vitamin D deficiency. A cross-sectional study conducted on 825 dialysis patients showed that 78% of those patients had a vitamin D deficiency with values < 30 ng/mL and 18% of those patients had severe deficiency with values <10 ng/ mL. That study also showed that low vitamin D values were associated with an increased risk of early mortality.[7] In addition to a native vitamin D deficiency, there is also reduced calcitriol synthesis in CKD. In fact, the progressive loss of renal function is frequently associated with reduced 1-alpha-hydroxylase activity and consequently reduced production of 1,25$(OH)_2$D [2]. In CKD, vitamin D deficiency should be seen in a broader context because it underlies (even though it cannot be seen as the only causative factor) the alterations in calcium, phosphorus and PTH. The development of secondary hyperparathyroidism typically follows the onset of these alterations, which is a clinical and laboratory situation that is peculiar to CKD. Furthermore, among these patients, the altered homoeostasis of mineral metabolism not only affects the skeletal system, but is also closely associated with other important alterations, such as the development of vascular calcifications and, above all, the progression of cardiovascular disease [4].

VITAMIN D IN MINERAL METABOLISM DISORDERS INDUCED BY CKD

CKD is closely associated with the presence of alterations in bone metabolism including dysregulation of calcium and phosphorus metabolism as well as the pathophysiological axis represented by vitamin D-PTH-FGF23. In 2006, the KDIGO (Kidney Disease Improving Global Outcomes) guidelines coined the definition of CKD-MBD (Chronic Kidney Disease-Mineral Bone Disorder) to describe alterations in mineral metabolism and the resulting diseases, such as bone and cardiovascular disorders, associated with increased fracture and cardiovascular risk [8]. These alterations have been found to already be present in approximately 40 to 80% of patients with stage 3 or 4 CKD [9].
Although the exact chronological sequence of the pathophysiological steps is not completely known, it is believed that the increased serum phosphate levels resulting from reduced kidney function stimulate the synthesis and release by osteoblasts and osteocytes of fibroblast growth factor 23 (FGF23), which inhibits PTH synthesis, whist it also inhibits 1-alpha-hydroxylase in the kidney, resulting in reduced calcitriol levels and increased PTH synthesis. Constant stimulation of the parathyroid cells and the failure to correct modifiable factors, such as vitamin D deficiency and hyperphosphatemia, induce a response that is initially "adaptive" but which later becomes, if not corrected by appropriate dietary and pharmacological intervention, "maladaptive", which is characterised by polyclonal hyperplasia of the parathyroid cells. The transition of polyclonal hyperplasia to a "nodular" form of hyperplasia leads to a further progression of secondary hyperparathyroidism, which is characterised, at the level of the parathyroid, by a series of morphological and functional adaptations (reduced expression of the VDR). All of this tends to make the clinical situation poorly responsive to pharmacological therapy, thereby making recourse to surgical treatment necessary (parathyroidectomy) [10].
Therefore, vitamin D does indeed play a key role in the genesis and progression of secondary hyperparathyroidism. Actually, physiological concentrations of 1,25(OH)D have an inhibitory effect on PTH transcription. Moreover, faced with a low affinity for VDR, high serum levels of 25(OH)D have been shown to activate VDR, thus mimicking the effect of 1,25$(OH)_2$D. Besides, 1-alpha-hy-

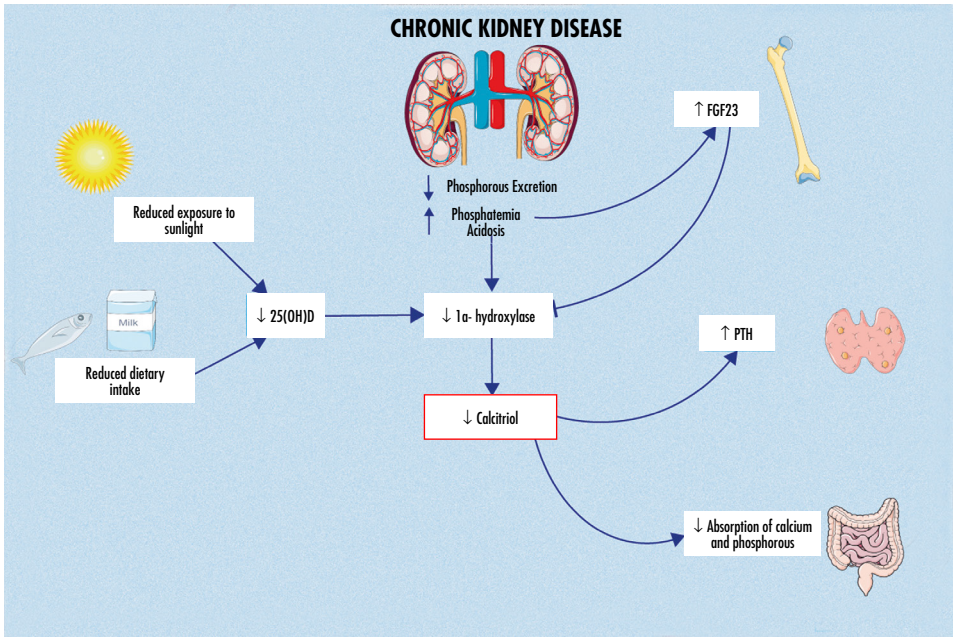

FIGURE 2.
Vitamin D and mineral metabolism disorders in CKD

droxylase, a key enzyme in the conversion of calcifediol to calcitriol, is found in the parathyroid glands and in many other extrarenal tissues, presumably for local production of the hormone.
In this regard, it has been shown that serum levels of 25(OH)D and $1,25(OH)_2D$ increase in response to the administration of nutritional vitamin D (cholecalciferol and ergocalciferol) in dialysed patients. Clearly, this suggests that 1-alpha-hydroxylase activity is also present in extrarenal tissues in CKD, which, in the presence of high levels of 25-hydroxyvitamin D, is able to allow sufficient extrarenal production of 1,25-dihydroxyvitamin D for PTH control.
Since the parathyroid glands express 1-alpha-hydroxylase, a possible autocrine mechanism through which nutritional vitamin D supplementation is able to reduce PTH production should be considered.

The latest KDIGO Guidelines (2017) for the management of CKD-MBD indicate the importance of monitoring serum levels of calcium, phosphate and PTH at the onset of stage G3a CKD and of assessing their trends over time, as well as suggesting that 25(OH)D levels be measured to diagnose vitamin D deficiency (Fig. 2) [8].
With regard to vitamin D values in the general population, reference is made to the recommendations of the Endocrine Society, which establish deficiency with 25(OH)D concentrations at < 20 ng/mL, insufficiency with concentrations between 21 and 29 ng/mL and normal levels or sufficiency with serum levels that are >30 ng/mL [12]. Several guidelines have been formulated over the years concerning the population with CKD that have made different claims regarding the diagnosis and treatment of vitamin D deficiency.
The most recent indications from the National Kidney Foundation, have established that 25(OH)D concentrations at >20 ng/mL can be considered "adequate", whereas concentrations at <15 ng/mL should be treated. For 25(OH)D levels between 15 and 20 ng/mL, consideration should also be given to PTH levels and the counter-regulatory activity of vitamin D on this hormone [13].
Vitamin D supplementation in patients with CKD is still a much debated topic. The KDIGO guidelines suggest supplementation with nutritional vitamin D (cholecalciferol and ergocalciferol), as for the general population, to improve the deficiency status and prevent the onset and progression of secondary hyperparathyroidism [8]. However, there are no conclusive studies currently available on the effect of native vitamin D supplementation on PTH values, although those that are available show no alterations in calcium and phosphorus levels nor any adverse events. It has been hypothesised that nutritional vitamin D supplementation tends to be more effective in preventing the onset and progression of hyperparathyroidism rather than actually reducing PTH values when these have already become elevated in the advanced stages of the disease.
Secondary hyperparathyroidism is a process whose onset begins slowly from the earliest stages of CKD (conservative phase), whilst its onset and/or progression may be prevented by correcting the vitamin D deficiency with early and adequate supplementation treatment. For 25(OH)D levels between 15 and 20 ng/mL, PTH levels should also be considered, whilst the activity of nutritional vitamin D, may reduce the negative effects of secondary hyperparathyroidism on bone remodelling [14], whereas supplementation may also reduce the risk of having PTH levels above the target ranges recommended by KDIGO along with the need for increased drug prescriptions during the subsequent dialysis phase [15].
Furthermore, in light of preclinical and clinical studies, it is likely that in the pathophysiological context of CKD, the antagonising action of the nutritional vitamin on the onset of secondary hyperparathyroidism would be expressed in the presence of higher serum levels of 25(OH) [> 40 ng/mL] than those considered "effective" for the general population [16]. All of this suggests that within a specific pathophysiological context, such as CKD, the currently recommended 25(OH)D levels (> 30 ng/mL) may not be effective, i.e., sufficient for the treatment of SPHT.
Both the KDIGO guidelines and the recommendations of the National Kidney Foundation submit that supplementation with nutritional vitamin D (ergocalciferol, cholecalciferol) should be prioritised first, and only afterwards should active vitamin D compounds (vitamin D receptor activators: VDRA) be introduced, reserving the latter for more advanced stages of CKD and for cases of severe hyperparathyroidism that cannot be controlled by nutritional vitamin D alone. Moreover, treatment with VDRAs should be undertaken when the stage of CKD is advanced, when high PTH values associated with adequate 25(OH)D levels are present and in the absence of elevated levels of calcaemia or phosphoremia [8,17].
In fact, VDRAs should be used with caution since cases of hypercalcaemia and hyperphosphoremia have been reported. Furthermore, their ability to induce excessive PTH depletion may increase the risk of adynamic

bone disease, whilst the increase in FGF-23 levels [17], which in itself is a negative effect, should always be taken into account.

In conclusion, clearly, vitamin D plays a key role in CKD considering that, in light of the ubiquity of vitamin D receptors, its role is crucial for the body's homoeostasis in general and its action cannot be reduced to bone metabolism alone. Therefore, vitamin D deficiency should be diagnosed and treated promptly, even more so in patients with CKD in light of its important impact on hyperparathyroidism and on the regulation of bone metabolism.

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