NATIVE VITAMIN D IN CHRONIC KIDNEY DISEASE

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VITAMIN D AND KIDNEYS

Kidneys are certainly among the most important organs with regard to the metabolism of the vitamin D endocrine system. It is known that 1,25 $(OH)_2$ vitamin D (or calcitriol) – the system's most active metabolite in terms of function – is indeed produced within kidney tissue, where cytochrome CYP27B1 is maximally expressed. This gene is responsible for synthesizing the 1-alpha-hydroxylase enzyme, which is able to convert 25 (OH) vitamin D – which mostly comes from the liver – into calcitriol (Fig. 1). Calcitriol is the most powerful stimulator of the vitamin D receptor (VDR) (Fig. 2), whose activity generates the most important functions of this hormonal system within the human body [1].

For this reason, it has always been believed – and still is today – that the progressive loss of renal function can reduce calcitriol synthesis. This, in turn, triggers complex metabolic and clinical alterations which lead to the onset of the condition known as CKD - MBD (Chronic Kidney Disease - Mineral and Bone Disorder): this disorder is largely responsible for skeletal and vascular complications, which quite frequently afflict those with CKD [2]. The most notable of the complications caused by an impaired function of the vitamin D endocrine system is the increase in parathyroid hormone (PTH). Although also plays a significant role in the increase of phosphatemia, a typical symptom of CKD, it has always been held that treatment of secondary hyperparathyroidism, which is characteristic of CKD, should be effected with active vitamin D metabolites (calcitriol and analogs) [3].

In recent years, however, new scientific evidence has been collected that has led scientists to reconsider this idea, at least in part. If it is indeed true that renal synthesis of calcitriol decreases with a reduction of kidney function, today it is known that the nearly total cessation of 1-alpha-hydroxylase activity of the kidney occurs when the glomerular filtration rate (GFR, mL/min) is less than 15. In previous stages of CKD, this activity is present and efficient, at least in part (Table I). It then became increasingly clear that expression of cytochrome CYP27B1 and the resulting activity of 1-alpha-hydroxylase enzyme is actually present in tissues and organs other than the kidneys [4], thus rendering possible a significant degree of extra-renal calcitriol synthesis. This synthesis is largely carried out through the local actions, autocrine and paracrine, rather than the systemic ones, of this metabolite (Table II). Nonetheless, the most relevant fact is certainly an increasingly evident prevalence of reduced levels – sometimes markedly reduced – of 25 (OH) vitamin D, which is surely not attributable to the loss of renal function.

This observation has given rise to a long series of studies which aim to assess the importance of "pre-renal" hypovitaminosis D in the genesis of various complications related to chronic kidney disease (CKD) and the possible role of native vitamin D in the treatment of this condition [5].

HYPOVITAMINOSIS D IN CHRONIC KIDNEY DISEASE: PREVALENCE, POSSIBLE COMPLICATIONS AND THERAPY

As we have seen, in the last ten years many studies have focused on the role of 25 (OH) D status in patients with CKD. Most of these show that serum levels of this hormone tend to decrease, in parallel with what takes place with calcitriol, with a progressive deterioration of renal function [6]. Already in patients with stage 1-2 CKD, it is estimated that the prevalence of 25 (OH) vitamin D serum values < 30 ng/mL is close to 80% [6], reaching almost 85% in patients with terminal stage CKD. In particular, it has been shown that 25 (OH) vitamin D levels below 15 ng/mL are found in ca. 50% of patients with stage 4-5 CKD. Quite similar data indicate that low

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VITAMIN D - UpDates
2018;1(2):32-34; https://doi.org/10.30455/2611-2876-2018-04

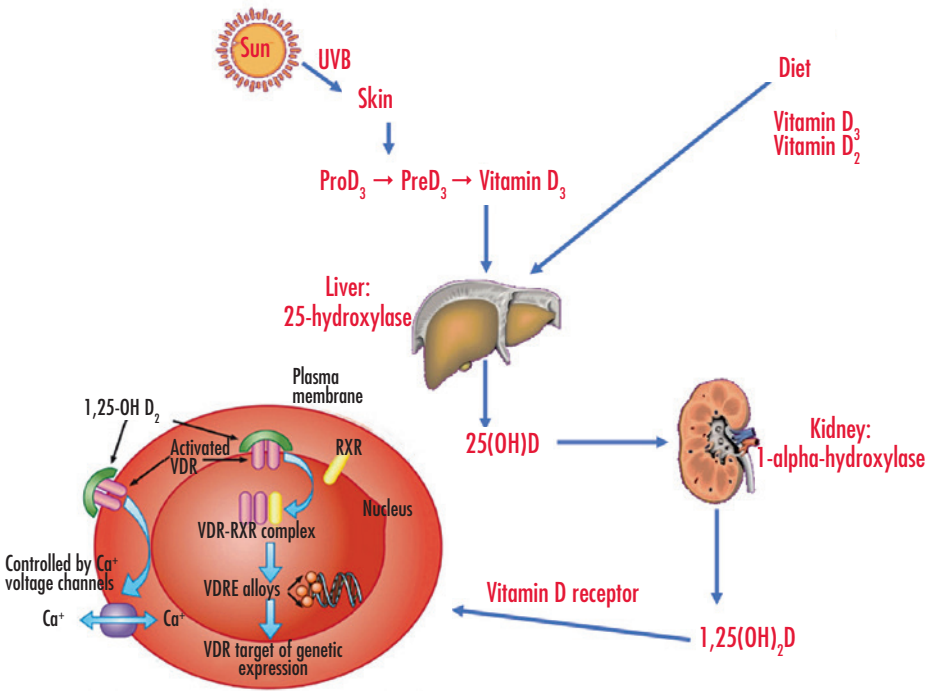

FIGURE 1.
Vitamin D endocrine system.

vitamin D levels are also present following kidney transplants, with a prevalent tendency toward 25 (OH) vitamin D deficiency.
The reason for this very high prevalence of hypovitaminosis D is not completely clear. One possibility is that, as in the general population, insufficient exposure to sunlight could in part explain this phenomenon. It has in fact been demonstrated that exposure to UVB rays in terminal stage CKD patients is able to significantly raise 25 (OH) D serum levels [8]. On the other hand, it is also clear that the seasonal boost of these blood levels is, on the whole, rather modest in these patients. Indeed, one study has shown that a prevalence of severe vitamin D deficiency of 96% during winter months dropped to only 86% in summer months in subjects undergoing hemodialysis [9]. This datum should not surprise us, given that these patients suffer from significant morbidity, which is little compatible with adequate exposure to sunlight during the warm months.
The complications of this widespread condition are still not clear today. There are still very few studies which aim to show the cause-effect relationship between hypovitaminosis 25 (OH) D and morbidity in CKD patients. Nonetheless, a number of interesting suggestions backed by sound scientific evidence have been produced in the last few years. Bone fragility and subsequent fractures are quite common conditions in CKD. They result from a series of impairments of bone tissue, which constitute the basis of renal osteodystrophy and which frequently include the concomitance of various stages of osteomalacia, high turnover bone disease and adynamic bone disease. Secondary hyperparathyroidism is certainly a distinctive characteristic of the first two forms; it is therefore not surprising that a significant portion of scientific work has focused on the role of low 25 (OH) vitamin D levels in the genesis of this condition. Although no sound studies are available to show the ability of therapy with native vitamin D to reduce the risk of fractures in the course of CDK, recent data indicate that it plays a clear role in the pathogenesis and correction of the main metabolic alterations related to them.
In subjects with kidney transplants, 25(OH) D serum levels were quite low in the majority of evaluated individuals and represented the greatest predictive factor for high parathormone levels, as the latter were correlated to a high risk of vertebral fracture in these patients [7]. Indeed, several studies regarding this category of patients have shown that therapy with cholecalciferol – even if different doses were used – was able to broadly and significantly reduce serum parathormone levels [10]. Even more interesting results come from a randomized double-blind controlled study which involved stage 3-4 CKD patients with 25 (OH) vitamin D serum levels < 20 ng/mL. These subjects were administered either 300,000 IU of cholecalciferol on two occasions at a distance of 8 weeks, or a placebo. At the end of the study, after a follow-up conducted at 16 weeks, researchers found that those treated with cholecalciferol had fully normal 25 (OH) vitamin D serum levels.

Activation of the vitamin D receptor produces:

- genomic actions
- non-genomic actions – rapid intestinal absorption
- endocrine function – systemic
- paracrine and autocrine functions – local

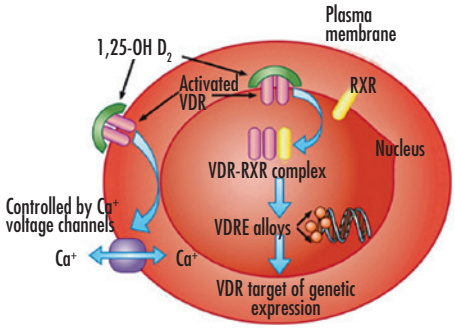

FIGURE 2.
Vitamin D receptor and its activation.

TABLE I.
Stages of chronic kidney disease (CKD).

STAGE	DESCRIPTION	GFR (ML/MIN)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with slight GFR reduction	60-89
3	Kidney damage with moderate GFR reduction	30-59
4	Kidney damage with severe GFR reduction	15-29
5-5D	Kidney failure (D = Dialysis)	< 15

TABLE II.
Main organs and tissues that express mRNA for CYP27B1 in (1-alpha-hydroxylase synthesis).

Adrenal Gland	Mammary Gland
Bone	Muscle
Bone Marrow	Neoplastic Cells
Brain	Ovary
Cartilage	Pancreas
Fat	Parathyroid Glands
Heart	Placenta
Intestine	Prostate
Kidney	Skin
Liver	Testicle
Lung	Thyroid
Lymphocyte	Uterus

Nonetheless, the most relevant finding of this study was certainly that of a reduction of ca. 25% in PTH values, which are high at basal conditions, and of 30% and ca. 18% of bone alkaline phosphatase and of the Cross-Laps of the pyridinium, respectively, which are known to be reliable bone-remodeling markers. These results allow us to postulate a positive effect of cholecalciferol in terms of bone morbidity in CKD patients [11].
In both of the studies cited above, as in others that we are forced to omit, no significant or clinically relevant modification of serum calcium values or renal function was observed, indicating that this therapy has safety characteristics that are completely reassuring.
Vitamin D insufficiency has, moreover, been associated with the genesis of other possible CKD complications. Even though, in this context, we still lack sufficiently solid evidence to confidently recommend the use of native vitamin D in the course of CKD, some interesting scientific data are already available. In these patients, it is known that residual proteinuria following maximum therapy with angiotensin-converting enzyme inhibitors constitutes an independent risk factor for the progression of CKD and for the onset of cardiovascular events.
A recent prospective and controlled study of pre-dialysis CKD patients with hypovitaminosis D found a significant (41%) reduction in proteinuria in subjects treated with cholecalciferol (666 IU/day for 6 months), while no variation was observed in untreated subjects. In this study, stage 3-4 CKD patients with 25 (OH) vitamin D serum levels < 20 ng/mL were given either 300,000 IU of cholecalciferol on two occasions at a distance of 8 weeks, or a placebo: it was observed that vascular function – defined as the variation of the endothelium-dependent flow in the brachial artery and of the carotid-femoral pulse-wave velocity – improved significantly in the treated subjects, but not in the placebo group [12].
It is clear that sufficient data are lacking in order to draw realistic conclusions and that further studies are still necessary; even so, the available literature seems to suggest that low levels of 25 (OH) vitamin D can be correlated to a worsening of anemia and a progression of renal dysfunction in patients with CKD [5].

CONCLUSIONS

Solid evidence from different studies provides increasingly convincing indications that insufficiency of 25 (OH) vitamin D (and not only of calcitriol) may be responsible for many clinical consequences of CKD. Undoubtedly, the challenge over the next few years will be to definitively show the importance and the wide range of potential applications of therapy with native vitamin D, including in this complex and common clinical condition.

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