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Vitamin D in the Patients with Chronic Kidney Disease: When, to Whom and in Which Form

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ABSTRACT

Alteration in vitamin D metabolism has a central role in the pathogenesis of secondary hyperparathyroidism (SHPT) and is also associated with increased cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). For more than sixty years, vitamin D, nutritional vitamin D (ergocalciferol, cholecalciferol or calcifediol) and nonselective vitamin D receptor (VDR) activators (calcitriol, alfacalcidol) have been used in the prevention and treatment of SHPT. In the last twenty years, selective VDR activators (paricalcitol, maxacalcitol) have been used to target SHPT. However, there are many open questions regarding use of nutritional vitamin D or VDR activators. The K/DOQI and KDIGO guidelines recommended testing for vitamin D insufficiency and deficiency in patients with CKD, but there is no consensus on the definition of vitamin D insufficiency in CKD. There are a many open questions, for example, regarding the optimal nutritional vitamin D type and the dose and co-administration of nutritional vitamin and VDR activators. Therapy with VDRAs is required in the majority of patients with CKD, particularly in dialysis patients. However, when to start with VDRAs is not so apparent. Is PTH level the only indication of when to start therapy? Although VDRAs are very effective in lowering PTH levels and bone metabolism the effect of patients mortality is not so straightforward. Despite many unanswered questions, there is a large body of experimental and clinical data to support vitamin D use in patients with CKD. To obtain answers to the open questions, we need more randomized controlled trials.

Key words: vitamin D, chronic kidney disease, bone disease.

1. INTRODUCTION

Traditionally, vitamin D was perceived as a vitamin essential for the regulation of calcium metabolism. In the 19th century the importance of exposure to the sun was recognized in the prevention and treatment of rickets. At the beginning of 20th century, vitamin D was structurally identified and chemically synthesized. Although it is still named vitamin, in fact it is hormone, a fat-soluble steroid hormone found in two forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Today, it is well known that vitamin D is important not only for the regulation of bone and mineral metabolism, but due to its capability of inhibiting the proliferation and differentiation of many cells it has an important function in modulating the immune system (1). Moreover, there is much clinical and experimental data that vitamin D can influence insulin secretion and inhibit renin secretion (2, 3). Over the last decade evidence has suggested that low serum vitamin D level is associated with a number of non-skeletal disorders including cancer, heart disease, high blood pressure, diabetes, age-related cognitive decline, Parkinson's disease, multiple sclerosis, skin disease and arthritis (4). In chronic kidney disease (CKD) alteration of vitamin D metabolism is one of the most important factors in the pathogenesis of secondary hyperparathyroidism and features of chronic kidney disease-mineral bone disease (CKD-MBD). In addition, many observational studies have shown an association with vitamin D disturbance, i.e. low levels of vitamin D in CKD and cardiovascular disease (left ventricular hypertrophy and vascular calcification, hypertension and faster progression of kidney disease) (4, 5). Thus, in recent years there has been renewed interest in vitamin D metabolism and action.

2. VITAMIN D PHYSIOLOGY

There is a double origin of vitamin D. It can be ingested orally or it can be formed endogenously in the skin after exposure to sunlight, or better to say, to UVB light (Figure 1)(1, 6). Very briefly, in the skin under the influence of UVB radiation 7-dehydrocholesterol is converted to previtamin D. By a temperature dependent process previtamin D is very quickly converted to vitamin D3 (cholecalciferol). Vitamin D3 is transported in the blood by vitamin D binding protein (VDBP). Orally ingested

vitamin D is vitamin D2 (ergocalciferol) and is also transported by VDBP to the liver. In the liver cholecalciferol, i.e. vitamin D3, and ergocalciferol, vitamin D2, are converted to 25-hydroxivitamin D by the enzyme 25-hydroxylase. This process is not tightly regulated and the half-life of these metabolites is very long, up to 19 days. Therefore, the measurement of these metabolites is used to define vitamin D deficiency and insufficiency (see later). 25-hydroxivitamin D (D represents D 2 and D3) is biologically inert and much less potent than so-called active metabolite, 1.25 dihydroxivitamin D. Under the influence of 1 α hydroxylase, 25-hydroxivitamin D (named calcidiol) is hydroxlated to the above-mentioned 1.25 dihydroxivitamin D, named calcitriol. More than 85% of circulated 25-hydroxivitamin D is hydroxylated in renal tubules and about 5 % is hydroxylated in other cells, e.g. monocytes. Calcitriol from the kidneys has an endocrine function and calcitriol from other peripheral tissues and cells has autocrine or paracrine function. Calcitriol synthesis in kidney is regulated by PTH, calcium, phosphate and fibroblast growth factor 23 (FGF 23). While PTH increases 1 α hydroxylase activity, the effect of calcium, phosphorus and FGF 23 is the inhibition of calcitriol synthesis. Moreover, FGF 23 increases the activity of 24, 25 hydroxylase, i.e. synthesis of 24, 25 dihydroxivitamin D (Figure 1).

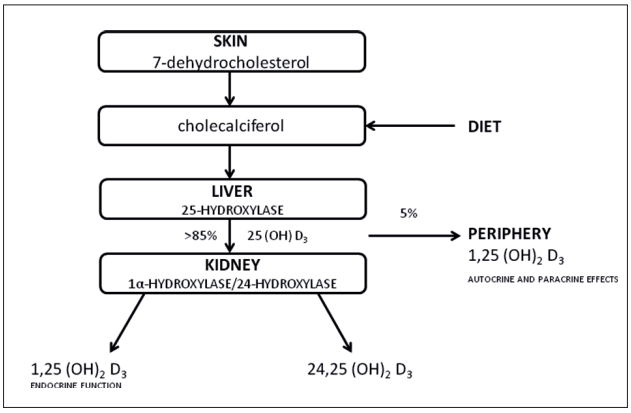

Figure 1. Vitamin D metabolism

3. ASSESSMENT OF VITAMIN D STATUS

Over the last 25 years, there have been many studies showing the association between decreased calcidiol concentration in the blood and mortality, cardiovascular disease, bone fractures, diabetes mellitus, increased incidence of some malignant diseases and autoimmune disease (6, 7). Therefore, it was obvious that vitamin D status, as a deficiency of insufficiency, should be defined. Several professional societies defined a deficiency as a calcidiol level < 20 ng/ml (< 50 nmol/L) and insufficiency as a calcidiol level of 20-29 ng/mL (50- 60 mmol/L)(6). Recently, there have been many discussions about the optimal definition of vitamin D status that could be find in literature (8). There are several reasons for that. First, we still do not have a standardized method to measure calcidiol level. Another reason is that optimal level of calcidiol is based on PTH level, i.e. the PTH plateaued level. Some experts suggest that the reference interval for calcidiol should be defined in the same way as other reference intervals, i.e. as the central 95% of the values found in a healthy normal population. Finally, and no less important, measured calcidiol is total calcidiol, 80% of which is bound to VDBP, and the other 20% is made up of calcidiol bound to albumin and free calcidiol. Albumin-bound and free calcidiol are bioavailable. At this moment, we do not have a biochemical method to measure bioavailable calcidiol, it must be calculated. It seems that this form is more important, at least in mineral and bone metabolism (8).

4. VITAMIN D IN CKD

Among many other complications, CKD is characterized by low calcidiol and calcitriol level (9, 10, 11). Alterations in vitamin D metabolism in CKD, together with hyperphosphatemia and hypocalcemia leads to secondary hyperparathyroidism. Moreover, vitamin D alterations in CKD is one of the major reasons for increased all-cause mortality and cardiovascular mortality in CKD patients (12).

There are several reasons for low levels of calcidiol and calcitriol in CKD. Calcidiol deficiency is due to reduced sun exposure, reduced skin synthesis, reduced ingestion of foods rich in vitamin D, and loss of VDBP with proteinuria. Reduced calcidiol availability, reduced renal 1α hydroxylase availability, down regulation of renal 1α hydroxylase from hyperphosphatemia and FGF-23, reduced endocytotic uptake by megalin, increased degradation of calcitriol by PTH and FGF-23 are the reasons for low calcitriol level. Even more in CKD, there is also calcitriol resistance due to loss of vitamin D receptors (13).

Based on the above criteria, the prevalence of vitamin D deficiency in the CKD population is much higher than in the general population. It is estimated to be as much as 80%. Vitamin D deficiency is also prevalent in early stages of CKD, beginning before other mineral metabolism disturbances. It must be pointed that there is no consistent association between bone disease in CKD and calcidiol level. In addition to other factors, one explanation might be the fact that we measure total calcidiol not bioavailable calcidiol (see above). At this moment, there are no guidelines for when and how often to measure calcidiol level in CKD patients.

5. THERAPEUTIC USE OF VITAMIN D IN CKD

The use of vitamin D compounds in CKD has been known for more than 60 years. Cholecalciferol and calcidiol were the first vitamin compounds used in CKD, and from late 1970s calcitriol, a so-called active metabolite, was introduced into clinical practice. Since then, newer drugs have been introduced with more or less the same advantages (14). Despite the long use of various forms of vitamin D in CKD, there are still many open questions about its use – when to start, what compound to use, oral vitamin D supplement or active metabolites or the so-called analogs (15). It is interesting to note that there are no specific recommendations for vitamin D supplementation for CKD in KDIGO and European Renal Best Practice Groups guidelines, i.e. the recommended treatment strategy is the same as for the general population. KDOQI guidelines from 2003 recommended oral or intravenously ergocalciferol in a dose based on calcidiol level. There are several studies showing different effects of ergocalciferol or cholecalciferol on PTH level. It seems that cholecalciferol may have some advantage in the supplementation of vitamin D in CKD (5, 16).

There are various active forms of vitamin D in clinical practice: calcitriol, paricalcitol, doxercarciferol 1-α calcidiol and 22-oxacalcitrol. In majority of guidelines the decision when to start, the dose and the route of the treatment is based on

PTH and calcium level (17, 18). It must be underlined that all active forms of vitamin D are not available everywhere and no less important is the significant difference in the price. In our county we have calcitriol and paricalcitol, the latter in two forms, oral and intravenously Based on our clinical experience and international guidelines, we have created a way for the therapeutic use of vitamin D in CKD. In patients with PTH level between 150-250 pg/mL and hypocalcemia we start with low doses of calcitriol, e.g. 0.25 to 0.5 mcg orally. If PTH is higher, low doses of paricalcitol are used, 3-6 mcg orally three times per week. If there is a trend for PTH to rise, we increase the dose, and if PTH is higher of 600 pg/mL we use paricalcitol with an intravenously three times per week in a total weekly dose of not less than then 15 mcg. Despite new forms of vitamin D prevention and treatment of mineral metabolism disturbance and bone disease in CKD is still a great challenge.

Many guidelines might be helpful in our everyday practice, but one should keep in the mind the adage that guidelines should inform but not dictate, guide but not enforce, and support but not restrict (19).

CONFLICT OF INTEREST: NON DECLARED.

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