Vitamin D and Kidney Disease. What we know and what we do not know

Vitamina D e doença renal. O que nós sabemos e o que nós não sabemos

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Abstract

Vitamin D deficiency is common in the chronic kidney disease (CKD) population. CKD has been recognized as a significant public health problem and CKD patients are at increased risk of total and cardiovascular morbidity and mortality. There are increasing epidemiological data suggesting that vitamin D deficiency may play a role in overall morbidity and mortality associated with CKD. The vitamin D hormonal system is classically implicated in the regulation of calcium homeostasis and bone metabolism but there is ample evidence to support the claim that extra renal conversion of 25(OH)D to $1.25(OH)_2$ has significant biological roles beyond those traditionally ascribed to vitamin D. Based on the current state of evidence this review intends to give an update on novel biological and clinical insights with relevance to the steroid hormone vitamin D specifically in patients with kidney disease.

Keywords: 25-hydroxyvitamin D_2; kidney failure, chronic; vitamin D deficiency.

Resumo

A deficiência de vitamina D é um achado comum em pacientes com doença renal crônica (DRC). A DRC é reconhecida como um problema de saúde pública importante, com elevado risco de morbimortalidade total e cardiovascular. Inúmeras publicações epidemiológicas sugerem que a morbimortalidade nesses pacientes pode estar associada à deficiência de vitamina D. O sistema hormonal da vitamina D é classicamente implicado na regulação do metabolismo ósseo e da homeostase do cálcio; entretanto, há uma grande evidência de que a conversão de 25(OH)D para $1.25(OH)_2$ tem um papel biológico significante além daquele tradicionalmente descrito. Baseada em atual evidência, esta revisão pretende ressaltar os aspectos clínicos e biológicos relevantes no sistema hormonal da vitamina D especificamente em pacientes com doença renal.

Palavras-chave: 25-hidroxivitamina D_2; deficiência de vitamina D; insuficiência renal crônica.

Introduction

Vitamin D deficiency/insufficiency is an increasingly recognized public health problem in the general population.[1] Chronic kidney disease (CKD) has been known to be a risk factor for development of vitamin D deficiency/insufficiency and is associated with increased morbidity and mortality.[2] The vitamin D hormonal system is implicated in the regulation of calcium homeostasis and bone metabolism but also potentially has extra-mineral metabolism functions through activation of non-renal vitamin D receptors (VDR) and over the last decade, interest in the therapeutic potential of vitamin D has grown.[3]

The active form of vitamin D are present in many tissues which are not associated with calcium or bone metabolism. Indeed, 1.25-dihydroxyvitamin D regulates cell proliferation, differentiation and apoptosis in many normal and cancer cells. Epidemiologic studies have shown that vitamin D deficiency increases the risk of cancer, cardiovascular disease, autoimmune disease, type 2 diabetes mellitus, and infectious disease; however, in this review we will focus our attention on highlighting new information from recent

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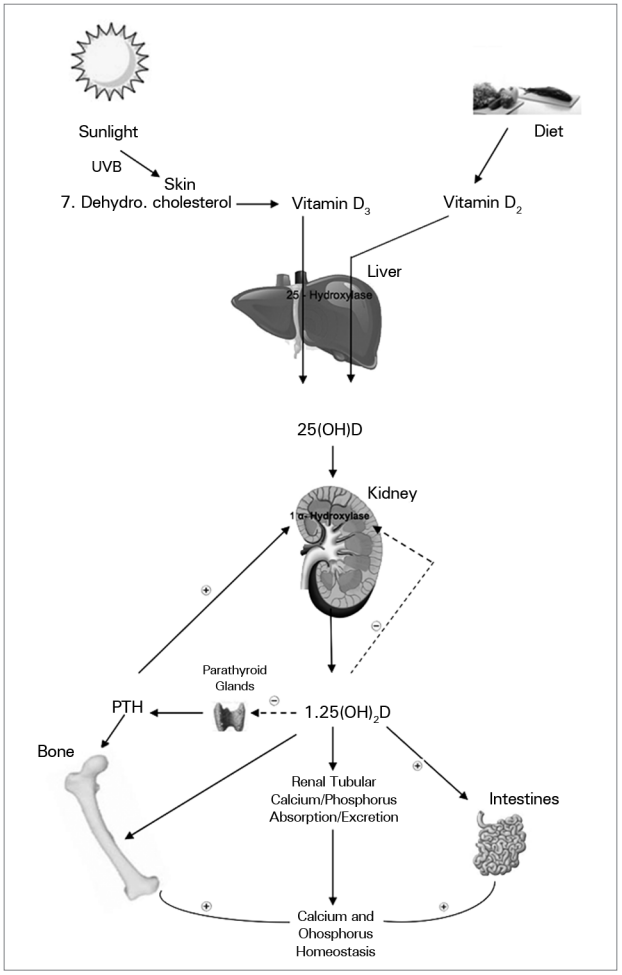
studies on vitamin D deficiency/insufficiency and pathogenesis in renal disease, and vitamin D replacement therapy and outcomes in renal disease.

Sources and metabolism of vitamin D

In nature, vitamin D can be obtained in two forms - dietary ingestion or sunlight-induced endogenous synthesis by the skin (Figure 1). Humans derive vitamin D mostly from skin-exposure to sunlight and, to a lesser extent, from the diet and dietary supplements.[4,5] Few foods naturally contain or are fortified with vitamin D. Therefore, without daily regular consumption of naturally-rich or fortified foods, individuals may be deficient in vitamin D. In the absence of daily exposure to sunlight, or with the use of sunscreens, this deficiency will be more pronounced. Solar ultraviolet B radiation converts 7-dehydrocholesterol in the epidermis to pre-vitamin D_3, which is immediately converted to biologically inactive vitamin D_3 in a heat-dependent process.[4]

Figure 1. Sources and metabolism of vitamin D. UVB: Ultraviolet B; Vitamin D_3: cholecalciferol; Vitamin D_2: Ercalciferol; 25(OH)D: 25 hidroxyvitamin D; 1.25$(OH)_2$D: 1.25 dihydroxyvitamin D (calcitriol); PTH: Parathyroid hormone.



Vitamin D refers to two biologically inert precursors or prohormones: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol).[5] They behave in a similar manner and are subsequently referred here only as 25-hydroxyvitamin D (25(OD)D). Vitamin D in these forms must be converted to the active hormone to be able to exert biological influence affecting mineral metabolism and other physiological functions. Vitamin D is transported in the blood by the vitamin D-binding protein (DBP) to the liver. In the liver vitamin D is hydroxylated at the C-25 position by one or more cytochrome P450 vitamin D 25 hydroxylases, resulting in the formation of 25(OH)D. 25-hydroxyvitamin D is the main storage form of vitamin D. In the proximal renal tubule (PCT), the enzyme 1-α-hydroxylase catalyzes the hydroxylation of 25(OH)D (Figure 1) at the position of carbon 1 of the A ring resulting in the hormonally active form of vitamin D, 1.25-dihydroxyvitamin D (1.25$(OH)_2$D). Also called calcitriol, this is the biologically active form of vitamin D that acts on receptors in different target organs.

The renal synthesis of 1.25$(OH)D_2$ is a tightly regulated step in itself, given its potent activity in calcium homeostasis (Figure 1). Dietary calcium can regulate vitamin D directly through changes in serum calcium and indirectly by altering parathyroid hormone (PTH) levels. 1-alpha hydroxylase can be suppressed by other factors such as phosphorus and chronic metabolic acidosis.[6,7] However, high circulating calcium and fibroblast growth factor-23 (FGF-23) levels directly suppress renal 1-α-hydroxylase activity, via regulation of 1-α-hydroxylase gene transcription and indirectly through PTH suppression via cAMP-mediated changes.[8] FGF-23 is a hormone produced by osteocytes and is a critical circulating hormone involved in phosphate metabolism.[9]

Vitamin D in the extra-renal milieu

Evidence suggests that the physiological significance of vitamin D extends beyond regulating the classical calcium-phosphorus-PTH axis domain. Research in the last few years has demonstrated the expression of 1-α-hydroxylase in tissues and organs other than kidneys. Evidence suggests that 1.25$(OH)_2$D exerts a wide range of non-classical actions, including effects on modulation of the immune system, regulation of cellular differentiation, programmed cell death, inhibition of cell growth, control of the central nervous

system, regulation of cardiomyocyte hypertrophy, regulation of insulin secretion and regulation of blood pressure via the renin angiotensin aldosterone system (RAAS).[8,10-14] Laboratory experiments have demonstrated the expression of 1-α-hydroxylase in non-renal tissues and therefore the synthesis of $1.25(OH)_2D$ in extra-renal sites.[15] Also, it has been shown that intracellular VDR are expressed such as breast, skin, prostate, lymph nodes, colon, pancreas, adrenal medulla, brain, and placenta.[16] It is likely that $1.25(OH)_2D$ is locally produced in these sites to mediate local biological effects in the immediate cellular environment.

FGF-23 and vitamin D

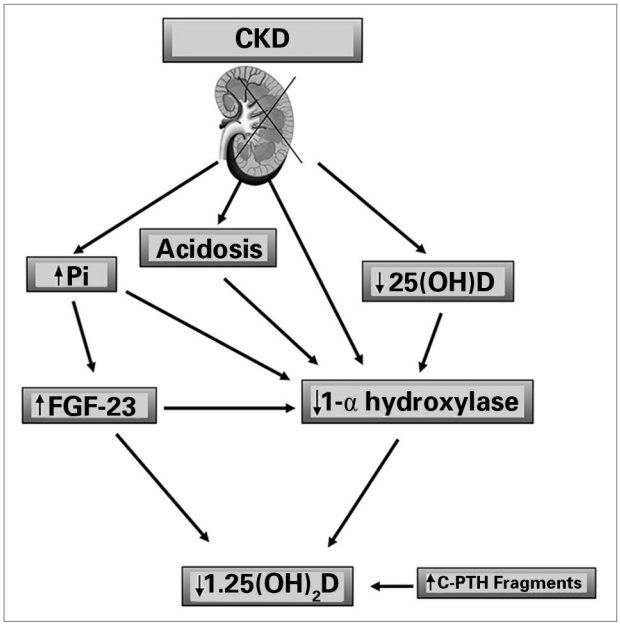
The discoveries of FGF-23 and Klotho have added an interesting dimension to our understanding of vitamin D homeostasis.[17] FGF-23 is an approximately 32-kD (251 amino acids) protein and its N-terminal region contains the FGF homology domain.[17] FGF-23 induces phosphaturia and has been shown to directly suppress the activity and expression of 1-α-hydroxylase.[18] Also, FGF-23 production induces the expression of 24-hydroxylase the enzyme responsible for the degradation of $1.25(OH)D_2$ thus decreasing vitamin D bioavailability.[3,19]

Klotho is a type 1 membrane protein, with a single transmembrane domain near its C-terminus that is hypothesized to anchor the protein to the membrane.[20] The FGF-23 receptor, Klotho, is involved in aging and both the klotho knock-out mouse and the FGF-23 knock-out mouse experience rapid aging and vascular calcification.[21-24] Further research has suggested that Klotho can bind to multiple FGF receptors, and that the Klotho-FGF receptor complex binds to FGF-23 with much higher affinity than either the FGF receptor or Klotho alone. The binding of this complex can then activate downstream signaling events.[25] The phosphate-lowering effect of FGF-23 is partly mediated through the reduced expression of naPi-2a and 1α hydroxylase in the proximal tubular epithelial cells. The interaction of proximal and distal tubules to facilitate FGF-23-Klotho-mediated functions is an important and unsolved issue, and an active area of research.

Vitamin D metabolism in CKD

The kidney is the key organ involved in production of bioactive forms of vitamin D from inert precursors. Consequently, chronic kidney disease is an important risk factor for development of vitamin D deficiency.[2] There are several mechanisms by which $1.25(OH)_2D$ are lowered during the course of CKD, starting with decreased availability of the 25 (OD)D substrate for the production of $1.25(OH)_2D$[26-28] (Figure 2). A reduction in glomerular filtration rates (GFR) limits the delivery of 25(OH)D to the 1-α-hydroxylase enzyme in the proximal renal tubule, and therefore restricts the ability of the kidney to produce $1.25(OH)_2D$.[29] Levels of phosphaturic hormone FGF-23 also increase early in CKD, presumably in response to phosphate retention, which also suppresses production of $1.25(OH)_2D$.[30] In addition to these factors, there may be additional contribution from potential suppressive effects of Carboxyl (C)-terminal fragments of PTH on $1.25(OH)_2D$ synthesis.[31]

Figure 2. The mechanism contributing to the progressive decrease in the levels of 1.25 - dihydroxyvitamin D (calcitriol).



Vitamin D deficiency in CKD

The debate and speculation surrounding the role of Vitamin D supplementation is hindered in the inability to achieve consensus on a cut-off point to define Vitamin D deficiency. Adopting criteria based on levels of 25(OH)D required to suppress PTH in mostly white populations, some experts have defined Vitamin D deficiency at serum 25(OH)D levels < 20 ng/mL and relative insufficiency as 21-29 ng/mL.[30-33] A target ≥ 30 ng/mL has been suggested to be desirable for optimal health.[33] It is important to remember that circulating $1.25(OH)_2D$ provides essentially no information with respect to the patient's nutritional vitamin D status.

The Workshop Consensus for Vitamin D Nutritional Guidelines, published in 2010, estimated that more than 50% of the older populations in the world do not have satisfactory vitamin D status.[34] The situation in younger subjects and pediatric population seems to be not different.[35,36] Epidemiological studies have demonstrated a high prevalence of insufficient or deficient vitamin D status in the general population,[37,38] CKD patients in pre- and chronic dialysis.[26,39]

The Study for the Evaluation of Early Kidney disease (SEEK) investigated more than 1800 CKD patients over a wide range of renal function and detected $1.25(OH)_2D$ deficiency (< 22.0 pg/mL) in more than 60% in those with eGFR < 30 ml/min/1.73 m^2 and 25(OH)D deficiency (< 15 ng/mL) in 12% of patients overall.[27] In a cross sectional study, LaClair *et al*.[39] measured serum 25(OH)D levels in 201 patients with a mean estimated GFR of 27 ± 11 mL/min/1.73 m^2 (GFR range 6-69 mL/min/1.73 m^2). The overall mean serum levels of 25(OH)D were 19 ± 14 ng/mL. Only 29% of the 65 patients with stage 3 CKD and only 17% of the 113 patients with stage 4 CKD had a serum 25(OH)D level above 30 ng/mL. Furthermore, 14% of patients with stage 3 CKD and 26% of those with stage 4 CKD had 25(OH)D level below 10 ng/mL.[39]

Even in a sunny country like Brazil, a cross-sectional study including 144 nondialyzed CKD patients at stage 2 to 5 found 57 patients (39.6%) 25(OH) D insufficient (16 to 30 ng/mL).[40] However, while this one study suggests that vitamin D status in Brazil may be better than in other countries, it still needs to be addressed due to the present knowledge of the proposed non-calcemic effects of vitamin D and vitamin D's potential beneficial role in vascular health, insulin resistance and immune function.

The high prevalence of 25(OH)D deficiency/insufficiency in CKD patients can be partially explained by poor sunlight exposure in chronically ill patients, decreased skin synthesis of cholecalciferol in response to sunlight, diminished ingestion of food that are natural sources of vitamin D, and urinary loss of 25(OH)D and DBP in proteinuric nephropathies.[41] Moreover, renal megalin, the binding protein for 25(OH)D in the proximal tubule, decreases as GFR falls, thus reducing 25(OH)D tubular reabsorption.[42] Additionally, renal retention of phosphorus in early stages of CKD may contribute the impaired production of 1.25(OH)D directly and by increasing FGF-23.[43] Recently, in a cross-sectional study, Figuiredo-Dias *et al*.[44] analyzed 120 patients with CKD at stages 2 to 5. They found diabetes mellitus (Odds Ratio (OR): 3.8; 95% CI: 1.2 to 11.7; p = .02) and BMI ≥ 30 Kg/m^2 (OR: 4.3; 95% CI: 1.2 to 15.3; p = 0.02) as independent risk factors for hypovitaminosis D in nondialyzed patients even after adjustment for sex, skin color, and season of the year.

Vitamin D in CKD and Mortality

CKD with or without hemodialysis has been consistently shown to be an independent risk factor for all-cause and cardiovascular mortality across diverse clinical populations.[45] Within the CKD population, evidence gathered from epidemiological studies point to a potential role the levels as well as supplementation of vitamin D play in survival outcomes in CKD patients regardless of dialysis status.[46-48] A recent meta-analysis of prospective studies by Pilz *et al*.[49] estimated a significant decrease by 14% in mortality risk [RR 0.86, 95% CI (0.82-0.91)] per of 10 ng/ml higher 25(OH)D levels. Current evidence also suggests a survival benefit with vitamin D supplementation that is independent of changes in serum calcium, phosphorus or PTH levels, and supports a growing body of literature on non-classical effects of vitamin D beyond regulation of bone and mineral metabolism.[47-50] While there is no direct explanation for the apparent survival benefits associated with vitamin D, indirect supportive evidence can be derived from studies showing an association of low levels of 25(OH)D and $1.25(OH)_2D$ with cardiovascular risk factors, including increased renin activity, hypertension, left ventricular hypertrophy (LVH), inflammation, insulin resistance, diabetes mellitus, and albuminuria.[51-54]

Vitamin D in CKD and cardiovascular disease

25-hydroxyvitamin D deficiency/insufficiency has been recently associated with higher risk of cardiovascular disease (CVD) in CKD and in the general population.[55] Evidence suggests that the non-traditional risk factors arising from CKD mediate vascular damage with activation of inflammatory pathways.[56] In CKD patients not on dialysis with a mean eGFR 38 ml/min/1.73 m^2 (SD 15), using non-invasive brachial artery flow-mediated dilatation (FMD) methods to evaluate endothelial function, Chitalia *et al*.[57] found a correlation between decreasing 25(OH)D levels and worsening FMD (r = 0.44,

p = 0.001). This association between Vitamin D levels and FMD persisted in further analysis using regression models adjusting for traditional cardiovascular risk factors. Endothelial dysfunction is posited to be a marker of atherosclerosis and thereby surrogate for cardiovascular disease. These findings should encourage future clinical trials to further investigate the impact of vitamin D supplementation on endothelial function in an attempt to establish a biological mechanism. Despite of small number of patients studied, the absence of a control group, and a short time of supplementation, two recent studies have shown that cholecalciferol supplementation on hemodialysis patients decrease inflammatory parameters represented by increased serum albumin and reduction of both C-reactive protein and interleukin-6.[58,59] Also, they showed improve cardiac dysfunction reflected by lower BNP levels (58) and left ventricular mass index decrease.[59]

Animal models have shown that there are others pathways by which Vitamin D may ameliorate or prevent cardiovascular disease. Decreased VDR activity increases circulating renin levels and blood pressure and causes left ventricular and myocyte hypertrophy in genetically manipulated mouse models.[51,53] The 1α-hydroxylase knockout mice develop hypertension, cardiac hypertrophy, and depressed cardiac function, but the use of calcitriol seems to ameliorate hypertension and improve cardiac function in these animals.[60] These findings suggest that vitamin D is a regulator of the renin-angiotensin-aldosterone system (RAAS), and suppress the RAAS axis.

The Paricalcitol benefits in Renal Failure Induced Cardiac Morbidity (PRIMO) multi-center trial was designed to evaluate the beneficial effects of paricalcitol on left ventricular hypertrophy in pre-dialysis patients. However, results from the trial failed to demonstrate a reduction in ventricular mass index at the end of 48 weeks of daily paricalcitol supplementation in CKD patients with mild to moderate left ventricular hypertrophy.[61] There was, however, a decrease in hospitalizations, a secondary end-point. These results are contrary to multiple animal experimental and human observational data. One potential explanation for the results is that the paricalcitol may have increased FGF-23 levels and multiple studies have shown a link between FGF-23 and LVH.[62-64] More work is need in this area.

Vitamin D and albuminuria

Albuminuria is an important marker and major risk factor for progressive decline in renal function and is considered by many to be the first step in an inevitable progression to nephropathy and renal failure. Multiple studies have shown an inverse relationship between the level of vitamin D and degree of albuminuria[65,66] and an anti-albuminuric effect of vitamin D analogs.[67] Isakova *et al.*[66] showed that lower levels of 25(OH)D and 1.25$(OH)_2$D were associated with albuminuria in patients with CKD, independent of age, sex, race, blood pressure and diabetes mellitus. In this cross-sectional study of 1847 patients, they estimated 2-3 times increased odds of albuminuria for those in lowest tertiles of 25(OH)D [OR 3.0; 95% CI (1.3-7.0)] and 1.25$(OH)_2$D [OR 2.6; 95% CI (1.7-3.9)]. The linear relationship between 25(OH)D and albuminuria persisted after controlling for different eGFR levels and use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Additionally, in a subgroup analysis in 387 patients with data on inflammatory markers, they found a significantly higher plasma concentration of IL-6, IL-10 and TNF-α in the presence of albuminuria.

Findings from the VITAL Study[67] provide interesting clues to the renoprotective effects of vitamin D. This placebo-controlled randomized trial evaluated the anti-albuminuric effect of paricalcitol 1 or 2 µg/day *versus* placebo in 281 diabetic nephropathy patients with CKD stages 2-4, using standard therapy to control blood pressure and proteinuria. The primary outcome of reduced albuminuria (albumin/creatinine ratio) only showed a small trend but, significant reversible reductions in secondary outcomes at 24 weeks were seen in those randomized to receive high-dose 2 µg/day paricalcitol, including reductions in 24 h albuminuria of -28% (95% CI -43 to -8; p = 0.009), eGFR (range -3 to -5 mL/min per 1.73 m^2; p = 0.001 *vs.* placebo), and blood pressure (range -3 to -9 mm Hg; p = 0.033 *vs.* placebo). The reduction of eGFR observed could be possibly explained by the effect of VDR activation on increased creatinine generation and, consequently, increased serum creatinine in response to paricalcitol as has been shown by Agarwal *et al.*[68]

Vitamin D and progression of CKD

Reduction of albuminuria is a major target in renoprotective therapy and vitamin D has demonstrated

a positive effect.[67] At the same time, there exists supportive evidence that vitamin D therapy may have the potential to alter the progression of kidney disease. Vitamin D may possibly modify podocyte hypertrophy, podocyte function as a filtration barrier, expression of TGF-β, expression of MCP-1, recruitment of macrophage-like cells, and the T effector lymphocytes.[69-73] Animal models[71-73] and human clinical studies[74,75] have reported findings in support of vitamin D induced attenuation of kidney disease progression. Using data from NHANES III, Melamed *et al.*[75] reported 2.6 fold higher incidence of ESRD among individuals with 25(OH)D levels < 15 ng/mL compared to those with higher levels after adjusting for demographic, socioeconomic, and clinical and laboratory factors including diabetes mellitus, hypertension, estimated GFR, and albuminuria [IRR 2.64; 95% CI (1.00 to 7.05)]. We still do not have clearly what is the role of FGF-23 in the progression of CKD but some studies have shown it as a significant independent predictor of CKD progression in diabetic nephropathy patients and in patients with nondiabetic CKD.[76,77] Important contributions to the understanding of the role of vitamin D will come up in the next few years with the results from on-going clinical trials (NCT01214356); (NCT00552409); (NCT01029002) evaluating the following aspects, respectively: the effectiveness of vitamin D supplementation on progression of kidney disease in African Americans adults type 2 diabetes stage 1 or 2 CKD; the change in urine albumin excretion in adults type 2 diabetes stages 1-2 CKD, and the albuminuria in patients stages 3-4 CKD from various causes. Also, important contributions to the understanding of the role of FGF-23 on progression of kidney disease and to the effects of different forms of vitamin D on FGF-23 levels are coming from the on-going observational (NCT01317173), and interventional (NCT00957879) studies, respectively.

Vitamin D and immune system

Vitamin D deficiency/insufficiency may predispose to infectious disease by impairing innate immunity. Cells of the innate and adaptive immune system including macrophages, lymphocytes and dendritic cells express the VDR and respond to stimulation by $1.25(OH)_2D$.[78,79] Vitamin D treatment *in vitro* has also been demonstrated to modulate levels of systemic inflammatory cytokines such as TNF-α and IL-6, and to inhibit LPS-induced activation vasodilation of the vascular endothelium.[80,81] Recently, two studies showed a significant reduction in IL-6,[59,82] IL-8, and TNF[82] after cholecalciferol supplementation in ESRD patients were on hemodialysis. Therefore, it is reasonable to believe that a deficiency/insufficiency of nutritional 25(OH)D in ESRD may contribute to an altered immune response, predisposing to early morbidity and mortality from infection. Results from an ongoing randomized, placebo-controlled trial (NCT 00892099) evaluating cathelicidin, cytokine levels, and the incidence of infections in hemodialysis patients randomized to high and low dose of ergocalciferol will provide further clarity when they are published.

Vitamin D in CKD - What we need to answer

Given the high prevalence of vitamin D insufficiency and deficiency in CKD patients, the first step in the correction of vitamin D abnormalities in these patients would be to correct the levels of 25(OH)D levels in order to facilitate and maintain the production of $1.25(OH)_2D$. Current K/DOQI guidelines recommend treatment of CKD stage 3 and 4 patients with nutritional forms (ergocalciferol or cholecalciferol) of vitamin D when levels of 25(OH)D are below 30 ng/mL.[33] Our current understanding and experience with vitamin D mainly come from various observational and laboratory experimental studies. Epidemiological studies, even with rigorous methodology, are limited by their biases and the inability to prove causality. Many issues remain to be clarified such as an understanding of whether vitamin D therapy improves defined clinical end points in CKD patients, whether nutritional vitamin D plays a role in improving CKD outcome; the appropriate time to start vitamin D treatment; the frequency and dose of vitamin D administration (daily or bolus); the benefit of nutritional vitamin D supplementation in stage 5 CKD patients; whether vitamin D can slow the progression of CKD; understanding the role of non-classical effects of vitamin D and whether local production in non-classical tissues is critical for these actions; whether systemic $1.25(OH)_2D$ alone is sufficient to improve survival. Large rigorous randomized clinical trials (RCTs) are needed to answer at least some of these questions.

Conclusion

Vitamin D deficiency/insufficiency is a common condition affecting the general population and special

populations such as CKD patients. Aside from effects on bone and mineral metabolism, low serum levels of 25(OH)D have been associated with all-cause and cardiovascular mortality as well as increased risk of comorbidities such as cardiovascular disease, infections, and kidney dysfunction in general and CKD populations. The widespread expression of VDR in many organ systems constitutes the biological basis for the hypothesized pleiotropic and non-skeletal actions of vitamin D. These properties include RAAS inhibition, endothelial protection, immune modulation and anti-inflammatory actions. In this regard, vitamin D deficiency is associated with insulin resistance, left ventricular hypertrophy, proteinuria, atherogenicity, decreased thrombolysis, immune imbalances, susceptibility to infections and perpetuation of inflammation. More RCTs are needed to determine whether vitamin D supplementation could reduce future CVD events, the rate of progression of kidney disease and mortality risk in individuals with CKD as well more accurately define the precise therapeutic agent, dose, timing, monitoring parameters and indications for vitamin D therapy.

Referências

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81. PMID: 17634462
2. Echida Y, Mochizuki T, Uchida K, Tsuchiya K, Nitta K, et al. Risk factors for vitamin D deficiency in patients with chronic kidney disease. Intern Med 2012;51:845-50.
3. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol 2005;289:F8-F28. PMID: 15951480
4. Holick MF, Frommer JE, McNeill SC, Richtand NM, Henley JW, Potts JT Jr. Photometabolism of 7-dehydrocholesterol to previtamin D3 in skin. Biochem Biophys Res Commun 1977;76:107-14.
5. Lensmeyer GL, Wiebe DA, Binkley N, Drezner MK. HPLC method for 25-hydroxyvitamin D measurement: comparison with contemporary assays. Clin Chem 2006;52:1120-6.
6. Kawashima H, Kraut JA, Kurokawa K. Metabolic acidosis suppresses 25-hydroxyvitamin in D3-1alpha-hydroxylase in the rat kidney. Distinct site and mechanism of action. J Clin Invest 1982;70:135-40. PMID: 6282936
7. Portale AA, Booth BE, Halloran BP, Morris RC Jr. Effect of dietary phosphorus on circulating concentrations of 1.25-dihydroxyvitamin D and immunoreactive parathyroid hormone in children with moderate renal insufficiency. J Clin Invest 1984;73:1580-9. PMID: 6547151
8. Andress D. Nonclassical aspects of differential vitamin D receptor activation: implications for survival in patients with chronic kidney disease. Drugs 2007;67:1999-2012. PMID: 17883284
9. Quarles LD. Skeletal secretion of FGF-23 regulates phosphate and vitamin D metabolism. Nat Rev Endocrinol 2012;8:276-86.
10. Hewison M. Vitamin D and the intracrinology of innate immunity. Mol Cell Endocrinol 2010;321:103-11. PMID: 20156523
11. Diker-Cohen T, Koren R, Ravid A. Programmed cell death of stressed keratinocytes and its inhibition by vitamin D: the role of death and survival signaling pathways. Apoptosis 2006;11:519-34.
12. Holmøy T, Moen SM. Assessing vitamin D in the central nervous system. Acta Neurol Scand Suppl 2010;88-92.
13. Kristal-Boneh E, Froom P, Harari G, Ribak J. Association of calcitriol and blood pressure in normotensive men. Hypertension 1997;30:1289-94.
14. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, et al. Independent association between 1.25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Clin Chim Acta 2010;411:1354-60. PMID: 20515678
15. Townsend K, Evans KN, Campbell MJ, Colston KW, Adams JS, Hewison M. Biological actions of extra-renal 25-hydroxyvitamin D-1alpha-hydroxylase and implications for chemoprevention and treatment. J Steroid Biochem Mol Biol 2005;97:103-9. PMID: 16081283
16. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab 2001;86:888-94. PMID: 11158062
17. Liu S, Quarles LD. How fibroblast growth factor 23 works. J Am Soc Nephrol 2007;18:1637-47.
18. Perwad F, Azam N, Zhang MY, Yamashita T, Tenenhouse HS, Portale AA. Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1.25-dihydroxyvitamin D metabolism in mice. Endocrinology 2005;146:5358-64.
19. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004;19:429-35.
20. Nabeshima Y, Imura H. alpha-Klotho: a regulator that integrates calcium homeostasis. Am J Nephrol 2008;28:455-64.
21. DeLuca S, Sitara D, Kang K, Marsell R, Jonsson K, Taguchi T, et al. Amelioration of the premature ageing-like features of Fgf-23 knockout mice by genetically restoring the systemic actions of FGF-23. J Pathol 2008;216:345-55. PMID: 18729070
22. Tsujikawa H, Kurotaki Y, Fujimori T, Fukuda K, Nabeshima Y. Klotho, a gene related to a syndrome resembling human premature aging, functions in a negative regulatory circuit of vitamin D endocrine system. Mol Endocrinol 2003;17:2393-403.
23. Nakatani T, Sarraj B, Ohnishi M, Densmore MJ, Taguchi T, Goetz R, et al. In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (Fgf23) -mediated regulation of systemic phosphate homeostasis. FASEB J 2009;23:433-41.
24. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, et al. Regulation of fibroblast growth factor-23 signaling by klotho. J Biol Chem 2006;281:6120-3. PMID: 16436388
25. Medici D, Razzaque MS, Deluca S, Rector TL, Hou B, Kang K, et al. FGF-23-Klotho signaling stimulates proliferation and prevents vitamin D-induced apoptosis. J Cell Biol 2008;182:459-65. PMID: 18678710
26. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007;71:31-8.
27. Kawashima H, Kraut JA, Kurokawa K. Metabolic acidosis suppresses 25-hydroxyvitamin in D3-1alpha-hydroxylase in the rat kidney. Distinct site and mechanism of action. J Clin Invest 1982;70:135-40. PMID: 6282936
28. Murayama A, Takeyama K, Kitanaka S, Kodera Y, Kawaguchi Y, Hosoya T, et al. Positive and negative regulations of the renal 25-hydroxyvitamin D3 1alpha-hydroxylase gene by parathyroid hormone, calcitonin, and 1alpha,25(OH)2D3 in intact animals. Endocrinology 1999;140:2224-31. PMID: 10218975
29. Dusso AS, Tokumoto M. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease. Kidney Int 2011;79:715-29. PMID: 21270766
30. Liu S, Tang W, Zhou J, Stubbs JR, Luo Q, Pi M, et al. Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol 2006;17:1305-15.

31. Usatii M, Rousseau L, Demers C, Petit JL, Brossard JH, Gascon-Barré M, et al. Parathyroid hormone fragments inhibit active hormone and hypocalcemia-induced 1.25(OH)2D synthesis. Kidney Int 2007;72:1330-5. PMID: 17805236
32. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18-28. PMID: 16825677
33. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:S1-201. PMID: 14520607
34. Henry HL, Bouillon R, Norman AW, Gallagher JC, Lips P, Heaney RP, et al. 14th Vitamin D Workshop consensus on vitamin D nutritional guidelines. Steroid Biochem Mol Biol 2010;121:4-6. PMID: 20561983
35. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 2009;124:e362-70. PMID: 19661054
36. Peters BS, dos Santos LC, Fisberg M, Wood RJ, Martini LA. Prevalence of vitamin D insufficiency in Brazilian adolescents. Ann Nutr Metab 2009;54:15-21. PMID: 19194104
37. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res 2011;31:48-54.
38. Zadshir A, Tareen N, Pan D, Norris K, Martins D. The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis 2005;15:S5-97-101.
39. LaClair RE, Hellman RN, Karp SL, Kraus M, Ofner S, Li Q, et al. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. Am J Kidney Dis 2005;45:1026-33. PMID: 15957131
40. Cuppari L, Carvalho AB, Draibe SA. Vitamin D status of chronic kidney disease patients living in a sunny country. J Ren Nutr 2008;18:408-14.
41. Holick MF. Vitamin D and the kidney. Kidney Int 1987;32:912-29.
42. Takemoto F, Shinki T, Yokoyama K, Inokami T, Hara S, Yamada A. Gene expression of vitamin D hydroxylase and megalin in the remnant kidney of nephrectomized rats. Kidney Int 2003;64:414-20.
43. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004;19:429-35.
44. Figuiredo-Dias V, Cuppari L, Garcia-Lopes MG, de Carvalho AB, Draibe SA, Kamimura MA. Risk factors for hypovitaminosis D in nondialyzed chronic kidney disease patients. J Ren Nutr 2012;22:4-11.
45. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006;17:2034-47.
46. Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in nondialyzed CKD. J Am Soc Nephrol 2008;19:1613-9.
47. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernán MA, Camargo CA Jr, et al. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol 2005;16:1115-25.
48. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, et al. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney Int 2006;70:351-7. PMID: 16738536
49. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. Am J Kidney Dis 2011;58:374-82.
50. Vacek JL, Vanga SR, Good M, Lai SM, Lakkireddy D, Howard PA. Vitamin D deficiency and supplementation and relation to cardiovascular health. Am J Cardiol 2012;109:359-63. PMID: 22071212
51. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1.25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229-38. PMID: 12122115
52. Scragg R, Sowers M, Bell C.; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2813-8.
53. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab 2005;288:E125-32. PMID: 15367398
54. Bucharles S, Barberato SH, Stinghen AE, Gruber B, Meister H, Mehl A, et al. Hypovitaminosis D is associated with systemic inflammation and concentric myocardial geometric pattern in hemodialysis patients with low iPTH levels. Nephron Clin Pract 2011;118:c384-91. PMID: 21325871
55. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11. PMID: 18180395
56. Stenvinkel P, Heimbürger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999;55:1899-911. PMID: 10231453
57. Chitalia N, Recio-Mayoral A, Kaski JC, Banerjee D. Vitamin D deficiency and endothelial dysfunction in non-dialysis chronic kidney disease patients. Atherosclerosis 2012;220:265-8.
58. Matias PJ, Jorge C, Ferreira C, Borges M, Aires I, Amaral T, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol 2010;5:905-11.
59. Bucharles S, Barberato SH, Stinghen AE, Gruber B, Piekala L, Dambiski AC, et al. Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism. J Ren Nutr 2012;22:284-91.
60. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1.25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. Kidney Int 2008;74:170-9. PMID: 18385669
61. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA 2012;307:674-84.
62. Gutiérrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation 2009;119:2545-52. PMID: 19414634
63. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest 2011;121:4393-408. PMID: 21985788
64. Canziani ME, Tomiyama C, Higa A, Draibe SA, Carvalho AB. Fibroblast growth factor 23 in chronic kidney disease: bridging the gap between bone mineral metabolism and left ventricular hypertrophy. Blood Purif 2011;31:26-32.
65. de Boer IH, Ioannou GN, Kestenbaum B, Brunzell JD, Weiss NS. 25-Hydroxyvitamin D levels and albuminuria in the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2007;50:69-77. PMID: 17591526
66. Isakova T, Gutiérrez OM, Patel NM, Andress DL, Wolf M, Levin A. Vitamin D deficiency, inflammation, and albuminuria in chronic kidney disease: complex interactions. J Ren Nutr 2011;21:295-302.
67. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 2010;376:1543-51. PMID: 21055801

68. Agarwal R, Hynson JE, Hecht TJ, Light RP, Sinha AD. Short--term vitamin D receptor activation increases serum creatinine due to increased production with no effect on the glomerular filtration rate. Kidney Int 2011;80:1073-9. PMID: 21716260
69. Aschenbrenner JK, Sollinger HW, Becker BN, Hullett DA. 1.25-(OH(2))D(3) alters the transforming growth factor beta signaling pathway in renal tissue. J Surg Res 2001;100:171-5. PMID: 11592788
70. Krüger S, Kreft B. 1.25-dihydroxyvitamin D3 differentially regulates IL-1alpha-stimulated IL-8 and MCP-1 mRNA expression and chemokine secretion by human primary proximal tubular epithelial cells. Exp Nephrol 2001;9:223-8.
71. Tan X, Li Y, Liu Y. Paricalcitol attenuates renal interstitial fibrosis in obstructive nephropathy. J Am Soc Nephrol 2006;17:3382-93.
72. Kuhlmann A, Haas CS, Gross ML, Reulbach U, Holzinger M, Schwarz U, et al. 1.25-Dihydroxyvitamin D3 decreases podocyte loss and podocyte hypertrophy in the subtotally nephrectomized rat. Am J Physiol Renal Physiol 2004;286:F526-33. PMID: 14600034
73. Makibayashi K, Tatematsu M, Hirata M, Fukushima N, Kusano K, Ohashi S, et al. A vitamin D analog ameliorates glomerular injury on rat glomerulonephritis. Am J Pathol 2001;158:1733-41. PMID: 11337371
74. Coen G, Mazzaferro S, Manni M, Fondi G, Perruzza I, Pasquali M, et al. No acceleration and possibly slower progression of renal failure during calcitriol treatment in predialysis chronic renal failure. Nephrol Dial Transplant 1994;9:1520.
75. Melamed ML, Astor B, Michos ED, Hostetter TH, Powe NR, Muntner P. 25-hydroxyvitamin D levels, race, and the progression of kidney disease. J Am Soc Nephrol 2009;20:2631-9.
76. Titan SM, Zatz R, Graciolli FG, dos Reis LM, Barros RT, Jorgetti V, et al. FGF-23 as a predictor of renal outcome in diabetic nephropathy. Clin J Am Soc Nephrol. 2011;6:241-7. DOI: http://dx.doi.org/10.2215/CJN.04250510
77. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol 2007;18:2600-8.
78. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab 2008;4:80-90.
79. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-3.
80. Equils O, Naiki Y, Shapiro AM, Michelsen K, Lu D, Adams J, et al. 1.25-Dihydroxyvitamin D inhibits lipopolysaccharide--induced immune activation in human endothelial cells. Clin Exp Immunol 2006;143:58-64. PMID: 16367934
81. Sadeghi K, Wessner B, Laggner U, Ploder M, Tamandl D, Friedl J, et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. Eur J Immunol 2006;36:361-70.
82. Stubbs JR, Idiculla A, Slusser J, Menard R, Quarles LD. Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. J Am Soc Nephrol 2010;21:353-61.