Chapter 3

The Multiple Roles of Vitamin D Besides Calcium-Phosphorus Metabolism

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Abstract

Vitamin D is a kind of steroid hormone and is well known for its important role in regulating the levels of calcium (Ca) and phosphorus (P) as well as in mineralization of bone in body. But the vitamin D signaling also exhibits multiple effects, such as anti-inflammation effects, anticancer effect, and cardiovascular- and kidney-protective effects. From a practical point of view, vitamin D deficiency participates in many pathological progressions and diseases. In some diseases, the administration of vitamin D or vitamin D receptor agonist (VDRA) could rescue the clinical symptoms and improve outcomes. In this review, we briefly deal with these topics, limiting ourselves to comment on some novelty studies about vitamin D signaling, which might help us to understand the multiple effects of vitamin D in some pathological progresses and diseases, which are all worth to be studied further.

Keywords: vitamin D, vitamin D receptor, renal disease, inflammation

1. Introduction

Vitamin D is a kind of steroid hormone and presents naturally in very few foods. However, a number of foods have been fortified and sun exposure produces vitamin D in the skin. The final hormonal form of vitamin D was generated by undergoing two hydroxylation steps, the first to produce 25(OH)D3 in the liver and then second in the kidney to create the hormonal form, $1,25(OH)_2D3$, after consumed or made in the skin.

Vitamin D has been known for its important role in regulating the levels of calcium (Ca) and phosphorus (P) as well as in mineralization of bone in the body. But vitamin D deficiency has become a major health problem worldwide, which was thought to be related with several factors according to many researches, such as gender, age, sunlight exposure, cultures, dietary,

and so on. In 2012, the 25(OH)D of 2327 (1744 females and 583 males) healthy Caucasian outpatients were tested in the North-East of Italy. The results showed that the 25(OH)D values had no significant differences between females and males. A nonsignificant variation of 25(OH)D values was also found throughout four age cohorts (<21, 21–40, 41–60, and >60 years), in both genders. In each age group, the values of 25(OH)D did not significantly differ between genders [1].

But in 2016, a single-center analysis of patients from 136 countries showed that 82.5% of the studied patients (57.5% were female and 42.5% were male) have vitamin D deficiency to insufficiency; 26.4% of females and 18.4% of males have extreme deficiency of 25(OH)D. There was higher variability of vitamin D in the group of females than males according to coefficient of variation. The prevalence of hypovitaminosis D is significantly high among population of UAE, Saudi Arabia, and many Middle Eastern countries, especially among women, despite abundant sunshine. This study considered the difference between female and male [2].

Vitamin D deficiency also existed in Europe. According to an alternate suggested definition of vitamin D deficiency (<50 nmol/L), the prevalence was 40.4%. Dark-skinned ethnic subgroups had much higher (3- to 71-fold) prevalence of serum 25(OH)D <30 nmol/L than did white populations [3]. In Sweden, about 56.4% people, 25-OHD, were under 50 nmol/L, which was related to several unfavorable health outcomes [4].

Disorders in mineral metabolism and bone disease are common complications of chronic kidney disease (CKD). In 2009, the board of directors of kidney disease, improving global outcomes (KDIGO), published a new guideline for the treatment of patients of CKD and CKD-related mineral and bone disorders (CKD-MBD). The levels of 25(OH)D (calcidiol) were suggested to be measured and repeated testing determined by baseline values and interventions in patients with CKD stages 3–5 with CKD–MBD or CKD stages 1–5. And vitamin D deficiency and insufficiency should be corrected by using treatment strategies recommended in the general population [5].

However, an increasing amount of data has suggested a possible involvement of vitamin D activity in a great number of different pathophysiological fields not exclusively associated with mineral metabolism, such as modulation of inflammation and immune response, cell proliferation and differentiation, gene expression, and so on [6]. The functions of vitamin D have been widely found to be dependent not only on a widespread ability of different tissues to synthesize the active form of vitamin D but also on the almost ubiquitous distribution of the specific vitamin D receptor (VDR), which then translocates to the nuclei of target cells. In this review, we briefly deal with these topics, limiting ourselves to comment on some novelty studies about vitamin D signaling, which might help us to understand the multiple effects of vitamin D in some pathological progresses and diseases.

2. The effects of vitamin D

2.1. The effects of vitamin D in inflammation and immune response

Inflammation and immune response are the body's immediate responses to damage to its tissues and cells by pathogens, noxious stimuli such as chemicals, or physical injury. Recent

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studies have suggested that vitamin D signaling played critical roles in controlling inflammation and immune responses [7–9].

Immune cells such as activated CD8 (highest concentration), CD4 lymphocytes, and macrophages express VDR [10], which indicated that vitamin D signaling takes part in these cells'functional modulation [11]. Vitamin D signaling potently inhibited antigen- and mitogen-induced T-cell proliferation and cytokine production. Several key cytokines in T cells are direct targets of vitamin D signaling, in particular Th1 cytokines, such as IL-2 (interleukin-2) and IFN-g (interferon-gamma). Active vitamin D inhibits IL-2 secretion via impairment of transcription factor NF-AT (nuclear factor of activated T cells) complex formation, because the ligand-bound VDR complex itself binds to the distal NF-AT-binding site of the human IL-2 promoter. IFN-g has been found to be directly inhibited by vitamin D through interaction of the ligand-bound VDR complex with a VDRE (vitamin D-responsive element) in the promoter region of this cytokine [12]. In 2016, it was reported that 1α,25(OH)2 vitamin D3 modulates avian T lymphocyte functions without inducing cytotoxic T lymphocyte (CTL) unresponsiveness [13]. Another study, a cross-sectional study was from the National Health and Nutrition Examination Survey (NHANES) 2003–2006, showed sexually active women with cervicovaginal human papillomavirus (HPV) infection status and serum 25-hydroxyvitamin D (25(OH) D) levels (ng/mL) (n = 2353). Associations between serum 25(OH)D levels (continuous and categorical forms) and cervicovaginal HPV infection (high-risk HPV or vaccine-type HPV) were estimated using weighted logistic regression. The results showed that cervicovaginal HPV prevalence is associated with less-than-optimal levels of serum vitamin D [14].

Besides these, there are still some critical proteins through which vitamin D plays the modulation effect in inflammation and immune responses.

2.1.1. Toll-like receptor-9

The Toll-like receptor 9 (TLR9) expression could be downregulated by vitamin D in monocytes. In response to decreased TLR9, these cells subsequently secreted less IL-6 as a downstream functional effect. This phenomenon may have significant biological relevance and maybe a factor in the association of vitamin D deficiency with susceptibility to autoimmune disease [15].

2.1.2. Nuclear factor kappa-B

The antagonism between VDR and NF-**κ**B is mutual since overexpression of p65 but not p50 subunit of NF-**κ**B inhibited VDRE-mediated transcription in transfected cells. Similar NF-**κ**B-dependent mechanism has also been implicated in the inhibition of IL-8 promoter expression by vitamin D signaling [16].

2.1.3. Tumor necrosis factor-α

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic inflammatory cytokine produced by activated immune cells as well as stromal cells. It was also reported that vitamin D inhibits TNF-α in mycobacteria-infected macrophages and peripheral blood mononuclear cells from pulmonary tuberculosis patients. The vitamin D analog cholecalciferol reduces the circulating level of TNF-α in patients with ESRD (end-stage renal disease) [17].

Vitamin D signaling also inhibited the induced production of pro-inflammatory cytokines, IL-1α, IL-6, and IL17 [18]. These activities form the basis of vitamin D-mediated modulation of immune responses and inflammation.

2.2. The effect of vitamin D in cell proliferation and differentiation

Vitamin D has been demonstrated to alter cellular proliferation through multiple mechanisms in highly cell-specific manners. One of the most important mechanisms was the slowing of cell cycle progression induced by vitamin D, typically due to inhibition of advancement from the G1 to the S phase of the cell cycle. Many key regulators, which influence gene transcription and protein stability, including p21waf1, p27kip1, cyclin D1, and others, are taken effect on by vitamin D. The ligand-activated VDR directly or indirectly influences the cell cycle, apoptosis, and/or differentiation by interacting with important transcriptional regulators or cell-signaling systems [19, 20].

Anti-proliferative effects of vitamin D signaling are often, but not always, linked to the promotion of cellular differentiation. Vitamin D and the VDR also have important interactions with other transcriptional regulators and cell-signaling systems. In many cell lines including cancer cells, 1,25$(OH)_2$D3 and vitamin D analogs upregulate the expressions of TGF-β receptor type I protein or androgen receptors, and downregulate the expressions of estrogen receptors or IGF (insulin-like growth factor I). Vitamin D analogs also induce the expression of E-cadherin, promoting translocation of β-catenin from the nucleus to the cell membrane, to control cell growth and differentiation [19]. In our study, we found that VDR could be downregulated by high glucose and take part in the epithelial-epithelial-mesenchymal transition of podocyte in mice [21].

3. Vitamin D and diseases

3.1. Vitamin D and kidney diseases

Kidney is the major site of the synthesis of 1, 25-$(OH)_2$D3, the active form of vitamin D, under physiologic conditions. Additionally, the vitamin D receptor, which binds to, and mediates the activity of 1, 25-$(OH)_2$D3, is widely distributed in the kidney. Thus, the kidney is essential not only for the maintenance of normal calcium and phosphorus homeostasis but also for the activation of vitamin D. There is close relationship among vitamin D, VDR, and the kidney. Any problem of kidney may lead to the vitamin D-signaling deficiency, and vitamin D-signaling deficiency always causes the abnormal function of kidney [22].

3.1.1. Chronic kidney disease

It was reported that when the glomerular filtration rate declines below 60 mL/min, chronic kidney disease (CKD) was always associated with increased cardiovascular events and mortality. One of the most important reasons was that the reduction/absence of kidney α1-hydroxylase, which mediates the final hydroxylation step of 25(OH)D to 1,25-$(OH)_2$D, could lead to the vitamin D deficiency in CKD patients. Vitamin D deficiency causes parathyroid

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hyperplasia and increased parathyroid hormone; the consequent hyperparathyroidism and hyper-phosphatemia are important risk factors for mortality in CKD patients [23, 24]. Accordingly, vitamin D treatment is associated with a reduced rate of cardiovascular diseases (CVDs) and mortality [25].

It has been shown that calcitriol (the active form of vitamin D) decreases the glomerulosclerosis index and albumin excretion in subtotally nephrectomized rats (SNX rats). Those mice lacking the VDR were more susceptible to hyperglycemia-induced renal injury [26], which may be related to podocyte loss. And the scientists also found that the expression of renin could be inhibited by calcitriol, and a larger decrease in renal glomerulosclerosis in experimental CKD could be found for the combination use of enalapril and paricalcitol (VDR agonist, VDRA), which may be because of the decreased TGF-β expression and macrophage infiltration [27].

In CKD patients treated with paricalcitol, proteinuria decreased after 23 weeks, independently of glomerular filtration rate, blood pressure, or angiotensin-converting enzyme (ACE) inhibitor [28].

3.1.2. Diabetic nephropathy

Diabetic nephropathy (DN) is the most common renal complication of diabetes mellitus and a leading cause of end-stage renal disease (ESRD). Intervention of DN remains a medical challenge despite some success.

In recent years, renin-angiotensin system (RAS) inhibitors have been used as the mainstay treatment for DN because the renin-angiotensin system (RAS) was considered as a major mediator of progressive renal injury in DN. But the compensatory renin increase caused by the disruption of renin feedback inhibition becomes one major problem which limit the efficacy use of the RAS inhibitors. These most recent data demonstrate that vitamin D and its analogs have renoprotective and therapeutic potentials in DN through targeting the RAS. Vitamin D negatively regulates the RAS by suppressing renin expression and thus plays a renoprotective role in DN [26, 29]. The molecular mechanism underlying this regulation is that 1,25(OH)2D3 disrupted the cAMP-signaling pathway, a major regulatory pathway involved in renin biosynthesis [30]. It was reported that vitamin D analog therapy could increase long-term survival, reduces heart and kidney weights, and prevents overt renal tissue damage in mouse models. Combination therapy with a RAS inhibitor and a vitamin D analog was found to markedly improve renal injuries in the diabetic vitamin D receptor null-mutant mice which developed more severe renal injuries because of more robust RAS activation [30]. Another study found that combined therapy with losartan and paricalcitol completely reduced proteinuria in a model of experimental diabetic nephropathy, suggesting that the combination of an ACE inhibitor or an ANG II receptor blocker plus a VDRA may be a good therapeutic option [23, 24].

Results from two clinical trials have provided some initial insight into the benefit of vitamin D therapy in diabetic nephropathy patients. Selective vitamin D receptor activation with paricalcitol for the reduction of albuminuria in patients with type 2 diabetes (VITAL study)

investigated an active vitamin D analog exclusively in diabetic nephropathy patients. These patients were all the type 2 diabetics with a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The 281 patients were randomized into three groups: a single dose of placebo, 1 μg paricalcitol or 2 μg paricalcitol each day in a double-blind fashion. After 4 months of treatment, a significantly greater reduction in 24-h albumin excretion (measured by percent change from baseline) was found in the 2-μg paricalcitol group compared to placebo patients [31]. The second study about the measurement of the impact of vitamin D repletion with cholecalciferol on urinary albumin, MCP-1, and TGF-β1 was recently published by Kim and colleagues measured [32].

3.1.3. Immunoglobulin A nephropathy

The renoprotective effect of vitamin D was also investigated in immunoglobulin A (IgA) nephropathy. An open-label, non-placebo-controlled, randomized study about the effect of vitamin D and urinary protein excretion in 50 IgA nephropathy patients was operated on by using calcitriol. Patients who receive two doses (0.5 mg) of calcitriol per week or no treatment for 48 weeks were randomly assigned (1:1). The urinary protein excretion >0.8 g/d after renin-angiotensin system-inhibitor treatment for at least 3 months was considered as the main criterion for inclusion. The changes of 24-h urinary protein excretion from baseline to last measurement during treatment were compared and considered as the primary end point. The results showed that there was a significant decrease in proteinuria in the calcitriol-treated group compared with the control group (difference between groups, 41%; 95% confidence interval (CI), 5–79%; $P = 0.03$) the primary end point. At least a 15% decrease in proteinuria was set as the secondary end point. And the result were 7 of 24 (29%) controls and 17 of 26 (65%) of those treated with calcitriol ($P = 0.02$). These two groups showed the similar incidence of recorded adverse events, but had no significant differences in the decrease of estimated glomerular filtration rate and change in blood pressure. The conclusion was that the addition of calcitriol to a renin-angiotensin system inhibitor resulted in a safe decrease in proteinuria in patients with IgA nephropathy [33].

3.1.4. Other renal diseases

Vitamin D also play renoprotective role in other renal diseases. For example, cholecalciferol (vitamin D analog) treatment significantly increased serum 25-hydroxy vitamin D and decreased parathyroid hormone levels with no adverse effects in 25-hydroxy vitamin D-deficient renal-transplant patients [34]. Vitamin D receptor agonist doxercalciferol modulates dietary fat-induced renal disease and renal lipid metabolism [35].

Most of these studies have been reviewed recently and support the idea that vitamin D has therapeutic potential in slowing the progression of nephropathy. But these researches have their own limitations. The protection and mechanism of vitamin D need further study.

3.2. Vitamin D and cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death among patients with chronic kidney disease, with left ventricular hypertrophy (LVH) being a strong, independent risk

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factor. LVH is also a major risk factor for coronary ischemia, congestive heart failure, and cardiac arrhythmias [24].

There is a growing body of evidence linking vitamin D signaling and CVD in both experimental animals and humans. For instance, animals lacking the VDR or having vitamin D deficiency always show cardiovascular abnormalities, such as hypertension and LVH [36]. Cardiomyocytes isolated from VDR knockout mice developed contractile abnormalities, such as accelerated contraction and relaxation rates [37]. In humans, studies found that vitamin D deficiency is prevalent in neonates with congenital cardiac defects, and lower postoperative 25(OH)D levels are associated with the need for increased inotropic support in neonates undergoing cardiac operations. Low serum 25(OH)D level could also increase the incidence of sudden cardiac death both in healthy people and in hemodialysis patients. Some research showed that vitamin D deficiency may play a role in myocardial injury and postoperative recovery. Furthermore, two studies demonstrated that individuals with lower levels of active vitamin D were at a higher risk of developing hypertension [38, 39]. Vitamin D also was found to modulate the growth, hypertrophy, and differentiation of cardiomyocytes, pointing to a direct role for VDR agonists (VDRA) in cardiac physiology. These findings support that vitamin D deficiency is associated with poor cardiovascular outcomes in experimental animals and humans.

There were some reports about the improved cardiac function, which could be found in experimental animals or patients with administration of vitamin D or VDRAs. For example, after the treatment of paricalcitol, hypertensive rats showed a prevention of LVH and LV dysfunction accompanied with lower levels of brain natriuretic peptide and atrial natriuretic factor. VDRA therapy revealed similar results in another experimental model of LVH, the Cp/ rat model. Moreover, vitamin D is able to modulate contractility of cardiomyocytes in vitro by changing the distribution of the myosin chains and modulating Ca entry into cardiac muscle cells. In patients, the use of VDRA has been associated with improvements in left ventricular function and reductions in LVH [24].

Results from interventional trials, using either nutritional vitamin D or VDR agonists, supported the idea that VDR activation was beneficial for improving the underlying factors of CVD such as hypertension, endothelial dysfunction, atherosclerosis, vascular calcification, and cardiac hypertrophy.

3.3. Vitamin D and inflammatory bowel disease

Immune-mediated diseases such as inflammatory bowel diseases (IBDs) have increased in developed countries over the last 50 years. Scientists did much research to explain the increased incidence of IBD. They found that changing vitamin D status especially in prenatal as well as childhood could affect the development of the resultant immune response and the development of IBD.

There are reasons to believe that vitamin D could be an external factor that may play a role in the development of IBD. Animal models of experimental IBD had been used to explore the relationship between vitamin D signaling and IBD. The results showed that in IL-10 KO mice, the

development of IBD symptoms could be accelerated by vitamin D deficiency [40]. Additionally, a fulminating form of IBD resulted in ulceration of the intestine and the premature mortality of the double VDR and IL-10 KO mice within a very short time frame (3–5 weeks of age).

Vitamin D receptor knockout or vitamin D-deficient mice always have T cells deficient that have been implicated in the pathology of IBD. Actually, the active form of vitamin D directly and indirectly suppresses the function of these pathogenic T cells while inducing several regulatory T cells that could suppress IBD progressing [18].

People found that 1, 25$(OH)_2$D and analogs of 1,25$(OH)_2$D could suppress IBD in the IL-10 KO mice which required adequate dietary calcium, suggesting that 1,25$(OH)_2$D may directly and indirectly control immune function through calcium regulation in vivo. Many evidences from multiple different animal models suggested that the increased susceptibility of mice to experimental IBD could be caused by vitamin D and VDR deficiency, which could be suppressed by 1,25$(OH)_2$D [41].

Although at present there has not been a causal relationship between vitamin D status and IBD established in the clinic, there have been some clinic reports that show the influence of vitamin D in IBD. They found most of children and young adult patients in IBD had low vitamin D status (serum 25(OH)D concentration ≤15 ng/mL). Additionally, a randomized, controlled clinical trial from November 2007 to June 2010 at the Clinical and Translational Study Unit of Children's Hospital in Boston showed that most of the 71 patients (age 5–21) in IBD had low vitamin D status in serum (less than 20 ng/mL). A treatment of oral doses of 2000 IU vitamin D3 daily or 50,000 IU vitamin D2 weekly for 6 weeks could raise serum 25(OH)D concentration obviously and the basic conditions of children and adolescents with IBD could be improved. The change in serum PTH concentration did not differ [42].

Overall, the available data do suggest that vitamin D status and analogs would be useful for normalizing T cell function and in the prevention and treatment of human IBD. But there are still many problems that need to be studied, such as which mechanism of the vitamin D mediated occur in human cells and IBD patients.

3.4. Vitamin D and cancer

Numerous studies have suggested that lower vitamin D level is a risk factor for human cancers, and vitamin D deficiency linked with the incidence and mortality of many types of cancers, including breast, colon, and prostate cancers [43, 44].

Beneficial effects of vitamin D have been observed in experimental cancers induced by various chemical carcinogens or genetic mutations, and in studies using human cancer cells implanted in nude mice. The anticancer effects of vitamin D included alterations in cell growth, angiogenesis, tumor invasion and metastatic potential, and immune surveillance. Many studies have demonstrated that vitamin D signaling inhibited the growth of many cancer-derived cell lines in vitro, by inhibiting progression through the cell cycle, inducing apoptosis, and driving the cells to a more differentiated phenotype. VDR also played important role in anticancer effect. Some preliminary data suggested that VDR polymorphisms were more frequently associated with tumor genes which are Fok1, Bsm1, Taq1, Apa1, EcoRV, and Cdx2 [43–45].

And another study showed that vitamin D receptor expression is linked to potential markers of human thyroid papillary carcinoma [46].

Trials in clinic also have shown the potential therapeutic effects of vitamin D in different kinds of cancers. For example, in a pilot study of patients with recurrent prostate cancer, oral calcitriol (starting with 0.5 mg/day and escalating the maximum dose to 2.5 mg/day) for 6–15 months resulted in a significant decrease in the rate of prostate-specific antigen (PSA) rise during therapy (in comparison to PSA increase before therapy) in six out of seven patients [43]. In another research, scientists provided evidence indicating that vitamin D signaling protected the skin from cancer formation by controlling keratinocyte proliferation and differentiation, facilitating DNA repair, and suppressing activation of the hedgehog (Hh) pathway following UVR exposure [47].

Although the anticancer effect of vitamin D signaling has been discovered, there are still problems that need to be discussed both in experimental and in clinical trials. In vitro and in vivo studies have clearly demonstrated the antitumor effects of vitamin D. But the mechanisms of antigrowth effects of vitamin D are quite variable in different cell types, and even in different cell lines derived from the same type of cancer. In clinic, the results of vitamin D and cancer mortality were inconsistent and even oppositive associations. The majority of studies in cancer patients showed that patients with higher vitamin D levels had a decreased risk of mortality. But there were some other voice against this. In conclusion, the relationship of vitamin D status and anticancer effect is still unclear and warrants further studies.

3.5. Other diseases

There are many more reports and studies about vitamin D and its receptor which were found to play crucial role in many fields, such as vitamin D and obstructive sleep apnea in polycystic ovary syndrome (PCOS) patients [44], serum 25-hydroxy vitamin D levels in middle-aged women in relationship to adiposity and height trajectories [48], and vitamin D deficiency impairs skeletal muscle function in a smoking mouse model [49]. In engender, vitamin D deficiency and low ionized calcium are linked with semen quality and sex steroid levels in infertile men [50]. The same result was also found in subfertile women [51]. In cognitive behavior, low vitamin D levels were frequent in depression patients, especially 25-OH D levels <50 nmol/L were associated with cognitive/affective-depressive symptoms, and anhedonia symptoms in particular [52]. Vitamin D supplementation could prevent depression and poor physical function in older adults [53]. Some reports found that the concentration of vitamin D in the plasma of patients with metabolic syndrome was significantly lower than its recommendations [54], and a relationship was detected between vitamin D concentration and exponents of metabolic syndrome [55, 56]. But a randomized controlled trial for 1 year in a Chinese population found that the correction of hypovitaminosis D did not improve the metabolic syndrome risk profile [57].

4. Conclusion

It is now well recognized that vitamin D is involved not only in the control of bone health and mineral metabolism but also in many other physical progresses, such as the control of immune

responses, responses to infectious agents, and cell-proliferative mechanisms, particularly in cancer cells. The vitamin D signaling also exhibits multiple effects, such as anti-inflammation effects, anticancer effect, and cardiovascular- and kidney-protective effects. From a practical point of view, vitamin D deficiency participates in many pathological progression and diseases. In some diseases, the administration of vitamin D or VDRA could rescue the clinical symptoms and improve outcomes. In conclusion, vitamin D has many potential therapeutic effects and multiple roles in different diseases, physical and pathological progressions, which are all worth to be studied further.

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