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The Non-Calciotropic Actions of Vitamin D: Recent Clinical Developments

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Abstract

Purpose of Review—This review summarizes recently described actions of 1,25-dihydroxyvitamin D beyond its function in calcium homeostasis and bone metabolism.

Recent Findings—1,25-dihydroxyvitamin D stimulates the innate immune system, facilitating the clearance of infections such as tuberculosis. Hypovitaminosis D has been associated with several autoimmune disorders, various malignancies, and cardiovascular risk factors in a number of recent epidemiologic reports. Based on these observational reports, vitamin D and its analogues are being evaluated for the prevention and treatment of a variety of conditions, with early findings showing mixed results.

Summary—The broad tissue distribution of the 25-hydroxyvitamin D 1 α -hydroxylase enzyme and the vitamin D receptor establish a role for 1,25-dihydroxyvitamin D in the pathophysiology of various disease states and provide new therapeutic targets for vitamin D and its analogues.

Keywords

Vitamin D; Vitamin D Receptor; 25-hydroxyvitamin D 1 α -hydroxylase

INTRODUCTION

The major sources of vitamin D in humans are cutaneous synthesis, diet, and supplements. The initial step in vitamin D metabolism involves its hepatic hydroxylation, generating 25-hydroxyvitamin D (25-OH-D). 25-OH-D has a half-life in circulation of approximately 2 weeks, making its serum concentration the best biomarker of vitamin D status [1]. 25-OH-D is further hydroxylated by the mitochondrial 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) enzyme to form 1,25 dihydroxyvitamin D (1,25-(OH)₂-D), the physiologically active form of vitamin D. 1,25-(OH)₂-D signals via the vitamin D receptor (VDR), a nuclear receptor found in most organs (Table 1). The *calciotropic* actions of 1,25-(OH)₂-D include enhancement of intestinal calcium and phosphorus absorption, suppression of parathyroid hormone secretion, and stimulation of bone resorption via VDR in intestinal, parathyroid, and bone cells respectively (Figure 1). The wide tissue distribution of the VDR led to the recognition of the *non-calciotropic* actions of 1,25-(OH)₂-D (Figure 1), with roles beyond

the physiological regulation of calcium transport and bone mineralization. This review summarizes recent studies that have shed light on these non-calcitropic actions.

IMMUNOMODULATORY EFFECTS OF VITAMIN D

A major non-calcitropic function of 1,25-(OH)₂-D is in the regulation of the immune system. Recent studies have unraveled some of the underlying mechanisms, suggesting a potential therapeutic role of vitamin D, its metabolites and its analogues for infectious and auto-immune disorders in humans.

Vitamin D and infectious disorders

Patients with rickets have impaired macrophage phagocytic function [2], which could be reversed by 1,25-(OH)₂-D repletion [3]. In mice, targeted ablation of the 25-hydroxyvitamin D 1 α -hydroxylase enzyme resulted in enlarged lymph nodes and a reduction in CD4- and CD8- positive peripheral T lymphocytes [4]. These findings suggest that vitamin D plays an essential role in the ability of immune system to fight infections.

Vitamin D and Tuberculosis—A potential role for vitamin D in the control of tuberculosis was first indirectly described in 1849 by Williams who observed that administration of cod liver oil (a major source of vitamin D) to patients with pulmonary tuberculosis “was more beneficial ... than any agent, medicinal, dietetic, or regiminal, that has yet been employed” [5]. Recent studies have shed new light on the mechanism of the anti-microbial action of 1,25-(OH)₂-D, a mechanism that involves recognition of *Mycobacterium Tuberculosis* by toll-like receptors.

Toll-like receptors (TLRs) are a class of single membrane-spanning receptors that recognize structurally conserved molecules derived from microbes, and activate immune responses. TLR2 in particular contributes to innate immunity against *M. tuberculosis* [6]. A recent study investigating the underlying mechanisms in humans identified the 1 α -hydroxylase and VDR as two genes that are uniquely upregulated in monocytes/macrophages in response to TLR activation by *M. tuberculosis* [7**]. In the presence of sufficient 25-OH-D, this expression leads to a 1,25-(OH)₂-D-dependent induction of the antimicrobial peptide cathelicidin and enhanced killing of intracellular *M. tuberculosis* (Figure 2). In the same study, sera from African-American subjects with low 25-OH-D concentrations were inefficient in supporting cathelicidin mRNA induction [7**]. This may be the basis for the observation that African-Americans, in whom vitamin D deficiency is more prevalent, have increased susceptibility to tuberculosis [8].

While it appears that 1,25-(OH)₂-D plays a cardinal role in antimycobacterial immunity *in vitro*, most existing studies investigating the effects of vitamin D provision in TB treatment *in vivo* are methodologically flawed [9]. The only study examining the role of vitamin D added to standard anti-mycobacterial therapy is a randomized placebo-controlled trial in 67 Indonesian patients with pulmonary tuberculosis [10]. Compared with placebo, provision of 10,000 IU vitamin D daily for 6 weeks was associated with a higher rate of sputum conversion and a greater frequency of radiological improvement, with no cases of hypercalcemia observed [10]. In another recent randomized double-blind controlled trial, a

single oral dose of 100,000 IU vitamin D enhanced the ability of participants' whole blood to restrict growth of recombinant reporter mycobacteria *in vitro* [11]. More prospectively designed and controlled studies are needed to firmly establish whether correcting vitamin D deficiency, a relatively simple and inexpensive measure, reduces the incidence of tuberculosis in at risk populations, and facilitates clearance of the infection in affected individuals.

Other infections—Cathelicidin exhibits a broad spectrum of antimicrobial activity against a number of bacteria, fungi, and viral pathogens [12]. Since induction of cathelicidin expression was recently shown to be vitamin D-dependent [7**], vitamin D could potentially enhance host defense against infections other than tuberculosis, such urinary tract infections [13] and epidemic influenza [14]. Although case control studies have found associations between 25-OH-D deficiency and various infections [15,16], data from randomized trials is extremely limited. Intramuscular 1,25-(OH)₂-D co-administration with influenza vaccine in a randomized fashion did not appear to enhance humoral immunity in healthy young volunteers [17]. A trend to less frequent self-reported infections and antibiotic use was observed with vitamin D supplementation in the RECORD trial, a large randomized, placebo-controlled trial of oral vitamin D3 for the secondary prevention of osteoporotic fractures [18]. Additional randomized studies are clearly needed to assess whether vitamin D or its analogues can either prevent or alter the course of an infectious disorder.

Vitamin D and auto-immune disorders

Besides promoting innate immunity, another major effect of 1,25-(OH)₂-D on the immune system is the suppression of the adaptive immune system and generation of tolerance and anergy. At the cellular level, dendritic cells exhibit reduced expression of major histocompatibility complex (MHC) class II molecules and adhesion molecules necessary for full T-cell stimulation in the presence of 1,25-(OH)₂-D. Furthermore, 1,25-(OH)₂-D shifts the balance of helper T-cells from Th1 to Th2 and T-regulatory cells through inhibition of interleukin 12 production. Epidemiologic reports have correlated limited sunlight exposure, reduced dietary vitamin D intake and/or 25-OH-D levels with a number of auto-immune diseases, and studies have shown effectiveness of 1,25-(OH)₂-D and its analogs in a variety of animal models of these autoimmune disorders.

Multiple sclerosis—The prevalence of multiple sclerosis (MS) is well known to increase with latitude both north and south of the equator [19]. Although genetic predisposition likely plays a role in this variation [20], the role of sunshine was proposed several decades ago [21], and recent epidemiologic and experimental studies have provided evidence that high levels of vitamin D may decrease the risk of MS. Intake of vitamin D from diet and from supplements was inversely associated with risk of MS in the Nurses' Health Study and Nurses' Health Study II [22]. In a nested case-control study among > 7 million US military personnel who had serum samples stored in the Department of Defense Serum Repository, the risk of MS significantly decreased with increasing levels of 25-hydroxyvitamin D [23*]. Studies in experimental allergic encephalomyelitis (EAE), a widely used animal model for human MS disease, also suggest a protective role of 1,25-(OH)₂-D in MS, through inhibition

of monocyte trafficking to the CNS, and suppression of chemokine synthesis [24]. In a recently published small uncontrolled pilot study, administration of high doses of vitamin D (up to 280,000 IU per week) to MS patients was well-tolerated, with a tendency toward a decrease in the number of gadolinium-enhancing lesions per patient [25]. Randomized controlled studies will address whether vitamin D supplementation can alter the clinical course of MS.

Systemic Lupus Erythematosus—The threefold greater incidence of systemic lupus erythematosus (SLE) in African-Americans and increased morbidity and mortality compared to Caucasians [26] has been attributed to lower serum 25-OH-D concentrations [27]. In support of this hypothesis, 25-OH-D levels were significantly lower in recently diagnosed SLE patients compared to controls, and severe deficiency was associated with the presence of renal disease and photosensitivity [28]. In a different cohort of lupus patients, severe 25-OH-D deficiency was associated with higher disease activity measures consistent with a poorer general health status, but lower levels of antibodies to double-stranded DNA (dsDNA) than in patients with normal serum 25-OH-D [29]. In a murine model of lupus, the MRL/lpr mouse, treatment with 22-oxa-1,25-dihydroxyvitamin D₃, an analog of 1,25-(OH)₂-D significantly improved longevity and reduced proteinuria [30]. On the other hand, vitamin D intake from food and supplements was not associated with risk of SLE in two large cohorts, the Nurses' Health Study and Nurses' Health Study II (186,389 women) [31]. Thus, the role of vitamin D deficiency in the pathogenesis of SLE and whether vitamin D supplementation can improve the course of the disease is still not entirely proven.

Type 1 diabetes—Type 1 diabetes mellitus (T1DM) is another auto-immune disorder that may be modulated by vitamin D [32]. In non-obese diabetic (NOD) mice, a mouse model of human T1DM, vitamin D deficiency increases the incidence of diabetes [33], and oral administration of 1,25-(OH)₂-D prevents disease onset [34]. On the other hand, NOD mice lacking the VDR had the same course of disease as NOD mice with functional VDR, despite having worse immune abnormalities [35].

Low serum 25-OH-D levels have been reported in patients with T1DM from several countries [36,37]. While use of cod liver oil [38] or vitamin D supplementation [39,40] in infancy were associated with a decreased risk of T1DM in older uncontrolled studies, no association was found between an intermediate dose of vitamin D supplementation during infancy and development of diabetes-related autoantibodies at the age of 1 and 2.5 years [41]. An ongoing randomized controlled trial is currently recruiting individuals at risk for T1DM in Manitoba, Canada to address this issue [42].

ANTI-PROLIFERATIVE PROPERTIES OF VITAMIN D

A major non-calcitriolic action of 1,25-(OH)₂-D is its modulation of benign and malignant hyperproliferative conditions. This property was first clinically applied in the treatment of psoriasis, a recurrent inflammatory skin disorder, characterized by keratinocyte hyperproliferation and abnormal differentiation. Calcipotriol (calcipotriene or Dovonex®), a synthetic 1,25-(OH)₂-D analog chemically engineered to be metabolized quickly in systemic

circulation and hence a less calcemic compound than 1,25-(OH)₂-D, has become first-line therapy for plaque psoriasis, either as monotherapy or in combination.

Vitamin D and Cancer Epidemiology

Recent epidemiologic studies have described inverse associations between biomarkers of sunlight exposure, dairy products and/or dietary vitamin D and the risk of various malignancies including colon cancer [43], prostate cancer [44] breast cancer [45], and pancreatic cancer [46]. In Caucasians, solar UV-B exposure was inversely correlated with incidence and mortality for ten cancers: bladder, colon, Hodgkin lymphoma, myeloma, other biliary, prostate, rectum, stomach, uterus, and vulva [47]. Most recently, in data from the National Health and Nutrition Examination Study (NHANES) III, serum 25-OH-D levels was not associated with *total cancer mortality*, although in the same study, individuals with higher 25-OH-D levels had significantly lower risk of colon cancer mortality [48*]. A variety of experimental animal models and *in vitro* studies have shown that 1,25-(OH)₂-D exerts anti-neoplastic effects by regulating cellular proliferation, differentiation, apoptosis, and angiogenesis.

Vitamin D and Cancer Prevention and Treatment

While the association between hypovitaminosis D and the incidence of various malignancies is relatively well-established, the role of vitamin D supplementation in the prevention and treatment of cancer is still not entirely clear. In a 4-year study of 1179 community-dwelling postmenopausal women randomly assigned to calcium supplementation alone, calcium and vitamin D supplementation, or placebo, cancer incidence was significantly lower in the Ca +D women than in the placebo control subjects ($P < 0.03$), and serum 25-OHD level was a significant independent predictor of cancer risk [49*]. The results of this study are limited because of the small number of actual malignancies observed, but also suggest that calcium itself may play a big role beyond that of vitamin D. The largest randomized placebo-controlled study of vitamin D and the risk of colon cancer is the Women's Health Initiative, in which over 36,000 women were randomized to receive 400 IU vitamin D along with 1,000 mg elemental calcium or placebo daily [50*]. The incidence of invasive colorectal cancer after 7 years did not differ significantly between women assigned to calcium/vitamin D supplementation and those assigned to placebo. It is plausible that the dose of vitamin D used was too small to show an effect, and poor compliance and vitamin D use by placebo treated patients may have masked a potential protective effect. In men with advanced, androgen-insensitive prostate cancer treatment the use of DN-101, a 1,25-(OH)₂-D analog, along with docetaxel was associated with improved survival, although DN-101 did not produce a statistically significant improvement in the PSA response rate, the primary end point of the study [51]. A follow-up phase III clinical trial was halted early due to a higher death rate among DN-101-treated patients, although the cause of the excess mortality has not been reported.

The anti-neoplastic properties of 1,25-(OH)₂-D include regulating apoptosis and angiogenesis, and promoting cellular proliferation of normal and cancerous cells while inducing their terminal differentiation [52]. The major side effect of vitamin D and calcitriol that limits their expanded use and clinical development as anti-neoplastic agents is

hypercalcemia. Consequently, vitamin D analogs with less hypercalcemic liability have been / are being developed as preventative and therapeutic agents [53*], and certain compounds are currently in various stages of clinical investigation [54].

VITAMIN D AND CARDIOVASCULAR DISEASE / RISK FACTORS

In small case-control studies, 25-OH-D deficiency is associated with a greater incidence of myocardial infarction [55,56]. In the Framingham Offspring Study, 25-OH-D deficiency was associated with incident cardiovascular disease, particularly in hypertensive individuals [57*]. This link may be in part related to the association of lower 25-OH-D levels with a number of traditional cardiovascular risk factors including obesity, hypertension, hyperglycemia and hypertriglyceridemia [58*], the metabolic syndrome [59] as well as other confounders such as lower advanced age, socioeconomic class, and decreased physical activity.

A number of studies have described lower serum 25-OH-D levels among obese individuals, typically associated with elevation in serum PTH, and similar serum 1,25-(OH)₂-D when compared with non-obese controls [60-62]. The association between obesity and hypovitaminosis D may be in part due to reduced vitamin D bioavailability from sequestration in adipose tissue, as obese individuals exhibit a blunted rise in serum vitamin D in response to sun light and to orally supplemented vitamin D [63]. While reduced sun exposure related to a more sedentary lifestyle is another postulated mechanism linking obesity to hypovitaminosis D, this theory was refuted in a recent study [64]. Among morbidly obese individuals, 25-OH-D deficiency was more prevalent in those with the metabolic syndrome [60], suggesting that factors besides adiposity may be important. Relationships between hypovitaminosis D and insulin resistance and inflammation should be further explored in this observed clinical association.

The relationship between vitamin D and blood pressure was first described over two decades ago [65], and 1,25-(OH)₂-D was shown to negatively regulate the renin-angiotensin-aldosterone system (RAAS) in studies in VDR knock-out mice [66]. Recent reports on the relationship between vitamin D and the risk of hypertension from three large independent prospective cohorts, the Nurses' Health Study I and II, and the Health Professionals' Follow-up Study have yielded conflicting results: While *intake* of vitamin D was not associated with the risk of developing hypertension [67], lower serum 25-OH-D *levels* conferred a greater risk of incident hypertension [68].

Hypovitaminosis D has also been linked to greater risk for type 2 diabetes and worse glycemic control in a number of case control studies [69*]. In NHANES III, lower serum 25-OH-D levels was associated with a greater degree of insulin resistance as measured by HOMA (Homeostasis Model for Assessment of insulin resistance), and a higher prevalence of diabetes mellitus among Caucasians and Hispanics [70]. Potential mechanisms underlying this association include the influence of vitamin D on insulin secretion and peripheral actions. Interventional studies examining the role of vitamin D administration on insulin resistance and the risk of type 2 diabetes in humans are not entirely conclusive [69*]. Short-term interventional studies with a number of vitamin D metabolites did not show changes in

fasting serum glucose or insulin [71,72]. On the other hand, compared with placebo, combined vitamin D and calcium supplementation for 3 years was associated with a smaller rise in fasting serum glucose in subjects with impaired fasting glucose [73].

It remains unclear whether the association of 25-OH-D deficiency with increased cardiovascular disease can be entirely explained by traditional cardiovascular risk factors or if additional mechanism(s) are involved. In fact, 1,25-(OH)₂-D may have additional effects via modulation of pro- and anti-inflammatory cytokines linked to cardiovascular disease such as TNF- α and IL-10 [74], and through direct activation of the VDR expressed in cardiac myocytes and vascular smooth muscle cells [75,76]. On the other hand, a potentially detrimental action of 1,25-(OH)₂-D on the cardiovascular system is its promotion of vascular calcification [77].

IMPLICATIONS OF THE NON-CALCITRIOPIC ACTIONS OF VITAMIN D IN PATIENTS WITH CHRONIC KIDNEY DISEASE

The non-calcitropic effects of vitamin D are modulated by the presence of extra-renal 1 α -hydroxylase enzyme which metabolizes 25-OH-D to 1,25-(OH)₂-D locally in a number of tissues. This highlights the importance of adequate serum 25-OH-D levels as a substrate for these effects. The serum concentration of 25-OH-D estimated as optimal for both calcitropic (PTH suppression, intestinal calcium absorption, fracture prevention) and non-calcitropic outcomes (colorectal cancer, muscle strength) is >30 ng/ml (75 nmol/L) [78], although this level has been disputed by some [79]. The vast majority of patients with renal insufficiency are 25-OH-D deficient by this criteria [80], and repletion of 25-OH-D stores may potentially ameliorate the immune and cardiovascular function in these patients via non-calcitropic mechanisms. This is highlighted by a recent nested case-control study sample of 1,000 hemodialysis patients in whom severe 25-OH-D deficiency was associated with increased mortality within 90 days of hemodialysis initiation [80]. Thus, until data from prospective controlled studies become available, ergocalciferol administration to patients with stage 3 and 4 chronic kidney disease with serum 25-OH-D < 30 ng/ml should be strongly considered, especially since such a treatment also has a favorable effect on serum PTH [81].

Treatment of patients on hemodialysis with 1,25-(OH)₂-D or its analogs for PTH suppression has been associated with improved survival in several large cohort retrospective uncontrolled studies [80,82-84]. However, a recent meta-analysis of published randomized controlled studies did not substantiate this survival advantage [85*]. It is unclear whether this disparity in the findings is due to the small number of subjects reviewed in the meta-analysis or because of the nonrandom assignment of therapy in the observational studies (resulting in differences in baseline characteristics of patients, with sicker individuals not receiving vitamin D analogs). Large prospective randomized trials are needed to settle this debate. Even when such studies become available, it will be difficult to identify the isolated effects of vitamin D on mortality from effects of changes in serum calcium, phosphorus and PTH which occur during supplementation with 1,25-(OH)₂-D and its analogs.

CONCLUSION

The wide tissue distribution of the 1 α -hydroxylase enzyme and the VDR establish a role for vitamin D beyond its function in calcium homeostasis and bone metabolism. Accumulating evidence suggests that adequate vitamin D levels are required for prevention of malignancy and optimal function of the immune and cardiovascular systems. While vitamin D and its analogs have a potential therapeutic role for a range of medical conditions, clinical studies to date have not conclusively demonstrated efficacy.

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Figure 1. Vitamin D Metabolism and Actions

The calciotropic functions of 1,25-(OH)₂-D include the physiological regulation of calcium transport and bone mineralization. The synthesis of circulating 1,25-(OH)₂-D which mediates these calciotropic actions is tightly regulated. Non-calciotropic actions involve the activation of vitamin D receptors (VDRs) by locally produced 1,25-(OH)₂-D in a number of tissues in a paracrine and autocrine fashion.

Figure 2. Vitamin D and the Immune Response to Mycobacterium Tuberculosis

Activation of the Toll-Like Receptor 2/1 (TLR 2/1) heterodimer by *Mycobacterium tuberculosis* (A) upregulates the expression of 1α-hydroxylase and VDR genes in monocytes and macrophages (B). In the presence of sufficient 25-OH-D, this upregulation leads to a 1,25-(OH)₂-D-dependent induction of the antimicrobial peptide cathelicidin (C) and enhanced killing of intracellular *M. tuberculosis* (D). In a granuloma, surrounding T-helper 1 (T_H1) cells produce γ-interferon (IFNγ) which further enhances 1α-hydroxylase expression (E). Excess 1,25-(OH)₂-D inhibits the differentiation of undifferentiated T-helper cells (T_H0) to T_H1 cells in a paracrine fashion (E), providing a mechanism to prevent excessive 1,25-(OH)₂-D production.

Table 1

Cellular and Tissue Distribution of Vitamin D Receptor

Endocrine	Parathyroid gland, Thyroid, Pituitary, Adrenal
CNS	Brain neurons
Respiratory	Alveolar cells
Cardiovascular	Cardiac muscle
Gastrointestinal	Esophagus, Stomach, Hepatocytes, Small and Large Intestine
Renal / GU	Kidney, Urethra, Prostate
Reproductive	Testis, Ovary, Uterus, Placenta
Musculoskeletal	Osteoblasts, Osteocytes, Chondrocytes, Fibroblasts, Striated muscle
Epidermis	Skin, Hair follicle, Breast
Immune	Thymus, T-cells, B-cells, Macrophages