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Relation between Vitamin D Status and Other Diseases

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Abstract

Vitamin D plays a role not only in the proper functioning of the skeletal system and the calcium-phosphate equilibrium, but also in the immune system, the cardiovascular system and the growth and division of cells. Although numerous studies have reported on the analysis of vitamin D status in various groups of patients, the clinical significance of measurements of vitamin D forms and metabolites remains ambiguous. This article reviews the reports analyzing the status of vitamin D in various chronic states. Particular attention given to factors affecting measurement of vitamin D forms and metabolites. Relevant papers published during recent years identified by an extensive PubMed search using appropriate keywords. Measurement of vitamin D status proved to be a useful tool in diagnosis and progression of metabolic syndrome, neurological disorders and cancer. High performance liquid chromatography coupled with tandem mass spectrometry has become the preferred method for analyzing the various forms and metabolites of vitamin D in biological fluids. Factors influencing vitamin D concentration, including socio-demographic and biochemical factors as well as the genetic polymorphism of the vitamin D receptor, along with vitamin D transporters and enzymes participating in vitamin D metabolism should be considered as potential confounders of the interpretation of plasma total 25(OH) D concentrations.

Keywords: vitamin D, receptor; vitamin D status.

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1. Introduction

Two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 synthesized in the skin of humans and is consumed in the diet via the intake of animal-based foods, mainly fish oils, whereas vitamin D2 is derived from plant sources, is not largely human-made, and added to foods. Vitamins D2 and D3 forms differ only in their side chain structure. The differences do not affect metabolism (i.e., activation), and both forms have the prohormone function [1].Vitamin D_2 is a 28-carbon molecule derived from ergosterol (a component of fungal cell membranes), while vitamin D_3 is a 27-carbon derived from cholesterol [2]. UV-B irradiation of skin triggers photolysis of 7-dehydrocholesterol (pro-vitamin D_3) to pre-vitamin D_3, which is rapidly converted to vitamin D_3 by the skin's temperature [3]. Cutaneous synthesis of vitamin D is a significant source of vitamin D replenishment.

The amount of vitamin D synthesized by our skin depends on a number of factors: the age of the individual, the amount of skin exposed, the duration of exposure, geographic-related factors (i.e., latitude, season, time of day, shade, and air pollution), sun block use, and the skin pigment of the individual [4]**.** Studies have shown that children, especially infants, may require less sun exposure than adults to produce adequate vitamin D concentrations because of greater surface area to volume ratio and enhanced ability to produce vitamin D than older people may. Currently, there are no recommendations available to validate the appropriate duration of sun exposure in the pediatric population, and the variability of vitamin D synthesis between individuals would make such a recommendation difficult. The lack of data and the risks associated with prolonged sun exposure suggest food and supplementation as the preferred mode of repleting vitamin D stores [5].

1.1. Diabetes Mellitus

25OHD levels are typically lower in obese individuals who are more likely to develop diabetes mellitus and the metabolic syndrome. Adipocytes express the VDR, and 1, 25 (OH) 2D promotes increased lipogenesis and decreased lipolysis [6]. The pancreatic β cell expresses the VDR, and 1, 25 (OH) 2D promotes insulin secretion. Moreover, vitamin D deficiency is associated with insulin resistance [7]. Clinical trials in individuals with diabetes mellitus or who are prediabetic suggest a benefit from vitamin D administration with respect to improving or preventing the development of

frank diabetes, but longer and larger randomized clinical trials are required [8].

1.2. Cancer

The data from animal and cell culture studies are very promising that 1, 25 (OH) 2D or its analogs can prevent cancer development or retard its progress/metastasis once developed.The mechanisms by which 1, 25 (OH) 2D can suppress tumor development are numerous and in many cases cell specific. These include inhibition of proliferation by blocking elements of the cell cycle or interference with signaling by growth factors, inducing apoptosis, stimulation of DNA damage repair, prevention of tumor angiogenesis, and inhibition of metastasis. However, most of the clinical data stem from observational studies. These studies consistently show a likely benefit for vitamin D supplementation in colon and breast cancer, but randomized clinical trial data of sufficient size and duration with sufficient doses of vitamin D to be definitive are lacking. Development of an analog with tissue specificity relative to effects on calcium absorption/bone resorption would enhance the chances of success in treating malignancies [9].

1.3. Cardiovascular Disease

The vitamin D receptor (VDR) and cytochrome P450 (CYP27B1) expressed in the heart, both in the myocytes and in the fibroblasts [10]. 1, 25 (OH) 2D and its analogs suppress markers of cardiac hypertrophy, and deletion of the VDR specifically from the heart results in hypertrophy [11]. VDR and CYP27B1 null mice are also hypertensive with increased production of renin from kidneys and heart resulting in increased circulating angiotensin II levels. The increase in renin angiotensin may contribute to the acceleration of atherosclerosis observed in VDR null mice [12]. Severe vitamin D deficiency in humans is associated with cardiomyopathy, and in a number of large epidemiologic studies, the association of increased cardiovascular disease (CVD) risk with reductions in 25OHD levels has been found [13]. However, to date, no large randomized clinical trials have been performed specifically designed to test the role of vitamin D or any of its analogs in the prevention/treatment of CVD, and the results from fracture studies with CVD as a secondary outcome have not been compelling [14].

1.4. Inflammatory Bowel Disease

Vitamin D also acts as an enhancement of the intestinal defense mechanisms, locally regulating the mucosal immune system and preventing harmful microbial proliferation [15]. For instance, an association between lower vitamin D concentrations and an increased risk of developing IBD has been suggested [16]. For these reasons, according to recent interventional studies, a vitamin D supplementation can be considered a potential effective and safe therapeutic choice in patients with IBD [17].

1.5. Immune Disorders

The immune system is comprised of two distinct but interacting types of immunity: innate and adaptive. The innate immune response involves the activation of Toll-like receptors (TLRs) in polymorphonuclear cells (PMNs), monocytes, and macrophages as well as in a number of epithelial cells. TLRs are an extended family of host non-catalytic trans membrane pathogen-recognition receptors that interact with specific membrane patterns (pathogen-associated molecular pattern [PAMP]) shed by infectious agents that trigger the innate immune response in the host. Activation of TLRs leads to the induction of antimicrobial peptides (AMPs) such as cathelicidin and reactive oxygen species (ROS), which kill the organism. The expression of cathelicidin is induced by 1, 25 (OH) 2D in both myeloid and epithelial cells. Stimulation of TLR2 by a lipopeptide from an infectious organism such as M. tuberculosis in macrophages results in increased expression of CYP27B1 and VDR, which in the presence of adequate substrate (25OHD), results in the induction of cathelicidin. Thus, adequate levels of vitamin D promote the innate immune response [10].

The adaptive immune response is initiated by cells specialized in antigen presentation, DCs and macrophages in particular, activating the cells responsible for subsequent antigen recognition, the T and B-lymphocytes. Importantly, the type of T cell activated, CD4 or CD8, or within the helper T cell class Th1, Th2, Th17, Treg, and subtle variations of those, is dependent on the context in which the antigen presented by which cell and in what environment. Systemic factors such as vitamin D influence this process. Vitamin D in general exerts an inhibitory action on the adaptive immune system. 1, 25 (OH) 2D decreases the maturation of DCs decreasing their ability to present antigen and so activate T cells. Furthermore, by suppressing IL-12 production, important for Th1 development, and IL-23 and IL-6 production important for Th17 development and function, 1, 25 (OH) 2D inhibits the development of Th1 cells capable of producing IFN-γ and IL-2, and Th17 cells producing IL-17 [18]. Clinically, there are no approved vitamin D drugs for immune modulation. However, the association of tuberculosis with vitamin D deficiency is well known, but adequately powered randomized clinical trial data showing efficacy with vitamin D supplementation are lacking [19].

- ***Effects of vitamin D on the Immune system***

As skin, gastrointestinal tract and respiratory tract serve as a common portal of infections entry. While, as a part of innate immune system epithelial cover together with macrophages and neutrophils provide barriers against infection [20]. Circulated 25(OH) D absorbed by macrophages, neutrophils and epithelial cells. In the cellular level under the impact of extra renal 1 alpha hydroxylase 25(OH) D converted into the active form 1,25 (OH)2D. Consequently, active vitamin D banded to VDR and after the translocation into the nucleus attaches to the VDRE [10]. It is known that gene encoded for cathelicidin accommodate VDRE [21]. Cathelicidin is antimicrobial peptides produced by epithelial cells and neutrophils and relates to the function of innate immune systems [22].

1.6. Skin Diseases

The use of the 1,25(OH)2D analogs calcipotriol and maxacalcitol for the treatment of the hyper proliferative skin disease psoriasis represents another approved clinical application outside of the skeleton for vitamin D and its analogs. Psoriasis is a disorder with hyper proliferation and decreased or abnormal differentiation driven by an abnormal immunologic component. The successful use of 1,25(OH)2D and several of its analogs is likely due to their ability to inhibit the proliferation, stimulate the differentiation, and suppress the immune activity associated with this disease [23].

Nonmelanoma skin cancer also represents a condition of increased proliferation and decreased differentiation of keratinocytes. Mice lacking the VDR in their keratinocytes are predisposed to UVB and chemically induced skin cancer, and topical application of 1, 25 (OH) 2D appears to be photo protective However, this potential has not been examined clinically [24].

1.7. Vitamin D and Autoimmune Diseases

Role of low vitamin D levels in many other ADs are described, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, and vitamin D receptors polymorphisms have been associated with higher incidences of several ADs [25]**.** However, optimal vitamin D concentrations that could reduce the possible occurrence of ADs are not clear yet, even if levels higher than 20 ng/mL (about 50 nmol/L) should be considered sufficient to maintain the physiologic calcemic and non-calcemic functions of vitamin D [26]**.**

1.8. Infections

The recent immunological data indicates that conversion of vitamin D into the active form 1, 25 (OH) 2D is permanent process in the epithelial cells of respiratory tract and it accelerates during the viral infection. Therefore, sufficient status of vitamin D is essential for the adequate cathelicidin production as a part of defense reaction against respiratory infections [27]. Numbers of epidemiological studies have been conducted that have looked into possible association of vitamin D deficiency and acute low respiratory tract infections among pediatric group [28]. McNally et al., [29] conducted another case- control study in Canada, it has compared vitamin D status between children with pneumonia and healthy ones .It has been suggested that vitamin D deficiency is not associated with incidence of ALRI, but with severity of respiratory infections among pediatric group [29]. This conclusion has been confirmed by hospital based retrospective case study from Japan [30]. Furthermore, complementary analysis of the Canadian study by [31], identified association between genotype *ff* with less active VDR in the epithelial cells of respiratory tract**.**

Study conducted in a vitro model suggested that vitamin D highly likely diminishes inflammation in respiratory tract caused by RSV [32], also there is evidence that vitamin D is able to suppress release of pro inflammatory cytokines by macrophages [33]. It has been show that children with genotype *ff*susceptible to ARTI particularly towards RSV bronchiolitis, because of inability of vitamin D to implement immunomodulatory and antimicrobial effects [34]**.** Results from cross section and case-control studies conducted Triptoet al., [35] indicated strong association between vitamin D deficiency with ARTI. In fact, interventional randomized control trials were called to resume the vitamin's D effects on the susceptibility towards acute low respiratory tract infections in pediatric group. Several trials have been conducted at the different settings among the population at high risk of vitamin D deficiency [36]. The results vary from positive effect on the reduction of incidence of repeated cases to no effect of intervention.

Nevertheless, it has been suggested that intervention may require adjustment in dosage and regiment or effect from supplementation may be different for the different age groups and further research is needed [37]. As regards to the association of vitamin D status and tuberculosis, the meta-analysis and systematic review published in 2008, concluded that there is a strong correlation between vitamin D insufficiency and risk of development active tuberculosis [38]. In addition, the result from cohort study indicates, that the low status of vitamin D increases the probability to develop acute tuberculosis by 5 folds among healthy household contacts [39]. The reason is that in the low vitamin D status the synthesis of antimicrobial peptide cathelicidin by macrophages and respiratory epithelial cells is decreased, hence increase susceptibility towards Mycobacterium Tuberculosis [40]. Finally, role vitamin D can be summarize .Several immune modulatory effects of vitamin D have been described [41]**.** Vitamin D is believed to have effects on both the innate and the adaptive immune response by modulating the expression of antimicrobial peptides, like cathelicidin, in response to both viral and bacterial stimuli. The respiratory airway epithelium can generate active vitamin D [42]**.**

Alveolar macrophages need to be stimulated before converting inactive to active vitamin D**.** Toll-like receptor (TLR) 2/1 ligands (mycobacterial antigen) activate alveolar macrophages, induce 1α-hydroxylase and increase 1,25D which leads to an increase in the vitamin D regulated antimicrobial peptide cathelicidin [43]. Also it plays a key role in the balance between T-helper 1 and T-helper 2 (Th1-Th2) cytokines [44]**.** It has been shown that VD decreases the proinflammatory type 1 cytokines: IL-12, interferon-gamma (IFN-γ), IL-6, IL-8, tumor necrosis factor alpha (TNFα) and IL-17 and increase anti-inflammatory IL-10 and Th2 cytokines: IL-4 and IL-5 [45]. Vitamin D deficient individuals also report more frequent respiratory tract infections perhaps due to less production of cathelicidin and/or increased production of chemokines leading to uncontrolled inflammatory response [46]**.** Clinical and subclinical vitamin D deficiency in children has been reported to be a significant risk factor for sever acute lower respiratory tract infections [47]**.**

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