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Vitamin D and Infectious Diseases

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Abstract: In the early 1920s the antirachitic effect of food irradiated with ultraviolet light and cod liver oil has been recognized. The antirachitic substance was identified and called "vitamin D". Since then the key role of vitamin D in calcium and bone homeostasis has been investigated. Moreover, it has been recognized that vitamin D is able to modulate a variety of processes and regulatory systems such as host defense, inflammation, immunity, and repair. According to recent studies, vitamin D deficiency is likely to be an important etiological factor in the pathogenesis of many chronic diseases, as well as it has been associated with higher mortality rate for respiratory disease. In this regard, either observational studies aimed to verify an association between low vitamin D level and the incidence of respiratory tract infections (RTIs) or clinical trials on the effect of vitamin D as a supplementary treatment in RTIs patients have been presented in the emerging clinical literature. Conflicting results have been demonstrated in several randomized, double-blind, placebo controlled trials concerning the vitamin D treatment in tuberculosis. Some studies suggest a beneficial effect by vitamin D but it could not be reproduced in larger studies so far. In conclusion, although basic science research suggests that vitamin D may play an important role in modulating immune functions, no strong evidence exists whether correction of vitamin D depletion may be useful in the prevention or treatment of infections. Further and larger studies may clarify the role of vitamin D in infection.

Keywords: Antibacterial activity, immune, respiratory infections, sepsis, tuberculosis, vitamin D supplementation.

INTRODUCTION

In the 1920s an antirachitic effect was discovered in foods irradiated with ultraviolet light [1, 2] and an antirachitic substance, which was called "vitamin D", was independently identified in cod liver oil [3]. Since then the key role of vitamin D in calcium and bone homeostasis has been well described, whereas only in the last years the activities of vitamin D on several physiological and pathophysiological processes have been recognized. In this regard, the possibility that vitamin D might have a role in the development of certain lung diseases has been mainly supported by epidemiological data. More in general, the link between vitamin D supplementation and decreased total mortality has been hypothesized on the basis of both ecological and observational studies [4], although the mechanisms by which vitamin D supplementation would decrease mortality remain unclear.

FROM SUNSHINE VITAMIN TO BIOLOGICALLY ACTIVE VITAMIN

Vitamin D – the sunshine vitamin - is synthesized in the skin from 7-dehydrocholesterol (7-DHC) under exposure to sunlight (UVB: 290-315 nm) which promotes its non-enzymatic conversion to previtamin D3. Vitamin D3 (cholecalciferol) derives from previtamin D3 by its conversion by body heat. Excessive sunlight exposure degrades previtamin D3 and vitamin D3 to inactive photoproducts in order to avoid excessive production of the vitamin in the skin. Vitamin D3 is stored in adipose tissue or converted in the liver by the enzyme 25-hydroxylase to 25-hydroxy-vitamin D3 [25(OH) D3], also known as calcidiol, the form that circulates in the highest concentration and reflects from both solar and dietary exposure [5]. Then, it is converted in the kidney to the metabolitically active vitamin D hormone, 1α,25-hydroxyvitamin D [1α,25(OH)D] or calcitriol. The serum 1α,25-hydroxyvitamin D level is the best indicator of overall vitamin D status because its measurement reflects total vitamin D from both dietary intake and sunlight exposure. Defining a level of serum 1α,25-hydroxy-vitamin D3 as low or insufficient depends on the level that is defined normal. This interest in vitamin D status was exemplified by the 2011 Institute of Medicine (IOM) report which established a minimum serum 25-hydroxyvitamin D [1α,25(OH)D] concentration of 20 ng/mL as the optimal level for skeletal health in the US [6]. For optimal health benefits, the Endocrine Society recommended a concentration of at least 30 ng/mL [5]. According to recent studies, serum level of 25(OH)D < 20 ng/mL might be an etiological factor in the pathogenesis of many chronic diseases [7, 8], as well as a vitamin D deficiency was also associated with higher mortality rate for respiratory diseases [8].

INFECTION RELATED EXTRASKELETAL ROLES OF VITAMIN D.

A very interesting extraskeletal role of vitamin D is the modulation of the immune system, as it was suggested by the presence of vitamin D receptor (VDR) in nearly all types of immune cells [9], spanning the innate and adaptive immune response to pathogens. More in particular, vitamin D has

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been demonstrated able to modulate immune responses to gram-negative endotoxin (lipopolysaccharide) either *in vitro* or in rodent models of sepsis [10-15]. During bacterial infection, along with its capacity to affect the humoral response, vitamin D has been reported to act in the local tissue response [16], playing an integral role in the production of antimicrobial peptides (AMPs) [17, 18]. In particular, the critical role exerted by vitamin D in macrophage response to *Mycobacterium tuberculosis via* the AMP cathelicidin has been shown [19, 20]. The cathelicidin active fragment LL-37 is produced by phagocytic leukocytes, mucosal epithelial cells, and keratinocytes and is present in both plasma and mucosal secretions [21]. In addition to the promotion of phagocytosis and reactive oxygen species, as well as chemotaxis of immune cells to sites of infection, cathelicidin LL-37 has been demonstrated to disrupt *Pseudomonas* biofilms [22]. This direct bactericidal activity might represent a novel clinical application, mainly in patients suffering from cystic fibrosis. Similarly, the demonstration of vitamin D induction of cathelicidin in the urinary bladder [23] might be of importance in the next future for patients suffering from urinary tract infection. Furthermore, the involvement of vitamin D in the monocyte response to *Candida albicans* has been demonstrated [24].

THE CLINICAL IMPACT OF VITAMIN D

A link between vitamin D and respiratory tract infections (RTIs) is suggested by the observation that RTIs are more common in the winter period than during summertime. Because the food intake of vitamin D is insufficient, sunlight exposure seems to be of primary importance in determining its status in humans. Indeed, seasonal differences in vitamin D level in humans are well documented [25]. On the other hand, to compensate the limits of dietary intake of vitamin D supplements are commonly used. In consequence, the importance of vitamin D either in prevention or control of respiratory infections, which are among the very common sources of sepsis, has been investigated by a wide array of investigations. In this regard, either observational studies aimed to establish an association between low vitamin D levels and the incidence of RTIs or clinical trials on the effects of vitamin D as a supplementary treatment in patients suffering from RTIs will be discussed in the next paragraphs.

Among adults, two recent observational studies have shown an association between low vitamin D level and the incidence of respiratory infections. One study has shown that the highest rate of upper respiratory tract infections (URTI) is associated with a serum 25(OH)D level of less than 10 ng/mL. Serum 25(OH)D levels of 10 to less than 30 ng/mL also were associated with higher adjusted odds of URTI when compared with levels of 30 ng/mL or more, thus suggesting that serum 25(OH)D levels are inversely associated with URTI [26]. Along with this report, another study has shown that maintenance of 25(OH)D serum concentration of 38 ng/mL or higher should significantly reduce the incidence of acute viral respiratory tract infections [27]. On the contrary, not clear cut results were obtained by clinical trials. In one prospective cohort study including 800 young Finnish men, subjects with low 25(OH)D_3 levels had significantly more days of absence from duty because of respiratory infections in comparison with control subjects. However, in this study only one vitamin D measurement was performed at the beginning of a 6 months observational period, while the persistence of vitamin D status during the study was not evaluated. Furthermore, the study was not randomized [28]. In another clinical trial, the vitamin D-receiving group appeared to be favored on the basis of the statistical trend, thus suggesting that a larger sample size and a major vitamin D repletion, for a longer period, may lead to more conclusive results [29].

Some recent trials may be considered to verify whether vitamin D supplementation is successful on the basis of the baseline 25(OH)D level. In the randomized trial of 247 mongolian children vitamin D supplementation significantly halved the risk of acute respiratory infection [30]. In this study indeed the baseline 25(OH)D level was 7 ng/mL and at the end of the trial was 19 ng/mL in the group of children who exhibited a decreased occurrence of acute respiratory infection [30].

In a randomized controlled trial of 2259 participants supplementation with 1000 IU/day vitamin D did not significantly reduce the incidence or duration of URTI in those adults with a baseline 25(OH)D level $\geq$ 12 ng/mL [31]. Similarly, the monthly supplementation of 100000 IU of vitamin D in healthy adults did not reduce the incidence of URTI although the mean baseline 25(OH)D level was 29 ng/mL and the 25(OH)D level was maintained at greater than 48 ng/mL throughout the study [32].

Among children, observational studies about the relationship between low vitamin D and RTIs have also shown conflicting results [33-38]. On the contrary, in randomized controlled trials, when the effects of vitamin D supplementation to children were investigated, vitamin D reduced rates of recurrence of RTIs at 3 months [39] and decreased the incidence of influenza A infection [40].

VITAMIN D AND TUBERCULOSIS

The first observation on the putative role of vitamin D in the host defense to tuberculosis was that by the British physician C.B.J. Williams, who reported a "marked and unequivocal improvement in patients suffering from tuberculosis after treatment with cod liver oil [41]. On the other hand, before the antibiotic era, treatment of tuberculosis patients was mainly based on sunlight exposure in sanatoria. Nowadays this therapeutic approach can be easily interpreted by considering that the exposure to sunlight is responsible for the synthesis of 1α,25-dihydroxyvitamin D3. Since then manifold functions of vitamin D have been discovered and, with special reference to tuberculosis, in the 1980s the capacity of vitamin D to enhance bactericidal activity of human macrophages against *Mycobacterium tuberculosis* was demonstrated [42, 43]. Very recently, a novel, metabolic role for vitamin D in human tuberculosis has been described. Vitamin D treatment of infected macrophages was demonstrated to be able to suppress the intracellular storage of lipid droplets which are required for intracellular *Mycobacterium tuberculosis* growth [44]. Aside the basic science research, clinical research has been carried out. In addition to *in vitro* studies, the putative

role played by vitamin D deficiency in tuberculosis has been investigated by focusing the attention on vitamin D deficiency and susceptibility to mycobacterial infection in different parts of the world. Low vitamin D levels have been demonstrated in association to increased risk of active tuberculosis [45-48], even if independently of nutritional status [49], and this prompted studies to verify the hypothesis of a vitamin D treatment in tuberculosis. In this regard, several randomized, double-blind, placebo-controlled trials are available. In one study, 67 tuberculosis patients received at random vitamin D (0.25 mg/day) or placebo during the 6 initial weeks of treatment. A statistical significant difference in sputum conversion (*i.e.* the change of detectable to not detectable *Mycobacteria* in the sputum) was observed in favor of the vitamin D group [50]. In another study, 192 healthy adult tuberculosis contacts were randomized to receive a single oral dose of 2.5 mg vitamin D or placebo and followed-up for 6 months. In comparison with placebo, vitamin D supplementation significantly enhanced the ability of participants' whole blood to restrict BCG-lux luminescence *in vitro* without affecting antigen-stimulated INTERFERON-lux-γ-responses. The results allowed authors to conclude that vitamin D supplementation may primarily enhance innate response (as measured by the ability of whole blood to restrict luminescence) without any polarization of acquired immune response (antigen-stimulated IFN-γ-response) [51]. With the aim to test whether vitamin supplementation of tuberculosis patients might improve clinical outcome and reduce mortality, 365 individuals were studied in a double-blind, placebo-controlled trial. The intervention consisted in 100,000 IU of vitamin D administration or placebo at inclusion and again 5 and 8 months after the start of treatment. Two-hundred-eighty-one patients completed the 12-months follow-up. Vitamin D did not improve clinical outcome among patients and the trial did not show any effect on mortality, although the possibility that the dose used was insufficient should be taken into consideration [52]. In this regard it might be of interest that supplementation with higher doses of vitamin D (600000 IU) accelerated clinical and radiographic improvement in TB patients as well as increased immune activation in patients with baseline deficient serum vitamin D level (<20 ng/mL) [53].

VITAMIN D DEFICIENCY IN SEPSIS

The roles played by vitamin D in the functioning of the immune system have stimulated increasing interest in the connections between this steroid hormone and sepsis. Despite two decades of research, the pathogenesis of sepsis and the role of human immune system remains incompletely understood [54]. High prevalence of vitamin D deficiency has been documented in patients with sepsis [55-57] and a study of patients with sepsis in the ICU showed significantly lower plasma 25(OH)D concentrations in comparison to healthy controls [58]. Furthermore, the mean plasma levels of cathelicidin were significantly lower when compared to controls as well as vitamin D binding protein levels were significantly lower in critically ill patients with sepsis compared to critically ill ones without sepsis [58]. However, studies examining vitamin D insufficiency and sepsis, nested within the studies of critically ill patients, have had mixed results. In this regard, one study of 136 veterans admitted to the ICU demonstrated a significantly increased survival rate in those patients with serum 25(OH)D concentrations greater than 20 ng/mL [59]. In a larger multicenter observational study of 2,399 ICU patients an increase in all-cause mortality was shown among vitamin D-insufficient and –deficient groups [60, 61]. Aside this research in the larger population of the critical ill, investigation specifically examining the link between vitamin D and sepsis is needed. Although in this area the literature is mainly observational, some findings are of interest since they suggest that patients with serum 25(OH) concentrations less than 30 ng/mL were more likely to have more occurrences of severe sepsis and organ dysfunctions [62]. Potential causal relationship between vitamin D insufficiency and sepsis should however be supported by large randomized controlled trials carried out in order to establish whether 25(OH)D repletion might decrease sepsis incidence. In any case, the potential roles of vitamin D as "primary prevention", "acute intervention", and "secondary prevention" should be defined [63]. In the first role, as "primary prevention", vitamin D might be useful to either prevent infections or diminish the severity of sepsis in the community. The second potential role of vitamin D as an "acute intervention" represents a broad area of investigation where rigorous intervention trials should significantly demonstrate the benefits of vitamin D supplementation in ICU patients. Finally, the concept of "secondary prevention" should demonstrate that repletion of vitamin D, on admission and maintenance therapy over time may serve to protect patients against hospital-acquired infections and recurrence of sepsis in vulnerable populations [63].

CONCLUDING REMARKS

Basic science research suggests that vitamin D may play integral roles in modulating the immune system functions and, more in general, the host defense. Clinical research has shown the putative role of vitamin D in the prevention and control of respiratory infections, although the study designs, selected populations, and interventions have not demonstrated consistent results. However, the intake of vitamin D supplements seems to be associated with decreases in total mortality rates, although the mechanisms are not yet clear. In this light, the relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates should be further investigated in order to better delineating necessary changes in clinical practice and medical care of patients with vitamin D deficiency.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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