Austin Journal of Nutrition and Food Sciences

Open Access

Austin Publishing Group

Special Article - Vitamin D Deficiency: Clinical Cases & Short Reports

Vitamin D in Rheumatic Diseases: State of the Art

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Received: May 25, 2015; **Accepted:** September 15, 2015; **Published:** September 21, 2015

Abstract

Introduction: The classical role of vitamin is the regulation of calcium levels in the blood and in the interstitial fluids. In the last years the role of vitaminD has been studied in other diseases and in autoimmunity.

Aim: To revise the role of vitamin D in rheumatic diseases.

Results: Studies have suggested a potential role of vitamin D in autoimmune system and a possible negative correlation with disease activity in SLE patients that present many risk factors predisposing to low vitamin D serum levels. Patients with CTD may present low levels of vitamin D and it may relate to the development into a specific CTD. Patients with SSc present skin fibrosis that may influence serum levels of vitamin D; in RA a negative correlation between low levels of vitamin D and disease activity and bone loss has been suggested. The link between vitamin D and JIA is still discussed, however some studies showed a similar correlation than in RA. In Kawasaki disease low levels of vitamin D seem to have a role in coronary complications.

Conclusions: Low levels of vitamin D have been detected in rheumatic diseases and a negative link between vitamin D deficiency and disease activity has been suggested.

Keywords: Vitamin D; Systemic lupus erythematosus; Rheumatoid arthritis; Systemic sclerosis; Juvenile idiopatic arthritis

Introduction

Generality and metabolism

The classic role of vitamin D (Vit) is the regulation of calcium and phosphorus blood levels. Vit D can be orally ingested or produced endogenously in the skin with the ultraviolet B light (UV-B) exposure [1] converting the precursor 7-dehydrocholesterol in pre-vitamin D3 [2], and then in vitamin D3 (cholecalciferol).

Sun exposure is responsible for 80% of requirements, but dependent to many factors as skin color, creams/cosmetics occurrence, dress, and lifestyle factors. In the northern hemisphere from November to March, at latitudes greater than 40° north, sun exposure is inadequate to trigger the vit D synthesis.

Dietary intake of Vit D is often insufficient because it supplies only 20% of body's requirements [1,3]. It can be found in the cod liver oil and in several vegetables as its precursor ergosterol which is later converted to vitamin D in the body.

Vit D metabolism may be summarized into several steps: 1) Vit D intestinal absorption or cutaneous synthesis; 2) Vit D binding to albumin (11.6%) or a specific glycoprotein (VDBP or vitamin D-binding protein); 3) the transport in the liver where vitamin D3 is metabolized to 25-hydroxyvitamin D (25(OH)D) or calcifediol, the major circulation form in the blood [4,5]; 4) hydroxylation of 25(OH)D to 1,25-dihydroxyvitaminD ($1,25(OH)_2D_3$ or $_{calcitriol}$) in the kidney by the alpha-hydroxylase. Mechanisms regulating the $1,25(OH)_2D_3$ production are hypocalcaemia (stimulation of Parathormone (PTH) secretion and increased 25(OH)D conversion in $1,25(OH)_2D_3$), hypophosphatemia, and $1,25(OH)_2D_3$ levels (by feedback mechanisms).

The main role of Vit D, together with PTH, is the regulation of calcium levels in the blood and interstitial fluids; the activity of Vit D leads to the increase in calcium and phosphorus circulating levels [6]. Further, Vit D receptor is localized in organs involved in calcium metabolism, as intestine, kidney, parathyroid and bone. So, the interaction between $1,25(OH)_2D_3$ and its receptor (VDR), located in the small intestine, increases the transport of calcium from the intestinal lumen into the circulation, whereas at bone level, Vit D induces calcium mobilization and in the kidney leads to calcium reabsorption in the distal tubule [6-8].

Definition of vitamin D levels and prevalence of vitamin D deficiency

There is no general consensus on the definition of the optimal Vit D blood level [9]. However, ≤ 10, 11–20, 21–30, and > 30 ng/mL are defined as severe deficiency, deficiency, insufficiency, and sufficiency, respectively, in the absence of a consensus regarding appropriate levels for endocrine and extra-endocrine health [9,10].

Worldwide, Vit D deficiency is a major public health problem at all ages, even in areas of low latitude and in industrialized countries [11]. Still, most countries are still lacking data, with very limited information on infants, children, adolescents and pregnant women [12]. Based on the current literature, the prevalence of Vit D deficiency varies from 2 to 30% in adults, and until to 60% of children and adolescents [11,12].

Other pivotal roles of vitamin D

Beyond the effect played by Vit D on bone mineralization, there are other important roles. In fact, Vit D receptor is localized in other organs and tissues as brain, prostate, breast and colon. For example, Vit D receptors have been discovered in cardiomyocytes together with

Citation: Lepri G, Stagi S, Casalini E, Matucci-Cerinic M and Falcini F. Vitamin D in Rheumatic Diseases: State of the Art. Austin J Nutri Food Sci. 2015; 3(4): 1070.

its capacity to influence different cardiovascular risk factors [13,14]. Moreover, antineoplastic Vit D action includes the induction to the apoptosis of some tumors cells as breast cancer, colon and prostate cancers. Several studies have highlighted the link between the risk of cancer and the 25(OH) D serum levels [15,16].

Vitamin D and autoimmunity

The role of Vit D on immunity was supported by the fact that the VDR is present in almost all cells of immune system, as $CD8^+$ and $CD4^+$ T-lymphocytes, B-lymphocytes, neutrophils, APC (Antigen Presenting Cells) and macrophages [17]. In addition it has been shown that Vit D has an immunosuppressive effect with an enhancement of innate immunity and a regulation of adaptive immunity [18]. In some autoimmune diseases such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA) and inflammatory bowel diseases T cells target self and lead the immune system to inflammation in the peripheral tissue. Therefore the mechanism of these autoimmune reactions is still unknown, and Vit D status seems to be correlated to autoimmune diseases [19]. A correlation between the reduced intake of Vit D and the prevalence of autoimmune diseases (including type I Diabetes Mellitus (IDDM) and Systemic Lupus Erythematosus (SLE)) has been found. For example, deficient and insufficient Vit D serum levels were found in most children with PFAPA (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome) [20], and cholecalciferol supplementation seems to significantly reduce the typical PFAPA episodes and their duration, stressing the hypothesis that hypovitaminosis D might be a significant risk factor for PFAPA and supporting the role of Vit D as an immune-regulatory factor in this syndrome [20]. Additionally, reduced Vit D levels were discovered in Down Syndrome (DS), a genetic condition characterized by a higher prevalence of autoimmune disorders [21]; in DS subjects, hypovitaminosis D is more severe in those who developed autoimmune diseases [21].

Vitamin D and Innate Immunity

In the innate immunity the TLR (Toll-Like Receptor) are activated; these receptors are present in polymorphonucleate cells, macrophages and monocytes and recognizing the pathogens break out the immune response in the host [22]. The $1.25(OH)_2D_3$ has a key role in the activation of TLR and in the antimicrobial response of the host; studies have highlighted its role in the innate immunity in particular in tuberculosis infection [23]. In addition the autocrine production of Vit D in dendritic cells seems to have a role in the homing of T-cells [24]

Vitamin D and Adaptive Immunity

Vit D has an inhibitory action on adaptive immune system suppressing the proliferation and immunoglobulin production and retarding the differentiation of precursors into plasma cells [25]; on the other hand Vit D inhibits Th1 proliferation that is responsible of IFN and IL-2 production, and macrophages activation [26,27]. Vit D seems to have a role also on Dendritic Cells (DC) inhibiting with its intracrine activity their maturation and therefore modulating $CD4^+$ T-cell function [28]; in addition, acting DC APC (antigen presenting cell), Vit D promotes IL-4, IL-5 and IL-10 production and the differentiation of T into Th2 is promoted [18]. Finally, Vit D increases Treg CD4+/CD25+ that produces Il-10, so that the development of Th1 is blocked thus inhibiting IL-17 secretion by T effectors [24,29].

Systemic Lupus Erythematosus (SLE)

Many data showed a high prevalence of reduced Vit D levels in SLE, whereas in other studies the correlation between disease activity and Vit D deficiency has been ascertained [30,31]. The fact that SLE patients present reduced Vit D levels has not to be a surprise because of many risk factors, first of all the photosensitivity that leads patients to avoid sun exposure or to apply skin creams for sun protection. In addition, in SLE patient's kidney damage or chronic therapy with glucocorticoids may lead to an impaired Vit D metabolism. Also, antimalarials may represent other cause of Vit D low levels because of a reduced conversion of vitamin D2 to the biologically active vitamin D3 [32]. Finally, the presence of anti-vitamin D antibodies, in particular in patients with anti-phospholipid syndrome, has been reported [19,33]. Many data reported one low 25(OH) D concentration, demonstrating a common Vit D deficiency and insufficiency in SLE than in healthy controls [34], whereas other works did not confirm this datum. Besides, a not significantly different 25(OH) D concentration was found between patients who used supplements and those who did not, and among patients in therapy or not with antimalarial drugs [31]. Conversely, patients with fibromyalgia have comparable Vit D levels than SLE subjects [35]. Beyond the studies showing differences in Vit D levels between SLE patients and controls, recent works highlighted the possible immunomodulatory effect of Vit D in these patients as a negative correlation between Vit D levels and SLE disease scores, according both to the European Consensus Lupus Activity Measurement (ECLAM) and the SLE Disease Activity Index (SLEDAI). In conclusion, Vit D supplementation is recommended in these patients for its possible immunomodulatory role [19].

Undifferentiated Connective Tissue Disease (UCTD)

In UCTD patients some authors have shown significantly lower Vit D levels in comparison to healthy subjects [36]. As observed in SLE, also in UCTD lower Vit D levels seem to be correlated to skin symptoms as photosensitivity, erythema or chronic discoid rash. In addition, UCTD may progress into an established connective tissue disease, particularly in the first years of the disease; the same study detected a lower Vit D levels in patients who evolved into any CTD [36].

Systemic Sclerosis (SSC)

Recent studies reported a high prevalence of reduced Vit D levels in systemic sclerosis (SSc) [37,38]. In addition, SSc patients have a low Bone Mineral Density (BMD) and a high risk of fractures [39]. Nevertheless, other data did not confirm any significant correlation between Vit D and bone status [38]. However, evaluating patients with juvenile onset SSc [40], in all Vit D level was <20 ng/mL and a correlation between Vit D insufficiency and BMAD (bone mineral apparent density) was found. Other data suggested that Vit D deficiency may influence the fibrosis progression with a decrease of antifibrotic factors' expression [41]. In fact, Arnson Y et al. showed a significant difference in Vit D levels between healthy controls and SSc patients, in particular those with a Rodnan skin score≥10 suggesting an inverse relationship between fibrosis and Vit D concentration [42]. Data regarding the effect of Vit D on SSc skin led to the development of studies addressed to evaluate the effect of topical Vit D on skin

fibrosis, suggesting the potential role of calipotriol (CPT), a Vit D analogue for skin fibrosis in experimental scleroderma [43].

Rheumatoid Arthritis (RA)

Several studies have investigated the role and levels of Vit D in patients with polyarthritis [44] providing support to hypothesis of a possible role of Vit D in the disease. A negative correlation between Vit D levels and tender joint count, DAS28 score and HAQ score has been found in adults with inflammatory arthritis [44]. Yet, in rodents, $1,25(OH)_2D$ supplementation may prevent the onset and the progression of collagen-induced arthritis giving to this hormone a potential key role in the disease pathogenesis [45]. Few data suggest the presence of 25(OH) D low levels in patients with Rheumatoid Arthritis (RA) and its possible association to bone erosions and osteoporosis [46,47]. Other data demonstrated reduced levels of Vit D in patients with RA and a negative correlation between these levels and the disease activity and bone loss [48].

Juvenile Idiopathic Arthritis (JIA)

Whilst the association between Vit D levels and disease activity in RA has been clearly defined [49-51], the link between serum 25(OH) D levels and JIA is not yet clear. Some works reported that Vit D levels may influence the prevalence and the outcome of this disease [52,53], even if no significant difference in 25(OH) levels were observed between JIA polyarticular and oligoarticular forms by other authors. Additionally, higher 25(OH) D were found in patients with active JIA when compared to inactive form [54]. In a large study involving 152 subjects with JIA, all subtypes presented lower Vit D levels if compared to controls. Also, in patients with active disease and frequent relapses, 25(OH) D is lower than in patients with inactive disease. Noteworthy, JIA patients with Vit D deficiency showed increased PTH levels, and a lower bone density in comparison to those with normal value. The relationship between Vit D deficiency and disease activity has been studied in Maroccan JIA children, showing a negative correlation between Vit D levels and DAS28 in oligoarticular and polyarticular forms, confirming the previous study of Stagi et al. [55]. In a systematic review, correlation between Vit D and JIA was studied concluding for a lack in the interpretation of the link between Vit D and disease activity; however the attention was focused on the need to standardize 25(OH) D serum levels in the pediatric population, and in JIA. In another study no association was found between Vit D and JIA activity. Conversely, others authors stressed the role of Vit D and calcium in the protection of bone density in JIA children [56-59].

Kawasaki disease (KD)

Some data seem suggest low Vit D levels in patients affected by Kawasaki disease [60], the most common systemic febrile vasculitis in children, and the major cause of coronary injury in industrialized countries, suggesting a potential role of Vit D deficiency in the development of coronary artery complications in KD children.

Conclusion

The data reported have focused the effect of Vit D beyond its classical role in calcium homeostasis, and highlighted its potential influence in the development of autoimmune diseases. In the literature the role of Vit D has been studied in different autoimmune and inflammatory diseases, as neurological, endocrine, intestinal, and rheumatic illnesses. Other studies are now mandatory to understand its role in the pathogenesis of the diseases and its immune-modulatory and anti-inflammatory effect such as the role of Vit D has been studied and understood in rachitism and osteoporosis. Moreover, additional investigations are required to find the best way to Vit D supplementation.

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