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Vitamin D and Dysimmunity: State of Art in 2018

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ABSTRACT

Several physiopathological, epidemiological and clinical arguments argues in favor of a close relationship between dysimmunity and its consequences and vitamin D deficiency. This link, if definitively confirmed, could have particularly important consequences for the diagnostic and therapeutic management of these conditions. However, several questions remain unresolved regarding indications of systematic vitamin D dosing and supplementation during infections, cancers and autoimmune diseases.

INTRODUCTION

Vitamin D deficiency is a frequent disorder that has seen recently several advances in the understanding of its physiopathological and clinical aspects. Currently, it is known that besides conventional bone manifestations, the vitamin D deficiency is increasingly incriminated physiopathologically, epidemiologically and clinically in several other diseases including infections, autoimmune diseases and cancers [1-4]. In this article, we will discuss the main etiopathogenic bases linking vitamin D to dysimmunitary diseases and their epidemiological and therapeutic translation [1-4].

Pathophysiological aspects

Vitamin Dis provided at 20% by diet, at 80% by de novo skin synthesis and the transformation of 7-dehydrocholesterol into previtamin D_3, then into vitamin D_3, and ergosterol into previtaminD_2, then vitamin D_2, under the action of solar exposure. Vitamin D binding protein (DBP) ensures the passage into the bloodstream of vitamin D that will subsequently undergo hydroxylation in position 25 in the liver and in position 1 in the kidney. The resulting 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is the only active form of vitamin D. The enzymes CYP24A1, CYP27B1 and CYP2R1 have a crucial role in all of steps of vitamin D metabolism [5]. The intestinal and osteoblastic VDR receptors of $1,25(OH)_2D$ allow vitamin D to exercise its main functions, which are the activation of digestive phosphocalcic absorption and bone remodeling through the activation of the RANK-RANKL system. Recently, one of the greatest advances has been the demonstration of the presence of these receptors in immune cells, particularly antigen presenting cells (monocytes, macrophages, and dendritic cells), B-lymphocytes and T- lymphocytes [5-8]. An influence of vitamin D has also been observed in the transition of the immune cytokine profile from TH1 status to TH2 status. Moreover, Vitamin D can increase the antimicrobial effects of monocytes and macrophages by increasing their capacity for phagocytosis, chemotaxis and the synthesis of antimicrobial peptides. In the context of adaptive immunity, it has been discovered

that calcitriol can play a great role in the regulation of cytokine balanceand avoiding the appearance of autoimmunity phenomena [9]. The logical consequence of these several discoveries was a supposed immune-modulatory physiological function of vitamin D and a possible immunopathological impact of vitamin D deficiency.

The pathophysiological link between cancer and vitamin D deficiency would be through the increasingly obvious role of vitamin D in the mechanisms of immunity and inflammation that are the key components of the carcinogenesis process. In a Ma et al. study but also in many other more recent studies, a link between vitamin D receptor gene polymorphism and cancer risk was identified [10]. Furthermore, a reduction in the proliferation of certain cancer cells has been shown in vitro after exposure to vitamin D, in particular melanoma and myeloproliferative cells [11]. Finally, it is currently known that colonic, prostatic and mammary tissues possess a high hydroxylation capacity in the 1α position and therefore local production of $1,25(OH)_2D$ that would play several autocrine and paracrine roles, including regulation of cell proliferation, induction of cancer cell apoptosis and blockage of angiogenesis [4,12].

In general, the big question remains whether vitamin D deficiency is more a cause or consequence of dysimmunity. The link appears bi-directional and vitamin D deficiency appears to be part of a multifactorial set of genetic and environmental factors.

Epidemiological aspects

The prevalence of vitamin D deficiency in Europe and North America is on average 70% for the elderly, 50% for postmenopausal women, 40% to 50% for young people, 80% for pregnant women and finally 32% of healthy young adults [4,13-16]. It is also important to note in many highly sunny countries, the potential influence of clothing habits, which cover a large part of the body surface, which could greatly limit the beneficial effect of sun exposure [17].

Vitamin D and cancer: In cancer patients, the presence of severe vitamin D deficiency is associated with a relative risk of death of 2.5 [18]. Porojnicu et al. have also found a significant reduction in mortality of around 20% in breast, colon or prostate cancer patients diagnosed in the summer compared to those diagnosed in winter, suggesting thus a possible protective influence of vitamin D [19]. Futhermore, a sufficient vitamin D intake would be protective and an already present tumor would be less aggressive when the vitamin D intake is adequate. The main tumors for which this observation has been made are melanoma, gynecological cancers, digestive cancers and lymphomas. Furthermore, in vitro studies have shown that the exposure of tumor cells to a high dose of vitamin D contributes to considerably weaken their proliferative potential in vitro. Historically, the epidemiological link between vitamin D deficiency and cancer has been evoked since the 1940s, but with an observational and non-randomized character, all the studies that were interested in this question. Results from NHANES-III showed a slight benefit of supplementation in terms of reducing mortality for colorectal cancer and breast cancer. In another study involving more than 47,000 participants, an increase of 10 ng / ml of 25(OH)D was associated with a 17% reduction in cancer incidence and 29% overall cancer mortality. Similar data have been found in other studies including the LURIC study, which found a reduction in overall cancer mortality of 55% in patients with normal vitamin D levels compared to severely deficient patients [4,20]. In patients with colon cancer, Ferrer-Mayorga et al., had demonstrated specific anti-tumor effects of vitamin D through the inhibition of fibroblasts of the cancerous tissue. This effect would be quantitatively proportional to the number of VDR receptors present on the fibroblastic surface [21].

It should be finally noted that a recent study questioned this link by showing a large population of 43,770 people that there was no genetic correlation between the decrease in plasma vitamin D concentration and the risk of to develop cancer [22].

Vitamin D and infections: Vitamin D deficiency is particularly common in some infections such as tuberculosis and HIV infection. In two dedicated studies in 3085 and 2044 patients, 25(OH)D less than 30 ng / ml were found in more than 85% of HIV-infected patients, with the main risk factors being female sex, smoking, unfavorable immunological status at the time of diagnosis and finally the presence of an ongoing antiretroviral treatment containing in particular efavirenz. We should also note that solar exposure has been used historically for over a hundred years in the treatment of tuberculosis [23,24]. Many years later, a stimulating effect of vitamin D on macrophages

and TLRs directed against Mycobacterium tuberculosis has been demonstrated. Most immune cells, particularly antigen presenting cells, B cells and thymocytes, in addition to the presence on their surface of VDR receptors, possess the ability to produce $1,25(OH)_2$Din situ [11,12]. Furthermore, $1,25(OH)_2$D would exert an activating effect on dendritic cells and macrophages thus potentiating several of their antimicrobial properties, especially against Mycobacterium tuberculosis. Experimentally, Martineau et al., showed that supplementation with an oral vitamin D_3 monodose improved in vitro the quality of the anti-tuberculous immune reaction, data more recently consolidated by a double-blind randomized clinical trial but only for patients with specific genotypes of certain vitamin D receptors [11,25].

Vitamin D and autoimmune diseases: With regard to autoimmunity, it is currently accepted that the presentation of the antigen by an immature dendritic cell promotes immune tolerance. Vitamin D plays an important role in inhibiting the maturation of dendritic cells and may play a protective physiological role against autoimmune diseases. Of all autoimmune diseases, lupus and Rheumatoid arthritis (RA) are the most physiopathologically documented for their relationship to vitamin D. In human and mouse models of RA, there was considerable influence of VDR receptors on the outcome profile of the disease as well as an effect of $1,25(OH)_2$Dsubstitution in the prevention of severe synovitis and progression of the disease [11,26,27]. In lupus, in vitro tests had shown that exposure of lupus B cells to vitamin D led to a decrease of up to 60% in their antibodies production, especially anti-DNA. There is also an inducible overexpression of interferon during lupus disease in the presence of vitamin D deficiency. This phenomenon is reversible after supplementation. In multiple sclerosis, T cells are inhibited in the presence of vitamin D with a decrease in their production of IL17 and IFN gamma. Similarly, the production of IL1 and TNFα by monocytes would be lower in the type 1 diabetic patient exposed versus the unexposed to vitamin D [28,29].

A particularly high prevalence of vitamin D deficiency was found in several autoimmune diseases such as RA, type 1 diabetes and systemic lupus. Case-control studies have shown a significant prevalence of 30-63% in RA patients. In addition, the severity of the disease, as determined by the sedimentation rate, the C-reactive protein, the DAS28 and HAQ indices, the cumulative dose of corticosteroids and the number of DMARDs used would be higher in patients with particular genotypes BB and bb of the VDR receptor. In an open-label study in 19 patients with RA, vigorous alfacalcidiol supplementation was associated with a reduction in symptom severity in 89% of patients and complete remission in 45% [3].

In spondyloarthropathies, it is now well established that a high BASDAI activity index is associated with a higher frequency of osteopenia and metabolic alterations of vitamin D probably related to chronic inflammation, iatrogenic lack of physical activity in patients with active disease [30].

In Lupus patients, the prevalence of vitamin D deficiency is close to 50%, higher than in the general population and in patients with other chronic inflammatory rheumatism [31]. This high prevalence can be explained by the decrease in solar exposure related to photosensitivity, long-term treatment with corticosteroids and antimalarials, frequent renal damage or high prevalence of lupus in black patients. Carvalho et al. found in a series of 171 lupus patients antibodies against 25(OH)D in 4% of cases, suggesting a specific autoimmune mechanism for vitamin D deficiency during lupus disease [32]. Finally, the proportionality between a low level of vitamin D and an increasing activity of the disease is a fact unconstantly found in the studies.

Decreased serum vitamin D levels are a very common abnormality in chronic Inflammatory bowel disease (IBD) due to chronic inflammation, long-term corticosteroid therapy, and malabsorption. The administration of $1,25(OH)_2$D, for a period of 2 weeks, has allowed animal models to reduce the severity and progression of symptoms. In humans with active colitis, there has been a reduction in the proliferation of rectal epithelial cells and T cells following activation of VDR receptors [33].

Type 1 diabetes is thought to be more common in northern populations, raising the hypothesis of a possible physiopathological role of vitamin D deficiency. In mouse models, $1,25(OH)_2$Dactivates regulatory T cells and inhibits the production of IL-12 which is a major player in TH1 immunity incriminated in type 1 diabetes. The early administration of $1,25(OH)_2$Din the mouse also allows the reduction of insulitis [33].

Diagnostic implications

The abnormalities of phosphocalcic metabolism, hyperparathyroidism, granulomatosis and the suspicion of vitamin D intoxication are the only definite diagnostic indications of the dosage of vitamin D. Vitamin D intoxication is usually due to patients confounding between milligramme and microgramme during substitution [34]. Dosage of vitamin D is useless in elderly because of the high prevalence of deficiency and usual secure supplementation. Cancers, infections and autoimmune diseases are also included in situations where the dosage is not indicated due to the absence of a well-defined target value and the epidemioclinical link not yet definitely established between these conditions and vitamin D deficiency [35]. In Table 1, we summarize the main clinical indications for screening for vitamin D deficiency.

Table 1: Main indications of Vitamin D deficiency screening.

Confirmed indications
Abnormalities of phosphocalcic metabolism
Hyperparathyroidism
Granulomatosis
Renal insufficiency
Suspicion of vitamin D intoxication
Potential indications
Pregnancy – Breastfeeding
Atherosclerosis
Autoimmune diseases
Neoplasms
Neurodegenerative diseases

Therapeutic implications

In practice, there are also well-defined indications for vitamin D supplementation, such as malabsorption, hepatic insufficiency, Paget's disease, osteoporosis, osteomalacia, chronic renal failure and idiopathic falls of the elderly (Table 2).

Table 2: Main indications of Vitamin D supply.

Malabsorption
Hepatic insufficiency
Paget's diseas
Osteoporosis
Osteomalacia
Chronic renal failure
Idiopathic falls in elderly

Randomized placebo-controlled studies did not show a significant impact in terms of cancer incidence and mortality of daily vitamin D supplementation at 400 IU. The explanation that was given to this result was the probably lowdosage used. Indeed, Lappe et al. had subsequently been able to achieve a 60% to 77% reduction in cancer incidence but with daily supplementation of 1100 IU in a population of postmenopausal women [23,36]. The data also remain hypothetical for infections and autoimmune diseases. However, an additional exogenous supply of vitamin D is to be encouraged in infected patients, cancer patients and those with autoimmune diseases. The dosing has yet to be defined and is for the moment modeled on the usual dosing regimens and modalities based on sun exposure, artificial exposure to UVB and pharmacological supplementation with vitamin D_3. The recommended dose would then be an initial average daily 1000 IU or fortnightly 100 000 IU for 3 months and then a relay with a maintenance dose of 10000 IU every 3 month.

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