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Mini Review

The Unexpected Effects of Vitamin D

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Abstract

The role of Vitamin D related to sunlight, has always been recognized in the past fundamental for the reduction of rickets in children. The 1,25-dihydroxy-vitamin D (1,25-OH2)D is the steroid hormone, involved in the regulation of mineral homeostasis and bone metabolism. Vitamin D is synthesized in the skin, due to the effect of ultraviolet radiation (cholecalciferol) and is also introduced with the diet (ergocalciferol), but minimally. The biological effects of 1,25 (OH2) D are manifested thanks to the binding with the Vitamin D receptor (VDR) which belongs to the family of nuclear super-receptors and are expressed in numerous cell types and tissues. The 1,25(OH2)D, like parathyroid hormone (PTH), represents the mechanism which induces bone resorption. In recent years the beneficial effects of Vitamin D it also known in cancer prevention and treatment in several epidemiological studies. In laboratory studies, Vitamin D demonstrate a potential and important role in the tumorigenesis process as the cells regulation and proliferation or apoptosis. Also, in the immunomodulation process seem that the Vitamin D can be involved, both for innate and adaptive immune system. A possible association between Vitamin D deficiency and autoimmune disease (i.e. psoriasis, type I diabetes, multiple sclerosis, etc) has been published. The recent pandemic COVID-19 infection around the world seems that could be influenced by multiple factors (as age, comorbidity, obesity, diabetes, etc.), one of that, seems related to the deficiency of Vitamin D. Vitamin D deficiency is associate with an increasing susceptibility of infection diseases as upper respiratory tract producing antimicrobial peptides that might help to reduce the inflammatory response to COVID-19 infection. This review critically examines the current information on the role of Vitamin D in humans.

Keywords: *Vitamin D; Vitamin D Receptors (VDR); 1-25-Dihidroxyvitamin D; Cholecalciferol; Rickets; Parathyroid Hormone (PTH); Bone Metabolism; Inflammation; Immune System; Autoimmune Disorders; COVID-19*

Introduction

Vitamin D is a fat-soluble vitamin and steroid hormone that plays an important role in calcium-phosphorous regulation and bone structure [1]. Vitamin D is synthesized in the skin due to the effect of ultraviolet radiation (cholecalciferol) and is also introduced with the diet (ergocalciferol) but less than 10%. Vitamin D from vegetable's origin is represented by Vitamin D2, while, the one's that come from animal origin (as the humans), by Vitamin D3 [2]. Vitamin D, absorbed from the intestine or synthesized in the skin, is present in the blood linked to an α-globulin synthesized in the liver. Subsequently, Vitamin D is hydroxylated in position 1,25-hydroxyvitaminD (25 (OH) D in the liver and represent the main storage circulating Vitamin D. It's transported to the liver, where it undergoes hydroxylation at position 25. The last metabolic step, hydroxylation in the α-position, leads to the formation of the active hormone and occurs in the kidneys [3]. The biological effects of 1,25 (OH2) D are manifested thanks to the binding with the Vitamin D receptor (VDR) which belongs to the family of nuclear super-receptors. VDR is expressed in numerous cell types and tissues. 1,25 (OH2) D is a potent activator of calbindin

9k, a calcium-binding protein expressed in the intestine and which plays an important role in the active transport of calcium through the enterocyte. The 1,25(OH2) D increases the absorption of intestinal calcium and permit to have more important skeletal formation [4].

Vitamin D deficiency

Vitamin D deficiency is present worldwide and is important that the level not come down than 20 ng/ml. Vitamin D insufficiency has been defined as a Vitamin D of 21 - 29 ng/ml [1]. In accordance with these definitions, it has been estimated that 20 - 100% of people around the world, elderly men and women, children and young and middle-aged adults are Vitamin D deficient [5]. Vitamin D deficiency results in metabolism alterations of calcium, phosphorus, and than bone formation. Specifically, Vitamin D deficiency causes a decrease of intestinal calcium and phosphorus absorption, resulting in an increase in parathyroid hormone levels (PTH) [3] leading to the secondary hyperparathyroidism that don't modify the level of calcium in the blood. The PTH-mediated increase in osteoclastic activity, causes loss of bone mineral density (BMD), resulting in osteopenia and osteoporosis [6,7].

Causes of vitamin D deficiency

The major source of Vitamin D for children and adults is exposure to natural sunlight [3,8]. Then, the major cause of Vitamin D deficiency is inadequate exposure to sunlight [8,9]. However, during the exposition more people use the sun protection factors that reduce the synthesis of Vitamin D [10]. People with a white skin have a more synthesis of Vitamin D with respect to black people at least three to five times [11]. An other factor that reduce the absorption of Vitamin D is represented by obesity, in fact when the body mass index (BMI) is more than 30 kg/m^2 and thus it may associate with Vitamin D deficiency [12]. One other cause of Vitamin D deficiency is fat malabsorption syndromes, obesity patients treated with bariatric surgery and patients with nephrotic syndrome [1].

Benefits of vitamin D

Vitamin D receptors are represented in most tissues and cells in the body and Vitamin D supplementation, in several laboratory studies, it may reduce the risk of more than a dozen cancers but not change total mortality [13-15]. Also in autoimmune diseases, including both diabetes type 1 and 2, rheumatoid arthritis, Crohn's disease, Hashimoto's thyroiditis, and multiple sclerosis, infectious diseases can be involved. These studies demonstrated a correlation with Vitamin D deficiency [16,17]. In addition to autoimmune diseases, Vitamin D has also been implicated in the control of other inflammatory conditions, increasing the antimicrobial activity [18], promoting the production of antimicrobial peptide by macrophage and monocyte keratinocytes. The Vitamin D stimulate the interleukin (IL)-15 producing macrophages and increasing their antimicrobial activity [19,20]. The pandemic COVID-19 involve the respiratory tract and the production of antimicrobial peptides in the respiratory epithelium. Indeed the supplementation of Vitamin D, could reduce the symptoms less likely and reduce the inflammatory response to infection with SARS-CoV-2. The renin–angiotensin system improve the better prognosis by the supplementation of Vitamin D, in fact the Vitamin D interact with a protein in this pathway-angiotensin-converting enzyme 2 (ACE2) which is also exploited by SARS-CoV-2. Vitamin D supplementation promotes expression of *ACE2*, while SARS-CoV-2 downregulates this expression [21].

Conclusion

1,25(OH2) D or Vitamin D is a unique hormone, because it can be made in the skin from exposure to sunlight. Only a small part is introduced with food, but in an insufficient way. For this reason most of the world's population has a deficiency of Vitamin D. Both the population living in the geographic areas less exposed to sunlight and those living in the countries most exposed to sunlight, have a chronic Vitamin D deficiency (except periods of exposure to the sun). This chronic Vitamin D deficiency causes both problems with phosphocalcium homeostasis and bone metabolism, in particular in children (risk of rickets), young and adult people (osteomalacia), pregnant women (preeclampsia) and postmenopausal women (osteopenia or osteoporosis). The Vitamin D induce your own effects thanks to the

binding with the Vitamin D receptor (VDR), that are expressed in numerous cell types and tissues. The Vitamin D increases the efficiency of intestinal calcium absorption and also exerts several important skeletal transformations. VDR is expressed by osteoblasts and regulates the expression of numerous genes in these cells. Target genes include those for the bone matrix proteins osteocalcin and osteopontin, which are stimulated by Vitamin D. To obtain a good level of circulating Vitamin D, it's necessary to introduce about 1000 IU of Vitamin D daily, even if the body surface plays a fundamental role in obtaining a good level (between 40 and 60 ng/ml). In fact, in the obese subject, the quantity of Vitamin D to be introduced is about 2 - 3 times compared to the normal weight subject. Unfortunately, often many people are not properly informed of the importance of taking Vitamin D and this determines the lack of Vitamin D (< 20/30 ng/ml). Vitamin D deficiency may determine more abnormalities in calcium, phosphorus and bone transformation. Specifically, Vitamin D deficiency causes a decrease of intestinal calcium and phosphorus absorption, that mean to an increase in PTH levels. Secondary hyperparathyroidism don't modify the level of calcium in the blood. The PTH-mediated increase in osteoclastic activity, determine the focal loss of bone and a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis. Furthermore the Vitamin D, seem to permit to have more control of the immune system. The role of Vitamin D in the regulation of immune system is to improve it and has been published in recent years, Vitamin D has also been implicated in the control of other inflammatory conditions. Low Vitamin D status is also associated with increased susceptibility to infectious disease, as upper respiratory tract infections. Many authors have published the involvement of Vitamin D in reducing the risk of infections. The pandemic COVID-19 involve the respiratory tract and the production of antimicrobial peptides. The supplementation of Vitamin D could reduce the symptoms less likely and reduce the inflammatory response to infection with SARS-CoV-2. The renin–angiotensin system improve the better prognosis by a supplementation of Vitamin D, in fact the Vitamin D interact with a protein in this pathway-angiotensin-converting enzyme 2 (ACE2) which is also exploited by SARS-CoV-2. While SARS-CoV-2 downregulates expression of ACE2, Vitamin D supplementation promotes expression of this gene.

In the end, the Vitamin D supplementation play an important role both in the bone metabolism, and in inflammatory and autoimmunity diseases. In the last year of world pandemic COVID-19, several published studies have demonstrated that Vitamin D supplementation could be useful to reduce the risk of infection. To confirm this recommendation, it would be necessary to propose many randomized and controlled studies in a large series of population in the world.

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