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Vitamin D supplementation: Hypothetical effect on medication-related osteonecrosis of the jaw

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ABSTRACT

Vitamin D is an important nutrient for bone health and skeleton growth. Few foods are natural sources of this secosteroid; this is the reason why the consumption of vitamin D as a dietary supplement is becoming common in developed countries. For many years vitamin D has been considered crucial in the treatment and prevention of the Global Burden of Disease and in a reduction in mortality among elder people. Many health care providers prescribe these supplements in the management of osteoporosis and metabolic bone diseases; specifically in the primary prevention of fractures. Recently medication-related osteonecrosis of the jaw (MRONJ) has been reported as severe late sequelae of antiresorptive therapies (i.e., bisphosphonates and some monoclonal antibodies). Although MRONJ-related pathophysiology is not fully understood, there are three fundamental theories to explain it: (1) the inhibition of osteoclasts, (2) the inhibition of angiogenesis and (3) the processes of inflammation-infection. Recent advances in Vitamin D research have shown that this secosteroid can play a potential pivotal role in many of the different etiological pathways of MRONJ. Furthermore, there are a large number of co-morbidities between the deficit of this vitamin and other MRONJ concomitant outcomes. Our hypothesis argues that the low-risk and low-cost vitamin D dietary supplementation may prove to be suitable for use as a practical MRONJ prevention strategy. The described framework gives more insight into the study of disease mechanisms, search of potential biomarkers, and therapeutic targets in MRONJ.

Background

Vitamin D is an unsaponifiable heterolipid of the secosteroid group. Several vitamers of this steroid are known, of them the two most relevant vitamers in human physiology are jointly identified under the name of calciferol (i.e., vitamin D_3 or cholecalciferol and vitamin D_2 or ergocalciferol) [1]. This nutrient in humans is mainly obtained through food and dietary supplementation. Nonetheless, the main endogenous source of vitamin D in humans is through sunlight-mediated ultraviolet B (UV-B) skin synthesis; specifically through the conversion of 7-dehydrocholestrol into cholecalciferol [2]. These units of vitamin D obtained from diet and skin are biologically inactive and require a hydroxylation at the level of the liver and kidney. At the level of the hepatic system cholecalciferol is hydroxylated in 25-hydroxycholecalciferol or calcifediol; this molecule is released into the plasma, where it binds to the vitamin D binding protein (DBP or gc-globulin) traveling to the kidney where it is hydroxylated to 1,25-dihydroxycholecalciferol or calcitriol. Finally it binds to the vitamin D receptor (VDR); this ligand regulates the bioavailability of this molecule during its journey through the bloodstream in almost all of its physiological functions [3,4].

The pivotal role of vitamin D in physiology is calcium homeostasis (Ca^{2+}) at the level of the skeletal system [5]. Briefly, when the basal Ca^{2+} concentration decreases, the parathyroid glands react by secreting parathyroid hormone (PTH). This hormone stimulates the previously described hydroxylation reactions thus it increases the calcifediol circulating levels. This increase leads to greater intestinal absorption of calcium, a greater renal reabsorption of calcium and phosphates and a stimulation of osteoclastic activity. On the other side, when the serum concentration of Ca^{2+} increases, the C cells (also called parafollicular cells) of the thyroid release calcitonin. An increase in the serum calcitonin level produces the inhibition of PTH delivery, which inhibits the enzymes necessary for hydroxylation of the different metabolites involved in the synthesis of vitamin D and stimulates the osteoblastic

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activity [6].

Besides the maintenance of calcium homeostasis at bone, a large number of genes responsible for modulating cell proliferation, cell cycle arrest, and apoptosis are related to this steroid [7]. Also at the level of the immune system, vitamin D increases the expression of tyrosine hydroxylase, a pivotal enzyme in oxidative stress (OE) [8]. OE is part of the etiology of a large number of autoimmune-based pathologies in humans.

The Food and Nutrition Board (FNB) established a Recommended Dietary Allowance (RDA) for vitamin D of 600 IU (15 mcg) for both men and women. However, in adults above 70 years the recommendation goes to 800 IU (20 mcg) in both sexes [9]. There is a growing epidemic in terms of vitamin D deficiency in first-world countries, especially in North America and Europe. Multiple explanations arise for this deficit such as geographical latitude, lack of sunlight exposure, pollution or the prevalence of certain diseases and physiological conditions that hinder vitamin D intestinal absorption (i.e., obesity, metabolic syndrome, digestive disorders, frailty etc.) [10].

Few foods are natural providers of vitamin D; the flesh of fatty fish and some mushroom species are an inarguably great source, that's why a lot of foods like dairy, cereals, flours and juices are fortified with vitamin D. In addition the consumption of vitamin D as a dietary supplement is becoming more and more common in developed countries [9]. Several studies have attempted to show the influence of vitamin D supplementation on the management and prevention of the global burden of disease (i.e., cardiovascular diseases, cancer, autoimmune diseases, cognitive disorders and bone-related diseases) [11–14]. In turn, vitamin D supplementation has also been linked to a decrease in mortality in elderly people [15].

There is a growing interest in dietary supplementation due to the its large number of consumers globally and its easier introduction into the market in relation to conventional pharmaceuticals [10]. One out of every two North American adults consumes these supplements [16]. Vitamin D is a key component of many of these products. This steroid is especially indicated in certain pathologies related to osteolysis, such as osteoporosis (OS) or bone-related cancers. There is growing evidence in favor of the use of this supplementation in the prevention of OS-related bone fractures [17]. Another late sequelae associated with the use of certain anti-reabsorptive therapies, such as bisphosphonates (BPs) and some monoclonal antibodies (mABs), is medication-related osteonecrosis of the jaw (MRONJ) [18]. Nowadays, both outcomes are considered the most feared in the long-term prognosis in OS-affected patients [19].

Despite the existence of numerous clinical trials to find a relationship between vitamin D supplementation and the prevention of OS-related fractures (ie, NCT03337971, NCT01798030), at the present time there are no clinical trials to determine whether the use of these dietary supplementations could be useful in the prevention of MRONJ.

Hypothesis. *The hypothesis argues that vitamin D supplementation could play a pivotal role in the prevention of MRONJ. This secosteroid plays part in many of the different etiological pathways of MRONJ, while there are a large number of co-morbidities between the deficit of this vitamin and other MRONJ concomitant outcomes. This possibility would open a new therapeutic approach in the prevention and management of these complex sequelae and be one step towards the clarification of its etiopathogenesis.*

Evaluation of the hypothesis

MRONJ is defined as an exposed bone in the jaw persisting for more than 8 weeks with no history of radiation therapy while having under gone an anti-resorptive drugs therapy (i.e., BPs and mABs). The current etiopathogenic model of MRONJ is based on three fundamental pillars, which are: [1] the inhibition of osteoclasts [2], the inhibition of angiogenesis and [3] the processes of inflammation-infection. Other alternative hypotheses have also been raised regarding this complication such as drug-related soft tissue toxicity or the possible role that a possible suppression of innate or acquired immunity may have [20–23].

The co-morbidities and frequent risk factors related to the development of MRONJ are commonly classified as systemic and local (i.e., oral). At the local level, the risk of derived from a tooth extraction and the presence of periodontal disease (PD) are highlighted [24,25]. At the systemic level, different types of treatments such as chemotherapy, corticosteroids and antiangiogenic therapies are relevant risk factors [18,26–28]. On the other hand, the characteristics of the specific drug are also fundamental in the development of MRONJ [29].

The MRONJ onset is linked to a genetic predisposition related to a polymorphism in the CYP2C8 gene (related single nucleotide polymorphisms (SNPs) rs1934951) [30]. Diz et al. [31] suggested that in individuals with Mediterranean ancestry the probability of MRONJ onset was higher based on the origin of published cases series. This explanation points to a possible MRONJ endemicity.

Below we discuss some of the functions that vitamin D can play in each of these co-morbidities and biological pathways.

Suppression of bone turnover

Ardine et al. [32] demonstrated that hypocalcemia and hyperparathyroidism were risk factors for the development of osteonecrosis of the jaw specifically in patients undergoing treatment with BPs. At the same time it is accepted that the consumption of vitamin D dietary supplements helps in the prevention of certain side effects of BPs consumption (ie, fractures) [33]. The pivotal role of vitamin D in the homeostasis of calcium metabolism makes it a clear candidate to correct the high bone turnover ratio at maxillary bones secondary to antiresorptive treatments [34]. At the same time, biomarkers related to bone turnover described in the management and prevention of MRONJ (i.e., Serum C-terminal telopeptide of type I collagen (s-CTX); parathormone (PTH), osteocalcin (OC)) are easily alterable with the consumption of vitamin D supplementation [35,36]. Patients suffering from vitamin D deficiency tend to higher levels of CTX, BAP, OC and PTH. This altered biochemical profile could correlate this deficit with a greater susceptibility to suffer MRONJ [37], which could mean that supplementation with this vitamin could generate a bone homeostasis that mitigates the variations in these biomarkers and prevent the long-term MRONJ onset [38]. In spite of this, there are currently no conclusive biomarkers for the management or prediction of osteonecrosis of the jaw [20].

It should be noted that the use of glucocorticoids has been described as a risk factor in the development of MRONJ [23]. In turn, these drugs are known to decrease the expression of VDR by reducing the physiological bioavailability of vitamin D [39], and ultimately affecting the ratio of bone turnover. Recently, comorbidity between MRONJ and atypical bone fractures in patients chronically treated with BPs has been reported [40,41]. The management of these outcomes with the use of calcitriol supplements was raised in this type of clinical scenarios.

Secondary hyperparathyroidism in rickets and osteomalacia is classically linked to low levels of vitamin D. Recently Bedogni et al. [42] identified osteomalacia as a risk factor for the MRONJ onset. Sensitivity of biochemical test (specifically vitamin D concentration in blood serum) in comparison with other methods for the diagnosis of osteomalacia in human has been proved [43]. This link could mean an interesting hypothesis in the search for novel biomarkers for MRONJ.

Inhibition of angiogenesis

Numerous anti-angiogenic therapies have been related to MRONJ onset (i.e., bevacizumab, rituximab y cabozantinib) [19]. In addition, the successful use of biomarkers in relation to angiogenesis, such as Vascular Endothelial Growth Factor (VEGF), in the MRONJ prevention has been confirmed [44]. The active form of vitamin D (1, 25 (OH) 2D3) is a relevant regulator of angiogenesis and vascular function [45].