Vitamin D and its Impact on Oral Health — An Update

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continuing education
TD JOURNAL
EXAM #29

ABSTRACT

Vitamin D has been shown to regulate musculoskeletal health by mediating calcium absorption and mineral homeostasis. Evidence has demonstrated that vitamin D deficiency may place subjects at risk for not only low mineral bone density/osteoporosis and osteopenia but also infectious and chronic inflammatory diseases. Studies have shown an association between alveolar bone density, osteoporosis and tooth loss and suggest that low bone mass may be a risk factor for periodontal disease. Several recent reports demonstrate a significant association between periodontal health and the intake of vitamin D. An emerging hypothesis is that vitamin D may be beneficial for oral health, not only for its direct effect on bone metabolism but also due to its ability to function as an anti-inflammatory agent and stimulate the production of anti-microbial peptides.

CLINICAL SIGNIFICANCE:

The purpose of this review is to evaluate the impact of osteoporosis and vitamin D levels on periodontal health.

KEY-WORDS:

Vitamin D, osteoporosis, periodontal disease, innate immunity

Introduction

Vitamin D plays a critical role in mediating calcium absorption and regulating musculoskeletal health.[1] It has also been demonstrated to function in the regulation of cardiovascular health, immune responses, wound healing and cancer prevention.[2-6] Vitamin D is a fat soluble vitamin obtained from three sources. Endogenous synthesis of vitamin D occurs in the skin and is induced via ultraviolet radiation. It may also be obtained exogenously through dietary sources that include oily salt fish (mackerel, salmon, sardines and tuna), cod liver oil and egg yolk. Many countries, including the United States of America, fortify dairy products with vitamin D due to its scarcity in natural foods. Finally, various forms of vitamin D are available in over-the-counter dietary supplements. Vitamin D obtained through supplements is converted to 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D through the same pathway that keratinocytes utilize when ultraviolet radiation stimulates its synthesis from a cholesterol precursor in the epidermis. The current recommended daily intake for vitamin D and calcium are 400-600 IU and 1,000 to 1,200 mg, respectively, for people over 50 years of age.[7] Higher doses (800-1,000 IU) of vitamin D are recommended for osteoporosis prevention.[8] It is estimated that 1 billion people worldwide have vitamin D deficiency.[9-10]

Effects of Vitamin D on Metabolism and Osteoporosis

As an important component of interactions among the kidney, bone, parathyroid gland and intestine, vitamin D helps to modulate skeletal and mineral homeostasis.[1] Through its role in maintaining proper extracellular calcium levels, vitamin D is essential in maintaining skeletal integrity. After its formation in the skin, via exposure to ultraviolet light and modification in the liver and kidney, vitamin D is released into the circulation. In plasma, it binds to carrier proteins which transport it to target organs and tissues.[11] Vitamin D then mediates its effects via binding to the vitamin D receptor (VDR), a member of the steroid superfamily receptors. Binding of vitamin D activates the VDR, which acts as a transcription factor for target genes.[12] Vitamin D increases the ability of the small intestine to absorb dietary calcium and phosphate. In intestinal epithelial cells, via binding and activation of the VDR, vitamin D stimulates calcium uptake and transport by upregulating expression of epithelial calcium channels, a cytosolic calcium binding protein, and plasma membrane proteins that mediate delivery of calcium to the bloodstream.[13] By enhancing intestinal uptake of both calcium and phosphate, vitamin D helps to create optimum conditions for bone mineralization and is necessary for the development and maintenance of the mineralized skeleton.[1,14]

Several molecules, including receptor activator of NF-kB ligand (RANKL), and a RANKL antagonist (osteoprotegerin or OPG) are produced by osteoblasts and other cells such as activated CD4+ T lymphocytes and are important regulators of bone remodeling.[15-18] Binding of RANKL to RANK, expressed on the surface of osteoclast progenitor cells, causes them to differentiate into mature osteoclasts. OPG acts as a soluble receptor for RANKL, inhibiting RANK-RANKL interaction and the maturation of osteoclast progenitor cells. The relative ratio of RANKL to OPG in the osteoclast precursor microenvironment can thus determine mature osteoclast formation.

The RANKL gene promotor structure contains vitamin D and glucocorticoid response elements, and studies have shown that vitamin D-VDR stimulates RANKL expression in cells such as osteoblasts and bone marrow-derived stromal cells.[19-22] Vitamin D has been shown to downregulate OPG, and this combination of increased RANKL expression and decreased expression of OPG caused by vitamin D would favor differentiation and activation

of osteoclasts and increased bone resorption.[14,19,21-26] However, Hofbauer et al., have reported a stimulatory effect of vitamin D on OPG,[27] and Kondo et al., reported that while vitamin D initially represses OPG, long-term exposure to vitamin D led to a recovery of OPG expression.[24] This suggested that the catabolic effects of vitamin D can be transient. Indeed, vitamin D has several anabolic effects on osteoblasts, including stimulation of osteopontin and alkaline phosphatase, and in a rat model of osteoporosis, vitamin D also had anabolic effects.[28-31] Therefore, vitamin D appears to stimulate bone resorption (which is necessary for bone remodeling and formation of new bone), but after longer periods of exposure, it may facilitate osteoblast proliferation and differentiation.[24] Other studies have shown, however, that there is an association between lower serum vitamin D and increased expression of RANKL and other cytokines (i.e. IL-6 and TNFα) that stimulate osteoclastogenesis.[32-34]

Chronic low intake of Vitamin D and calcium leads to a negative calcium balance, impaired bone mineralization, and bone loss.[35] In children, vitamin D deficiency can cause rickets (characterized by limited growth and deformity of the long bones),[36-38] while in adults, it can cause osteopenia and osteoporosis, as well as increase the risk of fracture.[39-42]

Osteoporosis and Periodontal Disease

Jabbar et al., have noted that, like periodontal disease, osteoporosis is a chronic, multifactorial disease and that the two diseases may share certain risk factors such as genetic polymorphisms and hormonal and/or dietary deficiencies.[43-48] The contribution of generalized bone loss to oral bone loss and the extent of any relationship between osteoporosis and periodontal disease, however, is uncertain.[49,50] Several studies have suggested an association between systemic bone mineral density/low bone mass/osteoporosis and alveolar bone density and tooth loss.[48,51-77] However, data from some studies is difficult to accurately interpret and compare because of small sample sizes, insufficient control of confounding factors, different types of study populations and different methods or sites used to assess osteoporosis and periodontitis.[49] In addition, some studies have presented evidence that bone mineral density is not related to alveolar bone loss. For example, Elders et al.,[78] found no significant relationship between systemic bone loss and alveolar bone height, concluding that systemic bone loss is not important in the pathogenesis of periodontitis. Klemetti et al.,[79] found no strong correlation between existing trabecular or cortical bone density and the rate of alveolar crestal bone loss. In a longitudinal study of 398 post menopausal women, Famili et al.,[50] found little evidence to support an association between edentulism, periodontal disease and longitudinal changes in bone mineral density. Researchers in this field have cited the need for additional larger scale, well-controlled studies to determine the role of osteopenia/osteoporosis on the prevalence and severity of periodontitis, as well as prospective studies to determine if osteopenia/osteoporosis is associated with the incidence and progression of periodontal disease.[49] Despite conflicting studies in the literature, however, Jeffcoat[52] noted that most of the current evidence shows association between oral bone mineral density and some measure of systemic osteoporosis [i.e. dual energy x-ray absorption (DXA)]. This evidence suggests that osteoporosis/low bone mass may be a risk factor for periodontitis.[49,54]

Vitamin D and Periodontal Health

There are conflicting reports regarding the benefit of vitamin D and calcium supplementation in the treatment of periodontal disease. Some earlier studies from the 1970's and 1980's suggested that reduced tooth loss and alveolar bone resorption were observed with calcium and vitamin D supplementation but were criticized for heterogenous composition of the study groups or because they did not measure periodontal disease status directly.[80-83] More recent studies showed significant associations between periodontal health and intake of vitamin D and calcium,[84,85] and that dietary supplementation with calcium and vitamin D may improve periodontal health, increase bone mineral density in the mandible and inhibit alveolar bone resorption.[86,87] In a recently published longitudinal study, Garcia et al.,[35] reported that calcium and vitamin D supplementation may reduce the severity of periodontal disease if used at doses higher than 800-1,000 IU daily and supported the rationale for testing the potential beneficial role of vitamin D on periodontal disease in randomized clinical trials. They also noted that vitamin D, in addition to its role in bone and calcium homeostasis, acts as an anti-inflammatory agent because it inhibits immune cell cytokine expression and causes monocyte/macrophages to secrete molecules that have a strong antibiotic effect.[88-93] Indeed, vitamin D deficiency may be linked to increased risk of infectious diseases.[94] This suggests that vitamin D may be of benefit in the treatment of periodontitis, not only because of its direct effects on bone metabolism, but also because it may have antibiotic effects on periodontopathogens and inhibit inflammatory mediators that contribute to periodontal destruction.[95]

Vitamin D and its Effects on Immune Responses

Vitamin D was implicated in the regulation of immune responses following the discovery of VDRs on most immune cells including activated CD4+ and CD8+ T cells, B cells, neutrophils and antigen presenting cells such as macrophages and dendritic cells.[96,97] Vitamin D was also reported to exert pro-differentiation effects on monocytes, stimulating their acquisition of phenotypic features associated with macrophage.[98] In addition, vitamin D enhanced macrophage chemotactic and phagocytic capacity.[99] Vitamin D also inhibited the expression of monocytic inflammatory cytokines including IL-1, IL-6, TNFα, IL-8, and IL-12.[100-102] Recently, the antimicrobial effects of vitamin D were shown to be mediated via the VDR and associated with the upregulation of the cathelicidin hCAP-18 gene.[103] Importantly, toll like receptor activation of monocytes and macrophages results in the up-regulation of VDR and VDR target genes, with subsequent induction of cathelicidin antimicrobial peptide (CAMP) and killing of Mycobacterium tuberculosis.[92] Besides CAMPs, beta defensins, which are a separate class of anti-microbial peptides, have also been identified as a direct target of vitamin D.[104] Another recent report demonstrated the physiological link between vitamin D mediated innate immunity and enhanced macrophage

phagocytosis induced by cathelicidins.[105] These findings support the active role of vitamin D in clearing bacterial infections through augmented production of anti-microbial peptides.

Conclusion

Historically, vitamin D has been shown to regulate musculoskeletal health by mediating calcium absorption. Evidence has demonstrated that vitamin D deficiency may place subjects at risk for low mineral bone density/osteoporosis and osteopenia, as well as infectious and chronic inflammatory diseases. A recently conducted longitudinal study lends support to the protective role of vitamin D in promoting oral health. An emerging hypothesis is that vitamin D may be of benefit in the treatment of periodontal disease, not only for its direct effect on bone metabolism but also due to its anti-inflammatory and CAMP-stimulating properties.

Disclosure. None of the authors reported any disclosures.

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Questions for Continuing Education Article - CE Exam #29

1. Vitamin D has been shown to regulate musculoskeletal health by mediating:
   a. Striated muscle formation
   b. Fat absorption
   c. Co-Q-10
   d. Calcium absorption

2. An emerging hypothesis is that Vitamin D may be beneficial for oral health due to its:
   a. Anti-inflammatory properties
   b. Stimulation of the production of anti-microbial peptides
   c. a. and b.
   d. None of the above

3. The current recommendation for the daily intake of Vitamin D is:
   a. 250-500 mg.
   b. 400-600 IU
   c. 1000-2000 mg.
   d. 3000-5000 mg.

4. Chronic low intake of Vitamin D and calcium leads to a:
   a. Negative calcium balance
   b. Impaired bone mineralization
   c. Bone loss
   d. All the above

5. Recent studies showed a significant association between intake of Vitamin D and Calcium and:
   a. Periodontal health
   b. Kidney stones
   c. Decreased olfaction
   d. Benign migratory glossitis

Publication date: Spring 2011. Expiration date: Spring 2014.

Answer Form for TDA CE Credit Exam #29:

Vitamin D and its Impact on Oral Health — An Update

Publication date: Spring 2011. Expiration date: Spring 2014.

EXAM #29

Circle the correct letter answer for each CE Exam question:

1.	a	b	c	d
2.	a	b	c	d
3.	a	b	c	d
4.	a	b	c	d
5.	a	b	c	d

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