

The Role Of Vitamin D In Otolaryngological Diseases: Myth Or Truth

Ali Bayram¹, MD

¹Department of ENT, Kayseri City Hospital, Kayseri, Turkey

Abstract

In the present review, we aimed to evaluate the role of vitamin D in otolaryngological diseases. Since the recognition of vitamin D as a steroid hormone, it has attracted clinicians as a research issue due to its unique and complicated functions in human body processes. Numerous studies have investigated the association between vitamin D and human diseases, including in the otolaryngological field. However, although vitamin D alterations

may theoretically be involved in the pathogenesis of several otolaryngological diseases, a clear association has not been demonstrated due to inconsistent results from the studies to date. Further randomized controlled trials with large patient populations are required to determine the exact role of vitamin D in otolaryngological diseases.

Keywords: Vitamin D, otorhinolaryngologic diseases, immunity

Vitamin D is an essential nutrient that has a well-known regulatory function in calcium and phosphate metabolism. Recently, vitamin D has been recognized as a steroid hormone with the identification of vitamin D receptors in many tissues, such as lymphocytes, kidney, ovaries, stomach, thymus, pancreas, skin and parathyroid glands.^[1] In relation to recent discoveries regarding the vitamin D receptor, researchers have determined new functions for vitamin D including immunoregulation, induction of cell differentiation and control of other hormonal systems^[2], and vitamin D has now been accepted as a member of a complex endocrine pathway termed the 'vitamin D endocrine system'.^[3] Since the recognition of vitamin D as a steroid hormone, it has attracted clinicians due to its unique and complicated functions regarding human body processes. Numerous studies have investigated the association between vitamin D and human diseases including in the otolaryngological field. In the present review, we aimed to evaluate the role of vitamin D in otolaryngological diseases.

Vitamin D Physiology and Metabolism

The vitamin D endocrine system contains three forms of vitamin D; cholecalciferol, calcidiol (25-hydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D). Cholecalciferol is the natural form of vitamin D. It can be naturally synthesized in the skin through sunlight exposure or can be supplemented by dietary intake.^[4] Calcidiol is produced from cholecalciferol as a prehormone in the liver, which is generally accepted as a blood indicator of vitamin D status. Calcidiol is converted into calcitriol both in the kidneys and other tissues by enzymatic hydroxylation (25(OH)D3-1-hydroxylase and 25(OH)D3-24-hydroxylase). Calcitriol, as the physiologically active form of vitamin D, increases intestinal absorption of calcium and phosphorus, and promotes bone resorption in concert with parathyroid hormone.^[2,5]

Vitamin D and Immunoregulation

The immunoregulatory functions of vitamin D have been known for more than 30 years.^[6] Vitamin D directly regu-

Correspondence: Ali Bayram, MD, Kayseri City Hospital, Şeker Mah. Molu Village, Kayseri 38080, Turkey
E-mail: dralibayram@gmail.com

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lates B cell, T cell, dendritic cell, macrophage and monocyte functions.^[7,8] Vitamin D suppresses T-cell proliferation^[9,10], plasma cell differentiation and immunoglobulin secretion^[11], including IgE.^[12] Vitamin D also induces apoptosis of activated B cells and the switch from Th1 to Th2.^[13]

Vitamin D also has numerous effects on the innate immune system. Vitamin D decreases the immunostimulatory capacity of dendritic cells and provides them tolerogenic properties.^[14] It increases the antimicrobial activity of freshly isolated monocytes and decreases T-cell stimulation and macrophage inflammation.^[15] Chemotactic and phagocytic effects of monocytes and macrophages can be increased by vitamin D. Also, an increment in the synthesis of antimicrobial peptides, defensins and cathelicidin can be presented from natural killer cells and respiratory tract epithelial cells in an enriched active vitamin D environment.^[15] In addition, vitamin D causes the upregulation of calprotectin and S100 protein levels, which contribute significantly to the functions of the natural immune system.^[16] Vitamin D also has modulatory functions on a variety of cytokines that are considered to have an active role in the pathogenesis of many autoimmune diseases. In most studies, it is indicated that Th1-related cytokines such as interferon- γ , tumor necrosis factor- α and IL-2 are generally inhibited by vitamin D, whereas Th2-related cytokines including IL-4 and IL-10 are upregulated by vitamin D.^[13] In conclusion, vitamin D has several modulatory functions in the immune system that generate a positive correlation between the immune system and vitamin D status. Vitamin D deficiency causes impaired immune responses that lead to increased infection rates including in the upper respiratory tract.^[15] Also, vitamin D status has been investigated in recent studies concerning allergic and autoimmune pathologies including otolaryngological diseases due to its immunoregulatory effects.

Vitamin D and Otolaryngological Diseases

A high incidence of vitamin D deficiency has been reported in patients attending otolaryngology clinics in different studies. Bartley et al^[17] investigated plasma vitamin D levels in 48 patients who attended a general otolaryngology clinic and reported that 2% had a level of 17.5 nmol/L or less, 58% below 50 nmol/L and all were below 80 nmol/L. Similarly, Taneja and Taneja^[18] detected vitamin D deficiency in 83 out of 86 patients and concluded that the incidence of vitamin D deficiency is extremely common in

patients visiting outpatient otolaryngology clinics. Recently, the association between otolaryngological diseases (i.e. allergic rhinitis, otitis media, obstructive sleep apnea, etc.) and vitamin D status has gained a marked interest among clinicians and several reports have been introduced to the literature.

The role of vitamin D in allergic rhinitis (AR) is still a matter of debate, although several studies have investigated a possible relationship. A shift from a Th1 to Th2 phenotype in the proliferation of CD4+ T cells is a possible contributing factor in the pathogenesis of AR. In a similar manner, vitamin D induces a switch from Th1 to Th2 by enhancing the development of Th2 cells and suppresses the differentiation and functions of Th17 cells, which have an important role in the disease course of AR.^[19] Similarities between the pathogenesis of AR and vitamin D functions may suggest a role of vitamin D in the development of AR, although conflicting data have been acquired through epidemiological and clinical studies. Mai et al^[20] investigated the role of low vitamin D status in the development of AR in a large population-based health study and reported that low vitamin D status was related to an increased risk of AR in men and a seemingly reduced risk in women. On the contrary, in the study of Wjst and Hyppönen^[21], including 18,224 adults, they found that AR prevalence was increased with levels of vitamin D. A recent systematic review and meta-analysis investigating vitamin D status, aeroallergen sensitization and AR revealed a significant age- and sex-specific relationship between vitamin D status and the risk of aeroallergen sensitization and AR.^[22] The meta-analysis indicated that children with serum vitamin D levels lower than 50 nmol/L had an increased risk of aeroallergen sensitization. Also, vitamin D deficient men, but not women, were found to have an increased risk of AR according to the meta-analysis. Further studies conducted with large patient populations are required to clarify the exact mechanism of vitamin D in the pathogenesis of AR and the clinical implications of vitamin D supplementation on the risk of AR occurrence.

Due to its immunoregulatory functions, vitamin D has significant roles in improvement of immune function and reduction of inflammation.^[23] Therefore, vitamin D deficiency may be associated with respiratory tract infections (RTI) including acute otitis media, pharyngotonsillitis, rhinosinusitis, bronchiolitis and pneumonia, especially in children.^[24,25] Available data support a role of vitamin D deficiency in the risk of pediatric tuberculosis, recurrent

acute otitis media, and severe bronchiolitis, while further studies are required to clarify a relation in children with recurrent pharyngotonsillitis, acute rhinosinusitis and community-acquired pneumonia. However, the data are insufficient to allow definitive conclusions regarding a supplementation regimen for children.^[23] A systematic review of clinical studies including all ages determined a statistically significant relationship between low vitamin D status and increased risk of both upper and lower RTI, although vitamin D supplementation trials did not reveal consistent protective effects against RTI.^[26] Further studies are required especially to determine an optimal vitamin D supplementation regimen depending on the type of RTI.

Obstructive sleep apnea (OSA) is a serious disease that is characterized by apnea and hypopnea events during sleep. The severity of the disease depends on the number of apnea and hypopnea events per hour and particularly those with moderate and severe OSA have an increased risk of cardiovascular morbidities.^[27] Currently, several studies have investigated any association between vitamin D and OSA. Upala and Sanguankeo^[28] published the first systematic review and meta-analysis revealing the presence of lower vitamin D levels in patients with OSA compared to controls. In a more recent systematic review and meta-analysis, Neighbors et al^[29] reported that a relative insufficiency in serum vitamin D levels was present in OSA patients compared to controls, which was incrementally exacerbated with increasing severity of sleep apnea. On the other hand, the underlying mechanism of a vitamin D and OSA association is less clear than its presentation. One possible explanation is that low vitamin D levels arise due to a hypoxia-induced mechanism.^[30] Vitamin D insufficiency has been shown in obese patients regardless of OSA status.^[31] Since higher body mass index is a common morbidity in OSA, lower levels of vitamin D in OSA patients may be associated with obesity rather than OSA.^[29] In conclusion, further randomized controlled studies are needed to evaluate the association between OSA, vitamin D and obesity for a better understanding of underlying mechanisms.

Vitamin D related calcium channel proteins in the epithe-

lium are known to be involved in calcium metabolism of the vestibular organ. Vitamin D has a significant role in the development and maintenance of otoconia and proper otolith function.^[32] Decreased bone mineral density was shown in patients with benign paroxysmal positional vertigo (BPPV) in the literature. Vibert et al^[33] reported that the ratio of osteoporosis was higher among BPPV patients than controls and revealed an association between calcium metabolism disorders and the occurrence of BPPV. Since vitamin D has significant functions in maintaining proper bone structure and calcium metabolism, alterations of vitamin D levels may be seen in BPPV. In a retrospective study including 232 BPPV patients, vitamin D was suggested as a recurrence factor for BPPV, regardless of age, gender, follow-up period and type of BPPV.^[34] In severe vitamin D deficiencies, improvement of serum vitamin D levels was shown to diminish the recurrence rate of BPPV.^[32] On the contrary, Maslovara et al^[35] indicated the need for supplemental therapy due to a low level of serum vitamin D3 in most BPPV patients participating in their study, although no significant difference was shown in vitamin D3 levels in patients with and without recurrence. Future studies should be focused on clarifying the effect of vitamin D supplementation in decreasing recurrence rates in patients with recurrent BPPV.

Conclusion

Vitamin D attracts clinicians due its unique and complicated functions regarding human body processes. Numerous studies have investigated a possible association between vitamin D and otolaryngological diseases. Due to the inconsistency among the relevant studies, vitamin D seems to be an ongoing issue for further research in the otolaryngological field. Although further randomized controlled studies with large patient populations are required to demonstrate the clinical benefits, supplementation of vitamin D in deficient patients may have clinical implications for the course of otolaryngological disease.

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