American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Vitamin D, Zinc and Ear Nose Throat Disorders: Novel Findings

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To Cite This Article: *Fuat Bulut, Basak Ballica, Vitamin D, Zinc and Ear Nose Throat Disorders: Novel Findings. Am J Biomed Sci & Res. 2021 - 11(5). AJBSR.MS.ID.001672.* DOI: 10.34297/AJBSR.2021.11.001672.

Received: November 11, 2020; **Published:** January 29, 2021

Abstract

Vitamin D and Zinc (Zn) play a crucial role in human biochemistry. Over the last decade, there has been a better understanding on the significant role of vitamin D and zinc in ear, nose, and throat disorders. They are responsible for regulating mucosal immunity. Although vitamin D recognized as a key micronutrient, there is a pervasive vitamin D deficiency globally. Zinc as a critical trace element in human metabolism, facilitates the antioxidant activity and toxin excretion, plays a vital role in hearing system, acts as a cofactor in many enzymes. Zinc tasks in diseases related to mucosal defense, control of seasonal allergic rhinitis and healing of scar tissues. Zinc is an abundant intracellular trace element. Even though a mild zinc deficiency can manifest with serious clinical pictures like impaired immune defense.

Keywords: Vitamin D, Zinc, Mucosal, Nose, Hearing Disorders, Excretion, Micronutrient, Biochemistry, Vertigo, Predisposition, Rhinosinusitis, Laryngopharyngeal, Lymphatic, Epithelium, Granulomatose

Introduction

Otology and vitamin D

It has long been attested that vitamin D, in tandem with calcium, is effective in bone mineralization and linked with bone disease. Recent studies revealed the connection of vitamin D, which is a key actor as immuno-modulator, with otologic disorders. So far, numerous predisposing factors have been suggested in the formation of disease induced by otitis media with effusion. The relationship between otitis media with effusion and vitamin D deficiency has been reported [1]. This link can be attributed to an increased risk for allergic disorders in vitamin D deficiency or disordering effect of tuba eustachian in drainage system. Among kids implanted with tympanostomy tube, 25-hydroxy vitamin D [25(OH)D] levels have been classified [2]. Particularly, with a disorder in tuba eustachian functioning, there is a risk of post-otitis media retraction pocket unless a protocol is followed to address underlying cause.

Retraction pockets may be a risk factor for cholesteatoma formation. Due to vitamin D deficiency, osteoclastic activity of cholesteatoma may speed up [3]. Any jump in osteoclastic activity may be a risk factor for complications; hence vitamin D level estimation may be crucial among patients with cholesteatoma. It is effect in the pathophysiology of Benign Paroxysmal Positional Vertigo (BBPV), which is a common triggering factor in vertigo, has been shown. Some studies demonstrated that people with BBPV and low vitamin D levels experience vertigo attacks more frequently [4]. Among idiopathic BPPV patients, it is probable to detect a crack in calcium metabolism and this picture can be attributed to a decrease in vitamin D levels. At this stage, otoliths fall into posterior semicircular canal. They lead to vertigo lasting for seconds. BBPV patients that experience frequent attacks should be investigated with respect to their vitamin D store.

In allergic dermatitis, clinic manifestation of outer ear and outer ear canal is critical. Vitamin D deficiency may cause allergic

dermatitis or fuel this clinic view [5]. Hearing physiology is important for fetal development. Deficiencies during pregnancy could lead to irreversible hearing problems hence serum vitamin D levels should be monitored during pregnancy. Babies with low vitamin D levels may cope with critical levels of congenital hearing loss. Vitamin D deficiency plays a role in a range of diseases from cochlea induced hearing loss to Meniere's disease and cochlear otosclerosis [6]. Besides, vitamin D deficiency affects lymphatic flow adversely. Topical 1, 25-dihydroxivitamin D3 disturbs the migration of dentritic cells into lymph node the drainage system [7]. A disturbed lymphatic flow negatively affects muscle physiology. In case of ear nose throat disorders, malfunctions in muscle physiology may trigger cowl muscle dependent otologic pain which is seen in ear. Vitamin D levels should be evaluated when otalgia is concomitant with temporomandibular muscle and joint pain.

Rhinology and vitamin D

Upper respiratory tract infections are caused by a myriad of factors and bacterial biofilms are the most significant cause of recurrent infections. Decrease in nose mucosal defense may be originated from local causes or systemic factors. Vitamin D deficiency could create systemically adverse effects while also negatively affecting nose mucosal defense. It has been reported that there is a correlation between vitamin D levels and patients' response to the treatment [8]. So that, in influenza case, vitamin D levels may hold value with respect to disease inducted complications and response to treatment. Particularly in such infections, vitamin D deficiency should also be checked to provide required support. Allergic rhinitis as one of most frequent disorder of nose mucosa lining causes severe complications, labor force losses, and huge financial damages. Conducted studies emphasize the correlation between allergic rhinitis and vitamin D [9].

Among patients with allergic rhinitis, it is importantly suggested to estimate vitamin D levels of these patients to prevent complications due to redundancy of drug use or the disease itself. Changes in environmental factors and increased predisposition for yeast infections causing a rise in fungal sinusitis. Relevant studies demonstrated the link of vitamin D deficiency with allergic fungal sinusitis [10]. Allergic fungal sinusitis is a noninvasive disease most common in among youngsters. Among patients with allergic fungal sinusitis, nasal polyposis is seen nearly in every patient. Influenza infections are common during mid seasons. In that matter, researchers suggested the correlation between seasonal change and low vitamin D levels [11]. Rhinosinusitis, as a major health problem in both childhood age and adulthood period, develops chronic rhinosinusitis in tandem with recurrent attacks. A wide array of predisposing factors play role in the formation of chronic rhinosinusitis. Once the disease becomes chronic and patients experience decrease in quality of life. In that case, protocol of the treatment targeting the underlying cause has a great importance. Vitamins that are effective in mucosal defense mechanism are as important as other etiological factors including laryngopharyngeal heartburn, allergic predisposition, and environmental factors. Relevant case studies suggest that chronic rhinosinusitis could be attributed to low vitamin D levels. Specially, among patients with eosinophilic mucus, an increase in the mRNA levels of cathelicidin were observed [12,13].

To achieve success in treating chronic rhinosinusitis, preventing any complication and its high recurrence rate after endoscopic sinus surgery, it is beneficial to evaluate vitamin D levels as its key role in mucosal defense mechanism. Besides, some studies demonstrated the link between vitamin D deficiency and nasal polyp, [14] bone pains [15] and cancer [16] Furthermore, vitamin D deficiency is related to nevoid basal cell carcinoma syndrome [17]. Vitamin D deficiency has adverse effects on lymphatic flow. However, it was reported that topical 1, 25-dihidroxy (OH) vitamin D3 damages the migration of dentritic cells to draining lymph nodes [18]. According to anatomical studies, lateral nasal bone displays a rich lymphatic flow, therefore serum vitamin D levels could be estimated in suitable patients prior to nose aesthetic surgery or any nose tumor operation. Some patients may experience a bone pain in their nose but they cannot describe the pain very precisely. Vitamin D levels should be evaluated in patients that complain due to nose bone pain of which cause is unidentified.

Throat Disorders and Vitamin D

Due to recurrent mucosal infections in upper airway, risk for complication become higher. In recurrent infections, detecting the potential factors explaining the damage in mucosal defense may prevent these attacks. Particularly, bacterial biofilms are a major source of recurrent infections. As reported, vitamin D concomitant with production of cathelicidin and defensin β2 play a huge role in mucosal defense against bacterial biofilm formation [19]. Surprisingly, it has been reported that vitamin D deficiency is linked with the rise in chronic tonsil lit, autoimmune and contagious diseases [20,21]. It has also been revealed that low vitamin D levels elevated the risk for lower respiratory tract infection. In childhood age, rickets due to severe vitamin D deficiency is primarily linked with pneumonia followed by a higher risk for acute respiratory tract infection [22]. Also, it was detected that people with vitamin D levels lower than 40nmol/L has a greater risk for upper airway infection [23]. Another study is related with a decreased risk for upper airway infection among people having vitamin D levels above 75nmol/l [24]. Some studies suggest that optimal vitamin D level to be guarded against contagious disease and cancer prevention is up to 80nmol/L and even higher [25].

Biochemistry of Vitamin D

Almost 95% of vitamin D is acquired through sunlight. A very tiny portion can be received via foods. Once the skin is exposed

to ultraviolet B (UV-B) rays, there is an accumulation of vitamin D in human body. When this fat-soluble vitamin is exposed to UV ray on skin, it initially turns into 7-dehydrocholesterol, then to pre-D3 vitamin lastly to cholecalciferol and it becomes synthesized. Active vitamin D form is cholecalciferol or its D3 form. Vitamin D is processed by 25-alpha-hydroxylase enzyme stored in liver and its active form 1, 25 (OH) vitamin D is produced. Kidney is a crucial organ to produce 1, 25 (OH) vitamin D. Active form of vitamin D which is D3 can be provided in a natural form from specific animal foods, particularly in fatty fish such as salmon and mackerel. Vitamin D is also found in grains and milk.

Immunologic Effects of Vitamin D

Vitamin D3 (VD3) acts like an immune system regulator in many immunologic processes. Vitamin D, a major player of mucosal defense, must have a serum level 40-60ng/mL to warrant the continuity of immunologic functions [26]. VD3 plays a major role in immune system via directly affecting monocytes, macrophages, dendritic cells, and T cells [27,28]. VD3 inhibits IL-2, IL-6 and interferon-γ production which are potent mediators of infection response. VD3 induces suppressor-T cell activity and causes a reduction of helper T cells. It acts upon formation of cytotoxic natural killer cell [29]. VD3 is an effective immune system regulator, also it has roles in fibroblast proliferation, collagen synthesis and endothelium cell function [30,31]. At the same time, it plays a role in immune mechanism via decreasing macrophage mediated inflammation and T cell stimulation [32] [Figure 1]. As regards upper airway mucosal defense below-listed factors can be given: The first and most vital physical defense is a superficial gel mucus lining which is covering ciliated respiratory epithelium and physically eliminating the inhale pathogens [33].

Secondary defense mechanism is antimicrobial peptides. Among these proteins, defensin, cathelicidin and big antimicrobial proteins are effective on airway secretions for instance lysozyme, lactoferrin and secretory leucocycte protease inhibitor [34,35]. Third defense mechanism is initiation of inflammatory response and phagocytic cells fighting against a new developing infection [36]. Cathelicidins have a direct antimicrobial function. In addition to antibacterial effects like membrane disintegration, they provide antiviral action against herpes simplex viruses, adenovirus, and retrovirus [37]. Cathelicidins are synergic with both lysozyme and lactoferrin [38,39]. Vitamin D acts on the production of cathelicidin and b-defensin-2 [40]. Besides, it could cause a striking rise production of Vitamin D and cathelicidin in different types of cell including immune system cells and keratinocytes. Vitamin D receptor genes are closer to cathelicidin and two genes that code antimicrobial peptits of b-defensin-2 [41].

Vitamin D could cause a minor increase in b-defensin-2 ‘s cell production, external vitamin D supplementation also elevates cathelicidin production [42]. Peptide-cathelicidins with an antibacterial activity are synthesized as prepropeptits and via releasing C terminal they are dismantled by protease enzymes [43]. Human cathelicidin shaped by protease enzymes, H HCAP-18’s free t C-terminal peptide also termed as LL-37 peptide is a chemotactic factor for immune system cells. In vitro studies proved that LL-37, human cathelicidin has also antibacterial and antibiofilm activity preventing the growth of free C-terminal’s deformation product and formation pseudomonas aeruginosa biofilms [44,45] [Figure 2]. Particularly, in chronic tonsillitis and chronic sinusitis, formation of bacterial biofilm is the most prevalent cause of recurrent infections. The significant role of vitamin D in the prevention of bacterial biofilm is indicative of its importance.

Factors Acting Upon Vitamin D Levels

Vitamin D level can be affected by a range of factors which could be explained by a systemic disease or an environmental factor. Vitamin D is widely acquired through sun, may have a low level if not sufficiently synthesized by skin. These conditions may be explained with minimal sun exposure, dark human skin, patients having undergone surgical skin graft, old-age, disorders that diminish biavailability (malabsorption, cystic fibrosis, celiac disease, whipple disease, crohn disease). On the contrary, there may be conditions that elevate catabolism. Taking anti-convulsant drug and glucocorticoid could also increase catabolism. Vitamin D levels may change in certain liver, kidney, chronic granulomatose disorders, hyperthyroidism, and some genetic disorders.

Otology and zinc

It is estimated that approximately above 2 billion of people are afflicted with malnutrition induced zinc deficiency [46]. Lately, there has been a surge in studies related to the importance of zinc in otologic disorders. There may be a variety of factors causing sensorineural hearing losses including some drugs, past infections, and genetics. Importantly, some studies demonstrated that patients with zinc deficiency and progressive sensorineural hearing loss experience clinical manifestations decreasing the life quality [47]. The role of zinc has been demonstrated among patients with sudden sensorineural hearing loss and hearing loss with an unidentified cause [48]. In patients with sudden sensorineural hearing loss, zinc levels are critical due to their contribution to the treatment and progress of disease. Relevant studies demonstrated that suppurative otitis media which is a clinical manifestation mainly belongs to childhood otologic disorders is also affected by zinc levels of the body. In a large randomized prospective study covering children below age 2, zinc supplementation reduced incidence of suppurative otitis media in a dramatic manner [49].

With age-dependent sensorineural hearing loss is the most common otologic disorder. In some patients sensorineural hearing loss presents with tinnitus. In relevant studies, it was manifested

that hearing losses and tinnitus among elderly patients may be explained with zinc deficieny [50]. Zinc was measured to have high concentrations on cortiorgan and vestibule in inner ear. Particularly, high zinc concentrations in inner ear increased the importance of zinc blood serum levels in inner ear disorders. Zinc deficiency, by impinging upon vestibular system, may cause balance disorders. Zinc could minimize progressive hearing loss for old patients [47]. Zinc also acts on neuronal functioning of cochlear's core. Zinc was demonstrated to be protective of cochlear hair cells against pneumolysin and cadmium-induced ototoxicity in experimental studies [51,52]. Free radicals have been associated with many diseases in human body. Studies revealed that cochlear becomes vulnerable to damages and protection against free-radical cannot be achieved when Cu/ZnSOD deficiency presents [53]. Dermatitis is also a frequent otologic disorder.Zinc deficiency could be a factor in dermatitis patients [54].

Rhinology and zinc

Nose physiology is crucial because of the wide mucosal surface, presence of nasal cycle, heating, moisturizing and air filtration and state of mucociliary activity. Nasal airway resistance is responsible of more than 50% of total airway resistance [55]. Allergic disorders impinge upon nose physiology. Histamine plays a major role in allergic rhinitis. Allergens promotes mast cell degranulation and release of histamine into the nasal mucosa. In this sense, studies have found that zinc plays a major role in storing histamin in the body by inhibiting mast cell degranulation and lowering histamine release [56]. Frequency of allergic rhinitis in the general population appears to be increasing and it turns into a progressive disease, largely affects patient's daily life. Some studies revealed the correlation between low serum zinc levels and frequent allergic disorders [57]. Clinical manifestations concurrent with allergic rhinitis are also in tandem with nasal polyps and patients with nasal polyps had low zinc levels [58]. Olfactory systemic disorders may occur due to drug-induced environmental factors or secondary to surgical operation and relevant studies underlined the link between low zinc levels and olfactory disorder (dysosmia). Additionally, zinc deficiency accounts for wound healing [59]. Following to surgical operations it is important that wound marks on inner and outer part of the nose heal quickly. Zinc, aside from differentiations in epidermal keratinocytes, plays a critical role in anti-inflammatory and wound healing processes [60].

Throat disorders and zinc

Recurrent infections occur mostly because of bacterial biofilms which not only diminish mucosal resistance but also elevate the risk for complications. Research about the effect of in vitro bacterial biofilm on tonsil was conducted by our team [61]. Zinc deficiency is associated with impaired immune response [62]. As a result of immune failure, it is likely to develop bacterial and fungal infections. This condition can be explained with disturbed zinc mediated leukocyte functions. There is also a correlation between sense of taste and zinc levels. Studies demonstrated that among young adults and women in their twenties, insensitivity of taste buds may be explained with zinc deficiency [63]. Zinc supplementation could increase the level of saliva gustin concentrations, consequently, taste function could be ameliorated among atrophic glossitis patients with hypogeuisea [64]. Oral mucosal lesions may influence the daily life very negatively. Dry mouth, atrophic glossitis, burning mouth syndrome could all stem from zinc deficiency [65]. Specifically, oral mucosal aphthous could be painful. Recurrent aphthous could not only be caused by systemic disorders, but impairment of mucosal defense can also be the reason. Furthermore, it was reported that zinc levels of patients with recurrent aphthous stomatitis was measured to be low [66]. Zinc has a key role in repressing T lymphoid activity and maintenance of immune response [67]. It was proved that low zinc levels are related with perioral dermatitis, delayed wound healing and taste disorder (dysgeusia) [59] [Figure 3].

Biochemistry of zinc

Zinc plays a vital role in the synthesis and breakdown of carbohydrates, lipids, proteins, and nucleic acids. Moreover, zinc is a key component of most enzymes that affect the metabolism of other micronutrients. Zinc exhibits its antioxidant properties by means of Superoxide Dismutase (SOD). Zinc is a prerequisite for Superoxide Dismutase1 (SOD1) activity [68]. A vast portion of absorbed zinc, blood plasma zinc is bound to albumin and stored in muscles and bones (80-85%), skin and liver (8-11%) [69]. Since zinc is a major cofactor for over 1000 enzymatic reaction and more than 2.000 transcription factors, zinc is critical in the development, differentiation, and cell growth in many tissues [70]. Zinc is a key element for numerous proteins. Free radicals have damaging effects for tissues. Zinc has a mission in defense against free radicals, displays cell functions like repairing DNA damage [71]. Zinc is the most abundant intracellular trace element and second most abundant trace element in human body [72, 73]. Human body contains a total 2-3 grams of (30mmol) zinc [70]. Zinc has a low storage capacity hence healthy zinc levels could only be acquired via food intake. Daily need of zinc is 2-3mg Zn [46]. In cochlea, zinc exists as Cu/Zn SOD (superoxide dysmutase) and zinc level in cochlea is higher than other areas [74]. Interestingly, Zinc concentrations are measured high in the choroid layer of the eye [75].

Antioxidant and Immunologic Properties of Zinc

Oxidative stress presents in many immunologic and allergic diseases. Normally, there are enough antioxidants in the respiratory tract and the production of a small amount of reactive oxygen species is insignificant. Even direct exposure to environmental

air is a source of reactive oxygen species. In case antioxidants are reduced or production of reactive oxygen species is rised up (eg, during alergic rhinitis, allergic asthma exacerbation) the balance between antioxidants and reactive oxygen species is tilted toward oxidative stress. Airway inflammatory cells are major source of these elevations [76]. Zinc fights against free radical formation and prevents the injury during inflammatory processes. Zinc is a cofactor of cytosolic and extracellular Zn/Cu SOD enzyme, which acts as an ROS scavenger by catalyzing the dismutation of O2- radical which is crucial for the resolution of inflammation [77]. Secondly, zinc homeostasis is maintaining by intracellular zinc binding proteins. Nearly 20% of intracellular zinc is combined by Metallothioneins (MTs), they act as both zinc acceptor and zinc donor, also directly affecting the available zinc ion concentrations appears to be the main role of MTs. When a shift towards oxidative stress happens, zinc ions are fastly get released by MTs [78].

Moreover, as proved in the prior studies, metallothioneins act as potent electrophilic scavengers and cytoprotective agents against oxidative and inflammatory injury [79]. They can capture 3 main forms reactive oxygen species and nitric oxide [80]. Previous studies have demonstrated that in case of zinc deficiency, it was found a systemic elevation in inflammatory NF-kB activation and its target genes, A20 (TNFAIP3) and PPAR (peroxisome proliferator-activated receptor). A20 is a pleiotropically expressed cytoplasmic signaling protein, known as an anti-inflammatory, NF-kB inhibitory, and antiapoptotic protein. Zinc as a free radical scavenger, contributes to the enzymatic stability of A20 [81]. Similarly, zinc enhances the expression of PPAR-a (the two zinc finger proteins with anti-inflammatory properties), which plays a significant role in inflammation, glucose homeostasis and lipoprotein metabolism [82]. PPAR-a prevents NF-kB activation via negative crosstalk in the nuclear DNA binding level [83]. The downregulation of NF-jB activation by zinc via A20 and PPAR signaling pathways is most likely the mechanism by which zinc decreases inflammatory cytokines/molecules [84] [Figure 4].

To fully appreciate the importance of zinc to human biology, must understand the great variety of biological processes entails zinc-containing proteins. Zinc plays a crucial role in the continuity of antioxidant events. It also has a central task in cellular and humoral immunity [85]. It stabilizes molecular structure of membranes hence contributes to preserving cell and organ integrity. Zinc displays anti-inflammatory features. It has been reported that zinc supplement represses inflammatory cytokine production. Zinc deficiency is related to a drop in T lymphocytes and cytokine production [86]. Zinc is a physiological suppressor of apoptosis [87]. In addition, severe zinc deficiency can manifest itself with more severe clinical results including growth failure, delayed sexual and bone maturation, skin lesions, diarrhea, alopecia, anorexia, increased predisposition towards infections and behavioral changes [75]. Invitro studies proved that a fall in cellular zinc levels can lead to endothelium barrier dysfunction [89]. It is revealed that Zinc, a main actor in cell growth, is an important cofactor for cell proliferation and renewal [54]. In experimental animal studies, it was demonstrated that protein expression levels of inflammatory inducible nitric oxide synthase (iNOS) and interleukin (IL)-1β were enhanced and inflammation in lung tissue was aggravated in rats with zinc deficiency [90] [Figure 5].

Factors Regulating Zinc Levels

Adequate amounts of zinc can be obtained through dietary sources. Certain conditions affecting zinc absorption consequentially lower zinc level. In developed countries, people above 71 and consuming lower amounts of zinc, poses a high-risk group [91]. Zinc absorption takes place in small intestine also absorption rate of zinc could be impaired by medication use. Proton pump inhibitors could dramatically lower zinc absorption and storage levels of zinc in human body [92]. Certain ingredients of foods consumed may also affect zinc absorption negatively. High-fiber foods and phytic acid consisting of foods inhibit bowel zinc absorption. Zinc is excreted from body via kidneys, skin, and bowel. Endogen intestine losses may vary from 7mmol/day (0,5mg/day) to 45mmol/day (3mg/day) depending on zinc intake [93]. Intense exercise and high room temperatures could also lead to zinc loss through sweating. In cases, when muscle catabolism is elevated, urinary zinc excretion increases, too. Besides, zinc level is also prone to infections and inflammatory situations [94,95].

Stressful events like infection, fever, food intake and pregnancy lower plasma zinc concentrations whereas long-term fasting elevates zinc concentration. It has been reported that changes in endogen intestinal zinc excretion are more effective than changes in absorption efficiency as regards sustaining zinc homeostasis [94]. Lean red meat, whole grains, legumes, and pulses provide high concentration of zinc 25-50mg/kg (380-760mmol/kg). Soluble low-molecular weight organic compounds such as amino and hydroxyl acids facilitate zinc absorption. Phytate contents, the ratio and source of dietary protein intake are similarly effective. Phytates are abundant in whole grain foods, legumes and, to a lesser extent, in green vegetables. Molar ratio between phytate and zinc in foods or diets is an indicator of the effect that phytates lowering zinc absorption. Enhancement in zinc bioavailability can be achieved by lowering phytate content in the food and preferring animal protein sources.

Conclusion

Vitamin D and zinc insufficiency as a great health problem worldwide in all ages, recently has gained more attention since their remarkable role for immunologic mucosal defense mechanism. Awareness on the relationship between ear-nose-throat disorders and vitamin D and zinc levels becomes crucial to prevent disease

complications, lower labor force losses and treatment costs. Future studies on vitamin D and zinc can open new windows into role of these vitamins in the diagnosis and treatment protocols of ear nose throat disorders. In this paper, our aim is to present the importance of vitamin D and zinc in ear nose throat disorders.

Conflict of Interest Statement

The authors did not report any potential conflicts of interest in the research, writing and/or publication of this paper.

Financing Status of The Authors

The authors did not receive any support for the research, writing and/or publication of this article.

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