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Association between vitamin D and ear disease: a meta-analysis and systematic review

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Abstract

Background: Vitamin D deficiency is a suggested cause and risk factor for various ear diseases. This review assessed the role of vitamin D in ear diseases such as otitis media (OM); this study aimed to assess potential relationships between serum vitamin D level and OM risk; and determined the usefulness of vitamin D supplementation for ear disease prevention and treatment.

Material and methods: This systematic review searched the PubMed, EMBASE, Google Scholar, Web of Science, and the Cochrane Database for studies on vitamin D deficiency as a risk factor for ear diseases. A total of 55 articles were screened based on their titles. The abstracts were then reviewed to identify the 11 articles analyzed in the present study.

Results: Statistical heterogeneity was observed among the 11 studies for subgroup analysis of plasma vitamin D level according to disease type (acute otitis media [AOM], $P < 0.00001$; chronic otitis media [COM], $P = 0.00001$) and age (≤ 5 years, $P < 0.00001$; > 5 years, $P < 0.00001$). Heterogeneity was also observed in the frequency of participants with sufficient plasma vitamin D levels according to disease type (AOM, $P < 0.00001$; COM, $P = 0.00001$) and age (≤ 5 years, $P < 0.00001$; > 5 years, $P = 0.003$; $I^2 = 70\%$: substantial heterogeneity).

Conclusion: Vitamin D deficiency is common in otolaryngology patients, for which supplementation showed promising results. Vitamin D deficiency was associated with the etiopathology of ear diseases in adults and children. We recommend empirical supplementation of vitamin D in otolaryngology patients and further studies investigating this supplementation.

Keywords: Vitamin D, Otitis media, Vitamin D supplementation, Vitamin D deficiency, Ear disease, Meta-analysis

Background

Vitamin D is an essential nutrient with a well-known regulatory function in calcium and phosphate metabolism. It has been recognized as a steroid hormone with the identification of vitamin D receptors in many tissues, including lymphocytes, kidneys, ovaries, stomach, thymus, pancreas, skin, and parathyroid glands [1]. The vitamin D endocrine system contains three forms of vitamin D, namely, cholecalciferol, calcidiol (25-hydroxyvitamin D), and calcitriol (1,25-dihydroxy vitamin D).

Vitamin D deficiency is common in the Middle East, particularly among women, and most vitamin D deficiency patients are asymptomatic. Long-term mild vitamin D insufficiency, on the other hand, can cause hypocalcemia and hyperparathyroidism. This, especially in the elderly, may raise the risk of osteoporosis, falls, and fractures. In patients with long-term and severe vitamin D deficiency, secondary hyperparathyroidism manifests as bone pain, arthralgias, myalgias, weariness, muscular twitching, and weakness. Fragility fractures can be

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caused by chronic vitamin D insufficiency, which leads to osteoporosis [2].

Sun exposure is the main source of vitamin D, and there are various factors linked with maintaining a normal level of vitamin D [3]. Fatty fish, fish liver oil, and egg yolk are also high in vitamin D, making them the most important natural dietary sources [4]. Due to a range of lifestyle risk factors, vitamin D insufficiency is becoming a worldwide health concern [3]. Among these are differences in sun exposure, sunscreen use, and skin pigmentation, as well as age, obesity, and the incidence of certain chronic diseases [5].

Vitamin D affects the body's anti-inflammatory function, in addition to its other functions, by controlling the production of cytokines and immune cells, both of which are crucial in the pathophysiology of many immune-related illnesses [6].

Vitamin D receptor (VDR) and CYP27B1 are expressed in a wide range of immune cells, indicating that vitamin D regulates immune function [7]. According to mechanistic study, vitamin D controls inflammatory processes associated in cancer progression, such as cytokines, prostaglandins, MAP kinase phosphatase 5 (MKP5), the nuclear factor kappa B pathway, and immune cells. Vitamin D has been shown in a number of studies to inhibit tumor growth by interfering with the inflammatory system [7].

Numerous studies have investigated the association between vitamin D and human diseases, including in the otolaryngological field. The incidence of vitamin D deficiency is high in patients visiting outpatient otolaryngology clinics [8]. Several studies have demonstrated the correlation between vitamin D deficiency and BPPV development and recurrence [9], Meniere's disease [10], tympanosclerosis [11], and otosclerosis [12].

Otitis media (OM), an inflammation of the middle ear, is the most common pediatric disease and the leading cause of pediatric visits [13]. Vitamin D reduces inflammation by decreasing the production of interleukins and interferon-gamma [14]. The administration of vitamin D, in addition to common treatments, is a good option for the treatment of upper respiratory tract infections such as OM [15].

Methods

A systematic review was conducted after extracting data from five databases (PubMed, EMBASE, Google Scholar, Web of Science, and the Cochrane Database) as high-quality sources for the publications used in this study.

The first selection focused on the article titles and abstracts in English language. In this stage, all articles that did not directly address the subject of interest were excluded and duplicate titles were removed using Google Drive software. Furthermore, a total of 55 articles were identified using the following terms: ("otitis media" or "tympanitis" or "acute otitis media" or "AOM" or "adhesive otitis media" or "OME" or "catarrhal otitis media" or "catarrh tympanitis" or "middle ear inflammation") AND ("vitamin D" or "ergocalciferol" or "calciferol" or "cholecalciferol"). Articles that did not have one of these topics as their primary endpoint, repeated studies, and review studies were excluded.

No software was used to analyze the data. The data were extracted using a specific form containing the article title, author's name, objective, summary, results, and outcomes. These data were reviewed by group members to determine the initial findings. Double revision of each member's outcomes was applied to ensure the validity and minimize mistakes.

Results

The initial search identified 55 potentially relevant studies; among these, 11 studies including 17,614 study participants were included in the final analysis. The included studies included one randomized controlled trial [13], two prospective cohort studies [16, 17], seven case-control studies [15, 18–23] and one observational cohort [24]. Four studies included patients with AOM, while seven included patients with chronic otitis media (COM). Four studies included patients aged $\leq$ 5 years, and seven studies were included patients aged > 5 years. The sample size of all studies ranged from 40 to 16,063. The study participants' ages ranged from 2.2 to 50.2 years.

The plasma vitamin D levels of patients with AOM and COM were both significantly lower than those in the control group (mean difference [MD] = − 10.63; confidence interval [CI] = − 19.29, − 1.97; $P = 0.02$ and MD = − 3.63; CI = − 7.02, − 0.24; $P = 0.04$, respectively) (Fig. 1). However, one case-control study observed high plasma vitamin D levels among patients with COM compared to the control group (MD = 3.80; CI = 2.13, 5.47), while another study showed no significant difference in plasma vitamin D level between patients with COM and the control group (MD = 0.71; CI: .70, 0.72). The pooled MD for all patients with OM was − 6.26; CI − 10.51, − 2.00; $P = 0.004$, subgroup difference: AOM vs. COM; $P = 0.14$; no significant difference) (Fig. 1), indicating a significant association between patients with OM (i AOM or COM) and lower plasma vitamin D levels.

In terms of patient age, children aged $\leq$ 5 years with OM showed a significant association with lower plasma vitamin D levels compared to those in the control group (MD = − 13.14; CI: − 19.09, − 7.19). In contrast, those children at the age of > 5 years with OM had no significant association with the level of plasma vitamin

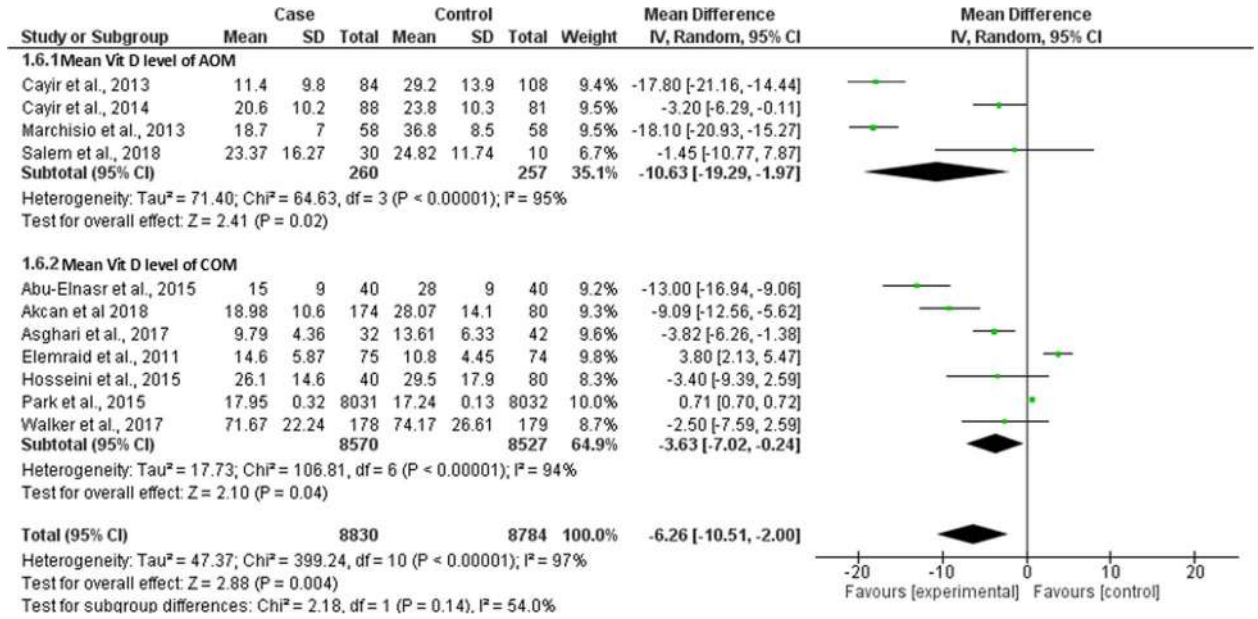

Fig. 1 Forest plot of plasma vitamin D levels by disease type (AOM vs. COM). AOM, acute otitis media; COM, chronic otitis media; SD, standard deviation; CI, confidence interval

D (MD = − 2.08; CI:-4.83, 0.67; $P = 0.14$). However, in the test for age group differences, those aged ≤ 5 years had significantly lower plasma vitamin D levels than those aged > 5 years ($P = 0.0009$) (Fig. 2). This indicated that younger children (≤ 5 years) with OM had lower plasma vitamin D levels.

As shown in Fig. 3, fewer participants with AOM had sufficient plasma vitamin D levels compared to the control group (odds ratio [OR[= 0.24; CI = 0.06, 0.92, $P =$ 0.04). In contrast, there was no significant difference in the number of participants with sufficient plasma vitamin D levels between the COM and control groups (OR =

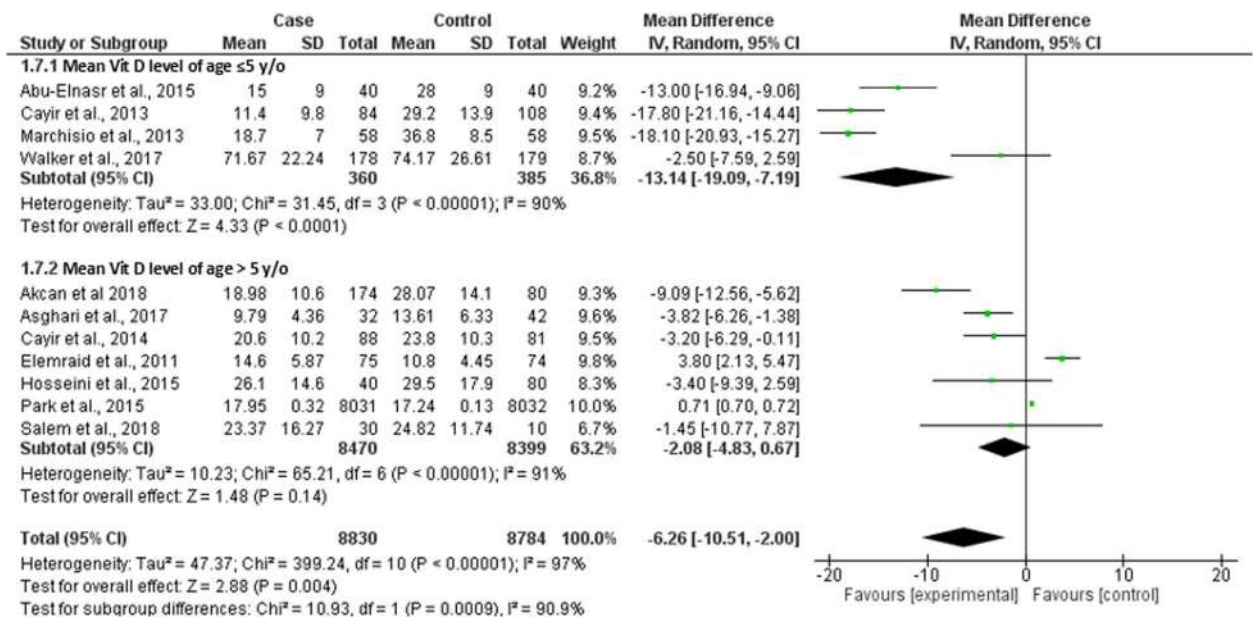

Fig. 2 Forest plots of plasma vitamin D levels by age group (≤ 5 vs. > 5 years). SD, standard deviation; CI, confidence interval

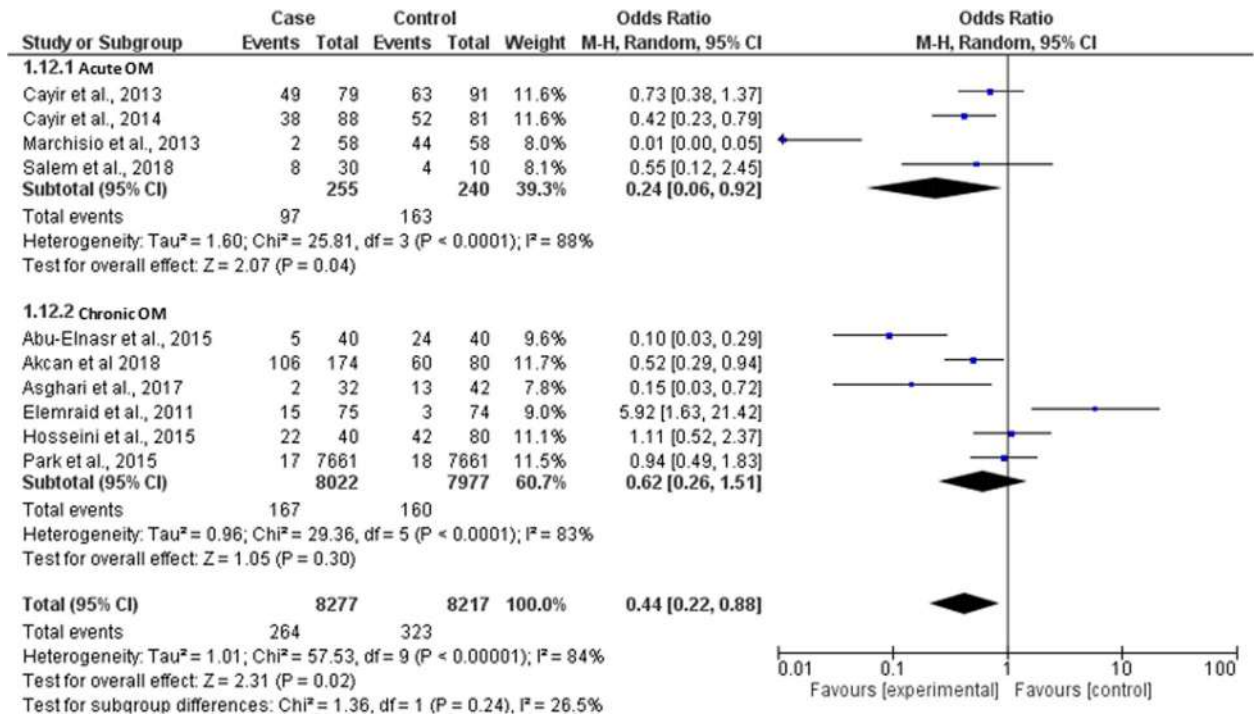

Fig. 3 Forest plot of the number of participants with sufficient plasma vitamin D level by disease type (AOM vs. COM). AOM, acute otitis media; COM, chronic otitis media; SD, standard deviation; CI, confidence interval

0.62; CI: 0.26, 1.51, $P = 0.30$). However, the test for group differences showed that all patients with OM (AOM and COM) had significantly lower numbers of patients with sufficient plasma vitamin D levels (pooled OR = 0.44; CI = 0.22, 0.88, $P = 0.02$; subgroup difference: $P = 0.24$) (Fig. 3). In terms of patient age, the number of participants with sufficient plasma vitamin D levels did not differ significantly between children with OM aged ≤ 5 and > 5 years and the control group (OR = 0.10; CI: 0.01, 1.07; $P = 0.06$; OR: 0.74; CI: 0.41, 1.35, $P = 0.33$, respectively; subgroup difference: $P = 0.11$) (Fig. 4). In the subgroup analysis for both disease types and age groups, a small proportion of OM patients had sufficient plasma vitamin D levels.

Statistical heterogeneity was observed among the 11 studies based on the results of subgroup analysis including plasma vitamin D level for disease type (AOM: ≤ 5 vs. > 5 years, $P = 0.003$, $I^2 = 70\%$; substantial heterogeneity).

Discussion

Vitamin D plays an indispensable role in innate immunity by producing antimicrobial peptides (AMPs) involved in destroying the invading microorganisms, modulating the inflammatory pathways, and increasing the conciliary clearance [25].

Recent decades have seen increased interest in the positive effects of vitamin D, not only on calcium metabolism but also on immune regulation, especially in autoimmunity. The role of vitamin D in infectious diseases has not been thoroughly investigated, but accumulating evidence suggests that 1,25-dihydroxy vitamin D3 exerts a protective effect during several types of infections [26].

This meta-analysis and systematic review investigated the association between vitamin D deficiency and ear diseases based on the analysis of one randomized controlled trial, two prospective cohort studies, seven case-control studies, and one observational cohort.

Our findings demonstrated an association between lower plasma vitamin D levels and AOM and COM compared to the controls ($P = 0.02$) and ($P = 0.04$), respectively. Another systematic review and meta-analysis conducted by Li et al. [25] showed that OM was associated with lower vitamin D levels. A similar systematic review of the evidence linking particular nutrient deficiencies, including vitamin D, with middle-ear diseases and infections, specifically chronic suppurative otitis media (CSOM), reported that no human-specific examinations on vitamin D deficiency or status demonstrated its association with CSOM. Additionally, of the 89 articles identified by the systematic search, 5 studies reported data of 16,689 individuals who were included in

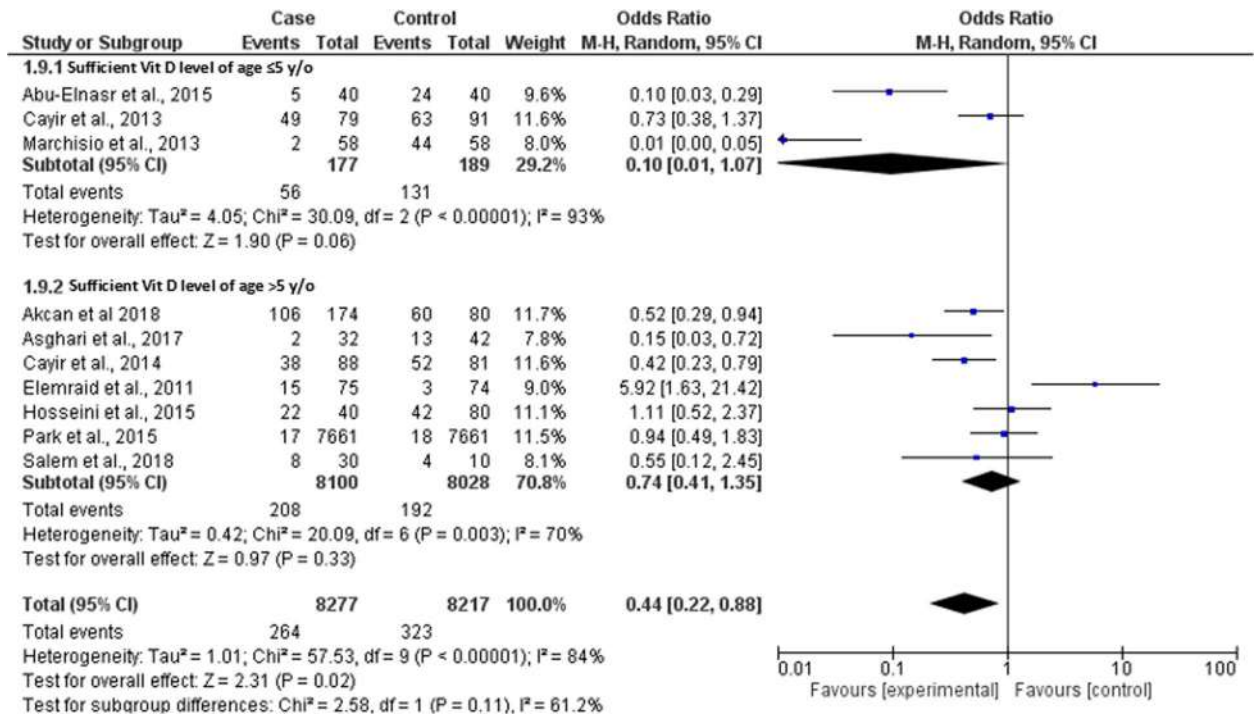

Fig. 4 Forest plot of the numbers of participants with sufficient plasma vitamin D level according to age group (≤ 5 vs. > 5 years)

the meta-analysis, observing that plasma vitamin D level might have a vital role in AOM progression [27].

Cayir et al. [15] compared vitamin D serum levels in 84 children with recurrent OM to those in 108 healthy children. They observed a statistically significant association between the two groups. Moreover, they also found that there is a decreasing OM recurrence on providing supplementary treatment with vitamin D. They also demonstrated that vitamin D deficiency could be a risk factor for upper respiratory tract infections, including OM. Marchisio et al. [13] conducted a randomized control trial of 116 children with AOM. They administered 1000 IU/day vitamin D supplements to 58 children; the other participants were administered a placebo. They found that children who received vitamin D supplementation had lower AOM rates. Additionally, the risk of AOM was significantly lower in participants with serum vitamin D levels > 30 ng/mL. Walker et al. [22] conducted a case-control study to investigate the relationship between vitamin D and OM. Their findings showed significant associations between vitamin D deficiency and several respiratory diseases, including otitis media with effusion (COME) ($P = 0.01$).

Abu-Elnasr et al. [18] conducted a case-control study to assess vitamin D serum levels in 40 children with recurrent OM compared to 40 healthy children. They observed a statistically significant association between the two groups. They administered 50,000 IU oral vitamin D weekly for 3 months to 17 children, while 18 children received a placebo. They observed significantly lower serum levels of 25 (OH) vitamin D in the supplementation group compared to those in the control group ($P < 0.05$). Low vitamin D levels increased the odds of OME occurrence by two times. Park et al. [24] assessed the vitamin D serum level in 16,063 participants aged > 20 years; the weighted prevalence of COM was 3.8%. High levels of vitamin D were associated with the development of COM, and this association was significant ($P < 0.01$).

In contrast, a case-control study conducted by Elemraid et al. [21] identified CSOM as a critical health condition among Yemeni children and recorded higher plasma vitamin D levels among patients with COM compared to those in the controls. They also found that children with vitamin D deficiency had a longer duration of infection. However, this relationship dissipated after adjusting for age. Generally, this high prevalence of vitamin D deficiency was probably due to its therapeutic or nutritional origin [24]. Alternatively, dark skin of children in the study population requires needs more prolonged exposure for sunlight penetration into the skin, which is a factor associated with increased risk of vitamin D deficiency [27].

Asghari et al. [23] conducted a cross-sectional study to investigate the relationship between otitis

media with effusion and vitamin D deficiency. While they observed lower plasma vitamin D levels in these patients, this difference was not significant when they considered seasons. It is well known that the main portion of vitamin D is made in the skin by exposure to sunlight [27]. Correspondingly, the etiological association between vitamin D deficiency and OME may not be clear in the aforementioned study, as they reported that 90% of the cases underwent surgery in winter. Additionally, patients with OME may have a prolonged course of illness that may affect their nutritional status. Linday et al. [28] also reported no significant association between OME and vitamin D levels. In their case-control study of 120 children with OME, Hosseini et al. [20] also observed no significant association between OME and vitamin D levels.

Regarding age, our findings revealed a significant association between children's age ($\leq$ 5 years), the development of OM, and lower vitamin D levels compared to those in the control group ($P < 0.00001$), indicating that younger children had lower plasma vitamin D levels. Akcan et al. [19] reported that the increasing average age of children was associated with decreased levels of vitamin D; however, the association was not significant ($P = 0.879$).

Moreover, we observed no significant association between the plasma level of vitamin D and OM in children over 5 years of age ($P = 0.14$). The numbers of children with OM aged $\leq$ 5 and > 5 years with sufficient plasma vitamin D levels did not differ significantly from that in the control group ($P = 0.06$) ($P = 0.33$). Most of the literature on the effects of vitamin D on infection in children was limited to age groups < 5 years of age. The impacts of vitamin D on respiratory infection vary among children of different ages as the causative pathogens differ. A prospective evaluation of immunocompetent hospitalized children with lower respiratory infections showed that the rate of viral infections was highest among infants. In comparison, the rate of identifiable bacterial infection was higher among children aged > 5 years [29].

Salem et al. [17] also reported a statistically significant relationship between vitamin D levels among children with AOM than normal children, with younger children aged 1–6 years showing abnormal vitamin D levels compared to older children aged 7–13 years. These age-related findings could be attributed to the fact that the two most two prevalent viruses in upper respiratory tract infections were rhinovirus and adenovirus. Adenovirus was associated with a higher rate of AOM-complicated respiratory infections; thus, the prevention of viral upper respiratory infections was proposed to reduce the incidence of OM in young children [28].

The results of the present study also revealed a lower number of patients with AOM with sufficient plasma vitamin D levels ($P = 0.04$), likely because invasive pneumococcal infection, group A streptococcal diseases, and meningococcal infections are commonly seen in patients with vitamin deficiency, particularly in the winter months. These bacteria are sensitive to the microbicidal effects of vitamin D. Additionally, vitamin D deficiency was reported to be a predisposing factor for upper and lower respiratory tract infections [22].

In contrast, the number of participants with sufficient plasma vitamin D levels did not differ significantly between patients with COM and the control group ($P = 0.30$). This could be because previous studies worldwide have reported a gradually decreasing prevalence of COM annually owing to the widespread use of antibiotics enhanced nutritional and hygiene status secondary to facilitated access to medical centers, and economic growth.

Conclusion

Vitamin D deficiency is common in otolaryngology patients, for which supplementation showed promising results. Vitamin D deficiency was associated with the etiopathology of ear diseases in adults and children. We recommend empirical supplementation of vitamin D in otolaryngology patients and further studies investigating this supplementation.

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Authors' contributions
MS: Collecting data and writing the manuscript. AA: Collecting data and writing the manuscript. KM: Collecting data and writing the manuscript. RA: Collecting data and writing the manuscript. HA: Writing the manuscript. MAlf: Writing the manuscript. MAlg: Writing the manuscript Production.

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Competing interests
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