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Original Research

Effect of vitamin D on chronic otitis media with effusion

Vitamin D and chronic otitis media

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Abstract

Aim: Vitamin D has a variety of functions other than well-known effects on calcium-phosphorus metabolism and is accepted as a steroid hormone. Identification of vitamin D receptors in immune system cells points to the immunomodulatory role of vitamin D. Vitamin D deficiency seems to be related to a higher risk of respiratory tract infections. This study investigates the relationship between vitamin D deficiency and otitis media with effusion.

Methods: This prospective study was conducted in a tertiary-care hospital in one fall season. The study group included children with chronic otitis media with effusion (COME), and the control group included children without any health problems. The diagnosis of otitis media with effusion was made with pneumatic otoscopy and supported by tympanometry. Serum levels of 25(OH)D3, calcium, parathyroid hormone, phosphorus, magnesium, alkaline phosphatase, and magnesium were investigated in both groups, and comparisons were made between the groups.

Results: 29 patients with COME and 30 controls were included between 6 and 12 years of age. Serum level of 25(OH) D3 was 17.15 ± 10.39 and 41.80 ± 18.23 ng/ml in the study and control groups, respectively (*P = .001*). Vitamin D deficiency was detected in 15 patients (51.7%) in the study group, whereas in 3 (10%) individuals in the control group. Significant differences were also found in the levels of alkaline phosphatase and magnesium, whereas levels of parathyroid hormone, calcium, and phosphorus were not significantly different between the groups.

Conclusion: We propose that lower vitamin D levels might play an important role in the etiology of chronic otitis media with effusion.

Keywords

vitamin D, vitamin D deficiency, 25(OH)D_3, immune system, infection, otitis media with effusion

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Introduction

Vitamin D has been demonstrated to have diverse effects on many different functions of the human body apart from its well-known effects on calcium metabolism and is accepted as a steroid hormone.[1] Skin exposure to sunlight results in the synthesis of vitamin D3 from 7-dehydrocholesterol. This intermediate metabolite is then hydroxylated in the liver and kidney to form 25-hydroxy-cholecalciferol (25(OH)D3) and 1.25-dihydroxy-cholecalciferol, respectively. 1.25-dihydroxy- cholecalciferol, also known as calcitriol, is the active form of vitamin D and exerts its effects through interaction with the vitamin D receptor (VDR).[2] Calcitriol is metabolized by the enzyme 24-α-hydroxylase. Expression of VDR in many different cells designates its wide range of functions. Antiinflammatory, antiapoptotic, and antiproliferative effects of vitamin D were also demonstrated.[3]

The impact of vitamin D deficiency on public health seems to be a very important issue, especially in developing countries. Vitamin D status is determined by circulating 25(OH)D3 levels.[4] Previously, vitamin D deficiency was defined by the presence of bone disease. The term 'vitamin D insufficiency,' on the other hand, has been used to describe suboptimal levels associated with some other clinical consequences.[5] A serum level less than 20 ng/ml is considered insufficiency, whereas a level less than 15 ng/ml is considered deficiency.[6] However, the cut-off value may change depending on many factors, including race, geographic location, and age.[7]

Otitis media with effusion (OME) is a common disorder of childhood and is characterized by fluid accumulation behind an intact tympanic membrane without symptoms and signs of local or systemic infection.[8] OME most commonly presents with hearing loss.[8] Risk factors for OME may be host-related and environmental. Eustachian tube dysfunction is one of the most important host-related factors that is closely related to viral and bacterial infections. Diagnosis of Eustachian tube dysfunction is based on a well-documented history and otoscopic examination and is supported by tympanometry. Other host-related factors include race, age, genetic susceptibility, anatomic defects, and allergy. Smoke exposure, daycare centers, seasonal changes, inadequate breastfeeding, pacifiers, and obesity are considered environmental risk factors.[9]

In this paper, vitamin D levels of the pediatric population with chronic otitis media with effusion were investigated, and the effects of vitamin D deficiency on middle ear fluid accumulation were analyzed.

Materials and Methods

Children with otitis media with effusion were investigated. The study was performed in one single fall season in 2012. All of the participants were between 6 and 12 years of age and were born and raised in the same city. Those children with chronic disorders and craniofacial abnormalities, including clefting, and those using any medication regularly were not included. Informed consent was taken from the parents of the children. Following a detailed physical examination, all patients were examined for any craniofacial anomaly, including cleft lip and/ or palate. Children with symptoms of allergy or previously diagnosed to have allergy, those with parental smoking habits, those with a history of breastfeeding less than one year, and those with any previous head and neck surgical intervention were excluded. All children were going to either kindergarten or primary school. Retraction and decreased mobility of the tympanic membrane and air-fluid levels behind the tympanic membrane were considered signs of middle ear effusion. Pneumatic otoscopy and tympanometry were performed at one-month intervals.

The age, sex, presenting complaints, the number of episodes of acute otitis media per year, and whether the patient has used vitamin D replacement therapy were recorded. Serum levels of 25(OH)D3, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), magnesium (Mg), and parathyroid hormone (PTH) were investigated. The diagnosis of OME was confirmed with pneumatic otoscopy and supported by tympanometry. Tympanometry was performed for all patients.

Before performing tympanometry, earwax was removed bilaterally. Tympanometry was performed with low frequency (226 Hz) stimulus. Results were recorded as type A, type B, and type C, demonstrating normal middle ear effusion and Eustachian tube dysfunction, respectively. Diagnosis of OME is made by otoscopic findings and supported by type B and C tympanometry.

Following a diagnosis of OME, a 10-day course of antibiotic treatment (amoxicillin + clavulanate, 40mg/kg) was given, and the patients were re-evaluated at one-month intervals. Persistence of OME for more than 3 months was considered as chronic otitis media with effusion (COME). Those patients with COME were included in the study group. Control individuals were randomly selected from the social pediatry outpatient clinic who were healthy with no documented past or present history of otitis media with effusion.

Serum 25(OH)D3 levels were measured by liquid chromatography for all participants in the study and control groups. The cut- off value for the lower limit for serum 25(OH)D3 was 20 ng/ dl. Serum 25(OH)D3 level less than 15 ng/dl was considered as vitamin D deficiency, whereas serum levels between 15-20 ng/dl were considered as insufficiency. The normal range for serum calcium, phosphorus, alkaline phosphatase, magnesium, and parathyroid hormone were 8.4-10.6 mg/dl, 2.3-4.7 mg/dl, 40-150 U/L, 1.5-2.5 mg/dl and 15-65 pg/ml, respectively.

Ethical Approval

This study was approved by the Ethics Committee of İstanbul Kanuni Sultan Suleyman Training and Research Hospital (Date: 2010-06-12, Decision No: 226).

Statistical Analysis

Statistical analysis was performed with SPSS version 20. Chi-square and Fischer exact tests were used for categoric variables, and the Whitney *U* test was utilized for group comparisons. Pearson test was used for correlation analysis. Results were evaluated within a 95% confidence interval, and $P < .05$ was considered significant.

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

Thirty patients with the diagnosis of chronic otitis media with effusion were included. The control group included 30 healthy children who were on follow-up in a healthy pediatric outpatient clinic. One of the patients in the study group was lost during the follow-up period, and the study was conducted with 29 patients (13 patients) of the control group were male, whereas 62.1% (18 patients) of the study group and 56.7% (17 patients) of the control group were female (Table 1). Sex differences between groups were not statistically significant ($P > .05$). Tympanogram curves were type B in 20 patients and type C in 9 patients. However, it was type A in all individuals of the control group. Mean 25(OH)D3 levels were

Table 1. Demographic Features and Serum levels of Variables Among the Groups and Comparison of Serum Levels of 25(OH)D3, Calcium, Phosphorus and Alkaline Phosphatase

Variable	Category	Study group	Control group	*P* value
Age, y		8.21 ± 2.01	8.80 ± 1.69	.149
Sex (male), n (%)		11 (37.9)	13 (43.3)	.673
25OHD3, ng/dl		17.15 ± 10.39	41.80 ± 18.23	.0001
PTH, pg/ml		31.85 ± 10.63	33.64 ± 10.32	.544
Ca, mg/dl		9.47 ± 0.56	9.39 ± 0.53	.610
P, mg/dl		4.97 ± 0.68	4.61 ± 0.84	.075
ALP, U/L		245.07 ± 94.51	186.97 ± 48.95	.021
Mg, mg/dl		1.78 ± 0.12	1.92 ± 0.19	.002
25(OH)D3, *n* (%)	deficiency	15 (51.7)	3 (10)	<.001
25(OH)D3, *n* (%)	insufficiency	5 (17.2)	1 (3.3)	<.001
25(OH)D3, *n* (%)	adequate	9 (31)	26 (86.7)	<.001
Ca, *n* (%)	low	1 (3.4)	1 (3.3)	.981
Ca, *n* (%)	normal	28 (96.6)	29 (96.7)	.981
P, *n* (%)	normal	12 (41.4)	17 (56.7)	.240
P, *n* (%)	high	17 (58.6)	13 (43.3)	.240
ALP, *n* (%)	normal	3 (10.3)	8 (26.7)	.108
ALP, *n* (%)	high	26 (89.7)	22 (73.3)	.108

25(OH)D3, 25-hydroxy-cholecalciferol; PTH, parathyroid hormone; Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; Mg, magnesium

Table 2. Number of Episodes of Acute Otitis Media in Patients With and Without Chronic Otitis Media with Effusion in the Last Year

Study group AOM episode	Study group *n* (%)	Control group AOM episode	Control group n (%)	*P* value
3	13 (44.8)	0	2 (6.6)	<.001
4	6 (20.7)	1	6 (2)	
5	5 (17.2)	2	12 (4)	
6	4 (13.8)	3	6 (2)	
8	1 (3.4)	4	4 (13.3)	

AOM, acute otitis media

Table 3. Correlation Between Serum Levels of 25(OH)D3 and Parathyroid Hormone, Calcium, Phosphorus, Alkaline Phosphatase and Magnesium

Variable	Study group (*r*)	Study group (*P*)	Control group (*r*)	Control group (*P*)
25(OH)D3 - PTH	-0.580	.001	0.298	.110
25(OH)D3 - Ca	0.044	.822	0.059	.756
25(OH)D3 - P	0.399	.032	-0.182	.335
25(OH)D3 - ALP	-0.373	.046	0.190	.314
25(OH)D3 - Mg	0.110	.570	0.299	.108

25(OH)D3: 25-hydroxy-cholecalciferol; PTH, parathyroid hormone; Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; Mg, magnesium

17.15 ± 10.39 and 41.80 ± 18.23 ng/ dl in the study and control groups, respectively. The difference was statistically significant (*P* < *.001*). Vitamin D deficiency was detected in 15 patients in the study group, whereas in 3 individuals in the control group. In the control group, adequate vitamin D levels were detected in 26 patients (86.7%), whereas in 9 patients (31%) in the study group (Table 1). PTH levels were lower, Ca and P levels were higher in the study group, with no statistically significant difference between the groups (*P* > *.05*) (Table 1). PTH levels were within the normal range in both groups. Mean ALP levels were 245.07 ± 94.51 and 186.97 ± 48.95 U/L in the study and control groups, respectively. The difference was statistically significant (*P* = *.021*). Mean Mg level was also statistically lower in the study group (1,78 ± 0,12 vs. 1,92 ± 0,19 mg/dl) (*P* = *.002*).

The most common complaints in the study group were frequent upper respiratory tract infections (48.3%), hearing loss (31%), and snoring (20.7%). Middle ear effusion was present unilaterally in 65,5% (41.4% on the right side, 24.1% on the left side) and bilaterally in 34.5% of patients. The median number of episodes of AOM in the last year was 4 (range: 3-8) in the study group and 2 (range: 0-4) in the control group. The difference was statistically significant (*P* < *.001*) (Table 2).

In the study group, 58.6% (17 patients) had used vitamin D supplementation for one year and 13.8% (4 patients) for two years, whereas 27.6% (8 patients) had no previous history of vitamin D supplementation. None of the children in the control group had a previous history of vitamin D supplementation in the last two years.

In the study group, a negative correlation was found between 25(OH)D3 and PTH and between 25(OH)D3 and ALP (*P* = *.001* and *P* = *.046*, respectively); however, a positive correlation was found between 25(OH)D3 and P (*P* = *.032*). No correlation was found

between 25(OH)D3 and Ca and Mg ($P > .05$). In the control group, no correlation was found between 25(OH)D3 and levels of PTH, Ca, P, ALP, and Mg ($P > .05$) (Table 3).

Discussion

Following the delineation of the protective function of vitamin D on inflammatory and infectious diseases in addition to calcium homeostasis, a wide range of research has been performed to explore the role of vitamin D in upper respiratory tract diseases. Due to an unexpected increase in the prevalence of rickets even in developed countries, a revision in vitamin D supplement doses may be needed. Accordingly, vitamin D has become popular again, and the extraskeletal effects of vitamin D have been explored gradually.[10]

Fluid accumulation within the middle ear without symptoms and signs of acute infection is defined as OME.[11] Persistence of effusion for more than 3 months is termed as COME. This clinical picture leads to decreased mobility of the tympanic membrane and insufficient conduction of sound and is generally related to dysfunction of the Eustachian tube. OME may also follow episodes of acute otitis media. Diagnosis of OME is made in more than 50% of pre-school children, and it depends on the season of the year and the age of the children.[12] Long- term results of OME include negative middle ear pressure and gradual development of chronic otitis media with or without cholesteatoma, as well as deterioration of speech and language skills and academic performance.[13] The primary diagnostic tool for OME is pneumatic otoscopy. Tympanometry is used to support the diagnosis of OME.[13] Treatment options include proper management of upper respiratory tract infections, watchful waiting, and surgical intervention, including ventilation tube insertion.

Since the status of vitamin D is dependent on the degree of sun exposure, nutrition, and skin pigmentation, the population in this study was chosen from the same geographical location within one single fall season of the year. The sex and age distribution of the patient and control groups were not significantly different. No child had documented allergic symptoms, and none of the parents had a history of smoking. All of the children were in the kindergarten or primary school. These findings indicate the homogeneity of the groups as much as possible. Serum 25(OH) D3 level was significantly lower in the study group compared to the control group. This result supports the hypothesis that vitamin D deficiency may be related to respiratory tract infections, including otitis media. The association between vitamin D deficiency and OME was also supported by some reports.[14-17] Lindsay et al. reported that 50% of children undergoing ventilation tube insertion had 25(OH)D3 levels less than 20 ng/ml.[14] Akcan et al. demonstrated that 39.1% of children with COME had vitamin D deficiency (less than 15 ng/ml), compared to 25% in the healthy control group.[15] The authors also reported that vitamin deficiency was detected in 32.4% of children with middle ear effusion with complete recovery without the need for ventilation tube insertion. Walker et al. stated that higher serum concentrations of 25(OH)D3 were associated with a lower risk of COME in their case-control study.[17]

An inverse relationship between the level of 25(OH)D3 and respiratory tract infections was demonstrated previously.[18] Vitamin D supplementation was stated to significantly reduce the risk of respiratory tract infections in children with vitamin D deficiency.[19] Similarly, vitamin D deficiency was proposed to increase the risk of pneumonia 13-fold in children younger than 5 years of age.[20] Oktaria et al. stated that 20% of children hospitalized for pneumonia had vitamin D deficiency.[21] Rickets are related to an increased risk of respiratory tract infections, including common colds, bronchitis, and pneumonia in infancy and early childhood.[14] These findings point to the fact that vitamin D is related to immune system-mediated diseases. Currently, vitamin D is known as one of the key modulators of the immune system.[22]

A decrease in calcium levels, along with an increase in the levels of P PTH and ALP, is expected in cases of low vitamin D levels. In this study, however, although the levels of Ca and P were higher in the study group, these were not statistically significant. PTH levels were higher in the control group, albeit within the normal range in both groups. The duration of time from the onset of vitamin D deficiency to the appearance of clinical symptoms may depend on PTH secretion capacity.[23] PTH secretion capacity is individual-specific specific, and this may be the underlying cause of normal PTH levels in our study group. Mg levels were significantly lower in the study group compared to the control group in this study. ALP levels in the study group were significantly higher compared to the control group.

In this study, a significant negative correlation was found between serum 25(OH)D3 levels and several attacks of acute otitis media. This finding may be interpreted as vitamin D may have a role in the etiopathogenesis of acute otitis media. Some reports similarly stated that serum vitamin D levels were lower in children with recurrent otitis media.[24]

Limitations

A relatively limited number of patients seems to be the most important limitation of this study. However, strict exclusion criteria were used to obtain homogeneous groups as much as possible.

Conclusion

The preventive role of vitamin D on upper respiratory tract infections has long been established. Vitamin D is accepted as one of the protective nutritional elements against infections in children. We may conclude from this study that vitamin D deficiency is associated with chronic otitis media with effusion. The frequency of acute otitis media is also higher in children with vitamin D deficiency. Determination of vitamin D levels seems to be necessary in the management of patients with otitis media with effusion.

Declarations

Ethics Declarations

This study was approved by the Ethics Committee of Istanbul Kanuni Sultan Suleyman Training and Research Hospital (Date: 2010-06-12, No: 226)

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Written informed consent was obtained from the parents of all participants.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Conceptualization: S.E., D.T.E.
Methodology: S.E., D.T.E., H.O.
Formal Analysis: S.E., D.T.E.
Investigation: S.E., D.T.E.
Data Curation: S.E., D.T.E.
Writing – Original Draft Preparation: S.E., D.T.E.
Writing – Review & Editing: S.E., D.T.E., H.O.
Supervision: H.O.

AI Usage Disclosure
The authors declare that no AI-assisted technologies were used.

Abbreviations
25(OH)D_3: 25-hydroxycholecalciferol
ALP: Alkaline phosphatase
AOM: Acute otitis media
Ca: Calcium
COME: Chronic otitis media with effusion
Mg: Magnesium
OME: Otitis media with effusion
P: Phosphorus
PTH: Parathyroid hormone
VDR: Vitamin d receptor

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