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Vitamin D Level in Children with Secretory Otitis Media

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Abstract

Background: Vitamin D has anti-inflammatory effects and has a modulation role in the immune system. In several studies, the role of vitamin D deficiency has been proven in respiratory and middle ear infections.

Aim: Study the effects of serum levels of vitamin D on the development of secretory otitis media and the adenoid hypertrophy.

Patients and methods: This prospective case control study included a total of 150 subjects, who were divided into two groups; cases group which included 100 cases diagnosed with secretory otitis media and adenoid hypertrophy, and control group which included 50 healthy children. All cases and controls were subjected to complete history taking, thorough ENT examination, and tympanometry. In addition, serum vitamin D was ordered for all subjects.

Results: The mean age of the study cases was 7.65 years, which significantly older than controls (mean age 6.1 – $p = 0.002$). However, no significant difference was detected between the two groups regarding gender ($p = 1$). The commonest season of presentation in the cases group was winter (70%), while the remaining cases presented at summer. The season of presentation was significantly different between the two groups ($p = 0.017$). Regarding vitamin D levels, it was significantly lower in the cases group (11.82 vs. 23.72 ng/ml in controls – $p < 0.001$). Using a cut-off value of 18.85, vitamin D had sensitivity and specificity of 100 and 90% respectively, with a diagnostic accuracy of 96.7%. All cases showed hypertrophied adenoids on X ray and type B tympanometry on tympanogram, while all controls showed normal sized adenoids in addition to type A tympanogram.

Conclusion: Our results suggest that low vitamin D levels are linked to both secretory otitis media with effusion together with enlarged adenoids. Therefore, measurement of the serum 25(OH)D level should be considered in children with these symptoms.

Key words: Vitamin D, otitis media, adenoid hypertrophy.

Introduction

Vitamin D has been suggested to play an important role in improving the efficiency of the immune system. Proposed mechanisms of such action include the production of defensin, cathelicidin, and other antimicrobial peptides. Additionally, this vitamin improves the function of macrophages through increasing chemotaxis and phagocytosis [1].

Although the relationship between vitamin D deficiency and infectious conditions was initially proposed in the context of tuberculosis, low levels of vitamin D are also shown to be highly associated with lower and upper respiratory tract infections. Furthermore, vitamin D has been suggested to have a role in some autoimmune diseases and inflammatory conditions such as allergy and asthma [2].

Otitis media (OM) is one of the most prevalent diseases in childhood and is the main reason for visiting a doctor, in children under three years of age. Almost 80% of children up to the age of seven are infected once, but some are infected frequently [3]. OM is seen as acute otitis media (AOM), recurrent otitis media, chronic otitis media and secretory otitis media or otitis media with effusion (OME) [4].

The pathophysiology of OME is associated with eustachian tube dysfunction [5]. The most common causes of this obstruction are adenoid hypertrophy, sub mucosal cleft palate, allergies, upper respiratory tract infection, tumours, sinusitis, AOM

and radiation. Obstruction of the eustachian tube causes accumulation of fluid in the middle ear [6].

In recent years, several studies have been conducted on the risk factors associated with the weakening of the immune system, in which the role of vitamin D can be pointed out. Vitamin D reduces inflammation by decreasing the production of interleukins and interferon gamma [7].

Cayir et al. studied the role of vitamin D in the treatment of children with recurrent otitis media and concluded that administration of vitamin D, in addition to common treatments, is a good option in the treatment of upper respiratory tract infections such as otitis media [8]. In another study by these authors, they studied the vitamin D levels in children with acute otitis media and concluded that vitamin D deficiency plays an important role in the incidence of middle ear infections [7].

Marchisio et al. investigated the role of vitamin D in reducing the risk of recurrent middle ear infections. They suggested that serum levels of vitamin D in children with acute recurrent otitis media should be tested, and in children with low levels of Vitamin D deficiency has been shown to be frequent in children with recurrent AOM, and low serum levels have been associated with an increased number of AOM episodes [9].

This study was conducted at Benha University Hospitals aiming to study the effects of serum levels of vitamin D on the development of secretory otitis media and the adenoid hypertrophy.

Patients and methods

This study is a prospective case-control one designed for patients having secretory otitis media and adenoid hypertrophy during the period between July 2019 and December 2019.

A total of 150 subjects were included in the current study. These subjects were subdivided into two groups:

-*Cases group:* 100 cases who were diagnosed with secretory otitis media and adenoid hypertrophy.

-*Group (B):* 50 children with normal adenoid and normal middle ear pressure.

Cases whose age between 2 and 12 years from both genders were included in the study. Nevertheless, other ages in addition to cases with normal adenoid or normal middle ear pressure were excluded.

All cases and controls were subjected to complete history taking, and thorough ENT examination. Lateral neck X ray as well as tympanometry were also ordered. Serum levels of 25-OH vitamin D were measured in all participants. A 5-mL blood sample was obtained from each patient in the clinical pathology laboratory. The serum level of 25-OH vitamin D was measured using the enzyme linked immunosorbent assay (ELISA) method via spectrophotometry with Diaplas Kit (ELISA reader, USA).

Ethical consideration

An informed written consent and local ethical committee approval.

was obtained from all parents of patients before the onset of this study.

Statistical analysis

Data entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS 21.0, IBM/SPSS Inc., Chicago, IL) software for analysis. Baseline characteristics of the study population were presented as frequencies and percentages (%) or mean values and standard deviations (SD) (after testing of normality by Kolmogorov-Smirnov and Shapiro-Wilk's tests).

For comparison of data, Fischer exact's test (FET) was used to compare two independent groups of qualitative data (as correction for Chi-Square test). For quantitative data, independent-Samples t-test (student's t-test) was used to compare two groups of parametric and non-parametric quantitative data respectively. The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation.

Results

The mean age of the study cases was 7.65 years, which significantly older than controls (mean age 6.1 – $p = 0.002$). However, no significant difference was detected between the two groups regarding gender ($p = 1$). The commonest season of presentation in the cases group was winter (70%), while the remaining cases presented at summer. The season of presentation was significantly different between the two groups ($p = 0.017$).

Regarding vitamin D levels, it was significantly lower in the cases group (11.82 vs. 23.72 in controls – $p < 0.001$). All cases showed hypertrophied adenoids on X ray and type B tympanometry on tympanogram, while all controls showed normal sized adenoids in addition to type A tympanogram. Table (1) illustrates these data.

Table (1): Comparing cases and controls.

	Case with secretory otitis media (100)		*Control group (50)*		*Statistical test*	*P value*
	No	*%*	*No*	*%*		
Age mean ± SD	7.65 ± 2.97		6.10 ± 2.77		St t= 3.08	0.002**
Sex n (%) Male Female	 40 60	 40.0 60.0	 20 30	 40.0 60.0	FET= 0.0	1.0
Season n (%) Summer Winter	 30 70	 30.0 70.0	 25 25	 50.0 50.0	FET= 5.74	0.017*
Vit D mean ±SD	11.82 ± 3.58		23.72 ± 6.03		St t= 15.15	<0.001**
X ray n (%) Hypertrophied Normal	 100 0	 100 0.0	 0 50	 0.0 100	FET= 150.0	<0.001**
Tympanometry Bilateral type A Bilateral type B	 0 100	 0.0 100	 50 0	 100 0.0	FET= 150.0	<0.001**

On analysing vitamin D level in the cases group, females had significantly lower vitamin D values compared to males (11.22 vs. 12.72 – p = 0.04). Nevertheless, the season of presentation did not have a significant effect of vitamin D levels. These data are illustrated at table (2).

Table (2): Vit D levels among cases group.

Case with secretory otitis media (100)	*N*	*Vit D*		*Statistical test*	*P value*
		mean	*±SD*		
Sex n (%) Male Female	 40 60	 12.72 11.22	 3.35 3.63	St t= 2.08	0.04*
Season n (%) Summer Winter	 30 70	 11.61 11.91	 3.57 3.60	St t= 0.38	0.71

On analysing serum vitamin D levels in controls, neither sex nor season of presentation had a significant effect on its level ($p > 0.05$). Table (3) illustrates these data.

Table (3): Vit D differences among control group.

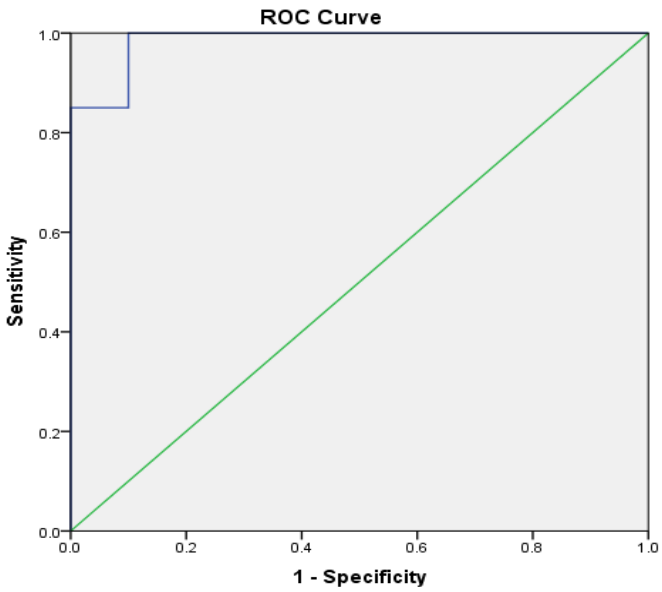
Control group (50)	*N*	*Vit D*		*Statistical test*	*P value*
		mean	*±SD*		
Sex Male Female	 20 30	 22.54 24.51	 3.74 7.11	St t= 1.13	0.26
Season Summer Winter	 25 25	 25.21 22.24	 4.25 7.17	St t= 1.78	0.081

Using a cut-off value of 18.85, vitamin D had sensitivity and specificity of 100 and 90% respectively, with a diagnostic accuracy of 96.7%. Table (4) and figure (1) illustrate these data.

Table (4): Validity of vit D in detection of cases with secretory otitis media.

	Case with secretory otitis media (20)		*Control group (10)*		*Statistical test*	*P value*
	No	*%*	*No*	*%*		
≤18.85 >18.85	100 0	100 0.0	5 45	10.0 90.0	FET= 128.57	<0.001**
AUC (95%CI)	0.985 (0.97-1.0)					
Cut-off point	18.85					
Sensitivity	100					
Specificity	90.0					
PPV	95.2					
NPV	100					
Accuracy	96.7					

Figure (1): ROC curve for vitamin D as a predictor for secretory otitis media.



Discussion

Otitis media in children may lead to speech delay and learning problems, and in the case of chronicity, serious complications, such as hearing loss, adherence or rupture of the tympanic membrane, ear ossicular problems and even behavioral problems, are to be expected [10]. Despite the considerable role of vitamin D in human health, its deficiency is a major health problem worldwide [11].

Vitamin D has anti-inflammatory effects and has a modulation role in the immune system. The effect of the immune modulating effects of vitamin D applies from its receptors on the majority immune cells [12]. Vitamin D reduces the activity of nuclease factor, interleukin and IFN γ, which results in lowering of the inflammation process [13].

In several studies, the role of vitamin D deficiency has been proven in respiratory and middle ear infections [7, 9]. Sabetta et al. stated that a vitamin D level of more than 30 ng/mL significantly ($P < 0.0001$) reduces the risk of respiratory infections [14].

This study was conducted at Benha University Hospitals aiming to study the effects of serum levels of vitamin D on the development of secretory otitis media and the adenoid hypertrophy.

We included a total of 150 subjects, who were divided into two groups; cases group which included 100 cases diagnosed with secretory otitis media and adenoid hypertrophy, and control group which included 50 healthy children.

In another study handling the same perspective, one hundred twenty children with and without otitis media with effusion were studied in two groups: a study group (40 individuals) and a control group (80 individuals) [15].

In our study, the mean age of the included subjects was 7.65 and 6.10 years for cases and controls respectively. Cases had significantly older age in the current study (p = 0.002).

Another study reported no significant difference between cases and controls regarding age (p = 0.180). The mean age of cases and controls was 5.08 and 7.7 years respectively [16].

Conversely, another study reported significant older age in controls compared to cases. The mean age of the study group was 5.7 ± 2.6 years-old and of the control group was 7.2 ± 2.2 years old (P = 0.002) [15]. Regarding gender distribution in the current study, it was not significantly different between the two groups (p = 1). Males represented 40% of cases and control groups respectively.

Another study also reported no significant difference between cases and controls regarding gender (p = 0.579). Males represented 57.5 and 53.7% of cases and controls respectively [16].

Regarding season of presentation, it was significantly different between the two groups (p = 0.017). Winter was the commonest one in cases group (70%), while both winter and summer had the same ratio in controls (50%).

Although there are many risk factors in the development of secretory otitis media, upper respiratory tract infections are among the most important of them. Upper respiratory tract infections are more common in winter, so the risk of having otitis media with diffusion increases in these seasons [16]. This agrees with our study results.

Furthermore, Season and ethnicity are the two main factors that determine the level of serum Vit D [17]. In winter and autumn, the lowest Vit D concentration was observed [16]. Some studies have revealed that vitamin D levels increases in the summer months and decreases in winter due to sunlight dependence [18, 19].

When it comes to vitamin D levels in our study, it was significantly higher in controls (23.72 ng/ml compared to cases (11.82 ng/ml – $p < 0.001$). Vitamin D level was significantly higher in boys compared to girls in the cases group ($p = 0.04$). Using a cut-off value of 18.85, vitamin D had sensitivity and specificity of 100 and 90% respectively, with a diagnostic accuracy of 96.7%.

In another study, the mean serum 25-OH vitamin D level in all patients was 11.96±5.85 ng/ml, with values of 9.79±4.36 and 13.61±6.33 ng/ml in the cases and control groups, respectively ($p=0.003$). Overall, only 15 (20.3%) patients had a normal serum 25-OH vitamin D level, while the remaining patients (79.7%) had a value below the normal range. Additionally, according to gender, the differences in 25-OH vitamin D levels between girls and boys overall and in each group were not significant [20].

Akcan and his associates confirmed our findings as the mean level of vitamin D was significantly lower in cases (18.98 ng/ml), compared to controls (28.07 ng/ml – $p < 0.001$) [16].

In a study conducted in Iran in 2004, the different levels of vitamin D deficiency in cases were as follows, severe, moderate and mild that were reported as 9.5%, 57.6% and 14.2%, respectively [21].

Cayir et al. reported the mean level of Vitamin D in 58 (69%) individuals was under 20 ng/mL (deficiency), compared to 32 (30%) in the control group [22].

Marchisio et al. performed a randomized controlled trial on 116 children with recurrent acute otitis media. Fifty-eight children received 1,000 IU/day vitamin D supplement and others were treated with placebo. The children who received vitamin D supplement had lower attack rates. Moreover, when the serum level of vitamin D was greater than 30 ng/ml, the risk of acute otitis media significantly decreased [9].

In another study, the mean vitamin D level in the cases group was 26.1 ± 14.6 ng/mL with a minimum of 6 ng/mL and a maximum of 67.6 ng/mL. In the control group, the mean was 29.5 ± 17.9 ng/mL with a minimum of 8.1 ng/mL and a maximum of 139 ng/mL. Vitamin D levels were not significantly different between the two groups (P = 0.27). Although there was not a significant relation shown between vitamin D levels between the two groups in that study, the vitamin D level in otitis media patients was less than in the control group. Therefore, authors recommended measuring the level of vitamin D in these patients, and a deficiency of vitamin D must be treated [15]. The modulator effect of Vit D on the immune system is well known. The increased chemotactic and phagocytic effects of monocytes and macrophages have been reported in an enriched active vitamin D environment. Active Vit D stimulates the synthesis of antimicrobial peptides, defensing and cathelicidin, from natural killer cells and respiratory tract epithelial cells [23, 24].

Additional, upregulated calprotectin and S100 protein levels were documented under the effect of active Vit D. These proteins are very important for effective natural immune system. There is a positive correlation between Vit D and immunity. In the event of Vit D deficiency immune response is impaired and leukocyte chemotaxis is affected. The rate of infections increases owing to impaired immunity [25].

Vitamin D deficiency has been shown to establish a predisposition to upper and lower respiratory tract infection and tonsillitis [26, 27]. A study showed decreased cathelicidin synthesis in the bronchial epithelial cells in patients experiencing frequent respiratory tract infections and suggested that inhaler Vitamin D could be used to increase cathelicidin synthesis [27]. Some studies have also shown that Vitamin D is effective as an adjuvant therapy in the treatment of several infections [24, 28].

Whereas the relationship between vitamin D deficiency and acute otitis media is undeniable, there is an insufficient body of research to draw the same definitive conclusion for otitis media. Linday et al. conducted a study on 16 children with a mean age of 3.7 years who underwent VT insertion, and reported that in 50% of these children, the serum level of vitamin D was below 20 ng/ml. However, this study did not demonstrate any significant relationship between the level of vitamin D and otitis media [29].

In our study, all cases showed adenoid enlargement on x ray. A few studies have shown the role of vitamin D deficiency in adenotonsillar hypertrophy [30, 31]. In one study, most of the children who underwent adenotonsillectomy had vitamin D deficiency, and the level of vitamin D inversely correlated with tonsillar size [32]. In another in vitro study by Nunn et al., vitamin D was shown to prevent the mitogenic-induced proliferation of tonsillar tissue [30].

Recent studies in adults showed that a large proportion of those with OSA also had a vitamin D deficiency [33, 34].

A Turkish study found that children with recurrent tonsillitis and allergic rhinitis had significantly lower 1,25-dihydroxyvitamin D [1,25(OH)2D] levels than controls [35]. Another study reported that the sizes of the tonsils and adenoids were negatively associated with the serum 25(OH)D level [36].

In the current study, Type B tympanometry was detected in all cases (100%), whereas type A was the only one detected in controls In another study, of 80 children in the control group, 70 (87.5%) were Type A and 10 individuals (12.5%) were Type C1. of 40 children in the OME group two patients (5%) were type C2 and 38 individuals (95%) were type B [15].

It has been reported in the literature that type A tympanogram normal pressure in the middle ear with normal mobility of the eardrum and ossicles. Conversely, type

B tympanogram may reveal fluid in the middle ear [37]. This agrees with our findings.

The main drawback of the current study is that we did not assess vitamin D administration on the resolution of otitis media and adenoid hypertrophy. Therefore, more studies regarding that matter should be cons=ducted in the near future.

Conclusion

Our results suggest that low vitamin D levels are linked to both secretory otitis media with effusion together with enlarged adenoids. Therefore, measurement of the serum 25(OH)D level should be considered in children with these symptoms.

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