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Original article

Effect of Vitamin-D Supplementation on Recurrence of Acute Otitis Media in Pre-School Children

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ABSTRACT

Background: Acute Otitis media (AOM) and its recurrence is a prevalent health problem among pre-school children. Different strategies to prevent recurrent have been established with questionable efficacy. Vitamin D is suspected as a possible preventable risk factor.

Aim of the work: To evaluate the effect of vitamin-D supplementation on recurrence rate of acute otitis media among Pre-school children.

Patients and Methods: 60 pre-school children with a recurrent episode of acute otitis media [by history and otoscopic examination] were included. After diagnosis, all children received standard treatment and after recovery, serum levels of vitamin-D were estimated; those with reduced vitamin D had been included, then divided into: Study group (30 children, received oral vitamin-D supplementation for 4 months; and **Control group** (30 children; received placebo). New attacks of AOM had been document during the regular visits for the six months. Vitamin D had been re-estimated after 6 months.

Results: Both groups were comparable regarding studied variables at the start. Upper respiratory tract infection and ear discharge significantly decreased; vitamin D significantly increased among study group at 6 months. Recurrent AOM after 6 months, had been significantly reduced among study vs control group (1.43±0.62 vs 3.46±0.62 respectively). Also, vitamin-D significantly increased at the end in study vs control group (21.76±5.95 vs 14.53±4.73 ng/ml respectively). The mean percentage of increase of vitamin-D in study group was 135.98% compared to 33.91%. In control group.

Conclusion: Vitamin D supplementation to children with a history of rAOM plays a significant role in reduction of attack frequency.

Keywords: Vitamin D; Recurrent otitis media; Upper respiratory infection; Pre-school; Children.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Acute otitis media (AOM) is defined as an acute inflammation of mucosal membrane of the middle ear cleft, most commonly occurred after upper respiratory tract infection, which may be either viral or bacterial; the most common viral organisms are respiratory syncytial virus (RSV) and influenza A virus, while the commonest two bacterial pathogens are *Haemophilus influenza* and *Moraxella catarrhalis*. Once pathogen invades the mucosal membrane, it induces inflammatory reaction and edema with subsequent exudate secretion, and later pus [1]. The winter is the most common season for repetition of AOM as upper respiratory tract infections are common and frequent [2]. AOM is the most frequent diagnosis in sick children who visit either ENT or pediatric out-patient clinics [3], and it is considered as the most common reason for antibiotic administration for them [4], the incidence of AOM in children is high all over the world, the incidence rate of AOM in children under 4 years of age is 61 new episodes per 100 individuals per year [5]. The basis for this age-related predisposition unclear, but it is may be related to particular characteristics of nasopharynx anatomy, Eustachian tube function or immune response [6].

Recurrent AOM (rAOM) is defined as ≥ 3 times documented and distinct attacks of AOM within 6 months or ≥ 4 episodes within 12 months, this does not include episodes of AOM which are diagnosed within 2-3 weeks of documented acute infection, as these may be misdiagnosed[7]. Infants with siblings with history of rAOM or who have their first episode before six months of age are risky for rAOM[8], also children have rAOM approximately 46% of them had already more than three episodes by the age of 3 years[9]. rAOM has an adverse effect on child's intellectual, speech and language ability, as well as their school achievement, also the longer a child has AOM, the poorer their performance in various tests assessing intelligence quotient and verbal and reading abilities. Therefore, it is essential to control episodes of AOM [10]. The first choice of treatment for rAOM relies mainly on antibiotic therapy, but its adverse effects as hypersensitivity and antibiotic-resistant bacteria are still a major health concern, as well as a recently widely recognized the role of viral infections in AOM, and a clear link with URTI episodes, so there is continuous search for alternative ways to control rAOM[11].

Vitamin D has an important role in human immunity, including increasing mucociliary clearance, influencing the production of antimicrobial factors, regulating epithelial cell production, modulating inflammatory pathways, and influencing the microbial communities [12]. Vitamin D is largely obtained from sunlight, on exposure to ultraviolet radiation B (UVB), skin synthesizes about 80 - 90 % of an individual's vitamin D, and a small amount is absorbed from certain foods, both forms are biologically inactive, hydroxylation is needed to activate them which occur in the liver and kidney. In the liver, cholecalciferol is converted to 25-hydroxycholecalciferol (25[OH] D), whereas ergo-calciferol is converted to 25-hydroxy-ergo-calciferol[13]. Part of the (25[OH] D) is converted by the kidneys to 1, 25-dihydroxyvitamin D (1, 25[OH] D) which is biologically active form of vitamin D [14], in turn it activates the vitamin D receptor (VDR) expressed in many immune cells including T and B lymphocytes, monocytes and epithelial cells. With this growing perspective on the role of vitamin D in general health, consumption of vitamin D can reduce respiratory tract infection susceptibility in children [15]. Deficiency of vitamin D is relatively a common problem; its prevalence is estimated about 30–40% [16]. The relationship between low serum levels of vitamin D and predisposition to respiratory tract infections was first described in cases of pulmonary TB, vitamin D had been investigated and found that its deficiency or insufficiency considered to be a risk factor for a many respiratory conditions including AOM, adeno-tonsillitis, rhinosinusitis, bronchiolitis and pneumonia [17-19]. Vitamin D supplementation has been considered as both a preventative measure and a treatment [20]. The daily vitamin D requirement as oral supplementation to children with vitamin D insufficiency or deficiency is a minimum 2000IU/ day for a minimum of 3 months [21].

The possible association between vitamin-D and upper respiratory tract infection had been studied. However, the role of vitamin-D and its supplementation in recurrent acute Otitis media has not been fully investigated.

AIM OF THE WORK

The aim of this study was to evaluate the effect of vitamin-D supplementation on recurrence rate of acute otitis media among Pre-school children.

PATIENTS AND METHODS

This randomized study included 60 pre-school children aged 3- 6 years. They were recruited from Otorhinolaryngology and pediatric outpatient clinics [Al-Azhar university hospitals] from June 2018 to December 2019. All patients in this study were matched for age and sex and enrolled during the same seasonal period and selected among children living in the same geographic area with similar sunlight exposure. Patients had been clinically diagnosed by history and examination (otoscopic or microscopic) as acute otitis media (AOM) on the basis of triads of sudden onset, symptoms of inflammation (otalgia or crying as the "otalgia equivalent"), and signs (severely congested tympanic membrane at least 2/3 of the drum with or without outward bulging), signs of occupation of the middle ear or otorrhea, with a history of repeated similar attacks. After diagnosis, all children received traditional AOM medication (amoxicillin clavulanic and analgesics) for 7-10 days, and after recovery, serum levels of 25-OH vitamin D were measured for all cases, and those with vitamin D-insufficiency (levels of 15-20 ng/dl) or deficiency (levels < 15ng/dl) were included in the study, then blindly (the principle investigators were unaware of groups) randomly divided into two groups: Study group included 30 children who had received oral Vitamin-D 2000 IU daily, in the form of ergocalciferol or cholecalciferol by gradual replenishment regimen continued for 4 months; and Control group included 30 children who had received placebo instead of vitamin-D supplement.

In both groups any new attacks of AOM had been recorded and children had been returned for follow up monthly, and parents had been asked to register every time children experienced a febrile episode accompanied by manifestations suggesting AOM, including disturbed sleep, irritability and/or ear pain. Episodes of AOM had been monitored for 6 months.

This study was approved by the Local Research and Ethics Committee [Faculty of Medicine, Al-Azhar University]. Informed consent had been signed by parents.

Prior to enrollment, the treatment regimen was explained to the parents of children. All cases were subjected to full history **(**onset, course, duration of ear symptoms and associated pain, fever and ear discharge, history of preceding upper respiratory tract infection (URTI) and history of previous similar attacks]. Then, complete otorhinolaryngological examination had been carried out (nasal and nasopharyngeal, otoscopic examination of the affected ear as regards to shape, color of tympanic membrane, and if there was associated ear discharge). Laboratory investigation had been requested and included serum calcium, creatinine, iron, and complete blood count. Serum levels of 25(OH) D was the best indicator of vitamin D status, and it had been measured twice for all children in the current trial, first at the beginning of the study, then on discontinuation of the supplementation. The measurement of vitamin-D levels had been achieved by enzyme-linked immunosorbent assay (ELISA) kit (Cal-biotic, USA, Cat# VD220B) according to the manufacturer instructions. The detection range of the kit is 2.5-150 ng/ml. Each sample had been run in duplicate and compared with a standard curve. The mean concentrations were determined for each sample. The normal serum levels of 25(OH) vitamin D was considered to be > 20ng/ml; vitamin D insufficiency as levels of 25(OH) vitamin D 15–20 ng/ml and vitamin D deficiency as levels of 25(OH) vitamin D <15 ng/ml and < 5 ng/ml as severe vitamin D-deficiency [22].

Exclusion criteria: Factors that can favor the development of AOM (e.g., chronic systemic diseases such as rickets or chronic renal failure, craniofacial anomalies, Down's syndrome, acquired or congenital immunodeficiency, history of cleft palate or lip surgery).

Statistical Analysis: Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). Age and temperature data showed normal (parametric) distribution while history of recurrence times and vitamin D-level data yielded non-parametric distribution. Data were presented as mean, standard deviation (SD), and range values. For parametric data, Student's t-test had been used to compare between the two groups. Paired samples (t) test had been used to compare participant's values in the two groups at base line and after 6 months. For non-parametric data, Mann-Whitney U test was used to compare between the two groups. Qualitative data were presented as frequencies and percentages. Chi-square test or Fisher's Exact test when

applicable had been used to compare between qualitative data in the two groups. Paired comparison for categorical data had been carried out by Wilcoxon signed rank test. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM statistical package for social sciences (SPSS) Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

A total of 60 patients were included in the current work. In the study group 18 (60%) were males and 12 (40%) females. In control group 15 (50%) were males and 15 (50%) were females. The mean age (±SD) in study group was of 4.3 ± 1.1 years compared to 4.4 ± 1.1 years in the control group with no significant difference between both groups regarding age or sex. (Table 1). Clinical presentation was depicted in table (2): At the beginning of the study, history of upper respiratory tract infection (URTI) in study group had been reported among 70.0% compared to 66.7% of the control group with no significant difference. After 6 months, the history had been reported among 23.3% of study group and 56.7% of the control group with significant reduction among study when compared to control group. In addition, running paired comparison in each group revealed that, there was statistically significant reduction of history of URTI among study group. On the other side, there was no significant difference between study and control groups as regard to ear discharge either at the beginning of the study or after 6 months (40% vs 46.7% at beginning and 20% vs 40% at the end). However, incidence of ear discharge significantly decreased in study group, but not in control group.

In the current work, the history of rAOM numbers ranged between 3 to 5 episodes at the beginning of the study with no significant difference between study and control groups (3.70±0.78 vs 3.60±0.67 respectively). However, at the end of the study (after 6 months), the history of episodes ranged between 1 to 4 and there was statistically significant reduction among study when compared to control group (1.43±0.62 vs 3.46±0.62 respectively). In addition, with paired comparison, the episodes were significantly reduced in study group, but the reduction among control group did not reach statistical significance. In addition, vitamin D levels had been ranged between 2 – 19 ng/ml at the beginning with no significant difference between study and control groups (10.93±4.37 vs 12.23±4.56 ng/ml respectively). After 6 months, the Vitamin-D levels ranged between 4 and 36, with statistically significant increase in study when compared to control group (21.76±5.95 vs 14.53±4.73 ng/ml respectively). Finally, there was significant increase of vitamin D-levels among each of study and control groups at the end of the study when compared to the corresponding basal values. But the increase is marked in study group, but minimal in control group. This evident from the percentage of increase of vitamin-D at 6 months when divided by the basal values. The mean percentage of increase in study group was 135.98% compared to 33.91%. In control group, some children had lower levels at 6 months when compared to original values (decreased by about 44.44%), while the minimum percentage of increase in study group was 14.29% (Table 3).

In addition, these results are confirmed by the categorization of vitamin D levels into (normal, insufficient, deficient and severely deficient). At inclusion, there was no significant difference between study and control groups, as there was 16.7%, 63.3%, 20.0% and 0.0% of the study group, who had severe deficiency, deficiency, insufficiency and normal values of vitamin D, successively; compared to 13.3%, 46.7%, 40.0% and 0.0% of the control group with the same order. After 6 months, none in the study group had vitamin D-deficiency, but 46.7% had insufficient levels and 53.3% had normal values. On the other side, only 13.3% of the control group had normal serum levels of vitamin-D, and 36.7% had insufficient values and 50% still in the deficient category; with significant difference between study and control group (Table 4).

Table [1]: Patient demographics among studied groups

		Study group (n = 30)	**Control group (n = 30)**	*P*-value
Age (years) Mean (±SD)		4.3 (±1.1)	4.4 (±1.1)	0.815
Gender [n (%)]	Male	18 (60%)	15 (50%)	0.43
	Female	12 (40%)	15 (50%)	

Table (2): Clinical presentations among studied groups

			Study group (n = 30)	Control group (n = 30)	*Test*	*P value*
History of upper respiratory tract infection	Beginning of study		21(70.0%)	20(66.7%)	0.07	0.78
	After 6 months		7(23.3%)	17(56.7%)	6.94	0.008*
	Paired Comparison	Z	3.75	1.73		
		P	<0.001*	0.08		
Ear discharge	Beginning of study		12(40.0%)	14(46.7%)	0.24	0.60
	After 6 months		6(20.0%)	12(40.0%)	2.85	0.09
		Z	2.44	1.41		
		P	0.014*	0.15		

Table (3): Number of rAOM episodes and vitamin D levels among studied groups

			Study group	Control group	**t**	**p**
Number of rAOM episodes	At beginning		3.70±0.78(3-5)	3.60±0.67 (3-5)	0.52	0.60
	After 6 months		1.43±0.62 (1-3)	3.46±0.62 (2-4)	12.55	<0.001*
	Paired comparison	t	14.29	1.44		
		p	<0.001*	0.16		
Vitamin D	At beginning		10.93±4.37(3-19)	12.23±4.56(3-19)	1.13	0.26
	After 6 months		21.76±5.95(15-36)	14.53±4.73(4-23)	5.20	<0.001*
	Paired (t)	t	14.61	2.57		
		p	<0.001*	0.015*		
	Vitamin D difference (after-before)		10.83±4.06 (2-18)	2.30±4.88 (-8-14)		<0.001*
	% of change		135.98±119.75 (14.29-466.67)	33.91±58.38 (-44.44 – 175.0%)		<0.001*

Table (4): Categories of vitamin D levels among studied groups

		Study group	Control group	X^2	*P-value*
Beginning of the study	Severe deficiency	5(16.7%)	4(13.3%)	2.86	0.23
	Deficiency	19(63.3%)	14(46.7%)		
	Insufficiency	6(20.0%)	12(40.0%)		
	Normal	0(0.0%)	0(0.0%)		
After 6 months	Severe deficiency	0(0.0%)	1(3.3%)	22.56	<0.001*
	Deficiency	0(0.0%)	14(46.7%)		
	Insufficiency	14(46.7%)	11(36.7%)		
	Normal	16(53.3%)	4(13.3%)		

DISUCSSION

AOM is a very common disorder affecting high percentage of pediatric populations in the first year of their lives worldwide. Regarding to children most of them have at least one episode in the first three years of their lives [23]. A group of children with AOM have a history of repeated attacks of AOM with significant medical, social and economic consequences for them and their parents[24]. Therefore, preventive approaches, including antibiotic administration, surgery, extended breastfeeding, and cigarette smoke prevention, pneumococcal vaccination, and influenza were reported as a means of reducing the hazards of frequent attacks of AOM in children with a history of rAOM, but none of them completely effective[25].

The current study included patients with history of recurrent acute otitis media and at inclusion, both groups had significant vitamin D-deficiency. After vitamin-D complementation, there was significant reduction of the number of acute attacks of otitis media. These results are of utmost importance as it confirms the beneficial role of vitamin-D supplementation in reduction of acute otitis media.

Carlberg and Molnar [26] reported that children with low levels of serum 25-hydroxy vitamin-D always suffering from recurrent respiratory infections. In addition, **Walker et al.** [19] reported that, both vitamin-D deficiency and otitis media sharing different risk factors, for example, vitamin D levels were lower in winter and in preschool children and similarly known risk factors for otitis media include

younger age, upper respiratory tract infections and winter season. The reduced values of vitamin-D in young children may be associated with increased risk of bacterial overgrowth and impede immune response to such infection.

Esposito and Lelii[27] suggested that maintenance of adequate vitamin-D may be an effective and inexpensive prophylactic method against respiratory tract infections. **Walker** [19] agreed that Vitamin D deficiency has been associated with several respiratory diseases; including otitis media therefore vitamin D supplementation may reduce the risk of otitis media. **Sun et al.**[28] reported the first study that suggests there is link between vitamin D and incidence of AOM which conducted on rats with rickets. **Li et al.**[29] in their meta-analysis systemic review that serum level of vitamin D might play an important role on the progression of acute otitis media. **Cayir et al.**[30] reported in their randomized, single-blind, case–control study, that serum levels of vitamin D were significantly lower in children diagnosed with rAOM than in controls without rAOM, suggesting that vitamin D deficiency plays a role in AOM risk. They also suggested in another study that a significant reduction in disease frequency was recorded following vitamin D supplementation [31]. This result was supported by **Marchisio et al.**[32] in their prospective, randomized, double-blind study on 116 children with a history of rAOM that supplementation of oral vitamin D 1000 IU /day for 4 months, showed that the number of children with at least one AOM episode during the study was significantly lower in the treatment group than in the group that received the placebo.

Other than rAOM, **Abdel-Rahman et al.**[33] evaluated the role of vitamin-D levels in patients with Sino-nasal polypi and compared these levels to values of healthy individuals, and reported significant reduction among patients with nasal polypi or allergic rhinitis. They concluded that, vitamin-D is a cheap therapeutic agent which could be used as a prophylactic therapeutic option in reduction of inflammation (working directly by itself or through a synergistic agent besides traditional therapeutic option]. This work with others in the filed of otorhinolaryngology and other systems signify the important role of vitamin-D as a systemic prophylactic agent.

Conclusion

Vitamin D supplementation to children with a history of rAOM plays a significant role in reduction of attack frequency.

Financial and Non-Financial Relationships and Activities of Interest

None

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