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ORIGINAL PAPER

Recurrent viral-induced wheezing in young children – the protective role of vitamin D supplementation

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ABSTRACT

Introduction: Vitamin D (VD) deficiency has been linked to recurrent respiratory infections in recent years. However, the impact of VD supplementation on recurrent viral-induced wheezing in early childhood remains unclear. Thus, we aimed to investigate the effect of daily VD supplementation on recurrent viral-induced wheezing episodes in young children.

Material and methods: This observational prospective cohort study involved 60 patients with recurrent viral-induced wheezing and 30 healthy children, all aged 6 months to 3 years. Patients with recurrent wheezing were assigned to receive 1000 IU of vitamin D_3 daily (VD group, $n = 30$) or no VD supplements (control group, $n = 30$) for a total of 12 months. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured in all study subjects at baseline and at the 12-month follow-up visit using electrochemiluminescence immunoassay.

Results: VD deficiency was detected in 75% of children with recurrent wheezing. VD levels below 20 ng/ml were linked to 4-fold increased odds of developing recurrent wheezing (OR = 4.35; 95% CI: 2.75-6.86; $p < 0.001$). At 12 months, the median number of wheezing episodes in the control group was twice as much than the VD group (2.0 [1.0; 3.0] vs. 1.0 [0.0; 2.0], respectively, $p < 0.001$). VD supplementation increased the median serum 25(OH)D concentration to 25.11 (12.14; 42.47) ng/ml. The vast majority (71%) of VD-insufficient recurrent wheezers attained sufficiency over 12 months. Among VD-deficient children, 54.5% remained deficient, 31.9% achieved insufficiency, and 13.6% achieved sufficient VD status.

Conclusions: VD supplementation of 1000 IU/day reduces the incidence of recurrent early wheezing. The supplemental dose of vitamin D3 was not optimal to achieve sufficient VD status in patients with baseline VD deficiency.

KEY WORDS:

vitamin D, supplementation, young children, wheezing.

INTRODUCTION

Acute respiratory infections (ARIs) of viral aetiology constitute one of the major causes of morbidity among children under 3 years of age [1]. Wheezing is a frequent symptom of a viral infection and the most common reason for hospitalization in the early years of life [2]. It is estimated that about 40% of children experience at least one wheezing episode before preschool age, and over half of them develop recurrent wheezing [3]. The majority of young wheezers are expected to improve symptoms by early school age [4].

The number of wheezing episodes can be triggered by a variety of factors [2], vitamin D (VD) status in particular [5]. Scientific interest in VD and its significant role in respiratory physiology and immune functions has increased substantially in recent years [5, 6]. VD has been recognized as a multifunctional hormone that supports innate

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immune responses to respiratory viruses. An adequate VD status is essential to maintain proper activity of the immune system aiding in the protection against ARIs [7]. VD deficiency, on the other hand, has been strongly associated with an increased risk of recurrent respiratory infections in children [1, 8]. Prior research has reported an association between VD deficiency and the number of wheezing episodes in preschool children [9].

VD supplementation for the prevention of paediatric respiratory tract infections has been the subject of controversial scientific discussions over the last few years. Some studies have shown the benefits of VD intake for the prevention of ARIs in children [10, 11], while others failed to demonstrate any efficacy [12]. Considering the potential role of VD in reducing the incidence rate of ARIs, the effect of VD supplementation on the recurrence of viral-induced wheezing in young children is of great interest. The currently available data on the impact of VD supplements on the incidence of viral-induced wheezing are limited and mainly address the aforementioned relationship between VD intake and ARIs in general. Furthermore, the optimal VD supplementation dose and intake duration for children with recurrent early wheezing have not been extensively studied. Hence, the aim of this study was to evaluate the effect of oral VD supplementation on the frequency of wheezing episodes in recurrent wheezers under 3 years of age.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

The observational prospective cohort study was conducted in Dnipro Children's City Clinical Hospital No. 6, Ukraine, from January 2016 to April 2018. All participants were recruited to the study after obtaining written informed consent from their parents or legal representatives. The principles of the World Medical Association Declaration of Helsinki were applied in the research.

We hypothesized that VD supplementation may decrease the number of viral-triggered recurrent episodes of wheezing in early childhood. In accordance with the aim of the research, we performed an assessment of the main baseline characteristics of the study subjects (number of wheezing episodes and serum VD levels) and investigated the impact of oral VD supplementation on wheezing recurrences as well as VD status.

We enrolled 90 children between the ages of 6 months and 3 years: 60 cases with episodic viral wheezing according to the European Respiratory Society symptom-based classification of preschool wheezing [3], and 30 healthy individuals with no previous history of wheezing. Recurrent wheezing was defined as 3 or more episodes per year [13].

The inclusion criteria were as follows: Caucasian ethnicity; formal diagnosis of episodic viral wheeze at admission verified in accordance with the national clinical recommendations and evidence-based medicine guidelines of the Finnish Medical Society Duodecim "Difficulty breathing in a child" (2017); a history of 3 or more physician-confirmed wheezing episodes related to viral infections in a preceding year.

All the study subjects met the following exclusion criteria: prematurity, growth retardation, chronic respiratory diseases, primary and secondary immunodeficiency, gastroesophageal reflux disease, malabsorption syndrome, chronic kidney failure, and history of glucocorticoid or anticonvulsant drug use. None of the patients met the diagnostic criteria for bronchial asthma on inclusion or during the study period.

VITAMIN D SUPPLEMENTATION

Patients with recurrent wheezing were randomly assigned to receive either oral VD supplements (VD group, $n = 30$) or no VD supplementation (control group, $n = 30$). The follow-up period for each participant was 12 months. Based on the practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe [14] and recommendations acknowledged at the V Congress of Paediatricians of Ukraine [15], we administered a daily dose of 1000 IU of VD for supplementation. Furthermore, an Endocrine Society clinical practice guideline suggests taking 1000 IU of VD per day to achieve and maintain optimal serum 25-hydroxyvitamin D (25(OH)D) levels above 30 ng/ml [16]. We did not consider higher VD doses because none of the enrolled patients had clinical signs of rickets. We mainly recommended vitamin D_3 (cholecalciferol) as the most common preparation used for supplementation and treatment of VD deficiency in Europe [17]. According to previous research, vitamin D_3 is more effective than vitamin D_2 in increasing and maintaining serum 25(OH)D concentrations [18]. The vast majority of patients were supplemented with micellized vitamin D_3. However, we did not give preference to water-soluble forms of VD because modern oil-based vitamin D_3 has excellent bioavailability as well.

All participants were asked to refrain from taking any vitamin supplements containing cholecalciferol or medicines that affect absorption, metabolism, or activation of VD for the 12-month period. In our study, the dietary sources were not considered to quantify daily VD intake. Firstly, young children do not consume fish as a major natural source of VD on a regular basis. Secondly, mandatory fortification of some food products is not widely provided in Ukraine. Lastly, dietary intake alone as well as sunlight exposure are usually insufficient to sustain optimal VD status in most individuals, and therefore use of VD supplements is often required [19]. The parents recorded their child's VD supplementation in diaries that were all collected at the end of the research.

ASSESSMENT OF SERUM VITAMIN D

The plasma 25(OH)D level is now the most accurate indicator of VD status [20]. The serum concentration of 25(OH)D was measured using electrochemiluminescence immunoassay (ECLIA) on a Cobas e411 auto analyser (Roche Diagnostics GmbH, Germany). According to the Endocrine Society's recommendations, the VD status of the study subjects was classified as deficient if the serum 25(OH)D concentration was less than 20 ng/ml, insufficient if ranging from 20 to 29 ng/ml, and sufficient if the serum 25(OH)D concentration was 30 ng/ml or higher [16]. Blood samples were taken at the time of recruitment (to determine baseline serum 25(OH)D levels) and at a 12-month follow-up visit. VD reference values were obtained from 30 healthy peers.

OUTCOME MEASURES

The primary outcome of the study was the number of physician-diagnosed wheezing episodes over a one-year follow-up. Participants were evaluated for evidence of wheezing by a paediatrician in the outpatient clinic or at inpatient appointments if hospitalization was required due to the severity of wheezing. The secondary outcome of the present study was changes in the median serum VD levels at the 12-month visit. We also interviewed families by telephone for compliance to study supplement use every 3-4 months after patient enrolment. Parental compliance with VD intake for children appeared to be high and remained unchanged during the follow-up period. A total of 60 (100%) children with recurrent wheezing successfully completed the 12-month follow-up study.

STATISTICAL ANALYSIS

All data were entered into a database in Microsoft Excel-2010 (Microsoft Office 2016 Professional Plus, Open License 67528927) and analysed using Statistica 6.1 (serial number AGAR909 E415822FA) and Statistica 10.0. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to evaluate the normality of data. Quantitative variables were represented as medians (Me) and the interquartile range (IQR, [Q25; Q75]) due to non-normal distribution. Qualitative variables were compared by using Pearson's χ^2 test, and quantitative characteristics by Mann-Whitney *U*-test. Comparisons of outcomes among wheezy children were performed using Wilcoxon test and McNemar's test for quantitative and qualitative variables, respectively. Measures of probability were based on the odds ratio (OR) with 95% confidence interval (95% CI), and *p*-value. $P < 0.05$ was considered statistically significant.

ETHICS COMMITTEE APPROVAL

The study was conducted in accordance with the Biomedical Ethics Committee of Dnipro State Medical University (Protocol No. 3 dated 4 April 2015).

RESULTS

Table 1 shows the baseline characteristics of the enrolled participants. There were no statistically significant differences between the VD and control groups ($p > 0.05$). The study samples were age-matched with a male predominance. The median number of wheezing episodes among recurrent wheezers was 4.0 (3.0; 5.0) at

TABLE 1. Baseline characteristics of the study participants

Characteristics	Vitamin D group	Control group ($n = 30$)	Healthy individuals ($n = 30$)	*p*-value
Age, months, median (Q25; Q75)	20.0 (15.0; 26.5)	19.5 (15.0; 27.0)	21.0 (7.0; 29.0)	> 0.05*
Male, *n* (%)	20 (66.7)	21 (70)	21 (70)	> 0.05**
Female, *n* (%)	10 (33.3)	9 (30)	9 (30)	> 0.05**
Number of wheezing episodes per year, median (Q25; Q75)	4.0 (4.0; 5.0)	4.0 (3.0; 4.0)	0 (0)	
Dietary vitamin D intake, *n* (%)	2 (6.6)	1 (3.3)	21 (70)	< 0.001**
Serum 25(OH)D concentration (ng/ml), median (Q25; Q75)	13.93 (9.60; 20.5)	13.21 (7.27; 18.52)	37.96 (26.47; 43.52)	< 0.001*
Vitamin D status categories, *n* (%)				
Optimal level (≥ 30 ng/ml)	1 (3.3)	0 (0)	21 (70)	< 0.001**
Insufficiency (20-29 ng/ml)	7 (23.4)	7 (23.4)	9 (30)	> 0.05**
Deficiency (≤ 19.9 ng/ml)	22 (73.3)	23 (76.6)	0 (0)	

** p-value is derived from the Mann-Whitney U-test for the comparison performed between recurrent wheeze sample and healthy individuals.*
*** p-value is referred to the Pearson's chi-square test for the comparison performed between recurrent wheeze sample and healthy individuals.*

TABLE 2. Median change in wheezing recurrences over a 12-month period

Vitamin D status categories	Vitamin D group ($n = 30$)	Control group ($n = 30$)	*p*-value*
Insufficiency (20–29 ng/ml)	–3.0 (–4.0; –1.0)	–2.0 (–4.0; –1.0)	0.620
Deficiency (≤ 19.9 ng/ml)	–3.0 (–3.0; –2.0)	–1.0 (–3.0; 0.0)	0.004
p-value**	0.592	0.523	

** p-value is derived from the Mann-Whitney U-test.*
*** p-value is referred to the Wilcoxon test.*
Me (Q25; Q75)

TABLE 3. Serum vitamin D levels in study participants

Serum 25(OH)D concentration (ng/ml), median (Q25; Q75)	Vitamin D group ($n = 30$)	Control group ($n = 30$)	*p*-value*
At baseline	13.93 (9.60; 20.5)	13.21 (7.27; 18.52)	0.633
At 12-month study visit	25.11 (12.14; 42.47)	14.48 (10.58; 23.47)	0.012
p-value**	0.002	0.228	

** p-value is derived from the Mann-Whitney U-test.*
***p-value is referred to the Wilcoxon test.*

recruitment. There was no difference in the incidence of wheezing between the VD group and controls ($p > 0.05$ by Mann-Whitney *U*-test). Of the 60 children with a recurrent pattern of viral-induced wheeze, 3 (5%) reported having taken vitamin D_3 at a minimum prophylactic daily dosage of 500 IU before the start of the study, whereas in healthy non-wheezing peers this characteristic had been at the level of 70%. We also found no difference between study groups in terms of median baseline serum 25(OH)D levels ($p = 0.633$ by Mann-Whitney *U*-test). Most recurrent wheezers were VD-deficient, while healthy children mainly possessed sufficient VD levels. VD deficiency demonstrated a strong positive association with an increased risk of recurrent wheeze (OR = 4.35; 95% CI: 2.75–6.86; $p < 0.001$).

A 12-month follow-up analysis showed a statistically significant reduction in the number of wheezing episodes among the children who were supplemented with vitamin D_3 compared to baseline characteristics: 1.0 (0.0; 2.0) versus 4.0 (4.0; 5.0), respectively, $p < 0.001$ by Wilcoxon test. Similarly, we observed a significant decrease in the frequency of wheezing in participants with no VD supplementation in comparison with baseline values: 2.0 (1.0; 3.0) versus 4.0 (3.0; 4.0), respectively, $p < 0.001$ by Wilcoxon test. However, the median number of wheezy episodes in the control group doubled that of the patients receiving cholecalciferol: 2.0 (1.0; 3.0) versus 1.0 (0.0; 2.0), respectively, $p < 0.001$ by Mann-Whitney *U*-test.

Table 2 represents a median change from baseline in wheezing episodes per year. We observed that the median decline in the frequency of viral wheeze in the VD group tripled that of unsupplemented controls: –3.0 (–3.0; –2.0) versus –1.0 (–3.0; –1.0), respectively, $p < 0.001$ by Mann-Whitney *U*-test. When we compared the VD group to the control group based on baseline 25(OH)D concentration, we found that the clinical benefit of VD supplementation was greater in patients who were deficient in VD.

VD supplementation resulted in a statistically significant increase in the median levels of serum 25(OH)D, whereas there were no significant changes in VD levels in children who did not receive VD supplements (Table 3).

In the primary comparison, we found that VD supplementation had a statistically significant effect on participants with a baseline of 25(OH)D ≤ 19.9 ng/ml versus those with a baseline of 25(OH)D 20–29 ng/ml. Simultaneously, the proportion of patients with optimal serum 25(OH)D concentrations increased significantly in the presence of a daily intake of VD. The results are presented in Table 4.

With the more detailed analysis of the efficacy of VD supplementation, we detected that among 22 participants with VD deficiency, 12 (54.5%) remained deficient, 7 (31.9%) patients improved VD levels to insufficiency, and 3 (13.6%) to sufficiency. Among 7 VD-insufficient children, 5 (71%) attained sufficient levels, and 2 (29%) remained insufficient. The patients with sufficiency did not change VD status category. In contrast to the VD group, no statistically significant improvement in VD status was seen for unsupplemented children. Among 23 deficient patients, the majority ($n = 20$, 87%) did not change their VD status category, and 3 (13%) children improved to insufficiency. Among participants with VD insufficiency, 6 (86%) remained insufficient, and one patient (14%) went into deficiency. Therefore, VD supplementation resulted in a statistically significant increase in the proportion of participants who improved VD status in both VD-deficient and VD-insufficient categories compared to those with no daily intake of VD ($p = 0.039$ and $p = 0.026$, respectively, by Pearson's χ^2 test).

We also performed an age-dependent analysis of the response to VD supplementation. Study participants

TABLE 4. Characteristics of vitamin D (VD) status in supplemented patients with recurrent wheezing

VD status categories, *n* (%)	Prior to VD supplementation ($n = 30$)	After VD supplementation ($n = 30$)	*p*-value
Optimal level (≥ 30 ng/ml)	1 (3.3)	9 (30.0)	0.016
Insufficiency (20–29 ng/ml)	7 (23.4)	9 (30.0)	0.771
Deficiency (≤ 19.9 ng/ml)	22 (73.3)	12 (40.0)	0.020

P-value is referred to McNemar's chi-square test.

were categorized into 2 major age groups: 6–24 months (n = 16) and > 24 months of age (n = 14). Our results revealed no significant age-related differences in the median number of wheezing episodes per year: 1.0 (1.0; 2.0) in children aged 6 months to 2 years versus 1.0 (0.0; 1.0) in patients older than 2 years, p = 0.182 by Mann-Whitney U-test. Similarly, there were no significant differences in the median serum 25(OH)D concentrations between the 2 age groups: 20.93 (12.14; 32.80) ng/ml for participants aged 6–24 months and 25.11 (15.26; 42.47) for children over the age of 24 months, p = 0.738 by Mann-Whitney U-test.

DISCUSSION

A significant body of research has demonstrated a clear association between VD deficiency and ARIs in recent years, while interventional studies on VD supplementation and its impact on the occurrence of recurrent respiratory infections among young children have had controversial findings [5, 21]. Our study aimed to assess the effectiveness of VD supplementation in decreasing the number of recurrent episodes of wheezing in Ukrainian children under 3 years of age. Our main finding is that VD supplementation of 1000 IU/day helps reduce the frequency of wheezing episodes in children with recurrent early wheezing, regardless of baseline VD status. However, the dose administered does not appear to be sufficient to achieve optimal 25(OH)D levels in patients with VD deficiency.

In this study, 75% of children with recurrent wheezing possessed VD deficiency, and nearly 1 in 4 patients was VD insufficient, while none of the healthy peers had VD levels below 20 ng/ml. The findings of our investigation are supported by Prasad *et al.* and Shyamajit *et al.* [13, 22]. Other similar studies conducted among children under 5 years of age in Turkey and Iraq detected serum 25(OH)D concentrations below 20 ng/ml in about half of the recurrent wheezers [23, 24]. Hence, our results highlight a relatively high prevalence rate of VD deficiency in young children with a recurrent pattern of viral-induced wheezing and point out the importance of VD supplementation in the given cohort of patients. VD deficiency can primarily be explained by the absence of adequate VD supplementation in most patients with recurrent wheezing. Although there is scientific evidence of a strong positive association between daily intake of VD and its serum concentration until 2 years of age [25], we surmise that most paediatric primary care providers do not routinely recommend prophylactic supplementation of VD to recurrent wheezers. We can also consider that increased time spent indoors due to frequent wheezing episodes may lead to decreased natural VD synthesis. In addition to this, it may be possible that some children did not receive VD supplements at the prophylactic dose due to a low level of parental compliance.

We found that VD supplementation of 1000 IU/day for 12 months was associated with a substantial reduction in the number of wheezing episodes. Similarly, we observed that unsupplemented patients also experienced a decrease in the frequency of wheezing during the follow-up period, although it was not as significant as in the VD group. This tendency could be explained by a natural decline in the incidence of wheezing by the age of 3 years. The protective effect of VD supplementation was seen for both VD-deficient and VD-insufficient patients at baseline. Our results support the findings that VD supplementation provided more benefits to children with deficient baseline VD status than VD-insufficient subjects in decreasing wheezing episodes when compared to unsupplemented peers. We speculate that these differences in results may be related to a small sample size of patients with VD insufficiency (n = 7). Although there is a lack of evidence on the administration of VD to infants and toddlers with recurrent viral-induced wheezing, several studies support the efficacy of VD supplements in the prevention of ARIs. For instance, Jolliffe *et al.* revealed a potent protective effect of a daily administration of 400-1000 IU of VD for up to 12 months on ARIs in children of all age groups [11]. Martineau *et al.* found that VD supplementation significantly reduced the risk of ARIs in participants with a baseline 25(OH)D concentration of less than 10 ng/ml [26]. Instead, Aglipay *et al.* and Hueniken *et al.* failed to show a considerable benefit of even higher-dose VD supplementation (2000 IU/day) in decreasing the incidence of viral upper respiratory tract infections among healthy children aged 1 to 5 years [12, 27]. However, these studies did not investigate baseline VD levels in the children enrolled. Overall, our findings support the protective effect of VD supplementation on viral wheezing. The precise mechanism of VD in the pathogenesis of wheezing has not been fully determined. Several research papers highlight significant immunomodulatory and antimicrobial activities of VD. It has been shown that VD enhances the production of defensin β_2 and cathelicidin antimicrobial peptides and decreases the proinflammatory type 1 cytokines [5, 7]. These mechanisms are considered to play an essential role in adequate antiviral defence, which might be associated with a decline in the frequency of viral wheezing in children supplemented with vitamin D_3 in the present study.

In our study, every second patient benefited from recommended supplementation and improved VD status category. The use of VD at a daily dose of 1000 IU resulted in a significant increase in median serum 25(OH)D concentrations over a 12-month period. There was evidence that the impact of VD supplementation on VD status varied depending on the baseline values. VD supplementation was more effective in increasing serum VD levels to sufficiency in VD-insufficient patients than in those with VD deficiency at baseline. Although 86% of VD-deficient children did not achieve optimal serum 25(OH)D levels after supplementation, 1 out of every 3 patients improved

to insufficiency by the end of the study. Our results indicate that higher doses of supplemental VD are required to attain the target level of plasma 25(OH)D above 30 ng/ml in VD-deficient subjects. Similarly, Chakhtoura *et al*. reported that a daily VD dose ranging from 1000 to 2000 IU may be necessary to reach a 25(OH)D level of 20 ng/ml and higher in the majority of children [28]. According to European VD supplementation guidelines, it is recommended to double the dose of VD to assess adequate 25(OH)D concentrations in individuals with VD deficiency [17]. Hence, it may be reasonable to administer 2000 IU of cholecalciferol daily to young children with recurrent viral-induced wheezing who are deficient in VD. Instead, our findings show that a daily dose of 1000 IU of vitamin D_3 is sufficient to achieve optimal serum 25(OH)D levels in participants with baseline insufficiency. Thus, optimal dosing regimens for VD supplementation in VD-deficient recurrent wheezers to achieve and maintain sufficient VD status remain to be determined.

There are certain limitations of our study. Firstly, the sample size of the patients with recurrent wheezing was relatively small ($N = 60$). Likewise, each VD status category included a small number of research participants, which could alter the statistical power. However, the prevalence rate of VD deficiency in the study cohort of patients concurs with earlier findings, which supports the validity of our data. Secondly, patients were assigned to the same supplemental dose regardless of baseline VD status. Lastly, VD was supplemented for 12 months without measuring probable changes in serum 25(OH)D levels in the middle of the follow-up period. Nonetheless, our findings highlight the strengths of the present study, which include a significant role of daily oral VD supplementation in reducing the frequency of recurrent wheezing episodes in early childhood, as well as the fact that VD supplementation was provided to study subjects knowing the baseline 25(OH)D concentrations.

CONCLUSIONS

Young children with recurrent viral-induced wheezing are at risk of VD deficiency and appear to benefit from VD supplementation. Daily administration of 1000 IU of VD for 12 months significantly reduces the number of wheezing episodes and improves serum 25(OH)D levels. However, a supplemental dose of vitamin D_3 at 1000 IU per day does not seem adequate to ensure VD sufficiency in recurrent wheezers with VD deficiency. Further research is required to investigate the response of VD-deficient children to a higher supplemental dose of VD to achieve sufficiency in the given cohort of patients.

DISCLOSURE

The authors declare no conflict of interest.

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