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Journal club

Can vitamin D_3 supplementation reduce the time to severe asthma exacerbations in children with asthma?

Commentary on:
Forno E, *et al*. Effect of Vitamin D_3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels: the VDKA randomized clinical trial. *JAMA* 2020; 324: 752–760.

Context

There is considerable evidence that the prevalence of asthma is increasing in industrialised countries, particularly in children and young adults [1]. Exacerbations of asthma constitute the main burden of the disease for children and their families. The majority of asthma exacerbations are triggered by respiratory viruses, most commonly rhinoviruses (RVs) [2, 3]. Host immune responses to respiratory viruses are important in asthma exacerbations. Mechanistic studies have identified immunomodulatory and anti-inflammatory roles for vitamin D [4, 5]. Figure 1 describes the actions of vitamin D on B-cells, T-cells and activated mast cells in the context of an allergen/virus-induced exacerbation of asthma. Vitamin D has also been shown to induce regulatory T-cell differentiation and interleukin (IL)-10 secretion that helps attenuate the airway smooth muscle cell hypertrophy which underlies severe asthma pathophysiology [6]. Particularly for RV, vitamin D has been shown to downregulate RV replication through induction of interferons (IFNs) and IFN-stimulated pathways [7]. Although the protective levels of vitamin D for bone health have been well described, we do not know what levels of vitamin D are needed for optimal immune responses to respiratory viral infections [8]. Vitamin D deficiency is defined as measurable levels of 25-hydroxyvitamin D below 20 ng·mL^{-1} and vitamin D insufficiency is defined as measurable levels of 25-hydroxyvitamin D below 30 ng·mL^{-1} [9], but these are based solely on bone markers.

There is evidence from observational cohort studies linking low 25-hydroxyvitamin D levels with asthma incidence in children [10, 11]. A systematic review of the literature on studies examining the impact of vitamin D supplementation in children with early diagnosed asthma failed to show clear positive impact [12]. Also, there is unclear evidence around the link between severity of asthma and low 25-hydroxyvitamin D levels [10]. Importantly, prior to the Vitamin D Kids Asthma (VDKA) trial [13], other studies including either preschool or school-age children had not focused only on children with low 25-hydroxyvitamin D levels or on those who are at high risk for severe asthma exacerbations (assessed by poor asthma control) [11, 14]. A recently published randomised controlled trial including younger children with vitamin D deficiency showed no positive impact of vitamin D_3 supplementation on incidence of asthma exacerbations and on asthma control [15]. It is important to understand the effect of age as a cofounder in these trial results. Preschool wheeze is

Cite as: Bokobza I, El Hadi N, Bush A, *et al*. Can vitamin D3 supplementation reduce the time to severe asthma exacerbations in children with asthma? *Breathe* 2021; 17: 210071.

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Vitamin D deficiency in children needs to be treated irrespective of asthma benefits. The VDKA trial showed that vitamin D supplementation in school-age asthmatic children with vitamin D insufficiency did not improve asthma control. https://bit.ly/2UF3j61

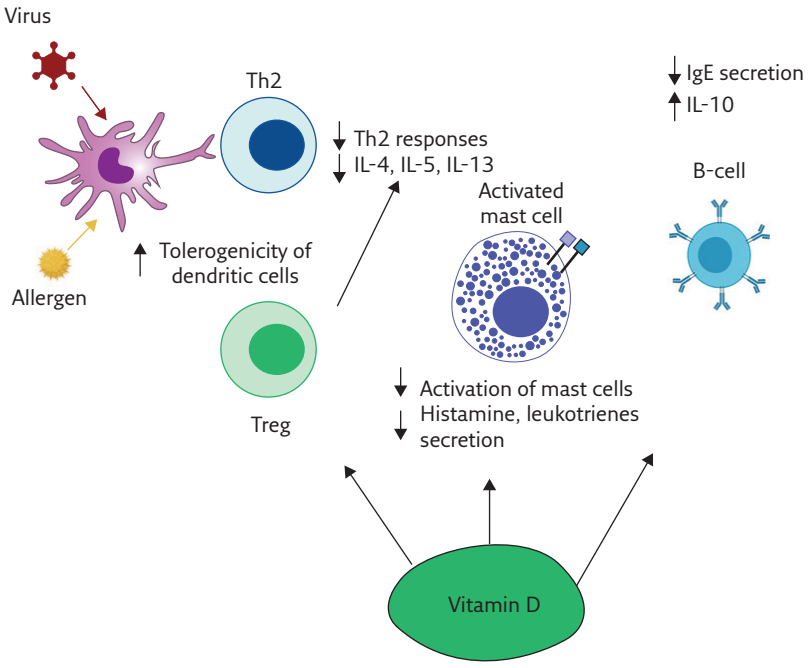

Figure 1 *Actions of vitamin D on B-cells, T-cells and activated mast cells in the context of an allergen/virus-induced exacerbation of asthma. Th: T-helper cell; Treg: regulatory T-cell; Ig: immunoglobulin.*

not asthma and all preschool children with wheeze do not have similar responses to treatments [16]. Table 1 summarises the main characteristics of randomised controlled trials in preschool and school-age children with asthma.

In view of the lack of conclusive evidence, a research study assessing possible protective effects of vitamin D_3 supplementation in children with low 25-hydroxyvitamin D levels and asthma was missing.

Methods

The VDKA study was a randomised, double-blind, placebo controlled clinical trial [13]. The primary outcome was the time to severe asthma exacerbation post vitamin D_3 supplementation. The secondary outcomes were the time to viral-induced severe asthma exacerbation, the number of patients who were able to reduce the use of their preventer medication by half, and the cumulative dose of inhaled steroids required over the study period.

Recruitment took place in seven US healthcare centres. Children at high-risk for asthma exacerbation with vitamin D deficiency and/or

Table 1 *Randomised controlled trials of vitamin D_3 supplementation in preschool and school-age children with asthma*

Study	Study type	Study population	Age, years	Baseline 25(OH)D, nmol·L^{-1}	Oral dose of vitamin D_3 (intervention arm)	Outcome
Urashima *et al*. [17]	Randomised controlled trial	School-age children with asthma	9.5 (2.1; 6.0–15.0)	Not determined	1200 IU·day^{-1}	Significant preventive effect against influenza A LRTIs
Majak *et al*. [18]	Randomised controlled trial with a cohort design	School-age children with asthma	10.9 (3.3; 6.0–17.0)	88.9 (38.2; 31.5–184.7)	500 IU·day^{-1}	Reduced the number of asthma exacerbations triggered by acute respiratory tract infection during 6 months of follow-up
Tachimoto *et al*. [19]	Randomised controlled trial with a cohort design	School-age children with asthma	9.9 (2.3; 6.0–15.0)	74.9 (24.6; 20.0–187.2)	800 IU·day^{-1}	Improved ACT at 6 months of follow-up
Jensen *et al*. [20]	Randomised controlled trial with a cohort design	Preschool children with recurrent wheeze	2.9 (1.1; 1.6–5.5)	64.2 (14.0; 42·0–87·0)	100000 IU bolus plus 400 IU·day^{-1}	No effect on use of oral corticosteroids during 6 months of follow-up
Kerley *et al*. [21]	Randomised controlled trial with a cohort design	School-age children with asthma	8.6 (2.8; 5.0–15.0)	54.4 (17.4; 26.0–92.0)	2000 IU·day^{-1}	No significant difference in asthma control during 4 months of follow-up
Jat *et al*. [15]	Randomised controlled trial with a cohort design	Preschool and school-age children with asthma	8.1 (2.3; 4.0–12.0)	18.6 (4.1; 21.7–32.9)	1000 IU·day^{-1}	No significant difference in asthma control and in the number of asthma exacerbations during 9 months of follow-up

Data are presented as median (minimum; interquartile range), unless stated otherwise. 25(OH)D: 25-hydroxyvitamin D; LRTI: lower respiratory tract infection; ACT: asthma control test.

insufficiency (age 6–16 years old) were recruited. Asthma was diagnosed by a physician at a clinic visit. Asthma diagnosis was based on a history of at least one severe asthma exacerbation that required systemic steroid treatment in the preceding year or use of any asthma medications for at least 6 months over the preceding year. A forced expiratory volume in the first second of expiration (FEV_1) ≥70% of predicted was a further entry requirement. Inclusion criteria for the serum levels of 25-hydroxyvitamin D were 10 to 30 ng·mL^{-1} (protocol changed to 14 to 30 ng·mL^{-1} during the study).

The participants were randomised to receive 4000 IU of daily Vitamin D_3 or placebo. Both groups received an inhaled corticosteroid (fluticasone propionate) (88 µg twice per day in children aged 6–11 years and 110 µg twice per day in children ≥12 years). Prior asthma medications were discontinued. 25-hydroxyvitamin D levels were measured at randomisation and every 16 weeks. Participants' asthma control was assessed 24 weeks after recruitment by using the Asthma Control Test (ACT). Adherence to medications was assessed electronically and *via* returned pill counts.

Results

The VDKA study aimed to recruit 400 participants, however the trial recruitment was stopped early based on interim analysis due to lack of efficacy of vitamin D_3 supplementation. The study recruited 192 participants equally distributed in both groups and showed that vitamin D_3 supplementation did not impact on the time to a severe asthma exacerbation as compared with placebo. The mean number of days until a severe exacerbation was 240 days in the vitamin D_3 group and 253 days in the placebo group with a mean difference of −13.1 days (p=0.63). The study also found no significant difference for any of the secondary outcomes.

Children who received vitamin D_3 supplementation were significantly more likely to achieve a 25-hydroxyvitamin D level higher than 30 ng·mL^{-1} compared with the placebo group (87.2% *versus* 30.1%, respectively, at 48 weeks; p-value <0.001). They reached mean 25-hydroxyvitamin D levels of 49.4 ng·mL^{-1} (95% CI 44.9–53.9 ng·mL^{-1}) at 48 weeks compared with 24.6 ng·mL^{-1} (95% CI 22.9–26.3 ng·mL^{-1}) in the placebo group.

The authors demonstrated statistically that both groups were similar in terms of baseline characteristics including age, ethnicity, parental education, household smoking, season of enrolment, weight, and lung function parameters.

Adverse events were similar in both groups, with hospitalisations for asthma exacerbations accounting for the majority. There were no cases of hypercalcaemia or vitamin D toxicity in either group.

Commentary

It is still unclear whether vitamin D_3 supplementation in children with vitamin D deficiency and asthma could impact positively on the incidence of asthma exacerbations. A Cochrane meta-analysis of the literature, only including double-blind, randomised trials in both adults and children with asthma, showed that vitamin D_3 supplementation could decrease the incidence of severe asthma exacerbations from 6% to around 3%, but did not have a positive impact on asthma control [22]. Interestingly, the recruitment in the VDKA trial was paused early in view of lack of efficacy of vitamin D_3 supplementation, assessed by failure to decrease incidence of severe asthma exacerbations by 16% (a high number considering previous trials [22]).

This resulted in 180 participants (92 patients in the treatment group and 88 patients in the placebo group) completing the trial with a median duration of follow-up of 332 days. Only 63 out of 180 participants (35% of the recruited patients) had serum 25-hydroxyvitamin D levels below 20 ng·mL^{-1}. Therefore, the impact of vitamin D_3 supplementation in asthmatic children with vitamin D deficiency was not assessed because of lack of statistical power. Hence the outcomes are only relevant to children with asthma and vitamin D insufficiency.

The daily dose of 4000 IU per day for vitamin D_3 supplementation is higher than the dose that has been used in other clinical trials [15]. This high dose for vitamin D_3 supplementation resulted in an increase of 25-hydroxyvitamin D levels in children with asthma from 22.5 ng·mL^{-1} to 57.2 ng·mL^{-1} at 16 weeks post supplementation.

Also, a total of 36 participants (37.5%) in the vitamin D_3 supplementation group and 33 participants (34.4%) in the placebo group had at least one severe asthma exacerbation during the trial. Although the authors commented that this asthma exacerbation incidence is lower than expected, US emergency department activity data have reported lower numbers of asthma exacerbations within a year in children with asthma [23]. Furthermore, this study enrolled participants with moderate asthma control, as defined by good lung capacity (FEV_1 more than 70% of predicted), and a mean baseline ACT score >19 [13].

The proportion of participants whose inhaled steroid dose could be reduced during the trial was not significantly different between the vitamin D_3 supplementation group (28 participants) and the placebo group (29 participants). Also, there was no impact of vitamin D_3 supplementation on the cumulative use of inhaled steroids during the trial. This is contrasting to evidence from the Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA) trial, where vitamin D_3 supplementation had a significant effect on reducing the overall use of inhaled steroids [24]. The VIDA trial used an extra initial dose of oral vitamin D_3

supplementation (100000 IU once); however, the effect on vitamin D levels following supplementation did not differ between the VKDA and the VIDA trials and could not explain the differences in the impact on use of preventive steroids.

What is clear is that vitamin D deficiency in children needs to be treated irrespective of asthma benefits. In intervention studies, patients with vitamin D deficiency or insufficiency who receive placebo need to be carefully monitored for any vitamin D deficiency-related symptoms.

Implications for clinical practice

Currently, children diagnosed with asthma do not routinely undergo vitamin D testing. They might already be on oral vitamin D_3 supplementation if diagnosed with insufficiency or deficiency. The VKDA trial showed that vitamin D_3 supplementation in children with asthma and 25-hydroxyvitamin D levels less than 30 $ng \cdot mL^{-1}$ did not impact positively on asthma exacerbations nor improve asthma control. It is of note that these conclusions cannot be applied in children younger than 5 years old, who are more likely to have non-eosinophilic asthma phenotypes. Also, the results cannot inform decisions around the use of vitamin D_3 in patients with vitamin D deficiency.

It is therefore important that clinical trials including younger children with vitamin D deficiency will be designed so that outcomes can inform clinical practice. It is also important that these clinical trials include ethnic groups who are at higher risk for vitamin D deficiency. Clinicians need to remember that mechanistic studies showed an effect on vitamin D treatment upon respiratory viral infection. A possible study design with an increase in the dose of oral vitamin D_3 supplementation with the first symptoms of a virus-induced asthma exacerbation, might better translate the laboratory findings into clinical practice.

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Conflict of interest

None declared.

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