Vitamin D reduces Exacerbation in Children with Asthma: A Systematic Review and Meta-analysis

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ABSTRACT

Aim: The question whether treatment with vitamin D improves asthma exacerbations in children and adults still needs to be addressed.

Background: Recent studies in children and adults found a higher prevalence of hypovitaminosis D associated with a higher severity of asthma and impaired pulmonary function. In asthmatic children, patients with vitamin D deficiency demonstrated increased airway hyperresponsiveness and corticosteroid requirements.

Results: Of 469 records/studies identified through database searching, 5 studies were included in this systematic review. The overall pooled effect showed a significant reduction in acute asthma exacerbation in the vitamin D group (odds ratio 0.45, 95% confidence interval 0.22–0.93). There were no studies that focus on the quality of life.

Conclusion: This systematic review supports the role of vitamin D in reducing the number of asthma exacerbations in children but not in adults.

Clinical significance: The present systematic review demonstrates reduction in asthma exacerbations in children. Most of the asthma children are on inhaled corticosteroid, which poses a threat for its side effects. However, vitamin D having multiple functions in body could be used as an alternative therapy in asthmatic children. In adults, more trials are needed wherein the deficient individuals are supplemented with vitamin D and further assessed for asthma exacerbations. There is no harm in supplementation of vitamin D to deficient and insufficient asthmatic individuals.

Keywords: Asthma, Exacerbations, Heterogeneity, Placebo, Pulmonary function test, Systematic review, Vitamin D.

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BACKGROUND

Asthma is a chronic inflammatory airway disease, characterized clinically by wheezing and intermittent dry coughing at night, and confirmed by documenting reversible airflow obstruction or airway hyperresponsiveness. The global prevalence of physician-diagnosed asthma, clinical/treated asthma, and wheezing in adults was 4.3, 4.5, and 8.6% respectively, and prevalence vary as much as 21-fold among the 70 countries.¹ Vitamin D plays an important role in calcium and bone metabolism as well as immunomodulation. Many cells (brain, colon, prostate, breast, immune cells) contain vitamin D receptors (VDRs) and respond to 1, 25-dihydroxyvitamin D (the active form of vitamin D).² There have been multiple reports of association between vitamin D deficiency and diseases, such as cancer, depression, cardiovascular diseases, diabetes, multiple sclerosis, osteoporosis, fertility, and asthma.^{3,4} There are few studies that show a negative association between vitamin D levels and asthma.⁴ The linkage between VDR polymorphisms on chromosome 12 and the diagnosis of asthma has been reported.³

Recent studies in adult and children found a higher prevalence of hypovitaminosis D in asthmatic individuals than in the normal population. In addition, low vitamin D levels are associated with higher asthma severity and worse pulmonary function.^{4,5} In asthmatic children, patients with vitamin D deficiency demonstrated increased airway hyperresponsiveness and corticosteroid requirements. In asthmatic children and adults, serum 25-hydroxyvitamin D levels less than 30 ng/ml have been linked to airway hyperresponsiveness, impaired lung function, increased exacerbation frequency, and reduced corticosteroid responsiveness.⁶⁻⁹ Vitamin D has been hypothesized to increase glucocorticoid response in patients with asthma. Greater lung function is associated with higher vitamin D levels with a 22.7 ($\pm$ 9.3) ml (mean $\pm$ SE) increase in forced

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expiratory volume in 1 second (FEV1) for each nanogram per milliliter increase in vitamin D ($p=0.02$). There is increased airway hyperresponsiveness in participants with vitamin D insufficiency (<30 ng/ml), with a provocative concentration of methacholine inducing a 20% fall in FEV1 of $1.03 (\pm 0.2)$ mg/ml *vs* $1.92 (\pm 0.2)$ mg/ml in those with vitamin D of 30 ng/ml or higher ($p=0.01$).^{6,7} Although the underlying mechanisms are still unknown, it has been suggested that vitamin D augment anti-inflammatory function of corticosteroids in asthma, either by enhancing the ability of T cells to produce interleukin (IL)-10 or through inhibition of Th17 cytokine production.^{10,11} Low vitamin D levels also create a proinflammatory state. These findings suggest that vitamin D supplementation could modify the steroid response and reduce airway inflammation. However, the question whether treatment with vitamin D improves the outcome in patients with asthma has not been reviewed and still needs to be addressed.^{10,11}

RESULTS

Inclusion Criteria

The studies included were randomized controlled trials, in which vitamin D supplementation was compared with placebo/no supplementation in patients with asthma (moderate to severe) diagnosed in accordance with Global Initiative for Asthma (GINA) guidelines. The inclusion of studies was not restricted by the dose of vitamin D received, concomitant use of corticosteroids (oral/inhaled) for treatment of asthma, and language of publication.

Objectives of the Study

The primary objective of the review was to determine the evidence supporting the role of vitamin D in decreasing the number of participants with acute exacerbations. The secondary objectives were improvement in the quality of life questionnaire and adverse events reported to be related to vitamin D supplementation.

Search Methods for identification of Studies

We attempted to identify all relevant studies, regardless of language or publication status (published, unpublished, in press, on-going). We searched the following databases: PubMed, Ovid, Embase, and Cochrane Central e-Appendix 1.

We also checked reference lists of all primary studies and review articles, and searched for errata or retractions from the included studies. We also manually searched index Medicus, CTRI, and ClinicalTrials.gov for any ongoing studies and snowball method for the manual searching.

Selection of Studies

Two authors independently screened the titles and abstracts of all the potential studies, removed the duplicates and coded them as "retrieve" (potentially eligible) or "do not retrieve" (not eligible). The retrieved full texts were then screened for inclusion and multiple reports/articles, if any, for the same study were collated. The reasons for exclusion of the ineligible studies were recorded. Any disagreements were resolved through discussion with the arbiter.

Data Analysis

Data were analyzed using RevMan software (version 5.0.2). GRADEpro software developed by Grading of recommendations assessment, development and evaluation (GRADE) working group was used to grade the evidence as low, moderate, or high quality.¹²

Continuous outcomes were presented as mean differences (MDs) with 95% confidence interval (CI) and dichotomous outcomes were presented as odds ratio (OR) with 95% CI. A meta-analysis was performed using a fixed-effect model unless there was evidence of heterogeneity (clinical and statistical) of effects across studies. We used Cochrane criteria to assess the risk of bias (quality) in the clinical studies.¹³

Heterogeneity was interpreted based on thresholds as identified in The Cochrane Handbook for Systematic Reviews of Interventions.¹⁴ We estimated statistical heterogeneity among studies using the chi-square test statistic and in turn used the result to calculate the heterogeneity statistics.¹⁴ (Prospero registration number: CRD42014013619).

Overview of Included Studies

Out of 469 records/studies identified through database searching and 14 additional records/studies, through other sources, 133 records were removed as duplicates. The remaining 350 records were screened for titles and abstracts. Nine studies were extracted as full-text articles. Four studies were excluded (two were nonrandomized controlled trials,^{15,16} one was a murine study,¹⁷ and one reported outcomes not relevant to the inclusion criteria¹⁸). Finally, five studies were included in the systematic review (Flow Chart 1). This systematic review was conducted in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement.¹⁹ Two review authors independently extracted the data from included studies and noted the characteristics of included studies (Table 1). Risk of bias graph was also prepared for the included studies (Graph 1).

The minimum dose of total cholecalciferol supplemented was 90,000 IU in 24 weeks and maximum

Table 1: Characteristics of the included studies

Study ID	Setting/ country	Participant details	Intervention	Control/placebo	Outcome	Randomization	Allocation concealment	Blinding	ITT
Castro et al (2014)	USA	Participants (> 18 years) with asthma and serum 25-hydroxyvitamin D < 30 ng/ml were on inhaled ciclesonide 320 µg/day and levalbuterol 180 µg/day	High dose vitamin D3 (100000IU once, followed by 4000IU/d for 28 weeks) Total = 8,84,000IU	Placebo	FEV1%, PEFR, Exacerbation, Asthma symptom score, Asthma control test	The study was a randomized, double-masked, parallel group trial	Yes	Yes	Yes
Martinaeu et al (2015)	London, UK	Two fifty adult patients (125 in patient group and 125 in control group) with a medical record diagnosis of asthma	Six 2 monthly oral doses (Vitamin D3) 120,000 IU Total = 720000 IU	Identical placebo	Severe asthma exacerbation, FEV1%, ACT, PEFR	Block randomization	Yes	ND	Yes
Urashima et al (2010)	Japan	School children aged 6–15 years with or without underlying diseases by influenza with asthma. Treatment not mentioned	The participants were asked to take 3 tablets twice daily (total: 1200 IU vitamin D3) for 17 weeks. Total = 142800 IU	Placebo	Exacerbation	A randomized, double-blind, placebo-controlled trial	Yes	Yes	Yes
Yadav and Mittal (2014)	Rohtak, India	100 children (3 and 14 years of age) with moderate to severe asthma	One group received vitamin oral vitamin D3 (cholecalciferol) 60,000 IU/month for 6 months Total = 360000 IU	Placebo powder	Exacerbation, PEFR	Double-blind, randomized control trial	Yes	Yes	No
Majak et al (2011)	Poland	5–18 years with newly diagnosed asthma	Steroid + vitamin D3 group (budesonide 800 µg/d administered as dry powder and vitamin D 500 IU cholecalciferol) for 6 months. Total = 90000 IU	Steroid group (budesonide 800 µg/d administered as dry powder and vitamin D placebo)	FEV1%	A randomized, double-blind, parallel group	Yes	Yes	Yes

Flow Chart 1: Prisma chart for identifying studies

of 8,84,000 IU for 28 weeks in the included studies. The duration and dose of vitamin D supplementation has been listed in characteristics of included studies (Table 1).

Five studies assessed the number of participants with asthma exacerbations as a primary outcome.²⁰⁻²⁴ In children, three studies had participants less than 18 years of age (n=482).²¹⁻²³ The number of participants with asthma exacerbations (any severity) in children (<18 years of age) was significantly reduced in the vitamin D supplemented group (OR:0.23, 95% CI:0.12–0.43). In adults (>18 years age), the number of participants with exacerbations was not significantly reduced in the vitamin D supplemented group (OR:0.89, 95% CI:0.47–1.68) (n = 630).^{20,24} The overall pooled effect showed a significant reduction in number of participants with asthma exacerbation in vitamin D supplemented group (OR:0.45, 95% CI:0.22–0.93, five trials; moderate-quality evidence; Tables 2 and 3).

There were no studies that reported data on quality of life questionnaire. A total of 23 serious adverse events in 20 participants and 1283 nonserious adverse events in 240 participants were reported by the single study.²⁴ The quality of the evidence was assessed according to GRADE using GRADEpro software (Table 3).

DISCUSSION

Summary of Results

This systematic review and meta-analysis on the evidence of vitamin D supplementation in patients with moderate to severe asthma has shown its effect on various aspects of asthma. Vitamin D supplementation has significantly reduced the asthma exacerbations in children.²¹⁻²³

Graph 1: Risk of bias graph

Table 2: Forest plot of comparison: Vitamin D vs placebo, outcome: Patients with acute exacerbation. Odds ratio relates the ratio of odds of frequency of acute exacerbations in individuals with asthma supplemented with vitamin D compared with placebo **Table 3:** Summary of finding table

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with vitamin D			
Patients with asthma exacerbation	Study population		OR 0.45 (0.22–0.93)	1112 (5 RCTs)	⊕⊕⊕O MODERATE ¹
	247 per 1000	129 per 1000 (67–234)			
	Moderate				
Patients with asthma exacerbation ≤ 18 years	Study population		OR 0.23 (0.12–0.44)	482 (3 RCTs)	⊕⊕⊕O MODERATE ²
	412 per 1000	240 per 1000 (134–395)			
	Moderate				
Patients with asthma exacerbation ≥ 18 years	Study population		OR 0.89 (0.47–1.68)	630 (2 RCTs)	⊕⊕⊕O MODERATE ³
	458 per 1000	163 per 1000 (92–271)			
	Moderate				

¹Urashima et al (2010) and Yadav and Mittal (2014) had attrition bias. Reporting bias was shown by Castro et al (2015) and Martineau et al (2015)

²Urashima et al (2010) and Yadav and Mittal (2014) have attrition biases

³Reporting bias by Castro et al (2014) and Martineau et al (2015)

However, in adults, two studies^{20, 24} did not report any reduction in the number of participants with asthma exacerbations. There were no studies that reported quality of life questionnaire. There were 23 serious adverse events and a total of 1283 nonserious adverse events reported by a single study.²⁴

Heterogeneity and Sensitivity Analysis

Heterogeneity was considerably higher in the trials included to determine asthma exacerbations in those >18 years of age. Thus, the sensitivity analysis was done by

using the random effect model. The higher heterogeneity was due to a single study done in children, having higher effect size than the other four included studies in children having low effect size (Table 4).²²

The results of our systematic review on asthma exacerbations were similar in comparison to a previous meta-analysis, but a subgroup analysis done in our review is not reported by the previous meta-analysis.²⁵ The results of the meta-analysis on exacerbation were not documented by the recent systematic review that included observational studies.²⁶

Table 4: Sensitivity analysis for the outcome of asthma exacerbation

Study or subgroup	Vitamin D		Control		Weight	Risk difference M-H, Fixed, 95% CI	Risk difference M-H, Fixed, 95% CI	
	Events	Total	Events	Total				
1.1.1 <18 years								
Majak 2011	4	24	11	24	6.2%	- 0.29 (-0.54, -0.04)		
Yadav 2014	14	50	30	50	12.9%	- 0.32 (-0.50, -0.14)		
Subtotal (95% CI)		74		74	19.0%	- 0.31 (-0.46, -0.16)		
Total events	18		41					
Heterogeneity: Chi² = 0.03, df = 1 (p = 0.86); I² = 0%								
Test for overall effect: Z = 4.11 (p < 0.0001)								
1.1.2 <18 years								
Castro 2014	26	201	39	207	52.4%	- 0.06 (-0.13, 1.01)		
Martineau 2015	50	108	47	114	28.5%	- 0.05 (-0.08, 0.18)		
Subtotal (95% CI)		309		321	81.0%	- 0.89 (-0.09, 0.04)		
Total events	76		86					
Heterogeneity: Chi² = 2.29, df = 1 (p = 0.13); I² = 56%								
Test for overall effect: Z = 0.62 (p = 0.54)								
Total (95% CI)		383		395	100.0%	- 0.08 (-0.14, 0.02)		
Total events	94		127					
Heterogeneity: Chi² = 13.47, df = 3 (p = 0.004); I² = 78%								
Test for overall effect: Z = 2.49 (p = 0.01)								
Test for subgroup differences: Chi² = 12.36, df = 1 (p = 0.0004), I² = 91.9%								

The moderate quality of GRADE reported in our systematic review is due to significant attrition shown by two of the included studies^{22,23} and no description of the method of randomization and allocation concealments in one included study.²² The GRADE analysis done in our review is not demonstrated by previous systematic reviews.^{25,26}

Strengths and Limitations of Review

The strength of the present systematic review lies in the inclusion of studies that report the outcomes in both children and adult asthmatic individuals. Our study reported the reduction in number of participants with asthma exacerbations in children, with the similar findings documented by the previous review.²⁷ However, there is no reduction in adult population and is not reported by previous review.²⁷ There are no studies that focus on the secondary outcome of the quality of life in the included studies. The data from the ongoing trials could not be added due to nondisclosure of results. The pooled sample size of the included trials is low, leading to a higher heterogeneity. Based on the results from our systematic review, it is recommended to design future randomized trials with primarily analyzing baseline levels of vitamin D, and then supplementing with higher doses of vitamin D for the deficient ones for a fixed duration of time.

CONCLUSION

This systematic review supports the role of vitamin D in reducing the number of asthma exacerbations in children but not in adults.

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