Does vitamin D supplementation reduce the frequency or severity of asthma exacerbations in children?

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INTEGRIS

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SUMMARY

Clinical Question:

Does vitamin D supplementation reduce the frequency or severity of asthma exacerbations in children?

Answer:

Inconclusive. Vitamin D is well tolerated in pediatric patients and should be considered as adjunctive therapy in asthma to reduce frequency and/or severity of asthma exacerbation.

Level of Evidence: B

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INTRODUCTION

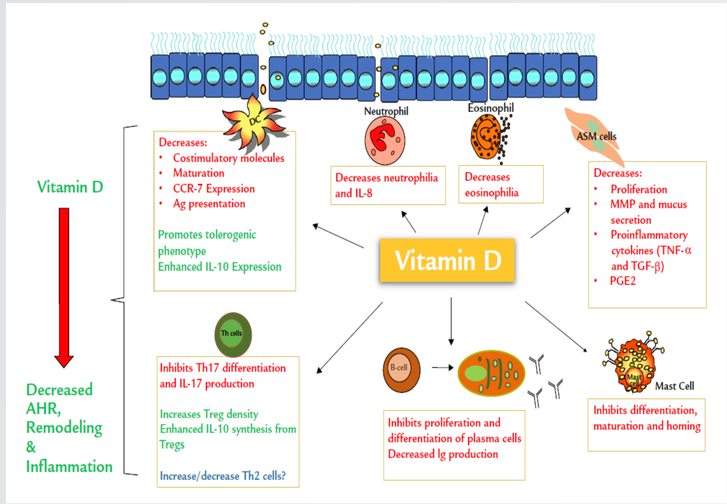
According to the CDC, over 25.9 million people in the United States are diagnosed with asthma; one third of these are pediatric patients.[1] Children who are at an increased risk of developing asthma include those exposed to household allergens (e.g. dust mites, mold, and cigarette smoke) and those who have had viral respiratory infections early in life. These same factors place children at an increased risk of experiencing an asthma exacerbation. Standard therapy for prevention and treatment of asthma currently includes limiting environmental exposure and using preventative medications (e.g. inhaled corticosteroids), rescue medications (e.g. albuterol), and acute exacerbation medications (e.g. IV corticosteroids). Vitamin D has been identified as potential asthma disease modifier, and it may be a therapeutic agent to reduce the frequency or severity of asthma symptoms with recent studies showing vitamin D deficiency being linked to the increased prevalence of asthma and risk of asthma exacerbations.[2]

The immunologic evidence behind vitamin D and inflammatory pathways has been well documented. It is known that vitamin D plays a role in lung function and in the reduction of pulmonary inflammation with vitamin D having been shown to increase surfactant synthesis, inhibit airway smooth muscle proliferations, and influence lung cell interactions during tissue maturation.[3] Vitamin D also has several other immunomodulatory properties including effects on epithelial cells, T & B lymphocytes, and antigen presenting cells.[4] Furthermore, virus-induced asthma exacerbations have been associated with interleukin 17A elevation, a proinflammatory cytokine present in allergic airway response. Vitamin D metabolites have been shown to inhibit production of interleukin 17A in peripheral blood mononuclear cells in asthma patients.[5]

This brings into question the possibility of adding vitamin D supplementation to standard asthma therapy to reduce asthma exacerbation frequency. This review will determine if vitamin D supplementation reduces the frequency or severity of pediatric asthma exacerbations.

DISCUSSION

Multiple prior studies have failed to consistently show a significant impact of vitamin D supplementation in asthmatic patients. There have been studies both supporting and refuting the effect of vitamin D blood levels and supplementation on asthma severity, prevalence, and exacerbations. Recently in 2016, a summary of evident report from published data up until January 2015 was released by the World Allergy Organization and concluded that clinicians should not use vitamin D supplementations to reduce allergic disease, including asthma. We review here



more recent studies in the past five years between 2014-2019.[2] Serum 25(OH) vitamin D is the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake, sun exposure, and adipose stores in the liver. The following studies used serum 25(OH) vitamin D to help determine study outcomes.

A relatively large study by Jolliffe et al in 2017 investigated a meta-analysis of 7 randomly controlled trials of asthmatic patients. This analysis included 978 patients in total, 297 children and 658 adults, spread across 3 continents who took either bolus doing (every two months) or daily dosing of vitamin D supplementation. The primary outcome of this study was the incidence of asthma exacerbations requiring treatment with systemic corticosteroids. Overall, results showed a significant reduction in asthma exacerbations requiring corticosteroids in patients who took vitamin D supplementation (RR 0.74, 95% CI 0.56-0.97). Further subgroup analyses showed that this effect appeared to trend strongest in patients with baseline 25(OH) vitamin D levels of less than 25 nmol/L (RR 0.33, 95% CI 0.11-0.98, 92 patients across 3 RCTs). This protective effect appeared to disappear with higher baseline 25(OH) vitamin D levels. However, this subgroup analysis did not meet statistical significance and no formal distinction in baseline vitamin D level could be made.[5]

Two prospective randomized, placebo-controlled trials in 2016 also showed a potential benefit of vitamin D supplementation. Kerley et all conducted a study in Ireland of 44 children who were randomized to receive 15 weeks of daily 2000IU vitamin D or placebo. Supplementation led to a significantly increased serum 25 (OH) vitamin D level as well as fewer school days missed due to asthma symptoms (1 vs. 5 days, p-0.04).[6] A separate study in Japan by Tachimoto et al investigated whether low-dose, short-term vitamin D supplementation improved control of pediatric asthma. They randomized 89 children to either take 800 IU/day of vitamin D or placebo for two months. Their primary outcomes were frequency and severity of asthma symptoms based on the Global Initiate for Asthma (GINA) asthma severity classification at two months and whether the effects persisted at six months. They concluded that vitamin D supplementation led to improved asthma control at two months and this effect was still statistically significant at six months.[7] While both of these randomized-controlled trials were small in size, they both highlight the potential benefit vitamin D supplementation may have.

In late 2014, a case-control trial by Hatami et al investigated the relationship between serum vitamin D levels and asthma severity in children. 200 children, ages 3-12, with asthma severity stratified by the GINA classification were matched with 200 controls. Their 25(OH) vitamin D levels were compared. A significant difference was observed between the concentration of 25(OH) vitamin D in the serum of healthy controls (25.39 +/- 4.1 ng/mL) and asthmatic patients (20.34 +/- 2.8 ng/ml: 95%CI: 1.46-3.86, P=0.01). Moreover, when stratified by the GINA asthma severity (intermittent, mild persistent, moderate persistent), while there was no statistical significance, there was a noticeable trend for vitamin D deficient (<20 ng/mL) patients to have higher prevalence of all three asthma severity categories when compared to vitamin D insufficient (20-30 ng/mL) and sufficient (>30 ng/mL) patients. The authors conclude vitamin D supplementation could be a tool to prevent or reverse allergic airway inflammation seen in asthma.[3]

CONCLUSION

Patients with vitamin D deficiency are more likely to have airway inflammation with some studies showing that vitamin D supplementation leads to a reduction in severity and frequency of asthma exacerbation. On the other hand, as documented previously by the World Allergy Organization, there has been conflicting evidence that did not show any improvement of asthma symptoms in patients receiving vitamin D supplementation. Further trials with adequate power and longer follow-up are necessary to confirm or refute these results. Unfortunately, nutrient-based clinical trials have continued to be difficult to control given differences in nutrient composition in different diets, amount of sunlight exposure, and nutrient levels in various supplements. Furthermore, the seasonality of asthma and confounding factors such as family history, cigarette smoke exposure, or pet dander exposure make result stratification difficult. It is also important for further research to determine the level of vitamin D at which patients would benefit from supplementation and the target vitamin D level for treatment. Despite these issues and the inconsistencies between studies, as a low cost and well-tolerated intervention, supplementation with vitamin D in patients with asthma should be considered.