

ously been described in other desensitization processes involving this same drug in cells of the epidermis⁷ and in peripheral blood⁸ as the mechanism responsible for resolution of the skin lesions. After induction of allopurinol tolerance in our case, the suppressing effect of IL-10 on the Th1 response has presumably prevailed and prevented the recurrence of a cutaneous reaction.

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Relationship of 25-hydroxyvitamin D and asthma control in children

Asthma prevalence and vitamin D deficiency rates have increased in parallel. We sought to address several critical issues in assessing the relationship of vitamin D and asthma.

It is accepted that serum 25-hydroxyvitamin D (25(OH)D) levels less than 10 to 12 ng/mL represent deficiency, levels less than 20 ng/mL represent insufficiency, and levels greater than 30 ng/mL represent sufficiency. A review of existing studies reveals associations between airway diseases and serum 25(OH)D using only a single measurement,^{1–4} and there are no dose-response data on the therapeutic effects of varying vitamin D levels in asthma.

We conducted a 1-year pilot study in children to examine whether increased serum 25(OH)D levels either through seasonal variations (placebo treatment) or with supplementation (vitamin D₃, 1,000 IU/d) result in improved asthma control (assessed by multiple measures, including Asthma Control Test [ACT] scores) in patients with chronic persistent asthma.⁵

Thirty patients, ages 6 to 17 years, with a physician diagnosis of chronic persistent asthma and current daily controller asthma medication were enrolled from Creighton University Medical Center. Patients were randomly assigned to either placebo or 1,000 IU of vitamin D daily. No differences were found in baseline characteristics between the placebo and vitamin D groups. At initial (winter), 6-month (summer) and 1-year (winter) visits, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), ACT score, spirometry, and serum 25(OH)D levels were measured. Twenty-four patients returned for a 6-month follow-up visit, with 3 patients lost to follow-up from each arm. Twenty patients completed the study, with 2 more patients lost from each arm.

The patient population was mainly nonwhite. Only 1 patient had a sufficient vitamin D level at baseline. The mean ACT score at baseline was 17.8 for both groups.

At the 6-month follow-up, the serum 25(OH)D levels in both the supplemented and placebo groups had increased significantly from baseline but did not differ significantly from each other (Fig 1A). However, only 33% of those in the supplemented group and 41.7% of those in the placebo group were vitamin D sufficient at 6 months (summer). At 1-year follow-up (winter), 50% of those in the supplemented group and 20% of those in the placebo group had sufficient

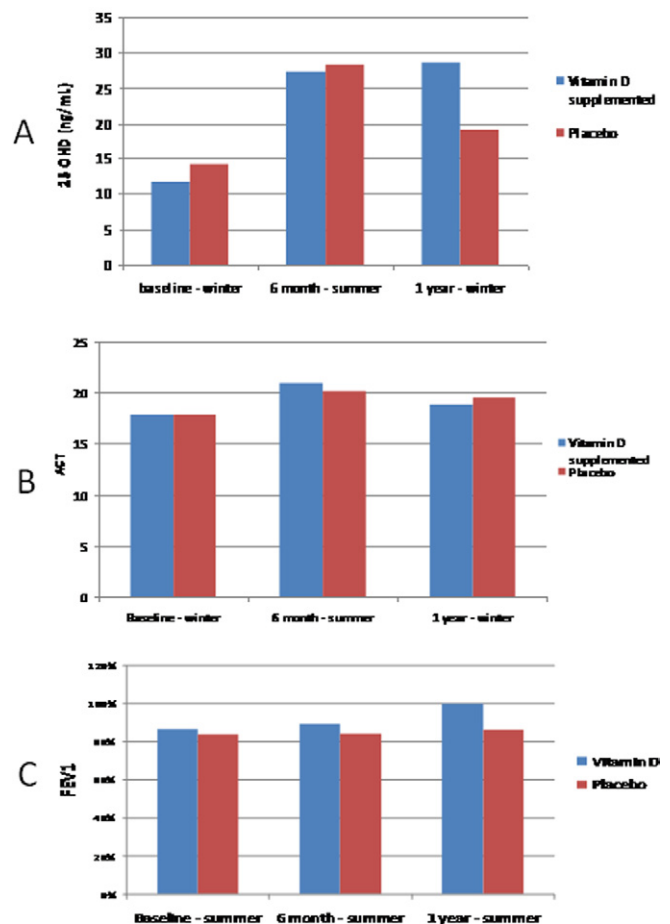


Fig. 1. Effects of season and vitamin D supplementation on serum 25-hydroxyvitamin D levels (A), Asthma Control Test scores (B), and forced expiratory volume in 1 second (C). Patients were enrolled in the winter and treated with either placebo or 1,000 IU/d of vitamin D for 1 year. The listed parameters were assessed at baseline in the winter, 6 months later in the summer, and 12 months later in the next winter. The numbers of patients for each of the 3 periods were 15 in each group at baseline, 12 in each group at 6 months, and 10 in each group at 1 year.

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25(OH)D levels. Vitamin D supplementation did not affect the ACT score or forced expiratory volume in 1 second (Fig 1B and C). However, because the patients' conditions were relatively well controlled at entry, this could have influenced the results.

When data were pooled using all serum 25(OH)D levels matched to the ACT scores for each of the 3 time points measured, a significant positive correlation was found (Pearson $r = 0.25$, $P < .05$). An inverse correlation of serum 25(OH)D and BMI was found (Pearson $r = 0.3$, $P < .05$).

There are important considerations from our data regarding the relationship of vitamin D and asthma. First, significant seasonal variation in 25(OH)D levels occurred, emphasizing the importance of obtaining multiple 25(OH)D levels throughout a study to allow for increases in 25(OH)D levels due to sun exposure. Even though those in the placebo group had an increase in serum 25(OH)D level in the summer, most individuals were still vitamin D insufficient (58.3%).

Second, to assess the therapeutic effect in asthma, a significantly higher dose of vitamin D supplementation will be necessary beyond the recommendation of the Institute of Medicine (600 IU)⁶ or the American Academy of Pediatrics (400 IU).⁷ We observed in our study population that 1,000 IU was inadequate to increase 25(OH)D levels more than 30 ng/mL in 50% of our study participants after 1 year of supplementation. This is likely dependent on the individuals because factors such as diet and sun exposure contribute to a person's 25(OH)D level. Most of our study participants were black or Hispanic, and many were overweight at baseline, with a mean BMI of 24.5. Vitamin D deficiency has been linked to being overweight and having darker skin color.⁸ Future studies should consider higher doses of vitamin D or, preferably, serial titration to sufficiency to ensure sufficient 25(OH)D levels.

Third, future therapeutic trials should be powered sufficiently, and patients supplemented to vitamin D levels greater than 30 ng/mL during the entire study to reveal the potential for vitamin D supplementation to improve asthma control. In this study, no significant differences were found in ACT scores or spirometry values between vitamin D–treated and placebo-treated individuals. This may have been a result of failure to achieve normal 25(OH)D levels in most vitamin D–treated patients. The study was likely underpowered with a relatively large dropout rate (33.3%). However, when the ACT data obtained from all visits were pooled, a positive correlation was found between serum 25(OH)D levels and ACT scores, suggesting an effect of vitamin D in asthma management.

Fourth, secondary end points for therapeutic benefit should be expanded, possibly adding serial methacholine challenges and nitric oxide measures, which might show interim benefit.

Because vitamin D has a number of potential important effects in asthma, this line of investigation is important. However, future studies need to be conducted for at least 1 year with higher levels of vitamin D supplementation and a larger number of individuals to truly determine the significance of vitamin D in asthma.

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Hypersensitivity reactions to marijuana

Allergy to marijuana is generally considered to be rare. *Cannabis sativa* is an annual plant in the Cannabaceae family that pollinates during the summer months. Various parts of this plant are used for both commercial and recreational purposes. Psychoactive cannabinoid compounds, mainly Δ^9 -tetrahydrocannabinol (THC), are present in the flowers and, to a lesser extent, in the leaves, stems, and seeds of the plant. When derived as dried preparations of the plant parts (marijuana), the cannabinoids are consumed by smoking, vaporizing, and oral ingestion. Teas and ointments are also common preparations.

The first report of allergic reaction to *C sativa* was in 1971, when a 29-year-old woman, after smoking a marijuana cigarette for the first time, had symptoms consistent with an anaphylactic re-

sponse.¹ Hypersensitivity was confirmed via skin prick testing (SPT) and passive transfer studies, suggesting an immunologic response to the THC component of the marijuana plant.¹ Since then, several case reports have been published describing allergic reactions to *C sativa* after exposures through inhalation, ingestion, or skin contact.^{2–4} Reactions, including rhinoconjunctivitis, urticaria, and angioedema, have been reported.

In addition to THC, sensitization to marijuana may involve IgE directed to proteins from *C sativa*.³ One case involved a 28-year-old man who had urticaria on contact and rhinorrhea after smoking marijuana.⁴ The investigators were able to isolate a 9-kDa IgE-binding protein and identified it as a lipid transfer protein (LTP). The patient's IgE to cannabis LTP cross-reacted with the LTP from peach.⁴ LTP is highly stable and cross-reacts with a large number of pollens and foods. Thus, individuals can have both type 1 hypersensitivity symptoms of rhinoconjunctivitis and anaphylactic symptoms when exposed not only by inhalation but also by ingestion

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