

EDITORIAL

Vitamin D supplementation in children with asthma

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Worldwide, asthma is a chronic inflammatory respiratory disease affecting over 300 million people, and some of these patients remain inadequately controlled by usual therapies and experience exacerbations.

In cross-sectional studies in asthmatic children, vitamin D deficiency has been linked to increased severity and exacerbations of symptoms (1, 2) and reduced asthma control (3, 4). However, it is difficult to find a temporal causal relationship in cross-sectional observations.

Biologically, as an adjunct therapy, vitamin D should improve disease control in severe asthma as it enhances glucocorticoid responsiveness; skews immune cells toward a regulatory phenotype; reduces the incidence of infections; mitigates airway smooth muscle hyperplasia, eosinophilia, and airway remodeling; and may lower the levels of IgE (5, 6).

At demonstration of the critical biologic role that vitamin D plays in human immunity and physiology, a systematic review and meta-analysis of five clinical trials, reporting asthma-related respiratory outcomes following vitamin D administration at a dose ranging from 500 to 2000 IU/day, found a 59% reduction in the risk of asthma exacerbation (RR 0.41) with supplementation (7).

Asthma exacerbations are mainly associated with viral respiratory tract infections, and there is evidence that deficiencies in antiviral activity and the integrity of the airway epithelial barrier could make individuals with asthma more susceptible to severe viral respiratory infections of the lower airway and thus to increased risk of exacerbation (8). At this regard, observational studies have documented an association between low vitamin D status and increased risk of acute viral respiratory infections in agreement with the immunomodulatory effect of vitamin D (9).

However, results from recent trials, assessing the effect of vitamin D supplementation on the prevention of childhood acute respiratory infections, have been inconsistent, and a recent systematic review of seven randomized controlled trials on vitamin D supplementation, for the prevention of childhood acute respiratory infections in children, found no significant effect on the reduction of childhood acute respiratory infections (RR 0.79) but, in subjects previously diagnosed with asthma, vitamin D supplementation resulted in a 74%

reduction in the risk of asthma exacerbation (RR 0.26) (10). At the same time, a systematic review and meta-analysis of eight randomized controlled trials provided some low-quality evidence to support vitamin D supplementation for the reduction of asthma exacerbations (11), a result which is strikingly different from the conclusion of other groups who analyzed in part the same studies.

So what is going wrong with vitamin D supplementation in asthma if we have conflicting results even from systematic reviews and meta-analysis?

In this issue of the Journal, Kerley et al. (12) evaluated the effect of vitamin D supplementation in children with not controlled asthma and found no effect of supplementation on subjective asthma control and lung function, but a significant decrease in school days missed due to asthma which seems clearly a contradicting and difficult to explain finding. If we observe conflicting results within the same study, we should not be surprised to see discordant results in studies performed with different designs with different patients and with different outcomes' evaluation.

Some cautions are needed interpreting this study results. In the Kerley et al. study, only 39 patients completed the trial and they were divided into four groups (VD deficient + supplementation, VD sufficient + supplementation, VD deficient + placebo, and VD sufficient + placebo) resulting in a small number of subjects in each group. The authors found that vitamin D supplementation was associated with decrease in school days missed and alkaline phosphatase, but no beneficial effects are founded regarding asthma control (c-ACT, mPAQLQ), IgE, ECP, and hsCRP.

However, ninety percent of the patients were allergic and total IgE level was lower in the vitamin D-supplemented group than in the placebo (not significant only because the limited number of patients), and thus, there was more room for increasing if exposed to relevant allergens (no information is available on allergen avoidance strategies eventually adopted).

Also, baseline eosinophils and EP levels were half in the supplemented group compared to the placebo.

If the negative outcome of vitamin D on several parameters is attributable to a biologic effect of vitamin D itself, this

should have been observed more in children who were vitamin D sufficient and supplemented rather than in those who were vitamin D deficient and supplemented, but this was not the case. So different events must be present to justify the author's results.

Also, the negative effect in spirometry observed in vitamin D-supplemented group, rather than being a biologic effect of vitamin D, can simply represent a regression toward the mean because lung function was better and normal in this group, and therefore, there was no room for improvement. The same could be true for the significant decrease in hsCRP in the PL group compared to the D3 Group as hsCRP in the PL group was significantly higher at baseline compared to the supplemented group.

In conclusion, well-designed clinical trials are warranted to define the optimal level of vitamin D, as well as dosing and duration of vitamin D supplementation, in pediatric patients.

Vitamin D has very complex biochemistry, and studies that evaluate the wide spectrum of vitamin D metabolites and intermediates, receptor polymorphisms, binding protein variants, and vitamin D metabolic enzyme should be performed to try to reach firm conclusions on the effect of this hormone on respiratory and allergic diseases in children.

Competing interests

AL Boner is consulting his son Company, Envicon Medical that manufactures products used for allergen avoidance and supplements nutraceuticals containing also vitamin D.

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