Editorial

Vitamin D in asthma: Panacea or true promise?

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Recent epidemiologic studies suggest that the prevalence of vitamin D insufficiency in the United States population is increasing,[1] a phenomenon attributed at least in part to dietary and behavioral changes over the last several decades. In this context, a growing number of studies investigating adverse health effects related to these population-level observations have emerged, including several investigating the role of vitamin D in asthma. To the skeptic, the results of many of these studies seem too good to be true, for they suggest that providing supplemental vitamin D to patients with asthma and low serum concentrations of vitamin D might (1) prevent the development of asthma, (2) reduce impairment and risk in patients who have the disease, and (3) enhance clinical response to glucocorticoids, the most widely applied and effective treatment for persistent asthma. Ongoing prospective studies will test each of these hypotheses and either assuage or fortify the skeptics, but examination of the current evidence does suggest a promising role for vitamin D supplementation in asthma.

There are at least 2 important aspects to the possible association between vitamin D and asthma. The first is the assertion that *in utero* and early-life vitamin D deficiency are associated with an increased risk of asthma, a conclusion based on birth cohort data suggesting that maternal vitamin D intake is inversely associated with risk of recurrent wheezing illness and the diagnosis of asthma in childhood.[2-5] This observation may be attributable to the fact that vitamin D modifies risk for viral infection, because these birth cohort studies have correlated maternal vitamin D intake or cord blood 25-hydroxyvitamin D (25[OH]D) levels with early childhood respiratory infections and wheezing, suggesting one pathway by which asthma risk reduction may occur. Some uncertainty remains in this area, however, because Camargo et al[6] recently reported that there was no association between cord blood 25(OH)D concentrations and incident asthma at 5 years in a New Zealand cohort of 922 infants.

The second important issue is the role of vitamin D in prevalent asthma, specifically related to phenotypic characteristics such as lung function, airway hyperresponsiveness, treatment response, and exacerbation risk. In this issue of the Journal, Brehm et al[7] report that insufficient vitamin D status (defined by serum concentrations <30 ng/mL) at enrollment was associated with a modest increase in the risk of severe asthma exacerbations over a 4-year follow up period in members of the Childhood Asthma Management Program cohort. Although this observation seems to suggest an important role for vitamin D in reducing exacerbation risk, we are unable to determine from this study the pathways through which the outcome is mediated. As noted by the authors, the study is limited by the absence of repeated vitamin D measurements over time, an issue that limits our ability to understand the extent to which fluctuations in vitamin D levels over time (because of seasonal, lifestyle, and demographic variables) might be relevant to the observed effect. Of note, the benefit with regard to exacerbations seemed to be accrued independent of significant effects of vitamin D status on markers of atopy or airway hyperresponsiveness, and in the setting of only small effects on absolute FEV_1. Although the exact nature of the relationship between vitamin D and severe exacerbations remains unclear, and although 1 limitation of the dataset the authors analyzed is the absence of specific data regarding respiratory tract infections, these findings suggest an effect that is mediated through enhanced resistance to respiratory tract infection rather than through direct modification of airway inflammation.

This conclusion is supported by *in vitro* data showing that vitamin D is important in inducing the production of antimicrobial peptides, including cathelicidin,[8,9] as well as by an analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) that identified a higher risk of upper respiratory tract infection in those with 25(OH)D <10 ng/mL compared with those with ≥30 ng/mL (adjusted odds ratio, 1.36; $P = .04$).[10] Interestingly, this association was strongest among those with asthma (adjusted odds ratio, 5.67; P for interaction = .007). Furthermore, a recent clinical trial in Japanese schoolchildren found that 1200 IU oral vitamin D_3 supplementation daily for 4 months reduced the incidence of influenza A compared with placebo (relative risk, 0.58; $P = .04$).[11] In this study as well, vitamin D supplementation appeared to have a stronger effect in the subcohort with underlying asthma (relative risk, 0.17; $P = .006$).

It is also possible that the effect of vitamin D may occur through enhancement of glucocorticoid responsiveness, a conclusion supported by the observation in this study of a greater protective effect of budesonide with regard to asthma exacerbations in those children with 25(OH)D concentrations ≥30 ng/mL. Previously, Xystrakis et al[12] reported that exposure of $CD4^+$ T cells from subjects with steroid-resistant asthma to both IL-10 and vitamin D_3 essentially reversed defects in glucocorticoid-induced IL-10 production by these cells. The authors also determined that ingestion of vitamin D_3 by subjects with steroid-resistant asthma enhanced IL-10 synthesis by T cells in response to dexamethasone, providing potential mechanisms by which vitamin D could enhance glucocorticoid responsiveness. More recently, Sutherland et al[13] reported that in a small cohort of adults with mild or moderate persistent asthma, lower serum 25(OH)D concentrations were associated with impaired lung function, increased airway

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hyperresponsiveness, and decreased *in vitro* corticosteroid response, with higher serum 25(OH)D concentrations associated with enhanced dexamethasone-induced expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) by PBMCs in an apparently IL-10–independent fashion.

In children, Searing et al[14] recently reported in the Journal that serum 25(OH)D concentrations were positively correlated with the use of both inhaled and oral steroids and total steroid dose, positively correlated with FEV_1 percent predicted and the FEV_1/forced vital capacity ratio, and inversely correlated with IgE and the number of positive aeroallergen skin prick tests. The authors also reported the results of *in vitro* experiments in which physiologic concentrations of vitamin D added to dexamethasone significantly enhanced MKP-1 expression in PBMCs compared with dexamethasone alone and suggested that the addition of vitamin D could decrease the dexamethasone dose requirement for steroid response by more than 10-fold. Separately, a recent population study in Costa Rican children, also reported by Brehm et al,[15] suggested an association between lower 25(OH)D concentrations and increased inhaled corticosteroid requirements in children, with a reduced odds of anti-inflammatory controller therapy use as 25(OH)D increased.[15] It is therefore interesting to note that, in the Childhood Asthma Management Program cohort, baseline 25(OH)D concentrations were not associated with many of the aforementioned surrogate markers of steroid response, leaving it to future studies to determine whether the effect of vitamin D on severe exacerbations is related to a reduction in respiratory tract infections or improvements in airway inflammation or glucocorticoid responsiveness, or whether it is mediated by the numerous demographic, lifestyle, socioeconomic, and other factors associated with vitamin D status in observational studies.

Given this framework, the emerging narrative relating vitamin D and asthma remains compelling and in need of further development. We look forward to the results of clinical trials of vitamin D supplementation, both for primary prevention and modification of prevalent disease, with strong mechanistic components which will help to elucidate further the role of vitamin D in asthma.

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