



## The Sun also rises

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Despite being present in minimal quantities, vitamins are essential for the proper functioning of the human organism. A healthy lifestyle and good dietary habits supply the minimum daily requirements, including that of vitamin D. Human beings have adapted over thousands of years to obtain vitamin D from natural sources, by synthesis in the skin from exposure in sunlight, or by consuming foods rich in its provitamin, such as eggs, cold-water fish, mushrooms, and cod liver oil.<sup>(1)</sup>

Adequate concentrations of vitamin D modulate the immune response and play a decisive role in respiratory health. In contrast, vitamin D deficiency (serum concentrations below 10 ng/mL) can result in inflammation of the airway smooth muscle, excessive mucus production, and bronchial hyperresponsiveness.

### WHY DOES THAT HAPPEN?

Vitamin D is one of the lipophilic mediators that participate in innate and adaptive immunity. The activity of vitamin D is of greater importance for health in innate immunity, because it stimulates dendritic cells and innate lymphoid cells, as well as molecules such as cathelicidins and  $\beta$ -defensins, which have antimicrobial properties, promote immune/metabolic training, bolster epigenetic adaptation, and stimulate apoptosis. Vitamin D also favors the proliferation of tolerogenic dendritic cells and inhibitory receptors, thus protecting against unwanted inflammation. As for adaptive immunity, vitamin D helps minimize Th1/Th17 hyperfunction and modulate the Th2 response.<sup>(1,2)</sup> Vitamin D inhibits the Th2 response by stimulating production of the immunomodulatory cytokines TGF- $\beta$  and IL-10. That production, together with stimulation of the Foxp3 transcription factor and regulatory T lymphocytes, blocks IL-13 and prevents exacerbation of Th2 inflammation. Likewise, B lymphocytes will predominantly produce IL-10 and IgG4 antibodies, thus blocking allergic phenomena. Therefore, vitamin D prevents eosinophilia and neutrophilia with excessive IL-8 production, inhibiting the proliferation and differentiation of plasma cells that secrete excess IgE, as well as the maturation of mast cells and their migration into the airways.<sup>(1,2)</sup>

### HOW DOES THE WELL-ORCHESTRATED SET OF RESPONSES TO VITAMIN D TRANSLATE INTO CLINICAL PRACTICE?

In recent decades, there have been a number of studies evaluating vitamin D deficiency/insufficiency as a biomarker/risk factor in the prophylaxis and complementary

treatment of asthma.<sup>(3)</sup> However, such studies, most of which were carried out in temperate countries with limited solar radiation throughout the year, have produced divergent results, as demonstrated in the conclusions of some systematic reviews and meta-analyses, such as one that included 36 studies evaluating serum vitamin D levels and complementary treatment of asthma with vitamin D versus placebo.<sup>(3)</sup> The authors of that systematic review and meta-analysis found that serum vitamin D levels were significantly lower among the children with asthma ( $n = 5,711$ ) than among those without ( $n = 21,561$ ). They also found that children who received vitamin D supplementation had fewer exacerbations than did those who received a placebo.<sup>(3)</sup> That finding is in keeping with those of other systematic reviews and meta-analyses, although such supplementation was not found to result in an improvement in lung function.<sup>(4,5)</sup>

One of the hypotheses raised to explain the lower number of exacerbations among individuals with asthma who receive vitamin D supplementation is that low levels of vitamin D predispose to viral infections, one of the main triggers of asthma exacerbations.<sup>(4)</sup> A comparison across studies indicates that there is statistical heterogeneity between clinical and functional outcomes. That could be attributed to several factors, including the serum vitamin D level at baseline, dose of vitamin D prescribed, and duration of supplementation; the age of the patients in the sample; latitude; sample variability; bias risk and control; follow-up time; and the use of medications, including oral corticosteroids, which are responsible for reducing serum vitamin D levels.<sup>(3-5)</sup> Another critical variable is inherent to the metabolism of vitamin D. It is known that vitamin D has a prolonged half-life and that daily supplementation for at least three months is necessary in order to reach a stable serum level. Therefore, different administration strategies and definitions of serum levels can generate different results.

The complexity of the relationship between vitamin D and asthma is amplified by the importance of variants in many genes that affect the regulation of vitamin D, which include the genes along the metabolic pathway, together with the genes of receptors in epithelial and bronchial smooth muscle, which increase the expression of various cytokines and interleukins, as well as contributing to the association between vitamin D and inflammation.<sup>(6)</sup>

A study published in this issue of the Brazilian Journal of Pulmonology sheds light on the whole range of comments, questions, and speculations regarding the relationship between asthma and vitamin D.<sup>(7)</sup> Despite the adoption

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of population-based sampling to obtain two comparable groups, that objective was not achieved for all of the study variables. For example, the statistically significant differences detected between age groups and school types, as well as the borderline difference in physical activity, could have introduced selection biases for both the prevalence of asthma and the serum levels of vitamin D. As pointed out by the authors, causal relationships cannot be established from cross-sectional studies; only cohort or case-control studies could provide an answer. In addition, it would be desirable to confirm the clinical diagnosis of active asthma through pulmonary function tests. However, the scarcity of studies of the issue carried out in tropical regions adds merit to the study conducted by Amaral et al.<sup>(7)</sup>

In the reality of clinical practice in Brazil and perhaps in its counterparts located in the tropics where, to paraphrase Ernest Hemingway, “the Sun also—and always—rises”,<sup>(8)</sup> vitamin D deficiency/insufficiency is not the first diagnostic hypothesis raised when a clinician encounters a child or adolescent with uncontrolled asthma. In fact, a lack of asthma control is most often associated with failure to use or the

inappropriate use of inhaled corticosteroids or other asthma medications, nonpharmacological measures, or comorbidity management. In the absence of a clinical response to such measures in children with low serum vitamin D levels, supplementation should be considered,<sup>(3)</sup> together with careful, systematic exposure to sunlight.<sup>(9)</sup>

Although there are many reasons for the rise of controversies around vitamin D, much of the blame can be laid at the feet of Dr. Michael Holick. Together with the discrepant findings published in scientific journals,<sup>(3-6)</sup> the subject has occupied editorial spaces in the lay press. According to an article published in The New York Times on 08/18/2018, Dr. Holick’s enthusiasm for vitamin D surpassed the limits of good science practice and entered the nebulous terrain of conflicts of interest.<sup>(10)</sup> The artificial elevation of the reference values to levels higher than those previously considered the standard caused a pseudoepidemic of vitamin D deficiency and heated up sales of the supplement, as well as of diagnostic tests that generate financial gains of approximately US\$1 billion a year.

We should always remember: the Sun also rises.

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