Allergol Immunopathol (Madr). 2019;47(5):409–410

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

EDITORIAL

The unpredictable levels of vitamin D and their effects on asthma

The research area of how vitamin D can be involved in the inception of asthma or in the better control of the disease is still a matter of discussion. The epidemiological data that appeared some time ago tended to show that asthma was less prevalent in areas with more sunny days (as ultra-violet B light on the skin is the main boost for skin synthesis). In an ecological study within the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three, Arnedo et al.[1] showed that when considering 32 western European centres found that sunshine hours in those centres were significantly and inversely correlated to the prevalence of markers of asthma (as measured by questionnaire) in the adolescent age (13-14 years of age). In schoolchildren (6-7 years of age) although only one of the markers was significant, the trend was similar. As the authors stated, this supported the idea of vitamin D being a protective factor for asthma, as hypothesized previously by Litonjua and Weiss in 2007.[2] The hypothesis, very attractive and consistent with some epidemiological findings that were common for vitamin D deficiency and asthma prevalence, at that time, has not definitely been proven. The authors based on the results of several general mother-child cohorts (not designed to prove the hypothesis) pointed out that a specific important population were pregnant mothers whose vitamin D deficit could cause disturbances both for the mother and the offspring. Thus, the suggested that a primary prevention could be possible when intervention were carried in pregnancy.

Vitamin D has important effects on the immune system. Vitamin D receptors have been found in many different cells of various tissues, including lymphocytes T and B, and dendritic cells. Apparently, the timing in which vitamin D acts can induce opposite effects in those cells, at least in the murine model. For instance, Vitamin D induces a shift of balance towards Th2-type cytokines, increasing IL-4 and decreasing IFN-γ in mature T cells; however, the effect on CD4+ and CD8+ cells from cord blood is opposite: the overall effect is an increase of IFN-γ and a reduction of IL-4.[3] There also seems that vitamin D has a role in innate immunity by upregulating certain antimicrobial peptides.

A recent meta-analysis on the effects of vitamin D inn the mother during pregnancy and respiratory conditions in the offspring[4] shows that, comparing the highest with the lowest levels, there is a clear association between higher levels in the mother and lower prevalence of respiratory tract infections; however, this association was not significant neither for wheezing nor for asthma. Furthermore, vitamin D in the mother was not associated to allergic markers such as atopic eczema, allergic rhinitis or allergic sensitization. Similar results have been found in a more recent cohort.[5] When this same methodology is applied to a cohort where mothers are asthmatics,[6] it seems that the lower levels of vitamin D (which was nevertheless low in all mothers) were again associated with greater risk of adverse respiratory outcomes during the first year of life. To what extent those respiratory conditions translate into later asthma is a matter of debate.

On the other hand, vitamin D offers some protection in asthmatics against severe attacks in adults with mild to moderate asthma.[7] Moreover, a clinical trial on the effect of prenatal supplementation with vitamin D to mother at risk of having asthmatic children found a substantial, albeit not significant reduction of recurrent wheezing at the age of 3 years.[8]

Overall, these results suggest that vitamin D may play a role as a protective factor for wheezing during the first years of life, although its effects on later asthma remain unclear. Although this vitamin apparently plays a role in the Th1/Th2 balance it does not seem that the mechanism of its protection against early respiratory conditions is related to atopic status but to defence against viruses.

Nevertheless, when performing such studies as the ones quoted above, which are of enormous public health importance it is crucial to have exact values of vitamin D. In this issue of Allergologia et Immunopathologia,[9] Sopo et al. show that vitamin D levels in children 6-16 years of age are quite unpredictable across seasons. It is true that, as expected, mean peak values are found in summer and lower values in December. However, when taken individually each child seems to have its own pathway which is not related

https://doi.org/10.1016/j.aller.2019.07.001

to sunlight exposure (measured in a non-precise way). Additionally, they did not find any correlation between vitamin D and IgE. They did find a correlation between vitamin D and circulating eosinophils, but only in December.

Under the light of the aforementioned information one ends up arriving to a question: what are we really measuring? It is itself very difficult to define asthma, especially during the first years of life; and what happens in terms of respiratory adverse outcomes from birth to 6-7 years does not necessarily translate into asthma. And on top of that, what happens if vitamin D levels are so unpredictable? Are we able to establish a consistent relationship between vitamin and asthma prevalence? Do we need to a kind of composite to redefine vitamin D levels?

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22 July 2019 24 July 2019