VITAMIN D AND RECURRENT INFECTIONS: Risk of hypovitaminosis and treatment effects

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IMMUNOLOGICAL BASES

Vitamin D plays an ever clearer role in regulating physiological processes concerning systems and organs which are involved in calcium homeostasis, such as bones, intestines and kidneys. Indeed the vitamin D receptor (VDR) – the receptor at the level of the vitamin nucleus which mediates many, if not all, of the functions of its preferred ligand (1,25-dihydroxyvitamin D [$1,25(OH)_2D$], or calcitriol) – is present in many body tissues. Many of these tissues contain the enzyme CYP27B1, which converts the most important circulating metabolite of vitamin D, 25-hydroxyvitamin D (25OHD), or calcifediol, into the active form $1,25(OH)_2D$. Vitamin D is able to influence the susceptibility and severity of infections through multiple mechanisms which involve the immune system in both its innate and adaptive forms [1]. As a pleiotropic agent, vitamin D is able to activate memory T cells (Tregs), to modulate the action of the toll-like receptors (TLRs) present on the dendritic cells, to regulate the production of cytokines (decrease of inflammatory cytokines, increase of IL-10), and to activate factors of innate immunity such as cathelicidins and defensins.

ASSOCIATION BETWEEN HYPOVITAMINOSIS D AND RECURRENT INFECTIONS

Data from an American study on a vast population of individuals over 12 years of age clearly showed that having deficient or insufficient vitamin D serum levels constituted a risk factor in developing a greater number of infections of the upper respiratory tract in the days prior to the evaluation. The association between infections of this type and hypovitaminosis was particularly significant in individuals with asthma or chronic obstructive pulmonary disease (COPD) [2]. This finding was then confirmed by various other studies carried out above all on pediatric subjects, taking other recurrent pathologies into account, such as gastroenteritis, otitis media and infections of the lower respiratory tract. In the clinical follow-up, the lowest vitamin D serum levels were accompanied by a heightened risk of this type of infection.

It is been emphasized that this correlation is particularly significant in cases of greater clinical severity. A study of pediatric patients under 5 years of age, who had been hospitalized for infections of the lower respiratory tract, showed a series of clinical conditions that were decidedly more complicated in patients that had low vitamin D levels, sometimes in association with low vitamin A levels. The clinical outcome, interpreted as a need for intensive therapy and/or mechanical ventilation, was particularly trying for children who showed hypovitaminosis correlated to the isolation of respiratory syncytial virus in cell culture or metapneumovirus [3]. The association between low vitamin D levels, failed response to treatment and duration of the pathology was once again demonstrated in a recent study on severe pneumonia in children [4], leading the authors to propose that vitamin D levels in children, especially in those at risk of recurrent infections, should be monitored and perhaps supplemented. It is clear that maternal serum levels can also influence the clinical prospects of the newborn: high vitamin D levels in the mother reduce the risk by half that the child will develop bronchospasm or persistent asthma.

Conversely, low levels in the mother or in the cord blood are linked to a more frequent and serious risk of bronchospasm, to reduced pulmonary function and to a greater risk of res-

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piratory infections in the first six month of life [5]. In this regard, some authors have shown that hypovitaminosis D can constitute one of the main factors of risk in developing asthma during the first 10 years of life. During the natural course of their lives, vitamin D can protect children from asthma by preventing the development of sensitivity to allergies, favoring the growth of intestinal and respiratory tract microbiome, developing normal pulmonary function and regulating the development and response of the immune system [6].

Indeed, a longitudinal study which evaluated vitamin D levels at six months, 1, 2, 3, 4, 5 and 10 years of age showed that individuals with repeated episodes of hypovitaminosis in the first decade of their lives are at a significantly higher risk for asthma, eczema and proneness to allergy, conditions which then persist past 10 years of age [7].

Prenatal vitamin D supplementation can be useful in preventing recurrent infections in children. A recent meta-analysis has demonstrated how the intake of vitamins and microelements, in particular vitamin D, may be useful in preventing infantile wheezing. The same does not, however, hold true for bronchial asthma, where other risk factors may play a role in the course of an individual's life. The two most recent studies on prenatal vitamin D supplementation compared the effects of a therapy of 400 IU/day, commonly used in Anglophone countries during pregnancy, with supplementation of 2400 IU/day or 4000 IU/day. In the first study, the risk of persistent wheezing was reduced, though not significantly, perhaps in part because of a wide confidence interval in the obtained results [8].

In the second study, by contrast, which used the higher supplementation dosage, a nearly significant trend was found for a reduction in the treated group for asthma or recurrent wheezing during the first 3 years of life [9].

In a third study, meanwhile, generous supplementation was effective in reducing the incidence of wheezing in newborns of African-American mothers who had good vitamin D serum levels from the first trimester of pregnancy [10].

Supplementation during pregnancy and which continues into the first years of infancy has proved to be effective in attaining normal vitamin D levels in mother and child from birth; it has also resulted in a later onset of the first viral infection and a decreased risk of proneness to allergies in the child [11].

Vitamin D supplementation in children can be useful in preventing recurrent infections.

Two landmark studies evaluated the effects of vitamin D supplementation in preventing respiratory infections in particular regional situations. In Mongolia, the administration of milk fortified with vitamin D (300 IU/day) produced significant effects in protecting against acute respiratory infections, thereby reducing this risk [12].

On the other hand, in another study conducted in Afghanistan, the administration of 100000 IU every 3 months did not produce protective effects against the incidence of pneumonia [13]. A more recent study compared two different supplementation regimes: one with 2000 IU/day, the other with 400 IU/day. The findings showed that the different doses did not have an effect in the prevention of the incidence of respiratory diseases [14].

In children with asthma, supplementing the basic therapy with vitamin D has led to a significant reduction of bronchial exacerbations caused by infective agents.

A 2013 meta-analysis compared the effects of supplementation on infections of the respiratory tract, finding a statistically relevant positive effect, especially when giving daily vitamin D doses as opposed to bolus administrations [15]. A more recent literature review and meta-analysis, which examined data gathered on nearly 11,000 patients from 25 randomized studies, found an overall protective effect in vitamin D supplementation against acute respiratory infections, though with a "number needed to treat" (NNT: the number of patients that need to be treated to have one who is protected) of 33, a rather poor ratio [16].

It is evident that systematic reviews take into account studies which are quite different in terms of doses, timing and modes of administration: in this case, the benefit was greater for patients who received daily or weekly supplementation compared to bolus doses (NNT = 20) and was particularly significant in those with serious vitamin D deficiencies (NNT = 4).

There is a clear need to further investigate clinical advantages through randomized clinical trials for supplementation, even if the results cited above are important for implementing public health measures, given the frequency with which values of hypovitaminosis D are found in our population. These review data may not change our clinical practices, but the observation that for the general population increased serum levels of 25-hydroxyvitamin D can reduce the risk of respiratory infections, and of influenza in particular, has led some authors to point to the savings in health care costs that could be achieved with vitamin D supplementation. These Canadian authors have in fact analyzed the costs of recurrent respiratory infections in terms of utilization of health care resources, absences from school, absence from work for parents and the use of medications [17]. As these pathologies are quite frequent, they have a notable economic impact; in this context, fortified foods or vitamin D supplements play an efficient and beneficial role, in part because they lead to economic savings.

CONCLUSIONS

Vitamin D therefore offers concrete prospects in terms of preventing and curing recurrent infections of the respiratory system. Aspects of the question, which until now have not been sufficiently understood, concern vitamin D supplementation for both pregnant mothers and children. The data at our disposal are very heterogeneous, such that the evidence is of low quality and ambiguous. Further large-scale studies on supplementation are needed to clarify such important questions as the timing, duration and dosage of the therapy. One of the most interesting supplementation strategies regards the period of prenatal life and the first stages after birth: adequate levels of vitamin D in these phases may constitute a window of opportunity during which the responses of the immune system can be programed in a stable and lasting manner.

Normal serum values of vitamin D are probably crucial in obtaining clinical efficacy, beyond that which is required for bone metabolism. Although one third of the population of western countries, including Italy, shows deficient vitamin D levels (serum levels < 20 ng/mL – 50 nmol/L), it has been suggested that levels that effectively maintain an adequate response of the immune system must be higher (at least 30-40 ng/mL – 75-100 nmol/L).

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