Review

Vitamin D and respiratory infections

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Abstract
Vitamin D or 1,25-hydroxyvitamin D (1,25(OH)\textsubscript{2}D) has a well-established role in calcium homeostasis. In recent years, the discovery of vitamin D-metabolizing enzymes and vitamin D receptor (VDR) in the lungs and various cells of the immune system has led to numerous studies conducted to evaluate its role in respiratory functions and, in particular, upper respiratory tract infections (URTIs). A PubMed literature search was done using vitamin D and respiratory infections as key words. Only clinical studies were considered. This study aimed to review recent clinical and epidemiological studies conducted in adults and children, and to evaluate the functional role of vitamin D in respiratory infections. The evaluated studies show an important immunomodulatory role of vitamin D, which reduces the incidence and risk of URTIs, both in children and in adults. Combating URTIs can be done prophylactically, associating the use of vaccines against Streptococcus pneumoniae with strengthening the immune system through supplementation with vitamin D. These actions can significantly contribute to reducing the number of URTIs, the use of antibiotics, and consequently, the rates of antimicrobial resistance.

Key words: vitamin D; respiratory infections; immunomodulatory effect.


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Introduction
A variety of recent studies have shown that vitamin D is a regulator of calcium and phosphate homeostasis, and also has numerous extra-skeletal effects. These include effects on the cardiovascular system, central nervous system, endocrine system, and immune system, modulating the innate and adaptive system, influencing the production of endogenous antimicrobial peptides, and regulating the inflammatory cascade [1,2].

Other studies suggest that vitamin D deficiency predisposes patients to respiratory tract infections and may play a role in the development and treatment of asthma [3].

Recently, there have been large numbers of publications involving the role of vitamin D in upper respiratory infections. Published studies are clinical and epidemiological, all of them involving the use of vitamin D and its activity in respiratory health [3,9,35,36,44-46]. Thus, this study aimed to review recent clinical and epidemiological studies conducted in adults and children, to evaluate the functional role of vitamin D in respiratory infections.

Source and homeostasis
The 1,25-dihydroxyvitamin D\textsubscript{3} (1,25(OH)\textsubscript{2}D\textsubscript{3}) is the biologically active form of vitamin D. It is a pleiotropic hormone, regulating calcium and bone homeostasis due to its modulation of Ca\textsuperscript{2+} ion absorption in the intestine [4]. It also regulates several genes, including those associated with the proliferation, differentiation, and apoptosis of cells [5].

The precursors of vitamin D are vitamins D\textsubscript{3} (cholecalciferol) and D\textsubscript{2} (ergocalciferol) [6]. Vitamin D\textsubscript{3} is formed by exposure to solar ultraviolet B (UVB) rays from its precursor, 7-dehydrocholesterol, present in the skin. It may also be consumed in the diet, particularly in fish fat [7-9].

Both precursor forms, whether synthesized in the skin or obtained through the diet, are hydroxylated in liver by the cytochrome P-450 to 25-hydroxyvitamin D (25(OH) D), its detectable and circulating form [8]. The 25(OH) D released by the liver is not the biologically active form of vitamin D, as that still needs a kidney hydroxylation to become an active compound. Action by the kidney turns 25(OH) D to 1,25 dihydroxyvitamin D (1,25(OH)\textsubscript{2} D) or calcitriol, the active form of vitamin D [6].

Vitamin D (1,25(OH)\textsubscript{2} D) thus synthesized may act directly on the receptor of vitamin D (VDR) [7]
that is not only present in bones and intestines, but can also be found in bone marrow, brain, pancreas, prostate, and especially in tumor cells and immune cells, suggesting a much broader range of vitamin activity than simply calcium homeostasis [4,10].

**Adequate levels**

Around 20 ng/mL of 25(OH) D in plasma [11] is considered adequate, and the risk of toxicity occurs when plasma concentrations reach 100 ng/mL [12]. The plasma concentration of 25(OH) D is strongly affected by seasonality, since the incidence of sun exposure varies greatly during all four seasons, interfering in a straightforward way in the concentration of vitamin D [9,13,14]. In a study that assessed the plasma concentration of 25(OH) D in British adults, it was found that in summer, concentrations were double those observed in winter [9]. Another important factor relates to the latitude of the location. Chilean children living in Coyhaique (45 degrees south of the Earth's equatorial plane) had severe degrees of vitamin deficiency due to the small amounts daily solar exposure in the region [15].

Hypervitaminosis D can occur at levels three times greater than normal range, or 100 ng/mL. People working or living in very sunny locations, such as lifeguards, can reach concentrations higher than this without showing effects of hypervitaminosis, manifested by hypercalcemia and renal stone formation [12].

On the other hand, deficiency occurs in individuals without appropriate diet or with low sun exposure. The deficiency is characterized by levels of 25(OH) D lower than 20 ng/mL [5,16,17]. Another cause of deficiency is age related, due to the decrease of the 7-dehydrocholesterol precursor in the skin. The difficulties of locomotion in the elderly, with a consequent decrease in sun exposure, also affect the levels of vitamin D [18-20].

Another factor related to decreased levels of vitamin D relates to skin color. In people with darker skin, melanin acts as a natural sunscreen, competing for UVB rays with 7-dehydrocholesterol and decreasing the formation of vitamin D [6,12]. People with darker skin need up to six times more sun exposure to produce the same amount of vitamin D that lighter-skinned individuals do [21,22].

Use of sunscreens has also been associated with decreased vitamin D production [23,24]. Some studies show that factor 8 sunscreens reduce vitamin production by 95%, reaching 99% for protection factors above 15 [25,26].

**Supplementation**

The recommended daily intake has been the focus of numerous discussions [27-31]. Recently, in 2011, the Institute of Medicine (IOM), by publishing dietary reference intakes for calcium and vitamin D, suggested a small increase in the recommended daily dose of vitamin. Table 1 shows the dietary reference intakes (DRI) for vitamin D for all life stage groups.

The tolerable upper intake level for children 0–6 months is 1,000 IU (25 μg); for children 6–12 months, it is 1,500 IU (38 μg); for children 1–3 years, it is 2,500 IU (63 μg); and for children 4–8 years, it is 3,000 IU (75 μg). From age nine to adulthood, the tolerable upper intake level was established to be 4,000 IU (100 μg) [11].

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>AI</th>
<th>RDA</th>
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<tbody>
<tr>
<td>Infants 0 to 12 months</td>
<td>400 IU (10 μg)</td>
<td>—</td>
</tr>
<tr>
<td>Children 1–8 years</td>
<td>—</td>
<td>600 IU (15 μg)</td>
</tr>
<tr>
<td>Adults (males and females) 9–70 years</td>
<td>—</td>
<td>600 IU (15 μg)</td>
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<tr>
<td>&gt; 70 years</td>
<td>—</td>
<td>800 IU (20 μg)</td>
</tr>
<tr>
<td>Pregnancy 14–50 years</td>
<td>—</td>
<td>600 IU (15 μg)</td>
</tr>
<tr>
<td>Lactation 14–50 years</td>
<td>—</td>
<td>600 IU (15 μg)</td>
</tr>
</tbody>
</table>

AI = adequate intake; IU = international unit; RDA = recommended dietary allowance. Adapted from IOM [11]
Activity of vitamin D in URTIs

The role of vitamin D in modulating calcium homeostasis has been fully discussed and established, and its action as an immunomodulator has been the subject of several publications that have confirmed its action on the immune system, especially in upper respiratory infections [4,32,36]. The recent discovery of the presence of vitamin D receptors (VDR) in nearly every tissue, especially in cells of the immune system and their ability to metabolize its active form, suggests a strong involvement of vitamin D in the immune system [37].

Recent studies have shown the direct role of vitamin D in several immune cells such as dendritic cells, B lymphocytes, T lymphocytes, and natural killer (NK) cells [38,39]. The production of peptides with antimicrobial activity by macrophages and even beta-defensins by endothelial cells is mediated and stimulated by vitamin D, which shows vitamin D’s activity as a mediator of the immune response [40,41].

Cathelicidin is a peptide that has antimicrobial activity against bacteria and viruses. In the presence of viral infections, lung epithelial cells convert inactive vitamin D into its active form so that it stimulates production of this antimicrobial peptide, helping to fight infection [2]. Animal studies showed a potent effect of cathelicidin in combating influenza A. The authors suggest that the antiviral activity should be controlled by a cathelicidin-mediated immunomodulator [42].

Vitamin D appears to combat infection via multiple mechanisms. It has a direct influence on the production of cathelicidin, which may lead to increased susceptibility to viruses and bacteria, and it influences cytokine profiles during infection via the innate and adaptive immune system [2].

Ginde et al. [3] conducted one of the largest studies of vitamin D in humans. Serum concentrations of vitamin D were assessed in 18,883 volunteers 12 years of age and older. The study correlated the concentration of vitamin D with the appearance of upper respiratory infections. The study concluded that serum concentrations of the vitamin were inversely related to the occurrence of these infections. The correlation was even stronger in patients with a respiratory disease (asthma and chronic obstructive pulmonary disease [COPD]). The study concluded that supplementation with vitamin D may reduce the incidence of URTIs and also reduce the severity of respiratory tract diseases [3].

Bergman et al. (2013) published a meta-analysis of 11 placebo-controlled studies and included a total of 5,660 patients. This meta-analysis assessed supplements of vitamin D versus placebos and the incidence of URTIs. After the evaluation of 11 randomized controlled trials, the meta-analysis concluded that the use of vitamin D may be effective in preventing respiratory diseases [35].

A study published in 2013 evaluated a possible correlation between serum 25-hydroxyvitamin D (25(OH) D) concentrations before admission and risk of hospital-acquired bloodstream infection (HABSI). The retrospective cohort study of 2,135 adult patients evaluated vitamin serum concentrations and correlated them with the emergence of HABSI. Patients who showed prehospital vitamin concentrations of less than 10 ng/mL were significantly correlated with increased odds of developing HABSI [43].

A meta-analysis published by Charan et al. (2012) evaluated five clinical trials. The outcome events were URTIs in the vitamin D group and the placebo group. The meta-analysis determined that the incidence of URTIs was significantly lower in the groups treated with vitamin D compared to the control groups [44].

A study published in 2011 evaluated the plasma concentration of 11,971 British adults, and correlated it with lung function assessed by spirometry and by episodes of URTIs. The results showed the expected seasonal variation of serum vitamin D concentration and an inverse relationship with the number of diagnoses of URTIs. There was also strong direct correlation between serum concentrations of vitamin D with lung function as measured by forced expiratory volume (FEV) and forced vital capacity (FVC). The study findings suggest that adequate intakes of vitamin D may have an important role in the appearance of URTIs [9].

In a prospective cohort study published in 2010, the authors evaluated, monthly, the serum concentration of vitamin D in 198 adults, correlating it with the appearance of URTIs. These findings show that concentrations of 38 ng/mL or more of vitamin D were associated with a twofold reduction (p < 0.0001) in the possibility of the appearance of URTIs. The number of days ill was also reduced in patients with adequate levels of vitamin D [36].

In 2010, a study evaluated the presence of polymerase chain reaction (PCR)-confirmed influenza A in 334 children ranging from 6 to 15 years of age. The children were divided into a treated group (1,200 IU/day of vitamin D) and a placebo group. The group treated with vitamin D showed an incidence of 10.8% influenza A, while in the placebo group, influenza reached 18.6% of children (relative risk [RR] 0.58, p =
The authors suggest that use of vitamin D in these children during the winter months may reduce the incidence of influenza A [45].

The activity of vitamin D on lung function was assessed by Choi et al. (2013), who determined the serum concentrations of vitamin D in more than 10,000 adults in Korea and correlated these with lung function (forced expiratory volume in 1 second [FEV1]). The authors found a positive correlation between the concentration of the vitamin and lung function. This correlation was more evident in patients with tuberculosis [46].

The observations linking vitamin D and innate immune response to infection suggest a possible link between vitamin D status and susceptibility to tuberculosis [47]. Before the etiologic cause of tuberculosis was determined, cod liver oil and sun exposure were commonly used to treat patients with tuberculosis [48]. Vitamin D levels lower than 30 ng/mL have been associated with a higher incidence of tuberculosis [49-51].

Several recent studies have suggested that there is a direct relationship between the concentration of vitamin D and clinical improvement in patients with tuberculosis [52-56]. A systematic review and meta-analysis in 2008 selected 151 articles published between 1980 and 2006. The meta-analysis concluded that low vitamin D levels were associated with a higher risk of active tuberculosis [49].

The association between sun exposure, the concentration of vitamin D, and the clinical improvement of patients with tuberculosis is well established. Future studies should seek detailed information about the mechanism of action and the best dose to be used in tuberculosis treatment.

In a study on other cases of lung diseases such as bronchiectasis, 402 patients with the disease were evaluated for serum levels of vitamin D. The results showed that patients with vitamin deficiencies had higher sputum levels of inflammatory markers and demonstrated a more rapid decline in lung function over three years of follow-ups [57].

The relationship between the umbilical cord blood concentration of vitamin D in neonates and the presence of respiratory syncytial virus (RSV), the most important pathogen causing lower respiratory tract infection (LRTI) in infants, was evaluated in 146 newborns by Belderbos et al. in 2011. The study showed that low levels of vitamin D in healthy neonates were associated with increased risk of RSV-LRTI in the first year of life. The authors suggest that supplementation of vitamin D in pregnant women could be an important strategy for the prevention of RSV-LRTI during infancy [58].

Another recently published prospective study assessed vitamin D supplementation in milk for children in Mongolia. The double-blind study compared a control group (n = 104) with a group that received milk fortified with 300 IU of vitamin D3 (n = 143). The number of respiratory infections was evaluated in both groups. The study concluded that supplementation of only 300 IU per day in Mongolian children was associated with a significant reduction in parent-reported URTIs [59].

There are also studies that have evaluated the relationship between the concentration of vitamin D and tonsillitis. Yildiz et al. compared the serum concentration of the vitamin in groups of healthy children and children with recurrent tonsillitis. In the group of children with tonsillitis, about 4.7% of the children had vitamin D levels below 50 nmol/L. No child presented levels below this value in the group of healthy children [60].

Other respiratory infections have been studied for the action of vitamin D. A study published in 2013 evaluated the association between serum concentration of vitamin D and the appearance of infections in 475 school-age children (mean 8.9 ± 1.6 years) in Bogotá, Colombia. Children were assessed for a year and their conditions were controlled. At the end of one year, the authors concluded that vitamin D deficiency was associated with increased rates of earache and discharge with fever [61].

Conclusions

Over the past 70 years, antibiotics have served us very well, dramatically reducing the indicators of global mortality and morbidity [62]. Evolution and adaptation of microorganisms, possible through reactive oxygen species [63,64], forced by the selective pressure caused by the indiscriminate use of antibiotics, has led to a significant decrease in the effectiveness and activity of these drugs through the phenomenon of antimicrobial resistance [65].

The adopted model in the man-microorganism relationship in the last 70 years, proposing to kill bacteria to stop infections, has shown to be flawed, and its time is running out; for that reason, it is essential that we find alternatives to the use of antibiotics. Vaccines have been shown to be extremely effective in making the individual less susceptible to bacterial infections; as a consequence, in countries with greater use of antibiotics, vaccination has resulted.
in decreased antibiotic consumption and a consequent reduction in the indicators of antimicrobial resistance [66].

Recently published studies show that supplementation with vitamin D in children seems to be a strong ally in fighting the onset of respiratory infections. The combination of vaccines and vitamin D supplementation can significantly reduce the appearance of URTIs and the use of antibiotics, with a consequent decrease of global indicators of bacterial resistance.

The large number of recently published studies and the great variety of actions attributed to vitamin D should show the scientific community that we still know very little about its action. Additional studies should be conducted in order to elucidate its role in human health.

References


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