VITAMIN D
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Vitamin D and asthma

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Asthma is a complex respiratory disorder of inflammatory origin, whose onset and progression are influenced by numerous elements, such as genetic, environmental and ethnic factors as well as socio-economic conditions [1]. The characteristics of asthma vary from person to person; it is manifested by different responses to a variety of triggers and therapies. Recognizing the heterogeneity of asthma and its relative characterization aids in determining an appropriate and specific treatment therapy for each patient [2].

Different hypotheses have been put forth to explain the increasing diffusion of asthma and other allergic diseases in western countries since the 1970's: some regard hygiene and intestinal microbiota, while others propose a connection between vitamin D status and the development of asthma, wheezing, allergic rhinitis, food allergies and atopic dermatitis [3]. The International Study of Asthma and Allergies in Childhood (ISAAC) analyzed the connections between the role of westernization – a lifestyle in which we spend more time indoors with resulting vitamin D deficiency – and the increase of cases of asthma and allergies. The study found a very high incidence of asthma symptoms in countries such as the UK, Australia, New Zealand and Ireland [4,5]. Some studies carried out in several Chinese cities with different socio economic profiles have shown a prevalence of asthma and allergic symptoms in Hong Kong, the most westernized city among those analyzed [6].

In recent years, vitamin D has been considered as a new factor possibly able to inhibit inflammation of respiratory tracts by virtue of its immunomodulatory properties through the regulation of the functions of the innate and adaptive immune systems. Indeed, vitamin D deficiency has been linked to an increase of respiratory tract inflammation, to compromised pulmonary function and to an increase of exacerbations and unfavorable prognoses in patients with asthma [7,8]. In particular, interest in a possible immuno-modulatory function of vitamin D in people affected by asthma has emerged from the fact that vitamin D receptors (VDRs) are present on immune cells and on various respiratory tract tissues. VDR receptors are located on epithelial cells of the respiratory tract and on immune cells (B cells, T cells, macrophages and monocytes), where the active form of vitamin D (1,25(OH)2D3) produces its physiological effects by binding to the VDR receptors [9,10].

EFFECTS OF VITAMIN D ON THE IMMUNE SYSTEM

The most known biological functions of vitamin D are calcium homeostasis and bone metabolism. However, because the vitamin D receptor, as a member of the nuclear receptor's family, has been localized in many tissues and cells of the human body, including the antigen-presenting dendritic cells (DC), it is reasonable to speculate that vitamin D is active in many ways [11,12]. Such actions take place in the immune system, given that vitamin D plays a very precise role in the course of autoimmune diseases, in which it inhibits the response and proliferation of T helper 1 and 17 cell lymphocytes [13]. Vitamin D plays a key role in the differentiation of T regulatory cells (Treg) [14]. Several studies show the positive effects of vitamin D in pathologies that lead to a hyperactivation of T helper 1 cell lymphocytes, such as rheumatoid arthritis, multiple sclerosis and psoriasis [15].

A beneficial effect of vitamin D has been observed on the progression of those allergic diseases in which the T helper 2 lymphocytes play an essential role, regardless of the underlying pathogenic mechanisms [16]. In one study, Pichler et al. examined the effect of 1,25(OH)2D3 on naïve CD4+ T helper and CD8+ cytotoxic T lymphocytes found in cultured human cells isolated from the umbilical cord. The study found that 1,25(OH)2D3 had inhibitory effects on the production of both IFN-γ promoted by IL-12 and on the production of IL-4 and IL-13 promoted by IL-4 in naïve cells [17]. In addition, vitamin D is able to inhibit IL-17A and to prevent the conversion of CD8+ T lymphocytes from cells which pro-

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Conflict of interest
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duce IFN-γ to cells which produce IL-13, as documented in asthmatic patients resistant to corticosteroids [18-20].
Regarding the possible role of vitamin D in the eosinophil immune response, it was found that those cells expressing the vitamin D receptor had longer survival rates [11]. Moreover, vitamin D reduces eosinophil necrosis and the cytolytic release of peroxidase. In addition, reduced production of immunoglobulin E (IgE) and an increase of IL-10 expression have been observed [21].
Filho et al. analyzed a non-selected population, that is, one in which allergic patients were not predominant, and found that patients affected by vitamin D deficiency had higher blood eosinophil counts. An inverse correlation of vitamin D has been observed between serum circulating levels of basophils and neutrophils [22].

GENETIC MODULATION OF VITAMIN D

The binding of vitamin D and its analogs to the VDR receptor regulates the expression of several genes associated with inflammation and immunomodulation [23] (Fig. 1). The biological effects of vitamin D can be altered by single nucleotide polymorphisms (SNPs) of the VDR gene. Specifically, many studies have suggested that SNPs in the vitamin D receptor VDR gene, such as rs2228570 (FokI), rs731236 (TaqI), rs1544410 (BsmI), and rs7975232 (ApaI), may represent risk factors for the onset of asthma. Masoud Hassanzadeh Makoui et al. observed a statistically significant correlation between the FokI and TaqI SNPs and asthma risk [24, 25]. Moreover, in the same study subgroup analysis was conducted to assess a potential ethnicity-specific effect, revealing that the presence of the FokI SNP in an African population decreases the risk of asthma below the dominant (OR = 0.60) and allelic models (OR = 0.54). The tt genotype of the TaqI SNP was associated with an increased risk of asthma in an Asian population (OR = 2.94) and with a decreased risk in American populations (OR = 0.64). This difference in outcome among ethnicities might originate from differences in dietary patterns and geographic locations, as well as from a significant influence of ethnicity on VDR gene expression and serum vitamin D levels [25,26]. Each of these four SNPs can disturb the stability of VDR mRNA, which in turn causes an imbalance between Th1 and Th2, with a resulting As a consequence, there will be a reduction in the production of IL-12 and of interferon gamma (IFN)-γ, which will lead to a production of mainly Th2 cytokines, such as IL-4 and IL-13 [25].

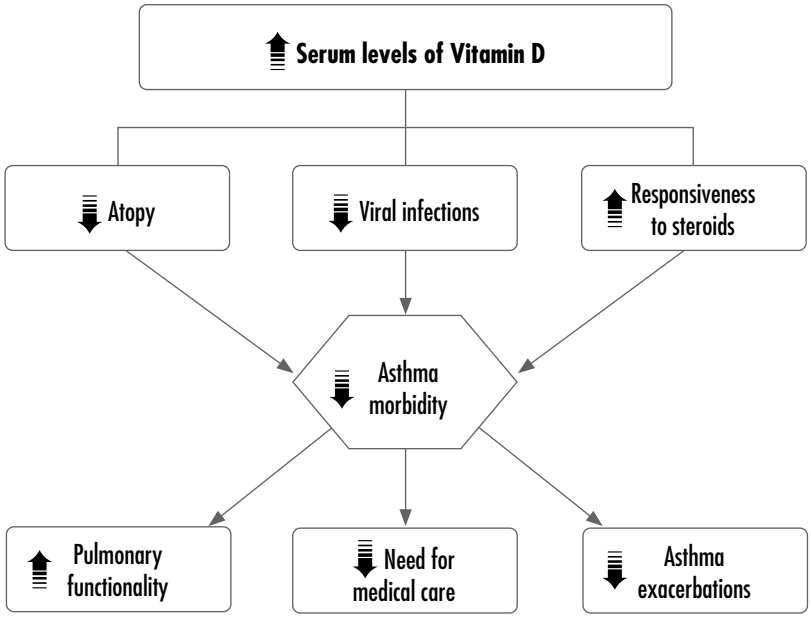

FIGURE 1.
Vitamin D and its network

ROLE OF VITAMIN D AND RESPONSE TO THERAPY IN PATIENTS WITH ASTHMA

Vitamin D may also influence the response to anti-inflammatory therapy, especially to glucocorticoids (GC), in patients with asthma [27]. Studies to evaluate the response to GC in patients with asthma suggest that up to 50% of these patients may not respond well to inhaled corticosteroids (ICS), while up to 25% of patients who have difficulty controlling asthma may not respond well to oral glucocorticoids, with high morbidity and a potentially life-threatening progression of the disease [28,29]. In patients with steroid-resistant asthma, defects in GC induced gene transcription of anti-inflammatory mediators such as IL10 and mitogen-activated protein kinase phosphatase-1 (MKP-1) may play a role [30,31].
In confirmation of this hypothesis, Xystrakis et al. have found that the addition of vitamin D and dexamethasone (Dex) to cultures of CD4+ regulatory T cells (Treg) in patients with steroid-resistant asthma increased IL-10 synthesis to levels observed in cells of steroid-sensitive patients cultured with Dex alone [30]. Zhang et al. have confirmed that vitamin D increased the GC induction of MKP-1 and IL-10 in peripheral blood mononuclear cells of children with asthma [32].

ROLE OF VITAMIN D IN COMBATTING RESPIRATORY TRACT INFECTIONS

Vitamin D also plays a crucial role in protecting against respiratory tract infections and therefore in the prevention of exacerbations of asthma. Observational studies have found a correlation between low serum concentrations of 25(OH)D and a susceptibility to acute respiratory tract infections and to exacerbations in patients with asthma [33,34]. In particular, *in vitro* studies of epithelial cell lines and of primary cultures of respiratory epithelial cells infected by a Rhinovirus-family virus demonstrate that vitamin D can increase antiviral defenses, generating an improvement of antimicrobial peptides (AMPs), such as cathelicidin and β-defensin [35,36]. Activation of innate immunity pathogen recognition receptors (PRRs) on respiratory tract epithelial cells upregulates antimicrobial peptide secretion through epithelial cells, programmed cellular death, and other intracellular responses, releasing proinflammatory mediators such as cytokines and chemokines. Vitamin D can interfere with many functions of PRRs [37,38].

Several studies report that oral supplementation of vitamin D in children suffering from recurrent respiratory tract infections (RRTIs) reduces the number of infections, consequently lessening their global socio-economic impact by assuming a prevention role [39]. Using an individual participant data (IPD) meta-analysis of randomized controlled studies, Martineau et al. found that vitamin D supplementation induces a reduction of the risk of contracting at least one acute respiratory infection. Daily or weekly vitamin D administrations brought significant benefits to those patients with serious baseline vitamin D deficiency; moreover, vitamin D administrations were also beneficial for patients with higher 25(OH)D concentrations [34]. Many studies show a correlation between vitamin D deficiency and a higher susceptibility to and greater severity of tuberculosis (TB) [40].

VITAMIN D AND EXACERBATIONS

Several meta-analyses have highlighted the role of vitamin D supplementation in reducing the rate of exacerbations, mainly in patients with vitamin D deficiency [41]. In fact, moderately acute recurrences were found after treatment with vitamin D supplementation only in patients with baseline 25(OH)D levels less than 25 nmol/L, but not in those patients with higher levels of circulating 25(OH)D [33].

Following treatment with $1,25(OH)_2D_3$, an inhibition of the production of cytokines expressed by Th 17 cells (IL-17 and IL-22) was observed in studies performed on the peripheral blood mononuclear cells (PBMCs) in patients affected by severe asthma. The importance of this finding is evident: given the inability of corticosteroids to inhibit the cytokines expressed by Th 17 cells, it suggests that vitamin D could improve the response to steroid therapy in patients with asthma [33,42].

VITAMIN D AND SARS-COV-2

In light of the protective role of vitamin D in many diseases associated with pneumonia, hypercytokinemia and acute respiratory distress syndrome (ARDS) – and therefore considering its antiviral effects that directly interfere with viral replications – it is legitimate to suppose that vitamin D could have important effects on the SARS-CoV-2 infection. Initially, the SARS-CoV-2 virus adopts mechanisms to evade immune defense, triggering immune hyper-action and a cytokine storm [43-46]. Preventive treatment with vitamin D has positive documented effects in ARDS animal models. Such effects consist in reducing pulmonary permeability, modulating the activity of the renin-angiotensin system, and reducing expression of the ACE2 receptor, which is known as the entry point of the SARS-CoV-2 virus in human cells [47,48].

Therefore, the possible use of vitamin D as adjuvant treatment or as a prophylaxis should be evaluated [49].

CONCLUSIONS

In light of the different mechanisms which are activated in respiratory diseases, the diverse pathways that can affect the individual capacity to produce adequate vitamin D concentrations at the local level, and the variability of this "beneficial" serum in each patient (including the side effects of vitamin D supplementation, such as hypercalcemia, hypercalciuria and kidney stones), the main message here is the importance of diagnosing, preventing and treating vitamin D deficiency. These observations should encourage us to view vitamin D not so much as a "universal" and independent factor for asthma, but as an important "regulator" of our immune system.

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