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Role of Vitamin D Deficiency in Allergic Diseases: Is this Due to an Impaired Patients' Response to Corticosteroid Therapy?

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Introduction

Accumulating evidence now shows that low level of vitamin D is associated with the development and/or aggravation of a number of lung diseases in both adults and children [1-3]. Clinically, low levels of vitamin D refers to *hormone deficiency* which is defined by a serum level <20ng/mL [4]. *Vitamin D insufficiency*, typically defined by levels ranging from 20-29ng/mL, has also been regarded as clinically important particularly in children [5]. Despite numerous reports associating vitamin D levels to allergic disorders, the cellular and molecular pathways explaining the protective role of vitamin D in lung diseases have not been fully investigated. The purpose of this short review is to describe the current evidence describing the importance of vitamin D in modulating patient's response to corticosteroid therapy.

Lower Levels of Vitamin D Correlate with Severity of Allergic Lung Diseases

A number of epidemiological studies from different countries have led to the same conclusion that low levels of vitamin D is associated with asthma in both children and adults. Studies performed in asthmatic children led to the demonstration that vitamin D insufficiency (<30ng/mL) was associated with asthma exacerbations and poor lung function in Puerto Rican patients [6] or poor asthma control and lung function in a British cohort [7]. In contrast, Wu AC, et al. [8] found that vitamin D deficiency rather than insufficiency was a feature in asthmatic children with a poor lung function characterized by a reduced improvement in pre-bronchodilator FEV_1 after inhaled corticosteroid treatment over the course of 1 year when compared to hormone sufficient patients [8]. A larger study involving 1024 children with mild-to-moderate persistent asthma from a multicentre clinical trial also found that higher odds of hospitalization and emergency department visits correlate with serum levels of vitamin D below <30ng/mL [9]. A more recent study by Bener A, et al. [10], conducted in Qatari children revealed that vitamin D deficiency was the strongest predicator of asthma although a deficiency in phosphorus or magnesium was also noticed in these patients [10]. In a cohort of Italian children (5-11 year-old), patients with partially controlled or uncontrolled asthma had insufficient levels of vitamin D while those with higher vitamin D levels had their disease well-controlled [11]. In a different study the same group described a poor lung response and >10% FEV_1 change in response to exercise challenge in children with intermittent asthma who had vitamin D insufficiency [12]. It is also important to mention that not all studies have found a correlation between low vitamin D levels and severity or the level of asthma control in children [13,14].

In addition to asthmatic children, vitamin D deficiency was also shown to impact on disease severity in adults. In a cohort of non-smoking adults with asthma, Sutherland ER, et al. [15], reported that patients with insufficient levels of vitamin D had increased airway sensitivity to methacholine challenge while patients with higher vitamin D levels had greater lung function [15]. Among the cohort of 121 Costa Rican patients, it was found that 74% of those with a vitamin D insufficiency or 91% of those with a vitamin D deficiency had higher risks of developing a severe disease. In contrast, those with higher levels of vitamin D were protected against the risk of hospitalizations or emergency room visits [16]. A German study involving 280 patients recently confirmed that serum levels of vitamin D <30ng/mL were more prevalent among adult patients with severe and/or uncontrolled asthma and were linked to lower forced expiratory volume in the first one second (FEV_1) and sputum eosinophilia [17]. A similar observation linking low levels of vitamin D and poor lung function assessed by air flow limitation was reported in a Chinese cross-sectional study involving 435 patients [18].

Taken together, these epidemiological studies from different parts of the globe reinforced the concept that the lack of vitamin D may have detrimental consequences on the management of asthmatic patients. It has been proposed that this could be due to a loss of the steroid-enhancing anti-inflammatory properties of vitamin D.

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Vitamin D and Corticosteroid Therapy in Asthma

The observation that levels of vitamin D were important in determining *in vitro* corticosteroid responsiveness and steroid requirements in asthmatic children strongly suggested that vitamin D directly or indirectly regulates the therapeutic responses of corticosteroids [19]. A study by Searing and colleagues in asthmatic children showed that patients with low levels of vitamin D not only presented with worse airflow obstruction but also had an increased need for inhaled and oral corticosteroids [20]. In addition, these authors found that combining vitamin D and dexamethasone was effective in inhibiting *ex vivo* steroid-resistant features such as T cell proliferation, raising the possibility that supplementation with vitamin D could be effective in restoring steroid efficacy.

An earlier study convincingly showed that in the presence of vitamin D, dexamethasone was able to induce secretion of the anti-inflammatory cytokine IL-10 by CD4+ T cells isolated from steroid-insensitive patients. This suggests that vitamin D is able to reinstate corticosteroid responsiveness, at least *ex vivo*, seen in steroid resistant conditions [21]. The potential role of vitamin D in managing steroid insensitive conditions was further suggested by Nanzer AM, et al. [22]. IL-17 expression is increased in steroid-insensitive asthmatic patients, however, vitamin D treatment suppressed the production of dexamethasone-resistant IL-17 by peripheral blood mononuclear cell (PBMCs) [22]. Furthermore, there was a superior damping of LPS responses of combining vitamin D/dexamethasone compared to individual treatments in PBMCs taken from patients who were either sensitive or resistant to corticosteroid therapy [23].

The greater therapeutic benefit provided by vitamin D/corticosteroid combination could possibly result from an enhanced corticosteroid receptor (GR) signalling. This hypothesis was recently supported by the observation that vitamin D/corticosteroid led to an increased induction of the GR-inducible anti-inflammatory protein called MAPK phosphatase 1 gene [24]. Another interesting anti-inflammatory protein induced by vitamin D/corticosteroid combination is IL-10. A study performed in children defined as severe-therapy resistant asthma reported a positive correlation between systemic levels of vitamin D and levels of IL-10 present in the bronchoalveolar lavage fluids. Although the underlying mechanisms of this association are not known, the authors showed that vitamin D was able to enhance IL-10 production induced by dexamethasone in PBMCs from these patients [25]. The role of IL-10 in the anti-inflammatory action of vitamin D has been previously described by Hawrylowicz CM's group [26-28], which showed that vitamin D significantly increased production of IL-10 by Foxp3+ T regulatory (Treg) cells [26-28]. Interestingly, a positive correlation was also found between serum vitamin D levels and circulating IL-10+Treg cells in asthmatic children [29]. These findings support previous observations made in patients suffering from Crohn's disease where vitamin D increased IL-10 while inhibiting IFNγ production in CD4+ T cells [30], providing further evidence for its therapeutic potential in managing other inflammatory diseases.

These studies provide undeniable *in vitro*/*ex vivo* evidence of a role of vitamin D in regulating corticosteroid responses via mechanisms that remain to be elucidated. The use of vitamin D as therapeutic supplement in asthmatics, therefore, suggested by multiple lines of evidence including that vitamin D inhibits steroid-resistant features and possesses immune-modulatory actions possibly via the regulation of Treg cells. More importantly, vitamin D also exhibits steroid-enhancing properties. These studies raise the interesting possibility that vitamin D supplementation could lead to a better control of asthma, in part by enhancing corticosteroid responsiveness particularly in patients with severe disease.

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