Vitamin D and corticosteroids in asthma: synergy, interaction and potential therapeutic effects

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Asthma is a chronic inflammatory disease of the airways. It is characterized by variable airflow obstruction and affects more than 300 million individuals worldwide of all ages and races [1], and it is estimated that by 2025, this number will increase by 100 million people. In the USA, asthma prevalence appeared to have reached a plateau in the mid-2000s, but a recent study from the CDC has shown that prevalence continued to rise between 2001 and 2009 [2]. Together with the rising prevalence, costs related to asthma are also increasing. In 2007, the estimated annual total cost of asthma in the USA was approximately US$56 billion [3]. Prescription medications accounted for the largest proportion of this cost. Asthma is responsible for more emergency room visits and hospital stays than any other childhood disease, and also accounts for a substantial amount of work day absences among adults [4], increasing the economic burden from asthma. While there are several classes of effective asthma medications, a significant proportion of patients have either no or inadequate responses to these agents [5], increasing costs related to asthma care. While genetic factors may explain the lack of response to these agents, other modifiable factors may also play a role. Therefore, identifying and correcting these modifiable factors will help in decreasing overall costs of asthma. In this article, I will summarize the evidence that vitamin D has synergistic effects on the administration of corticosteroids by either enhancing corticosteroid effects or reversing steroid resistance in the treatment of asthma.

Vitamin D & corticosteroids in asthma

Vitamin D deficiency is prevalent in Westernized countries, and has recently been recognized as a significant public health problem. Given vitamin D's effects on fetal lung development and immune development, it has been postulated that vitamin D deficiency, as a result of industrialization and Westernized lifestyles that have led to sun-avoidance behaviors and more time indoors, has a role in the development and treatment of asthma and allergies [6]. Other effects of vitamin D that have relevance for asthma treatment include upregulation of antimicrobial proteins that are involved in the defense against respiratory infections [7], and anti-inflammatory [8] and antiproliferative [9] effects on airway smooth muscle. Consistent with these effects, it has been shown that asthmatics with low vitamin D status (defined as circulating levels of 25-hydroxyvitamin D [25OHD] of <30 ng/ml) have increased risks for exacerbations [10], lower lung function [11] and indices of more severe disease [12].

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Corticosteroids are the most effective anti-inflammatory treatments for asthma and are one of the cornerstones of comprehensive asthma therapy [13]. Corticosteroids bind to the glucocorticoid receptors (GRs) in the cytosol, activating the translocation of GRs into the nucleus, where they bind to specific gene regulatory elements to induce expression of genes involved in the regulation of inflammation [5,14]. However, asthmatics exhibit a wide response to corticosteroids when measured in terms of lung function changes over a period of several weeks [15,16]. Furthermore, a subset of asthmatics do not respond to these medications and are considered steroid-resistant asthmatics [14]. The molecular mechanisms of steroid resistance have been studied and include reduced glucocorticoid binding to GR, reduced GR expression, enhanced activation of inflammatory pathways or lack of corepressor activity [14]. Finally, some asthmatics experience side effects from these drugs, particularly at high doses [17]. While genetic predictors of response to corticosteroids surely play a role in this variable response [5], identifying other reversible causes of steroid insensitivity is an important endeavor.

Evidence for synergy between vitamin D & corticosteroids in asthma

Can the administration of vitamin D enhance corticosteroid actions, and potentially reverse steroid resistance? Xystrakis *et al.* obtained peripheral blood $CD4^+$ T cells from steroid sensitive and steroid-resistant asthmatics [18]. They showed that the addition of vitamin D to $CD4^+$ T-cell cultures from steroid-resistant asthmatics restored IL-10 secretion in response to dexamethasone to levels seen in steroid sensitive asthmatics. More importantly, they showed that oral administration of vitamin D (calcitriol) reversed steroid resistance through induction of IL-10-secreting Tregs. Subsequently, several clinical and epidemiological studies have added support to the idea that there may be a synergistic effect of vitamin D and corticosteroids in asthma outcomes. In our analysis of data from 1024 participants of the Childhood Asthma Management Program, a randomized trial of inhaled budesonide versus nedocromil versus placebo, we showed that vitamin D insufficiency (<30 ng/ml) was associated with increased risks for severe asthma exacerbations leading to emergency department visits or hospitalizations [10]. In this study, the group with the lowest risk for exacerbations was the group who had 25OHD levels ≥30 ng/ml and who were on inhaled corticosteroids, suggesting a synergistic effect between vitamin D status and corticosteroid use on preventing exacerbations. We subsequently showed that the children who were on inhaled corticosteroids had poorer lung growth if they had vitamin D deficiency (defined as 25OHD <20 ng/ml) compared with those who were not vitamin D deficient [19]. In a cross-sectional study of 100 asthmatic children, Searing *et al.* demonstrated inverse associations between vitamin D levels and the use of inhaled or oral corticosteroids and total steroid dose [20]. More recently, Goleva *et al.* showed that both steroid requirements and *in vitro* steroid responsiveness were significantly inversely associated with vitamin D status in children [21]; while trends for association were also seen for adult asthmatics, these did not reach statistical significance, suggesting perhaps that the effects were stronger in childhood asthmatics where airway remodeling may not be as prevalent as in adults. This study was the first to compare corticosteroid responsiveness and vitamin D status between children and adults, although sample sizes were relatively small (50 adult asthmatics and 53 childhood asthmatics).

Potential mechanisms of synergy between vitamin D & corticosteroids

These clinical studies are very suggestive of a synergy or interaction between vitamin D and corticosteroids. Several studies in asthma (or asthma- or allergy-related models) and in other disorders have shed light on the potential mechanisms of this interaction, which appears to be primarily enhancement of the anti-inflammatory effects of steroids. The mechanism of induction of IL-10-secreting Tregs has been noted above [18]. This effect on IL-10 secretion has been seen by other groups [20]. In human airway smooth muscle cells, Banerjee *et al.* have shown that corticosteroids and vitamin D independently modulate the secretion of inflammatory chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and secreted), and their coadministration leads to additive inhibition of this chemokine [8]. In addition, they also showed that vitamin D inhibited fractalkine secretion, adding to the mechanism for reversal of steroid resistance. Another anti-inflammatory mechanism is through the increased expression of MAPK phosphatase 1 (MKP-1), leading to corticosteroid induced anti-inflammatory and immunosuppressive effects. Vitamin D has been shown to enhance corticosteroid induction of MPK-1 in peripheral blood mononuclear cells [20,22]. Finally, vitamin D and corticosteroids synergistically induce a tolerogenic dendritic cell (DC) phenotype [23] that may be important for immunomodulation and decreased responsiveness to self and external antigens (e.g., allergens). This study investigated differential protein pathways in human $CD14^+$ monocytes that were differentiated toward mature DCs, in the presence or absence of vitamin D and/or dexamethasone. The surprising suggestion from this study was that vitamin D was more potent than dexamethasone in skewing the cells from the proinflammatory phenotype seen in the untreated DCs. These findings bring up an important question that is also raised by studies on cancer cells as presented below.

Vitamin D and corticosteroids also interact on a genomic level, as elucidated in cancer cells. Vitamin D has antiproliferative properties, can activate apoptotic pathways and inhibit angiogenesis [24], and is being investigated as a therapeutic agent [25,26]. In these settings, corticosteroids are being used to enhance these vitamin D effects and for their anticalcemic properties [27]. Corticosteroids are known to stimulate vitamin D receptor protein expression by increasing *VDR* transcription [28], through binding of steroids to glucocorticoid response elements located in the promoter of the *VDR* [29], thus enhancing vitamin D effects on cancer cells. These mechanisms will need to be verified in model systems relevant for asthma and allergies. In addition, since the studies in cancer cell systems are unclear as to whether vitamin D enhances any effects of corticosteroids, these studies raise the question whether it is primarily the vitamin D effects or the steroid effects that are important in asthma.

Future work

The mechanisms reviewed above, in addition to the results of the clinical studies, strengthen the notion of a synergy between corticosteroids and vitamin D, which may have particular relevance for asthma and allergies. Larger studies in humans will be needed to verify this synergy, and to determine its clinical use. These studies will need to be of sufficient sample size, include both children and adults, and will need to clarify what circulating level and what dose of vitamin D affords the greatest potential for synergy with steroids. Furthermore, molecular and genomic studies in relevant asthma and allergy cell models are needed to further elucidate mechanisms and whether it is the vitamin D or the corticosteroid effects that are primarily operating in these disorders. The public health impact of these studies will be great, as vitamin D may be a relatively cheap and safe therapeutic option for patients with asthma.

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