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REVIEW ARTICLE

Vitamin D supplementation as a potential therapeutic mediator in asthma: does dose really matter? A critical review of the literature

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ABSTRACT

Around 400 million people across the globe will suffer from asthma in the next 10 years. Although most asthmatics use asthma medications regularly, they occasionally visit the emergency department for aggressive treatment amidst family anxiousness. Vitamin D (VD) not only regulates the expression of genes associated with calcium homeostasis, but also the genes associated with cancers, autoimmune diseases, and infection. VD has also non-genomic activities e.g. it is a potentially safe and effective novel strategy for decreasing the asthma episodes and controlling exacerbations. Our review assessed the dose, serum level, duration of administration and outcomes of VD in cases of asthmas. Although a body of research evidences the effectiveness of VD supplementation in asthma, other studies showed the insignificant response of VD to asthma either with low dose or low achieved serum VD levels. Nevertheless, recent reviews suggest that manipulating VD status holds promise for primary prevention and treatment of asthma. Future research on the relationship between VD and asthma should consider utilizing adequate doses of VD preparations for sufficient duration (likely to be >12 months) aiming to achieve appropriate level of serum VD (25-hydroxyvitamin D) concentration (likely to be at least >40 ng/mL).

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Introduction

Asthma is a chronic inflammatory airways disorder in which many cells and cellular elements play a role [1]. It is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, and coughing, particularly at night or early morning [1]. In asthmatics, some research has shown that serum Vitamin D (VD) levels positively correlated with lung function [2,3]; that lower VD levels were associated with worse asthma control [2], more asthma exacerbations, emergency department visits, and hospitalizations [4]; and that low VD was associated with poor control, increased exacerbation, decreased lung function, and increased medication usage [5]. Indeed adults with VD deficiency (VDD) had higher rates of asthma exacerbation than those who were VD-sufficient [6,7]; and the severity of asthma symptoms appears linked to winter season [8] and darker skin pigmentation [9], situations where VDD is likely. Certainly, VDD appears to be a significant risk factor for all-cause mortality in asthmatic adults [10]. Given such findings, a hypothesis of a potential effect of VD on asthma remains pertinent. If such data are true, why VD is, as a minimum, not used as a supplemental drug for asthmatic patients?

Vitamin D

In 1922, a new vitamin called VD was announced that cures rickets [11]. In the same year, VD was defined as a substance necessary for the cell's life and that it differed from other such substances in undergoing dilution by diffusion into the surrounding medium [12]. A hundred years thereafter, VD is now acknowledged for its importance for bone health and many other organs. Indeed, VD receptor (VDR) is expressed in most tissues, regulating cellular differentiation and function across many cell types [5,13–15].

VDR is a member of the steroid receptor superfamily. Over 3000 genes are responsive to VD [16], and VD's biological effects are mediated through binding to the VDR and inducing either genomic or non-genomic effects [14,17]. On VD binding, VDR translocates from the plasma membrane to the nucleus where it transcriptionally activates genes through the VD

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response element, thereby affecting transcription of other genes [17].

Many factors affect the prevalence of VDD e.g. region and latitude, diet and supplement use, clothing, obesity, smoking, concerns about sun damage, and the nature of the built environment. VDD is common, even in low latitude countries with abundant sunshine [18].

VD and asthma

The existing evidence is inconsistent, with some research showing an effect of VD in asthmatic patients, whereas other studies not supporting such an effect. Such inconsistencies and heterogeneous findings are probably due to important differences in study designs and other factors e.g. measured VD status vs. reported VD intake, VD dosing, outcome measures, and trial duration [5]. Nevertheless, the existing mechanisms, pathophysiology, and other data support an important role for VD in asthma. Across this current study, we used ng/mL as the unit for VD; for consistency, we converted other studies' 25(OH)D units (i.e. nmol/L) into ng/mL by dividing nmol/L values by ~2.5.

Empirical data/supportive results

VD and asthma: observational evidence

A review (25 case–control studies including 2568 asthmatics, 4376 controls) examined VD intake, status, and correlations with respiratory/atopic parameters in asthma cases vs. controls [5]. In the latter 25 case–control studies, the results were inconsistent about VD levels between cases and controls. Existing case–control studies regarding VD and asthma have compared asthmatics to healthy controls by assessing measurements, which were collected simultaneously and only at a single time point. Therefore, it is not possible to determine the temporal relationships between exposure and outcome [5].

An observational case–control study examined the metabolomics of exhaled breath condensate (breathomics) in severely asthmatic children vs. non-severe asthmatic children and healthy children, and reported that the absence of ercalcitriol (active VD metabolite) differentiated severe asthma from both children with non-severe asthma and healthy children. This is possibly the first report of VD being retrieved explicitly in the lung [19].

In agreement, a review (36 cross-sectional studies, 386,584 subjects) reported that low 25-hydroxyvitamin D [25(OH)D] was associated with poor control, increased exacerbation, decreased lung function, and increased medication usage in asthmatics [5]. Similarly, another large cross-sectional study found that adult patients with VDD had higher rates of asthma exacerbation than those who were VD-sufficient [6,7]. Similarly, a population-based study (3937 participants) also found that VDD patients were more likely to have current asthma than those with higher 25(OH)D levels [13].

In support, other published reports agreed on the evidence of effectiveness. A cross-sectional study (85 asthmatic; 85 non-asthmatic children) found that VD was significantly lower in asthmatic children, and VD was negatively correlated with emergency room/hospital admissions, asthma attacks, and severity [20]. Similarly, a case–control study (483 asthmatic children; 483 age, gender, and ethnicity matched controls) showed that VD was significantly lower and IgE significantly higher in cases than controls with an evident negative correlation. The cases had also less exposure to sunshine and lower exercise, and VDD was the strongest predictor of asthma in that population [21]. Furthermore, a meta-analysis (2 case–control, 12 cohort, 9 cross-sectional studies) showed that higher serum VD correlated with a lower risk of asthma exacerbations, particularly in children [22].

VD and asthma: interventional evidence

There have been 17 intervention trials of VD in asthma (1578 asthmatics, followed up for 52 weeks), characterized by varied VD doses and preparations, trial designs, VD dosing, outcome measures and trial duration, which may help explain the discrepancies of their findings [5].

No significant effect of VD on asthma: The "Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma" (VIDA) clinical trial is one of the largest double-blinded, randomized, placebo-controlled trials assessing VD supplementation effect on adults with symptomatic asthma and low VD. A total of 408 patients with VD insufficiency/deficiency on inhaled corticosteroids were randomized to add-on therapy with placebo or high VD dose (100,000 IU loading, followed by 4,000 IU/day) for 28 weeks [23]. The time to the first treatment failure, the rate of first asthma exacerbation or overall exacerbation rate did not differ between the VD and placebo groups, although the overall dose of inhaled corticosteroids to maintain asthma control was slightly lower in patients

taking VD. VD replacement did not yield superior clinical outcomes [23].

In agreement, in a recent intervention trial, all patients' (250 adults) serum VD level was <30 ng/mL (58% of patients had serum VD <20 ng/mL) before treatment [24]. They received six 2-monthly oral doses of 120,000 IU VD. The allocation to the trial's intervention arm resulted in an increase in serum VD (mean ≈10 ng/mL increase at 12 months). At 12 months, mean VD was 27.76 ± 8.4 ng/mL [24]. The study concluded that VD supplementation did not influence time to an exacerbation in asthmatic adults with a high prevalence of baseline VD insufficiency [24]. Similarly, a placebo-controlled study assessing the effect of 6 weeks of treatment with oral VD airway hyperreactivity, where 20 patients received VD (14,000 IU/week) and 19 received placebo showed no difference between the effect of VD and placebo, despite significant increases in serum VD levels [25].

Significant effect of VD on asthma: In contrast, a double-blinded, place-controlled randomized trial, 430 school-age children were randomized to receive VD (1200 IU/day) or placebo for 4 months during winter [26]. In a small subset of asthmatic children, VD supplementation led to a significantly lower rate of exacerbation than placebo, despite that the asthma prevalence was low, and VD status was not determined in this cohort [26]. In support, 100 asthmatic children attending the asthma clinic received monthly doses of 60,000 IU VD, which significantly reduced the number of asthma exacerbations, steroid requirement, and emergency department visits in the VD group compared to placebo [27]. Similarly, a randomized clinical trial (130 individuals) found that, at 24 weeks, the forced expiratory volume improved in both groups but improved significantly more in the VD supplementation intervention group (100,000 IU bolus intramuscularly plus 50,000 IU orally weekly) in addition to asthma controllers [28].

VD supplementation: does dose (and achieved serum level) really matter?

The VD dose that is administered and its duration in order to achieve a therapeutic serum level is of utmost importance. Total serum 25(OH)D concentration is an indicator of VD status [29,30]. Recommendations for optimal VD intake and serum VD i.e. 25(OH)D levels remain controversial. In terms of VD serum level, the 2010 Institute of Medicine (IOM) publication recommended a target serum 25(OH)D of >20 ng/mL [31]. However, this report was based almost exclusively on skeletal considerations and was criticized by VD experts [32,33]. The Endocrine Society defined VDD and insufficiency as a 25(OH)D < 30 ng/ml [34].

Dose: As for the appropriate VD supplementation dosage, in terms of serum VD level, IOM recommended a daily allowance of 600 IU for healthy subjects aged >1 year [31]. The Endocrine Society recommends adult VD supplements of up to 4000 IU/day [34]; and that obese children and adults be given at least two to three times more VD for their age group to satisfy their body's VD requirement. Certainly, higher levels of 2000 IU/day for children 0–1 years, 4000 IU/day for children 1–18 years, and 10,000 IU/day for children and adults 19 years and older may be needed to correct VDD [34].

When one contrasts such dose and serum level recommendations with the actual data reported across various published studies, a clearer picture emerges. For instance, Majak et al. reported that a 500 IU VD supplement daily for 6 months was insufficient to increase serum VD in asthmatic children at 51° North [35]. Comparing such a VD dose with international guidelines shows that it was clearly lower than the recommended levels. Similarly, Lewis et al. found that among asthmatic children treated with 1000 IU for 12 months, only 50% reached VD sufficiency defined as >30 ng/mL, where again, the VD dose in this instance was obviously insufficient [36]. Certainly, VD dosage needs adjustment according to patient's conditions in line with guidelines [34].

Many examples of such insufficient VD dosage exist. A double-blind randomized controlled study (48 children with newly diagnosed asthma, 500 IU/day) for 6 months found that while the placebo group had a significant increase in asthma exacerbations, the difference in serum VD and asthma therapy assessment questionnaire scores between the intervention and placebo group was very small and neither reached statistical significance [37]. This is not very surprising, given that the dose used (500 IU/day) seems much below the guidelines recommended by the Endocrine Society. Similarly, a study reported the administration of VD supplement of 14,000 IU/week for 13.5 ± 3.6-year-olds [25], clearly not in agreement with the international guidelines [34].

Serum level: The failure to reach an appropriate (therapeutic) level of serum VD may help to explain the inconsistent findings in terms of the effect of VD on asthma. In a recent intervention trial, all study participants' serum VD was <30 ng/mL (58% had serum VD <20 ng/mL) before treatment. The intervention patients (125 out of 250) received six bimonthly oral

doses of 120,000 IU VD, showing a mean increase of ≈10 ng/mL in serum VD at 12 months, where their mean VD reached 27.76 ± 8.4 ng/mL [24]. The study concluded that VD supplementation did not influence time to an exacerbation in asthmatic adults with a high prevalence of baseline VD insufficiency [24]. However, it is worth noting that serum VD levels of Martineau et al.'s patients were clearly in the insufficiency range i.e. <30 ng/mL, as defined by 'The Endocrine Society'[34], even after treatment [24,34]. If we consider that perhaps a VD level >40 ng/mL may be required for optimal respiratory (as opposed to skeletal) outcomes, Martineau et al.'s findings were inevitable.

Such VD dose considerations and the achievement of an appropriate serum VD level for a therapeutic effect to be apparent are further evident when 'subset analysis' is undertaken. For instance, VD supplementation did not yield superior clinical outcomes across 408 patients with VD insufficiency/deficiency on inhaled corticosteroids who were randomized to add-on therapy with placebo or high VD dose, although in the subset of patients who achieved VD sufficiency (>30 ng/mL), VD resulted in a significant (43%) reduction in asthma exacerbations [23]. In fact, each 10 ng/mL increase in serum VD concentrations was associated with a reduction in the overall rate of treatment failures [23].

Duration: there are no precise guidelines about the duration of administration of VD supplementation for bone health or lung wellbeing. However, some literature on the duration of VD supplementation for asthma appears to be of a too short duration in order achieving a therapeutic serum VD level. Such durations vary from 14,000 IU weekly for 1.5 months [25], 50,000 IU weekly for 6 months [28]. These range of durations seems to be unduly short (particularly if coupled with a suboptimal dosage) to increase serum VD to therapeutic serum levels.

VD modulation of asthmatic disease: potential mechanisms

In vitro and *in vivo* evidence highlight multiple potential mechanisms by which increasing VD status may influence asthmatic disease. These mechanisms include effects on lung development, immunomodulation, airway smooth muscle, genetic, and alteration of the effect of anti-asthmatic therapy.

Anti-inflammatory effects

VD inhibits the production of pro-inflammatory cytokines e.g. interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a) by monocytes via the inhibition of p38 MAP kinase [38]. VD dependently inhibited LPS-induced p38 phosphorylation at physiologic concentrations, as well as IL-6 and TNF-a production by human monocytes. MKP-1 expression was significantly upregulated in human monocytes, with increased binding of the VDR [38].

Adaptive immune system

In contrast to its effect on the innate immune system, VD seems to induce immunosuppressive effects on the adaptive immune system through inhibition of IL-12 secretion [39], inhibition of lymphocyte proliferation, and immunoglobulin synthesis [15], as well as impaired dendritic cell (DC) maturation, leading to the generation of tolerogenic DCs and T-cell anergy [40].

Airway smooth muscle (ASM) cells are key in asthmatic disease. ASM cells modulate bronchomotor tone in the airway lumen and airway resistance is principally influenced by airway diameter. Hence, small changes in airway radius can greatly influence airflow. An important VD role in asthma is a strong, direct anti-inflammatory ASM effect, evident from the suppression of both bronchial ASM proliferation, as well as mucus and matrix metalloproteinase secretion by cultured human bronchial cells [41,42].

Immunomodulation

VD has numerous effects on the immune system, with particular relevance to the respiratory system [43]. For example, VD has the potential to inhibit inflammation and infections [44] by modulation of both the innate and adaptive immune systems [45].

Interplay of genome and VD status to influence asthma

Asthma may develop as a consequence of a variety of gene-environment interactions. VD synthesis, transport, and degradation are controlled by several genes, particularly the genes encoding for the VD binding protein (VDBP) and the VD receptor (VDR). Polymorphisms in these genes may affect both 25(OH)D status and the effects of 1,25 D. For instance, human genome-wide linkage evaluation has shown strong genetic regulation of serum 25(OH)D levels, but not 1,25 D levels [46].

Strong affinity of VD (at higher concentrations) for testosterone nuclear receptors

Research strongly suggests an important role of sex hormones on asthma (Figure 1). Recent studies found

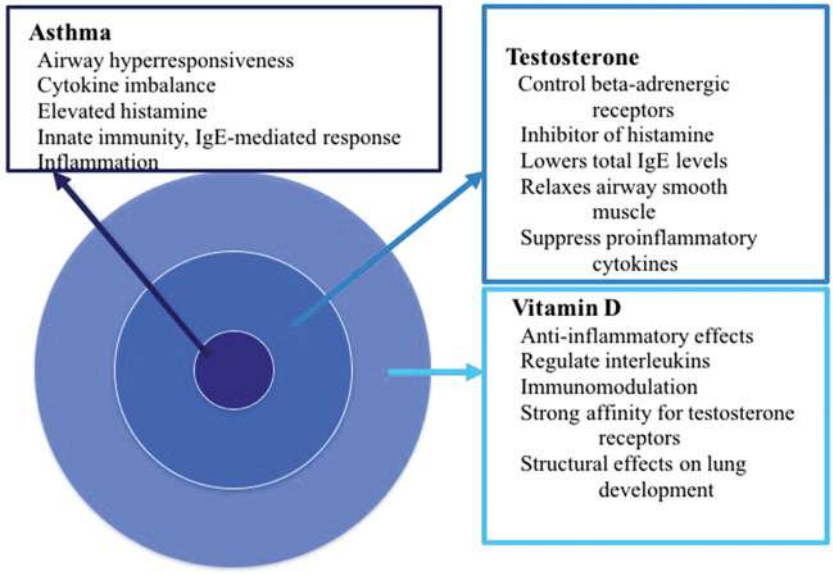

Figure 1. Vitamin D and testosterone modulation on asthmatic disease: potential mechanisms [1,5,52,55,56,65,66].

that there was a significant and positive association between serum 25(OH)D and total testosterone level [47–50]. Stimulatingly, latest literature showed a positive relationship between the IIEF-5 score that shows the erectile function of a man and 25(OH)D level [51]. Earlier, Canguven et al. demonstrated that VD treatment improves testosterone levels and erectile function in middle-aged men [48].

It was proposed that low testosterone levels might significantly alter immune processes and thus airway smooth muscle response, through genomic or non-genomic mechanisms, thus increasing the risk of asthma in susceptible individuals [52]. Changes in androgen levels in asthmatic patients may be associated with the severity of asthma [53]. Recently, androgens have been shown to be bronchoactive drugs that relax airway smooth muscle and prevent bronchospasm [53]. Previous research showed that testosterone and/or its metabolites maintain the physiological balance of autoimmunity and protective immunity by preserving the number of regulatory cells [52].

In silico (computer) modeling demonstrates that besides activating the VDR, VD also has a strong affinity for several of the body's other nuclear receptors. This indicates that at high concentrations, it can dislodging their native ligands [54]. When VD rises above its normal range, it binds the α/β thyroid receptors, glucocorticoid receptor (GCR), and androgen receptor (AR), displacing their native ligands [54].

During a molecular modeling of the actions of angiotensin receptor blockers on the nuclear receptors, investigators showed the symmetry with which endogenous ligands exhibited very similar affinities across several members of type 1 nuclear receptor family [55]. For example, VD docked into the VDR with an 8.48 Kd, but also exhibited an 8.05 Kd into the androgen receptor [55].

As testosterone is an immunosuppressant and is likely to be protective against processes that trigger asthma [52] and a bronchoactive drug, we might kill two birds with one stone by keeping VD levels in upper normal range levels according to *in silico* results [54].

Structural effects on lung development

VD appears to be an important regulator of lung growth *in utero* [56]. VD suppresses features of inflammation-induced airway remodeling in fetal airway smooth muscle cells, suggesting the importance of VD in preventing and treating detrimental structure changes in the developing lungs [57].

Conclusions

Asthma is one of the most common chronic diseases across the globe with around 300 million people afflicted. With the projected increase in the proportion of the world's population that is urban from 45% to 59% in 2025, there is likely to be a marked increase in the number of asthmatics worldwide over the next two decades [58]. It is estimated that there may be an additional 100 million persons with asthma by 2025.

Moreover, in many areas of the world persons with asthma do not have access to basic asthma

medications or medical care [58]. The burden of asthma in many countries is of sufficient magnitude to warrant its recognition as a priority disorder in government health strategies.

Manipulating VD status holds promise for primary prevention of asthma as recent reviews suggest [59,60]. Future trials should utilize adequate doses of VD preparations for interventions of sufficient duration (likely to be >12 months) [61] and VD concentration (likely to be at least >40 ng/mL) [30,34,62]. In addition, because reported VD intake and sun exposure are unreliable, 25(OH)D should be measured, preferably on more than one occasion. This will also help determine optimal serum 25(OH)D concentration and decrease the risk of VD toxicity (VDT). Although, VDT is very rare and has most reports of VDT have resulted from industrial accidents [63,64]. VD supplementation potentially represents a low-cost, low-risk method to treat and prevent asthma and therefore a further exploration of the effect of VD supplementation is encouraged.

Disclosure statement

No potential conflict of interest was reported by the authors.

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