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Vitamin D as an Adjunctive Therapy in Asthma. Part 1: A Review of Potential Mechanisms

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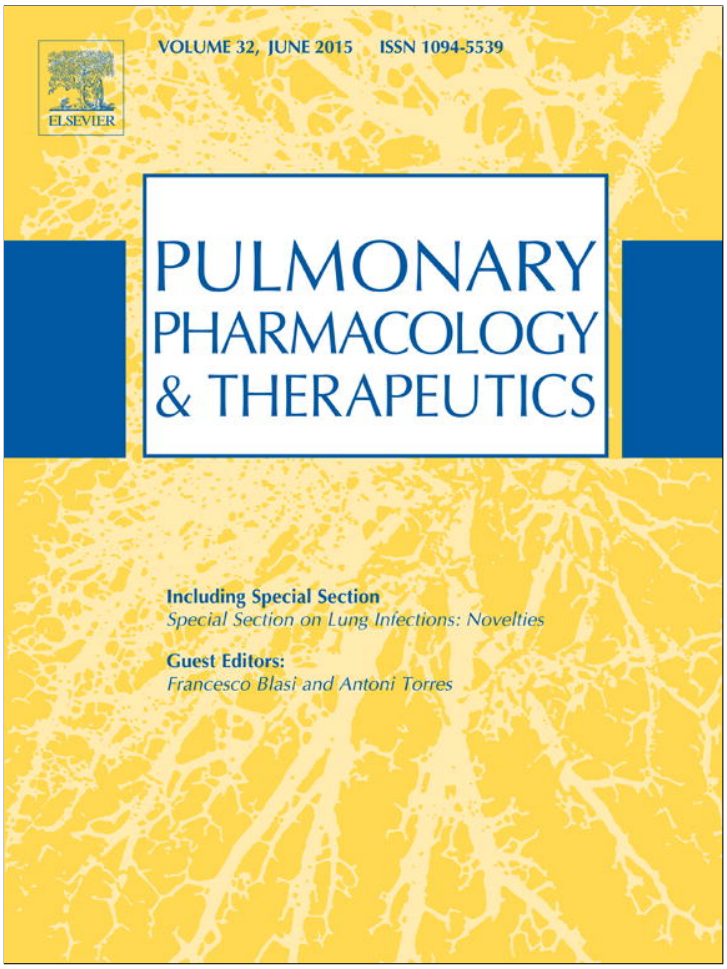

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Vitamin D as an adjunctive therapy in asthma. Part 1: A review of potential mechanisms

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ABSTRACT

Vitamin D deficiency (VDD) is highly prevalent worldwide. The classical role for vitamin D is to regulate calcium absorption form the gastrointestinal tract and influence bone health. Recently vitamin D receptors and vitamin D metabolic enzymes have been discovered in numerous sites systemically supporting diverse extra-skeletal roles of vitamin D, for example in asthmatic disease. Further, VDD and asthma share several common risk factors including high latitude, winter season, industrialization, poor diet, obesity, and dark skin pigmentation.

Vitamin D has been demonstrated to possess potent immunomodulatory effects, including effects on T cells and B cells as well as increasing production of antimicrobial peptides (e.g. cathelicidin). This immunomodulation may lead to asthma specific clinical benefits in terms of decreased bacterial/viral infections, altered airway smooth muscle-remodeling and −function as well as modulation of response to standard anti-asthma therapy (e.g. glucocorticoids and immunotherapy).

Thus, vitamin D and its deficiency have a number of biological effects that are potentially important in altering the course of disease pathogenesis and severity in asthma. The purpose of this first of a two-part review is to review potential mechanisms whereby altering vitamin D status may influence asthmatic disease.

1. Introduction

Asthma is a disease characterized by variable airway obstruction, respiratory symptoms, bronchial hyper-responsiveness and airway inflammation [40]. It represents a major public health problem, affecting ~300 million people worldwide [164]. Due its prevalence, asthma costs the US health care system an estimated $56 billion annually [17].

The exact cause of asthma remains unknown. For reasons not completely understood, asthma prevalence and severity has increased markedly since the ~1960s [39,69]. Further, asthma prevalence continues to increase in both children and adults and across ethnicities [164,178]. However, this increase does appear related to industrialization [9,38,164,229] and increased adiposity [23,221,231]. Additionally, asthma seems to be more prevalent at higher latitude [117,134]. Furthermore, the severity of asthma symptoms appears related to winter season [117,129,221] and darker skin pigmentation [9,102,121,177,187]. Finally, asthma is associated with exposure to cigarette smoke [103,254], pollution [190,278] and physical inactivity [256]. Although there is a complex interaction between these factors and asthma pathogenesis, one hypothesis that could potentially partially explain these associations is vitamin D deficiency (VDD).

This first part of a two-part review will introduce vitamin D metabolism and physiology. However, the main focus will be an exploration of the diverse mechanisms by which vitamin D may influence asthmatic disease. We have reviewed the evidence linking vitamin D and asthmatic disease from human studies in part two of this review [127].

2. Methods

References were identified by searches of MEDLINE, CINAHL, EMBASE and online Cochrane databases through January 2015.

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Abbreviations list

1,25D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
AAR	allergic rhinitis + allergic asthma
ACT	asthma control test
AMP	antimicrobial peptide
AR	allergic rhinitis
ASM	airway smooth muscle
BALF	**bronchoalveolar lavage fluid**
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
COX-2	cyclooxygenase-2
CRTAM	class I MHC–restricted T cell–associated molecule gene
d	day
DBRCT	double-blind, randomized, placebo controlled trial
DC	dendritic cell
FoxP3	forkhead box P3
GCS	glucocorticoids
GM-CSF	granulocyte macrophage colony-stimulating factor
h	hour
H_2O_2	hydrogen peroxide
HBECs	human bronchial epithelial cells
hCAP-18	human cathelicidin antimicrobial peptide-18
ICS	inhaled corticosteroid
IFN γ	interferon gamma
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
IL1RL1	interleukin 1 receptor-like 1
IP-10	interferon gamma-induced protein 10 is a protein that in humans is encoded by the CXCL10 gene and is a small cytokine belonging to the CXCchemokine family.
IU	international unit
LL-37	the protein precursor to hCAP-18 which undergoes extracellular cleavage to generate a 37-residue active cationic peptide
LPS	lipopolysaccharides
MAP	mitogen-activated protein
MKP-1	mitogen-activated protein kinase 1
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NK	natural killer
OCS	oral corticosteroid
OR	odds ratio
PBMCs	peripheral blood mononuclear cells
PGE2	prostaglandin E2
RANTES	regulated on activation, normal T cell expressed and secreted. RANTES is also known as Chemokine (C–C motif) ligand 5 (also CCL5).
RORC	retinoid-related orphan receptor C
ROS	reactive oxygen species
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RXRα	retinoid X receptor-α
SIT	specific immunotherapy
SNP	single nuclear polymorphism
SR	steroid resistant
SS	steroid sensitive
sST2	soluble decoy receptor for Il-33
T-regs	regulatory T cells
TGF	transforming growth factor
Th	T helper
TLRs	the toll-like receptors
TNF-α	tumor necrosis factor alpha
UV-B	ultraviolet-B radiation
VDBP	vitamin D binding protein
VDD	vitamin D deficiency
VDI	vitamin D insufficiency
VDR	vitamin D receptor
VDRE	vitamin D response element
WBCs	white blood cells
γδ T cells	gamma delta T cells

Keywords used included vitamin D and asthma, wheezing, airway inflammation, airway smooth muscle, and respiratory infection. Only manuscripts published in English are included. Articles were chosen according to their relevance for this review and their bibliographies were also searched for further references.

3. Results and discussion

3.1. Metabolism & physiology of vitamin D

Vitamin D can be described as a pre-prohormone. Vitamin D, either orally ingested or from ultraviolet B (UV-B) exposure is mostly inactive and must be dihydroxylated to its metabolically active form: 1,25-dihydroxyvitamin D (1,25D), also known as calcitriol. In the first step vitamin D is hydroxylated in the liver to form 25-hydroxyvitamin D (25(OH)D), also known as calcidiol. 25(OH)D is the storage form of vitamin D, which reliably indicates systemic vitamin D status [94,105,106]. The second hydroxylation to produce 1,25D occurs primarily in the kidney, but also extrarenally [99,282]. Unlike extrarenal production of 1,25, renal production of 1,25D is tightly regulated by serum levels of parathyroid hormone, calcium and phosphorus. However, tissue and intracellular 1,25 regulation is independent of serum 25(OH)D levels [151,222]. 1,25D has systemic endocrine, paracrine and autocrine effects.

3.1.1. 1α-hydroxylase

Animal and human studies demonstrate that the enzyme responsible for the second hydroxylation (1α-hydroxylase or CYP27B1) i.e. converting 25(OH)D into active 1,25D is present in many immune cells such as macrophages [83,151,193,194], including monocytes [132]; pulmonary alveolar macrophages [3], T cells [290], B cells [51] and dendritic cells [100,232] as well as many sites relevant to asthma for example lung fibroblasts [189], airway smooth muscle cells [15] and airway epithelial cells [91]. The presence of 1α-hydroxylase at these sites enables local hydroxylation of 25(OH)D into 1,25D and potentially enables high concentrations of 1,25D to increase the expression of vitamin D regulated genes with important immune functions. This however, depends on substrate availability (i.e. 25(OH)D). Supporting active hydroxylation of 25(OH)D to 1,25D in atopy/asthma airways, it has recently been demonstrated that 1,25D levels were low in airways but increased after allergen challenge and the increase correlated

with the inflammatory response and increases in cathelicidin [149] – see section 3.2.3.1.

3.1.2. Vitamin D receptor

The vitamin D receptor (VDR) is a member of the steroid receptor superfamily. Over 3000 genes are responsive to 1,25D [29] and its biological effects are mediated through binding to the VDR and inducing either genomic or non-genomic effects [59,182]. Upon 1,25D binding, VDR translocates from the plasma membrane to the nucleus where it transcriptionally activates genes via the vitamin D response element (VDRE), thereby affecting transcription of other genes [59]. VDR interacts with multiple proteins including the retinoid X receptor-α (RXRα) to mediate its transcriptional effects [22,202].

VDR is expressed in most tissues and regulates cellular differentiation and function in many cell types. VDRs were initially described in lymphocytes as far back as 1983 [201]. Since this discovery, VDR has been described in a variety of immune cells [258] for example macrophages [201], dendritic cells [4,34] as well as B- and T-cells [95,155,156] such as CD4+ and CD8+ T-lymphocytes [258] and natural killer (NK) T-cells [5]. VDR is also present at further locations relevant to asthma pathogenesis, including respiratory epithelial cells [91], fibroblasts [205,206] and in substantial quantities in airway smooth muscle [15,35,36]. Upon VDR activation, the expression of multiple target genes is altered, which has the potential to modify cellular processes for example inflammation and immune defense [151,220]. Once formed inside a cell/tissue, 1,25D will be metabolized and degraded inside that cell/tissue. Therefore, the presence of both 1α-hydroxylase and the VDR in these specific locations suggests local effects of 1,25D in these cells/tissues.

Despite recent advances in our understanding of vitamin D, its deficiency is highly prevalence worldwide [104] with many potential systematic effects. Recently, intense interest has focused on the influence of vitamin D for respiratory diseases, particularly asthma.

3.2. Potential mechanisms by which vitamin D may modulate asthmatic disease

There are multiple potential mechanisms based on both *in vitro* and *in vivo* research by which increasing vitamin D status may influence asthmatic disease. These mechanisms include: effects on lung development, immunomodulation, airway smooth muscle modulation, genetic effects, and altering the effect of anti-asthmatic therapy. This section is intended to summarize the existing mechanistic data regarding vitamin D and asthma pathways.

3.2.1. Structural effects

Early investigations in 50 day old rats born to mothers deprived of dietary vitamin D showed reduced lung compliance compared to rats born to mothers whose diet was supplemented with vitamin D [76]. Vitamin D regulated genes are found to be over-represented in developing human and mouse lung transcriptomes [128]. This finding suggests a significant association between early lung development and asthma related phenotypes for vitamin D pathway genes. Further, animal models have shown that VDD alters lung structure and creates deficits in lung function [287]. The same group used a community-based prospective birth cohort to show that forced vital capacity Z-scores in human children of both sexes at age 6 were positively associated with maternal 25(OH)D. This effect was not apparent at 14 years of age, however maternal VDD was positively associated with asthma at 6 years of age but only in males only [288]. Indeed, children who were on inhaled corticsteroids had poorer lung growth if they were VDD compared to those that were not VDD [274].

Using an *in vivo* rat model, it was recently determined that VDD was associated with increased airway resistance following methacholine challenge and that this defect was blocked by vitamin D_3 supplementation [280]. Therefore, it is plausible that transient and/or consistent VDD in early life may lead to permanent susceptibility to poorer respiratory outcomes, which may be independent of atopy. Additional studies suggest that vitamin D is an important regulator of lung growth in utero [68,188,189]. 1,25D has been shown to suppress features of inflammation-induced airway remodeling in fetal airway smooth muscle cells, suggesting the importance of 1,25D in preventing and treating detrimental structure changes in developing lungs [35,36]. See also section 3.2.5 on airway smooth muscle.

3.2.2. Anti-inflammatory effects

The broad spectrum anti-inflammatory effect of vitamin D on various pathologies, including asthma, was recently reviewed [271,277]. Briefly, Vitamin D has been shown to inhibit the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) by monocytes via the inhibition of p38 MAP kinase [285]. NF-κB is a ubiquitously expressed transcription factor. Free NF-κB translocates to the nucleus where it activates transcription of pro-inflammatory cytokines, anti-apoptotic factors as well as of enzymes involved in the generation of pro-inflammatory mediators such as COX-2 [125,247]. Activation of VDR inhibits NF-κB activation and signaling. Further, it has been shown that 1,25D down-regulates NF-κB levels in lymphocytes [279].

Compared to control airway epithelial cells from adult asthmatic during exacerbation, lipopolysaccharides (LPS) stimulated airway epithelial cells demonstrated increased reactive oxygen species (ROS), TNF-α, NFkB expression and phosphorylation as well as increased DNA damage. However, the addition of 1,25D blunted these effects significantly. Further, stimulation with hydrogen peroxide (H_2O_2) induced ROS production and decreased glucocorticoid receptor nuclear translocation as compared to untreated cells. Pre-treatment with 1,25D significant blunted this in a dose-dependent manner and enhanced the dexamethasone induced glucocorticoid receptor nuclear translocation in H_2O_2 stimulated cells [139].

3.2.3. Immunomodulation

Vitamin D has numerous effects on the immune system [56], many of which are of relevance to the respiratory system [162]. For example, vitamin D has potential to inhibit inflammation and infections [151,263,276] by modulation of both the innate and adaptive immune systems [60].

3.2.3.1. Innate immune. The addition of 1,25D to human monocytes inhibits their expression of the toll-like receptors (TLRs) 2 and 4 leading to reduced production the pro-inflammatory cytokine TNF-α [220,223]. *In vitro* studies have shown that 1,25D increases the proliferation and maturation of monocytes into macrophages [133,192]. Further studies have shown that VDD is associated with defective macrophage function, including impaired chemotaxis, phagocytosis and increased production of pro-inflammatory cytokines [193,194].

Antimicrobial peptides (AMPs) are a group of highly diverse micropeptides, which exert potent antimicrobial effects [74] and are key modulators of lung inflammation and infection risk in asthma [98]. Human cathelicidin antimicrobial peptide-18 (hCAP-18) is the only known member of the cathelicidin family of antimicrobial peptides that is expressed by humans [163]. LL-37 is a 37-residue

active cationic peptide and is the cleavage product of cathelicidin [237]. VDR activation by 1,25D regulates genes encoding for cathelicidin and other cationic peptides such as human defensin 2 and 4 by human cell lines [80,261], and multiple human cells including monocytes/macrophages and epithelial cells [81,226,261,263] and hence triggers their expression [80,150,151,261] at multiple sites including the airways of healthy individuals [91,276] and cystic fibrosis patients [276].

Additionally, the *in vitro* induction of hCAP-18 by 1,25D in various human cells, including monocytes, neutrophils and respiratory epithelial cells enhances antimicrobial activity against multiple respiratory pathogens including *Mycobacterium tuberculosis*, *Bordetella bronchiseptica* and *Pseudomonas aeruginosa* [151,163,261,276].

A cross sectional analysis 650 mostly black smokers revealed that participants with low cathelicidin had significantly lower forced expiratomy volume in 1 s compared to higher cathelicidin, a relationship which remained after adjusting for confounders ($p = 0.035$). Although, 25(OH)D was associated with cathelicidin levels, lung function decrements associated with low cathelicidin were greatest among individuals with lower 25(OH)D levels [138].

25(OH)D did not correlate with serum LL-37 levels in healthy individuals, but did correlate with the *in vitro* capacity to induce monocyte hCAP-18 expression [2]. Further, a positive correlation between serum 25(OH)D and cathelicidin levels has been noted among healthy adults [24,62], subjects in intensive care [116], as well as asthmatic children and adults [79]. Further, a significant change in LL-37 levels was observed in subjects after vitamin D supplementation, but only in those with the greatest increase in serum 25(OH)D [24]. Liu et al. assessed 1,25D and ll-37 responses to allergen exposure in bronchoalveolar lavage fluid (BALF) of allergic human. Compared to saline control, exposure to allergen resulted in significantly increased 1,25D ($p = 0.0006$) as well as significantly increased LL37 ($p = 0.0005$). Increases in 1,25D and LL37 correlated with each other ($P < 0.0001$) and with inflammatory cellular changes ($p < 0.0001$) [149]. These reports highlight a potential for vitamin D to influence cathelicidin and related peptide and potentially exert broad antimicrobial effects, which may have potential to affect infection risk and hence susceptibility to asthma exacerbation (see section 3.2.4).

3.2.3.2. Adaptive immune system. In contrast to its effect on the innate immune system, 1,25D seems to induce immunosuppressive effects on the adaptive immune system through inhibition of IL-12 secretion [57], inhibition of lymphocyte proliferation and immunoglobulin synthesis [86] as well as impairment of dendritic cell (DC) maturation, leading to the generation of tolerogenic DCs and T-cell anergy [4].

3.2.3.3. B lymphocytes (B cells). 1,25D has multiple effects on B cells, including inhibition of B cell proliferation, differentiation to plasma cells, and production of immunoglobulins [51].

Healthy adults supplemented with oral vitamin D_3 during the winter months (2000–8,000 IU/d) for 12 weeks had increased frequencies of circulating CD38 expressing B cells in peripheral blood but not CD23 expressing B cells. This effect was confirmed with *in vitro* experiments [66]. This is the first evidence that vitamin D supplementation targets peripheral B lymphocytes.

3.2.3.4. T lymphocytes (T cells). T lymphocytes have a central regulatory role in the pathogenesis of asthma. It has been known since 1985 that 1,25D has potential to inhibit T cell cycle and proliferation [212]. 1,25D directly targets T lymphocytes [257] and can act directly on T cells inhibiting the development and function of multiple T-helper (Th) cells including Th1, Th9 and Th17 cells while favoring the development of regulatory T-cells [122,243].

The role of vitamin D on Th2 cells is not consistent. Some have suggested a direct signaling effect of vitamin D on naive CD4+ T cells toward Th2 differentiation or maintenance [135,165]. Indeed, murine evidence suggests that vitamin D shifts the Th1–Th2 cytokine balance toward Th2 [27,135,142,165,166,169,193,194]; and thus potentially increases risk of asthma [264] and allergy [165]. However a recent animal model study demonstrated that perinatal VDD in mice resulted in Th2 skewing and reduced IL-10-secreting regulatory T cells. These effects were augmented by exposure to house dust mite. In contrast, vitamin D supplementation was associated with significantly reduced serum IgE levels, pulmonary eosinophilia and peri-bronchiolar collagen deposition [253]. These contradictory reports regarding the effects of 1,25D on Th2 responses are based mostly on animal or *in-vitro* models [118,140,165]. *In vitro* work with human cord blood cells has demonstrated inhibition of both Th1 and Th2 differentiation with 1,25D [198], whereas 1,25 decreased Th1 cytokines and increased Th2 cytokines in stimulated peripheral blood mononuclear cells (PBMCs) from subjects with inflammatory bowel disease [12].

The inconsistences regarding the effect of vitamin D on Th2 responses probably reflect varying protocols and differing doses of 1,25D, which may potentially explain the observation that both high and low 25(OH)OD levels have been associated with increased aeroallergen sensitization [216], elevated IgE levels [109], and adverse changes in lung function [245], raising the possibility that an optimal level of 25(OH)D exists regarding asthma and that levels above or below may be detrimental. However in this context, it is noteworthy that existing reports suggest that increasing 25(OH)D did not enhance Th2 cytokine levels in human peripheral blood [155,156,251].

3.2.3.5. T-helper cells. Asthma is considered mainly as a Th2 mediated disease, characterized by production of IL-4, IL-5, and IL-13 together with eosinophilic infiltration of the bronchial mucosa. However, a CD4+ Th17 mediated response has also been observed in asthmatics with chronic inflammation [8,171,195].

At the molecular level, 1,25D has been shown to be involved in the suppression of DC maturation and consecutive Th1 cell development [11,19,174]. In fact, vitamin D may suppress the production of IL-12, thereby reducing the production of Th1 cells and potentially leading to increased proliferation of allergy-associated Th2 cells [19,118]. Additionally, studies in mice have shown that treatment with 1,25D results in reduced secretion of the Th1 cytokines IL-2 and interferon gamma (IFN-γ) and an increase in Th2 type IL-4 [165].

CD4+ T cells, and associated Th2 cytokines are thought to have a pivotal role in the recruitment and activation of the effector cells of the allergic response [146]. It has been known since the late 1980s that 1,25D has modulatory effects regarding the function of CD4+ T cells [257].

Healthy adults supplemented with oral vitamin D_3 during the winter months (2000–8,000 IU/day) for 12 weeks had no effect on T cell subsets. However, in stimulated CD4+ T helper cells there were significant decreases of both IFN-γ producing T cells and IL-17 producing T-17 cells in the vitamin D group compared to the control group (both $p < 0.001$) [66]. Th9 cells are important in the asthma pathogenesis. *In vivo* work has demonstrated 1,25D is additive with dexamethasone in decreasing inflammatory cytokine production from Th-9 subsets, which are implicated in asthma [126].

Th17 cells constitute a subset of effector T helper cells functioning distinctly from other T helper cells. The pro-inflammatory role of Th17 cells and Th17 associated cytokines (IL-17A and IL-17F) is widely recognized [55]. There is an increased number of

Th17 cells in both blood and induced sputum in childhood asthmatics compared to non-asthmatics [90]. Chang et al. [47] observed a dose dependent reduction in IL-17A production when naive CD4+ T cells were cultured with transforming growth factor alpha (TGFα), IL-6 and increasing concentrations of 1,25D. A recent *in vitro* study demonstrated that stimulation of naive CD4+T cells under Th17 polarizing conditions in asthmatics showed a higher Th17 cell differentiation than healthy controls. The addition of 25(OH)D significantly inhibited Th17 cell differentiation dose-dependently, both from asthmatic ($p < 0.001$) and non-asthmatic children ($p = 0.001$). Further, 25(OH)D inhibited RORC, IL-17, IL-23R, and CCR6 gene. Additionally, treating DCs from asthmatics with 25(OH)D significantly inhibited IL-17 production ($p = 0.002$) and decreased the percentage of CD4(+)IL-17(+) ($p = 0.007$). Overall, these findings suggest that vitamin D_3 has an inhibitory effect on Th17 responses and this response is mediated via both T cells and DCs [289].

3.2.3.6. Gamma delta T cells (γδ T cells). γδ T cells represent a small number of T cells, which appear important in allergic airway inflammation. γδ T cells have been reported to be decreased in the blood of asthmatics compared to controls [49,130,239]. Decreased peripheral γδ T cell populations are thought to be due to their enhanced capacity to migrate from peripheral blood through the endothelium to the inflamed airways [14,239]. Moreover, γδ T cells have been demonstrated to be increased in the BALF of patients with allergic asthma and 1,25D has been found to significantly inhibit the proinflammatory activity of γδ T cells in a dose-dependent fashion [50].

3.2.3.7. Regulatory T-cell (T-regs). T-regs inhibit (effector/antigen specific) T cells by several inhibitory mechanisms to suppress overzealous immune responses and regulate immune responses [48,227,259]. Current evidence suggests that many of these inhibitory pathways are mediated through altered IL-10 and TGF-β production. Reduced T-reg number and function has been linked with glucocorticosteroid resistance [61,213]. VDD has been associated with reduced T-reg number and function both directly and indirectly through antigen presenting cells [46,61,92].

25(OHOD levels correlated with T-reg number and function in patients with multiple sclerosis [217,234,235]. In asthmatic human airway lymphocytes, Foxp3(+) and IL-10(+) T-reg numbers were correlated with 25(OH)D levels [250]. T-regs from steroid resistant (SR) asthmatics have been found to secrete less of the anti-inflammatory cytokine IL-10 in response to dexamethasone. However, culturing such T-regs in the presence of both dexamethasone and 1,25D seems to reverse this defect [275]. Further, 1,25D has been shown to increase the production of T-regs [46,84,85,251,275] and T-reg function [47,115,179], which may prove to be an additional mechanism for its immunomodulatory role.

3.2.3.8. Forkhead box P3 (FoxP3). FoxP3 is a transcription factor and is specifically expressed by CD4+CD25+ T-regs. FoxP3 controls CD4+CD25+ T-reg development and function [207]. 1,25D enhances the frequency of human Foxp3+ T-reg cells *in vitro* and directly enhances the production of T-regs from CD4+FoxP3+ T-regs [115]. 1,25D has been shown to promote a tolerogenic phenotype in human DCs, leading to the induction of FoxP3 T-regs [196]. Further, 25(OH)D levels have been found to correlate positively with CD4(+)FoxP3(+) T-cell numbers in moderate/severe asthmatics [44]. The effect of 1,25 on FoxP3 (+) T-reg cells seems to be magnified in the presence of certain cytokines, particularly TGF-β [45].

3.2.3.9. Interleukins. Interleukins are a subtype of cytokine that are secreted by white blood cells (WBCs). Many interleukins are relevant in asthma but we will limit our discussion to two main interleukins which can be influenced by vitamin D:

3.2.3.9.1. Interleukin-10 (IL-10). IL-10, which is produced by monocytes and to a lesser extent lymphocytes, including T-regs, is an anti-inflammatory and immunosuppressive cytokine. Its anti-inflammatory mechanisms include inhibition of antigen presenting cell function [176], inhibition of cytokine production by macrophages and DC [176], inhibiting T-cell, mast cell and eosinophil activation as well as inhibition of pro-inflammatory cytokine production [93,191]. This combination leads to profound inhibition of Th1 cell-mediated immunity [176].

Several studies have noted an inverse relationship between IL-10 levels and asthma severity [28,147]. In addition, alveolar macrophages from asthmatic subjects secrete lower IL-10 levels than non-asthmatic subjects [28,119,147]. Hence, it is widely believed that IL-10 has an important role in controlling the magnitude of human immune responses and in controlling airway inflammation.

Active vitamin D response elements have been identified in the IL-10 gene [96,167,168]. Cord blood 25(OH)D has been inversely associated with IL-10 concentration [286]. 1,25D administration has been associated with increased IL-10 gene expression in CD3+CD4+T cells from steroid refractory asthmatics [251]. Additionally, 1,25D has also been reported to increase IL-10 secretion from B cells *in vitro* [96]. Further, 1,25D has been demonstrated to potentiate the beneficial effects of allergen immunotherapy in an animal model of asthma through modulating of IL-10 and TGF-β [242]. Human *in vitro* evidence suggests that vitamin D supplementation could potentially increase the therapeutic response to glucocorticoids by restoring the impaired steroid-induced IL-10 response [275]. Clinical support was provided by a double-blind, randomized, placebo controlled trial (DBRCT) in heart failure patients demonstrating that daily supplementation with 2,000 IU vitamin D_3/day for 9 months increased plasma IL-10 [224]. Together these data suggest that sufficient 25(OH)D levels may be associated with increased IL-10 expression and/or function, which seems important for asthma control.

3.2.3.9.2. Interleukin 33. IL-33 is a cytokine that acts on multiple cells, including Th2 lymphocytes, to promote Th2 cytokine secretion and airway inflammation [75,146]. The genes IL33 and interleukin 1 receptor-like 1 (IL1RL1) have been identified as predisposing to asthma risk [87]. A 2014 *in vitro* study assessed IL-33 and IL1RL1 expression from human bronchial epithelial cells (HBECs), CD4 lymphocytes, CD8 lymphocytes, eosinophils, and mast cells when cultured in the presence or absence of 1,25D. Addition of 1,25D significantly increased expression of the gene hCAP as well as the total number of IL1RL1 mRNA transcripts expressed by HBECs and CD4 and CD8 lymphocytes but not in primary eosinophils or mast cells. Further, HBECs cultured with 100 nmol/L 25(OH)D resulted in increased expression of both IL1RL1 and the soluble decoy receptor for IL-33 sST2 (which inhibits the actions of IL-33). The authors suggest that 'the capacity of vitamin D to augment the synthesis of an inhibitor of IL-33 … is of potential benefit in the limitation of asthmatic mucosal inflammation' [197]. Clinical support comes from a 2014 human study demonstrated higher 25(OH)D in healthy controls compared to subjects with allergic rhinitis (AR) or asthma + allergic rhinitis (AAR), while plasma IL-31 and IL-33 were lower in subjects with AR or AAR. However, there was no correlation between 25(OHOD and either IL-31 or IL-33 [26].

3.2.4. Decreasing infection risk and/or severity

Early life respiratory tract infections (RTIs) have been associated with increased risk of asthma development [18,107,112]. Although

there is no evidence that asthmatics are more prone to RTIs than non-asthmatics, RTIs are a powerful trigger of asthma exacerbations [41,159] and typically lead to more severe symptoms compared to non-asthmatics [53,65]. Any intervention, which could decrease the susceptibility to either bacterial or viral RTIs, could potentially significantly decrease the frequency of asthma exacerbations and flairs.

Considering the immunomodulatory effects of 1,25D, it is plausible the vitamin D status could alter susceptibility and effects of RTIs [43] and it has been suggested that vitamin D may represent an important link between RTIs and asthma [77,78]. The association between RTIs and vitamin D can be seen with several studies associating rickets (classical vitamin D deficiency) with increased risk of RTIs [180,183,210] and wheezing [70]. In Hawaiian children (<5y), viral bronchiolitis, respiratory syncytial virus (RSV), and pneumonia vary with both season and skin pigmentation [82] suggesting a role for vitamin D. Additionally, single nucleotide polymorphisms in four of the innate immunity genes, including the VDR, seem to increase susceptibility to RSV bronchiolitis [113,131] and general lower RTI [215].

Vitamin D has potent bactericidal effects [101] and virucidal effects [157,249]. However, 1,25D appears to have little effect on virus replication in airway epithelial cells. Rather the anti-infective properties of 1,25D appear related to potentiation of CXCL8 and CXCL10 secretion from both infected or uninfected cells and alteration of cell morphology, including thickening of the cell layers ($p < 0.01$) and proliferation of cytokeratin-5-expressing cells. Indeed, any potential anti-viral effect of vitamin D appears due to altered growth and differentiation of airway epithelial cells as opposed to direct effects on viral load [37].

Recent observational studies have reported that low 25(OH)D is associated with increased incidence [77,78,124,137,219]; and severity of RTIs [143,172,262]. One study suggested that a serum level of 25(OH)D 95 nmol/L was associated with decreased RTI incidence compared to lower levels [219]. A detailed retrospective analysis from the UK, demonstrated a seasonal pattern of infection, which closely mirrored 25(OH)D levels [21]. Indeed, solar UV-B radiation exposure (a proxy for vitamin D) has been inversely associated with diverse respiratory tract symptoms [244], RSV incidence [265,281] and risk of invasive pneumococcal disease [267]. However, subsequent vitamin D supplementation DBRCTs have yielded conflicting results, with some reporting decreased risk [10,13,42,136,249,252], some reporting decreased duration [161] but others still reporting no difference [145,160,181].

These observed discrepancies may be partly be accounted for by differences in vitamin D dosing, interventional period, definition of RTI as well as baseline and endpoint 25(OH)D levels. Further, the protective effect of vitamin D against RTIs may be specific to high-risk populations, such as wheezing children [114] or those with asthma [32,77,78,157,249,252]. Indeed, two small intervention trials of vitamin D supplementation in pediatric asthma have demonstrated decreased RTI risk and hence decreased asthma exacerbations [157,249]. Therefore, increasing vitamin D as a RTI prevention strategy, particularly in asthmatics, warrants further investigation.

3.2.5. Airway smooth muscle

Airway smooth muscle (ASM) cells play a central role in asthmatic disease. ASM cells modulate bronchomotor tone in the airway lumen and airway resistance is primarily influenced by airway diameter. Therefore, small changes in airway radius can greatly influence airflow. Increased ASM hypertrophy and hyperplasia have been demonstrated in endobronchial biopsies from children with severe asthma and are significantly related to bronchodilator responsiveness [209]. Further, phenotypic changes to ASM, mediated by pro-inflammatory cytokines, are important for the airway remodeling process [63].

To date, there is little evidence that standard asthma therapies affect airway remodeling. However, vitamin D is a potential modifier of this process. Not only do ASM cells possess the enzymatic machinery to form 1,25D from 25(OH)D [15,30] and contain the VDR [15], but 1,25 modulates the synthetic activity of ASM cells and decreases expression of inflammatory chemokines. Treating ASM cells with TNF-α and/or IFN-γ mimics the inflammation of an acute asthmatic flare and facilitates the *in vitro* examination of the efficacy of potential anti-inflammatory therapies. TNF-α and/or IFN-γ treated ASM cells exposed to 1,25D had a dose-dependent decrease in inflammatory cytokine production [15]. In addition, both RANTES (a pro-inflammatory molecule that attracts monocytes, eosinophils, and T-cells) and IP-10 (a pro-inflammatory mediator that recruits activated T cells, NK cells, and mast cells) were noted to be significantly decreased with 1,25D treatment [15].

A potentially important effect of vitamin D on asthma is a strong, direct anti-inflammatory effect in ASM, evident from the suppression of both bronchial ASM proliferation, as well as mucus and matrix metalloproteinase secretion by cultured human bronchial cells [6,236], potentially because 1,25D downregulates the expression of MMP9 and ADAM33 (both known modulators of airway remodeling). Vitamin D treatment also increases ASM cell VDRs and at physiologic concentrations partially prevents ASM cells from becoming passively sensitized by exposure to asthmatic serum [236]. Further *in vitro* studies have demonstrated that 1,25D has a direct inhibitory effect on both passively sensitized ASM cells [236] as well as the growth of human ASM cells (both asthmatic and non-asthmatic)via growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1 [58]. Clinical evidence was observed by Gupta et al. who, using endobronchial biopsies, demonstrated that 25(OH)D levels were inversely related to ASM mass in children with severe asthma [89].

In vitro, 1,25D has been demonstrated to attenuate the pro-inflammatory and pro-fibrotic effects of pro-inflammatory cytokines (TNFα and TGF-β) in terms of extracellular matrix formation and cell proliferation in human fetal ASM and to suppress features of inflammation-induced airway remodeling in fetal ASM cells [35,36]. A recent study demonstrated that when human bronchial epithelial cells were stimulated with TGF-β1 or TGF-β2 cell motility was increased. However, the addition of 1,25D appeared to inhibit both migration and invasion induced by TGF-β1 and TGF-β2 [73].

Tissue repair and remodeling, a key feature of asthma, is partially mediated through fibroblasts which modulate tissue repair by producing and modifying extracellular matrix components and by releasing mediators that act as autocrine or paracrine modulators of tissue remodeling. Vitamin D, 25(OH)D and 1,25D all significantly reduced prostaglandin E2 (PGE2) production by human lung fibroblasts and stimulated an enzyme responsible for prostaglandin E2 degradation [152]. These findings suggest that vitamin D can regulate PGE2 synthesis and degradation which can modulate fibroblast-mediated tissue repair function. Further, fibroblast proliferation upon treatment with TGF-β1 (an important driver of many fibrotic disorders, including asthma) was inhibited by 1,25D in a dose-dependent fashion. Similarly, TGF-β1-induced upregulation of mesenchymal cell markers and abnormal expression of epithelial cell markers were blunted by 1,25D [205,206]. These observations suggest that under TGF-β1 stimulation, 1,25(D inhibits the pro-fibrotic phenotype of lung fibroblasts and epithelial cells.

Taken together, these findings suggest 1,25D may be a novel, important agent for the prevention and treatment of detrimental structure changes in the airways. The link between vitamin D and airway remodeling has recently been reviewed [20].

3.2.6. Vitamin D as an adjunct to anti-inflammatory therapy in asthma

Two major pharmacological treatments for asthma currently are glucocorticoids and immunotherapy. The anti-inflammatory and immunomodulatory effects of vitamin D, suggest potential to improve the efficiency of these anti-inflammatory therapies.

3.2.6.1. Immunotherapy. Allergen-specific immunotherapy is a unique form of therapy capable of changing the course of disease in allergen-sensitive rhinitis and asthma. This form of treatment increases allergen-specific immunoglobulin G (IgG) 1 and 4, induces T-regs and thereby peripheral tolerance leading to clinical improvement [1,7].

In murine models, pretreatment with 1,25D has the capacity to enhance the inhibitory effects of immunotherapy on allergic airway inflammation [97,153,242,255]. These preliminary results preceded human intervention work, whereby pre-treatment or adjuvant therapy with vitamin D, improved the efficiency of immunotherapy [16,157,158] – see section 3.1.6 in part two of this review [127].

3.2.6.2. Glucocorticoids. Glucocorticoids (GCS) are the first line anti-inflammatory treatment for asthma and are the most effective anti-inflammatory treatment currently available [248]. Their multiple inhibitory properties include inhibition of Th2 cytokine synthesis and enhanced IL-10 production by stimulated T cells [211] and airway cells [119]. Most patients with asthma respond to standard therapy with inhaled bronchodilators and GCS. However, approximately 15% of asthmatics fail to benefit from GCS. This is termed steroid resistant (SR) asthma [54]. SR asthma is associated with *in vitro* and *in vivo* alterations in cellular responses to exogenous GCS, including decreased IL-10 secretion by CD4+ T cells [92]. Despite the use of multiple high dose medications, individuals with SR asthma experience frequent exacerbations [266] and contribute excessively to the asthma-related morbidity and mortality [218]. In addition to SR asthma, GCS side effects – which have been shown to be strictly dose-dependent [214] – frequently limit long term GCS application. Therefore, it is desirable to lower the dose of GCS treatment while maintaining the anti-inflammatory effect.

3.2.6.2.1. Vitamin D status is associated with steroid response. An inverse association between 25(OH)D and the use anti-inflammatory medication (either inhaled corticosteroids or leukotriene inhibitors) has been noted in asthmatic children in Costa Rica [32] and America [228]. Conversely, vitamin D insufficiency (VDI) may lead to down-regulation of GCS pathways and thus a greater need for steroids, particularly in children. For example, there was an association between lower 25(OH)D and decreased *in vitro* steroid response in a small cohort ($n = 54$) of mild-moderate adult asthmatics [241]. However, GCS requirements and *in vitro* steroid responsiveness were significantly inversely associated with 25(OH)D level in childhood asthmatics. While trends for association were also seen for adult asthmatics, these did not reach statistical significance, suggesting a stronger that effect in childhood asthmatics [79]. Although the sample size was small (50 adult asthmatics and 53 childhood asthmatics), this study was the first to compare corticosteroid responsiveness and vitamin D status between children and adults. Further, it has been shown *in vitro* [275] and *in vivo* [184,275]. that co-administration of 1,25D with GCS could modestly improve GCS responsiveness in SR asthma.

3.2.6.2.2. Vitamin D may attenuate steroid resistance and work synergistically with steroids. An early report of the effect of dexamethasone + differing concentrations of 1,25D on PBMCs, demonstrated that 1,25D could act synergistically with dexamethasone to decrease Th1 cytokines (IFN γ) but increase Th2 cytokines (IL-5, IL-13) compared to dexamethasone alone [118].

T-regs from SR asthmatics have been found to secrete less of the anti-inflammatory cytokine IL-10 in response to dexamethasone. A subsequent *in vitro* investigation with CD4+ T cells from patients with SR asthma showed that the addition of 1,25D could potentially increase the therapeutic response to GCS by restoring the impaired steroid-induced IL-10 response [275]. Interestingly, they showed that oral administration of vitamin D_3 reversed steroid resistance in 3 adult asthmatics through induction of IL-10-secreting T-regs. 1,25D. Further, it is known that corticosteroids modulate ASM chemokine secretion *in vitro*. However, co-administration of both 1,25D and corticosteroids resulted in additive inhibition of chemokine secretion suggesting a synergistic relationship [15].

In a randomized trial of inhaled budesonide versus nedocromil versus placebo, VDI was associated with increased risk for severe asthma exacerbations leading to emergency department visits or hospitalizations. In this study, the group with the lowest risk for exacerbations was the group who had 25(OH)D levels >75 nmol/L and who were on inhaled corticosteroids (ICS), further suggesting a synergistic effect between vitamin D status and corticosteroids [33].

Increased expression of mitogen-activated protein kinase 1 (MKP-1), a protein involved in directing cellular responses to a diverse array of stimuli, leads to more effective corticosteroid induced anti-inflammatory and immunosuppressive effects. MKP-1 expression can be used as a marker of responsiveness to GCS. Another mechanism of GCS resistance involves the ability to regulate inflammatory gene expression and GCS receptors. *In vitro*, physiologic concentrations of 1,25D added to dexamethasone significantly enhanced MKP-1 expression in PBMCs compared with dexamethasone alone, suggesting that the addition of vitamin D could decrease the dexamethasone dose requirement by more than 10-fold. Interestingly, this relationship was stronger in patients who were steroid naıve [228].

Corticosteroid-exposed airway cells and PBMCs from asthmatics treated with 1,25D exhibited enhanced induction of MKP-1 and IL-10. Further, increased 25(OH)D levels were associated with improved lung function *in vivo* and with improved corticosteroid responsiveness *in vitro* [228]. The inability to trigger production of MKP-1 is one of the known mechanisms of SR, which is interesting because MKP-1 is considered a vitamin D target gene [285]. Indeed, it has been demonstrated that MKP-1 levels increase in parallel with 25(OH)D levels suggesting that vitamin D may improve GCS response [241].

Both 25(OH)D and 1,25D dose dependently inhibited LPS-induced p38 phosphorylation at physiologic concentrations as well as IL-6 and TNF-α production by human monocytes. MKP-1 expression was significantly upregulated in human monocytes and increased binding of the VDR was observed [285]. 1,25D stimulated GCS induction of MKP-1 and enhanced GCS inhibition of LPS-induced IL-6 signaling enhanced GCS responses in human PBMCs [284]. PBMCs from 11 SR asthmatics and 8 steroid sensitive (SS) asthmatics were pre-incubated with 1,25 D followed by dexamethasone treatment and LPS stimulation. Dexamethasone significantly inhibited LPS-induced phosphorylated p38 mitogen-activated protein kinase in monocytes from patients with SS asthma but not those from patients with SR asthmatics ($p < 0.01$). However, 1,25D inhibited LPS-induced phosphorylated p38 mitogen-activated protein kinase in monocytes from both patient groups ($p < 0.01$). Further, 1,25D enhanced dexamethasone suppression of LPS-induced phosphorylated p38 mitogen-activated protein kinase in monocytes, but only from patients with SS asthma ($p < 0.01$). 1,25D induced MKP-1 expression and enhanced dexamethasone induction of MKP-1 in SS asthmatics and SR asthmatics. However, the responses to GCS in SR asthmatics remained significantly lower than those with SS asthma ($p < 0.05$).

Vitamin D and corticosteroids synergistically induce a tolerogenic DC phenotype [72] 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. Vitamin D was more potent than dexamethasone in skewing the cells from the pro-inflammatory phenotype seen in the untreated DCs.

Both dexamethasone and 1,25D have the ability to inhibit production of pro-inflammatory cytokines (e.g. TNF, IL-6) from LPS stimulated PBMCs in cell culture. However, when administered concurrently the effects were additive. The mechanism was shown to involve stimulation of dexamathasone induction of MKP-1. *Granulocyte macrophage colony-stimulating factor* (GM-CSF) was shown to mediate the enhancement of dexamethasone-induced MKP-1 production in monocytes via increased production of mediator complex subunit 14 [284].

An *in vitro* study of PBMCs from SR asthmatics, SS asthmatics and healthy controls demonstrated that asthmatics produced higher levels of Th17-associated cytokines (IL-17A and IL-22). Stimulation of PBMCs with dexamethasone did not inhibit IL-17A cytokine expression. However, treatment of PBMCs with 1,25D, both in the presence and absence of dexamethasone significantly reduced both IL-17A and IL-22 levels. The inhibitory effect of 1,25D was evident in all patients studied, irrespective of their clinical responsiveness to steroids identifying novel steroid-enhancing properties of vitamin D in asthmatic patients [185]. *In vivo* work has demonstrated that 1,25D is additive with dexamethasone in decreasing inflammatory cytokine production from T-cell subsets implicated in asthma [126].

A recent animal study lends support to these *in vitro* studies. Monotherapy with vitamin D or dexamethasone attenuated the increased WBC count, serum IgE, nitric oxide and IL-5 levels observed among rats with ovalbumin-induced airway inflammation. However, combination therapy with vitamin D + dexamethasone was shown to be superior to either alone [173].

Several human studies have suggested a beneficial synergistic effect between vitamin D and GCS in asthma outcomes [33,79,157,228,274]. Possible mechanisms whereby vitamin D may mediate increased steroid responsiveness include inhibition of fractalkine secretion [15] and increased T-reg production and function (reviewed above) as well as increased GCS bioavailability in ASM cells induced by 1,25D [30].

Vitamin D supplementation may potentiate the anti-inflammatory function of corticosteroids in asthmatic patients. The evidence that vitamin D has additive effects on the administration of corticosteroids is reviewed fully elsewhere [148].

3.2.6.2.3. Vitamin D may prevent the adverse effects of anti-inflammatory therapies in asthma. Majak et al. conducted a double-blind, placebo controlled trial to assess specific immunotherapy (SIT) in combination with ICS (prednisone 20 mg daily) + either placebo or vitamin D_3 (1000 IU/week) [158]. Early administration of ICS prevented the benefits of SIT. However, the addition of low dose vitamin D (143 IU/day) preserved the benefits of SIT, despite concomitant ICS use. Indeed, all negative clinical- and immunological-effects of prednisone were prevented by the administration of vitamin D_3.

Children who were on ICS had poorer lung growth if they were VDD compared to those that were not VDD [274]. According to cross-sectional data from National Health and Nutrition examination survey (2001–2006), GCS users seem to be at higher risk of VDD (OR, 2.36; 95% CI, 1.25–4.45) compared to non-users. It was concluded that GCS use is independently associated with VDD, and the need for screening patients with chronic steroids usage was suggested [233].

These human studies are supported by a recent animal study. Dexamethasone-induced hyperglycemia, hyperlipidemia, and behavioral abnormalities in allergic rats but these effects were attenuated with vitamin D co-administration [173]. These studies suggest that optimizing vitamin 25(OH)D levels may be of importance in increasing the effectiveness of anti-inflammatory therapies and decreasing potential side-effects.

3.2.7. Interplay of the genome and vitamin D status to influence asthma

It is recognized that asthma may develop as a consequence of a variety of gene-environment interactions. Vitamin D synthesis, transport and degradation are controlled by several genes, particularly genes encoding for the vitamin D binding protein (VDBP) and the vitamin D receptor (VDR). Polymorphisms in these genes may affect both 25(OH)D status and the effects of 1,25D. For example, human genome-wide linkage evaluation has shown strong genetic regulation of serum 25(OH)D levels, but not 1,25D levels [268].

3.2.7.1. Vitamin D receptor (VDR). The biological effects of 1,25D are mediated via the VDR [182]. VDR polymorphisms have been significantly associated with asthma in studies of Chinese [218], American [200,203], African–American [199] and Tunisian [154] populations. However, further studies have failed to confirm this association among Chinese [71] and German [260,270]) populations. Indeed, a large cross sectional study in the UK found that 25(OH)D was not related to forced expiratory volume in 1 s and VDR genotypes were unrelated to lung function and did not modify the effects of dietary vitamin D intake or 25(OH)D concentrations on lung function [230]. However, a recent meta-analysis of case-control studies demonstrated that FokI polymorphisms were marginally associated with asthma risk (OR 1.187; $p = 0.088$) and that both TaqI polymorphisms (OR 1.488, $p = 0.040$) and BsmI k polymorphisms (OR 2.017; $p = 0.017$) were significantly associated with asthma [246]. Gender and age modified the association of these single nuclear polymorphisms (SNPs) with asthma, potentially explaining some of the discrepancies displayed from exiting observational and interventional research – see part two of this review [127].

A 2014 Greek study assessed, for the first time, potential associations between VDR polymorphisms (FokI, BsmI, ApaI, and TaqI) and asthma control as assessed with Global Initiative for Asthma score and Asthma Control Test (ACT) score. Although, there was no association between VDR polymorphisms and asthma prevalence, asthmatic children with the VDR ApaI-aa genotype had significantly higher ACT scores compared with asthmatic children carrying the ApaI aa/ac genotypes ($p = 0.011$). The frequency of VDR ApaI-aa genotype was significantly higher in controlled asthmatics ($n = 92$) compared to uncontrolled asthmatics ($p = 0.001$). Further, VDR ApaI-aa genotype was negatively associated with limitation in daily activities because of asthma ($p = 0.004$) but positively associated with well-controlled asthma [110]. This study has provided the first evidence that VDR SNPs may modulate both asthma control and response to vitamin D in asthma.

3.2.7.2. Vitamin D binding protein (VDBP). VDBP is a serum protein that binds the majority of circulating 25(OH)D and 1,25D with high affinity [238]. Bioavailable vitamin D is that 25(OH)D which is not bound to VDBP. VDBP possesses independent immunomodulatory functions, which predominantly relate to macrophage activation and neutrophil chemotaxis [52]. These immunomodulatory functions appear of particular relevance to RTIs [208] and inflammation [25,272]. VDBP variants have been associated with asthma susceptibility in a Chinese population [144]. Additionally, a recent study of 463 Hispanic children at 6 and 36 months of age

demonstrated that a specific genotype of VDBP might confer protection against the development of asthma [186].

Compared to non-asthmatic controls and moderate asthmatic children, children with SR asthma had significantly higher levels of VDBP in BALF but not in serum. Further, VDBP concentration in BALF correlated negatively with asthma control and percentage of predicted forced expiratory volume in 1 s but positively with ICS usage [88]. A recent study analysed the regulation of factors of the vitamin D axis during the early and late-phase reaction of asthma in 15 patients. A significant increase in VDBP and 25(OH)D_3 but not 1,25D in the BALF from mild asthmatics 24 h after allergen challenge was noted [31].

Specific VDBP- and VDR SNPs were significantly associated with pediatric asthma development in a case-control study among Egyptian children [111]. Other studies have associated non-VDR genetic variation to paediatric asthma [269], including 25-hydroxyalse [199]. There is evidence that SNPs in genes encoding for 25-hydroxylase can directly affect presence of asthma, and SNPs in the VDR gene can affect asthma morbidity and lung function, as well as number of positive allergen tests and IgE elevation [199].

3.2.7.2.1. Additional studies of vitamin D genetics relevant to asthma. A genome wide association analysis provided mixed conclusions regarding vitamin D-asthma genetics [141]. However, a subsequent genome-wide study of gene–vitamin D interactions in asthma exacerbations identified 3 common variants in the class I MHC–restricted T cell–associated molecule gene (CRTAM) that were associated with an increased rate of asthma exacerbations based on the presence of low 25(OH)D. These findings suggest an important gene-environment interaction whereby vitamin D status can influence CD8+ and NK T cells, as well as asthma exacerbation [67]. A 2013 study observed that vitamin D regulated genes were markedly over-represented in normal human and mouse developing lung transcriptomes [128]. This finding suggests a significant association between early lung development and asthma related phenotypes for vitamin D pathway genes, supporting a genomic mechanistic basis for the epidemiologic observations relating maternal and neonatal vitamin D intake/25(OH)D and childhood asthma susceptibility [175,204].

When human bronchial ASM cells were stimulated with 1,25D over 400 genes – including genes implicated in asthma were regulated [30]. The same research group went on to demonstrate modest associations of asthma with multiple genes in the vitamin D metabolism pathway, and multiple genes regulated by 1,25D [29]. Further, a recent DBRCT of low (400 IU/d) vs. high (2,000 IU/d) dose vitamin D_3 supplementation for 8 weeks demonstrated that improved 25(OH)D status was associated with at least a 1.5 fold alteration in the expression of 291 genes involved in expression of WBCs [291], which may be of relevance to asthma. A recent microarray analysis of adult non-smokers revealed that the expression of thirteen candidate genes from small airway epithelial cells were significantly altered by serum 25(OH)D ($p < 0.05$), and a genome-wide significant expression quantitative trait loci association was detected for sphingosine-1-phosphate phosphatase 2 – a gene associated with lung function [294]. Similarly to children, these finding suggests a significant association between lung function, immune homeostasis and vitamin D pathway genes, supporting a genomic mechanistic basis for the epidemiologic observations relating intake/25(OH)D and adult asthma susceptibility.

These interesting observations suggest a role for VDR, VDBP and potentially other genes as well 25(OH)D in asthma pathogenesis. The apparent discrepancies in vitamin D-asthma-genetic studies may be due to differences in phenotypes related to age or asthma duration and/or sample size issues. Nevertheless, the preponderance of currently available data suggest that genetic abnormalities may be an additional pathway by which inadequate 25(OH)D levels are linked with asthma pathogenesis and severity.

3.2.8. Additional health benefits for the asthmatic population? bone health

GCS are a mainstay of anti-asthmatic therapy. The current consensus indicates that long term treatment with GCS is associated with detrimental effects on bone [64,273,283]. Further, both airway hyper-responsiveness and asthma were related to clinically meaningful decreased bone mineral density (BMD) in a recent study of 7034 Korean individuals [123]. It is possible this finding may be explained by concomitant GCS use.

VDI is associated with a decreased response to GCS and therefore greater use (reviewed above). Vitamin D is best known for its beneficial effects of bone metabolism. During treatment with oral corticosteroids (OCS), VDI has been associated with decreased bone mineral accrual whereas vitamin D sufficiency seems to protect asthmatic children from loss of bone calcium [292].

The combination of vitamin D_3 (1,000 IU/day), calcium (1,000 mg/day) and ethane-1-hydroxy-1,1-diphosphonate (0.5 mg/kg body weight), has been shown to prevent decreases in BMD and perhaps increase BMD [273]. Because of the combination of therapies, it is impossible to assess the independent role of vitamin D based on this preliminary study. However, the addition of 600 IU vitamin D_3/day to inhaled budesonide (400 μg/d) for 4 weeks to asthmatic children did not affect short-term growth or markers of bone despite a significant increase in serum 25(OH)D [225]. Similarly, a subsequent DBRCT did not find any benefit of 1,25D (0.5 mcg/day) on bone health [170]. A small DBRCT ($n = 62$) of 50,000 IU vitamin D/week + 1,000 mg calcium/d in a diverse group of corticosteroid users demonstrated that although vitamin D + calcium blunted the initial decrease in BMD, there was no observable long-term benefit and differences between vitamin D + calcium vs. placebo did not reach statistical significance at any point [293]. However, the addition of 800 IU vitamin D_3 daily to 24 weeks of steroid therapy in children was associated with improvement in both calcium–phosphorus balance and collagen turnover [240]. These discrepancies may potentially be explained by serum 25(OH)D levels, differing vitamin D dose and intervention period.

The Cochrane Database of Systematic Reviews evaluated the data supporting the recommendation to use calcium and vitamin D as preventive therapy in patients receiving GCS [108]. The authors concluded that because calcium and vitamin D have low toxicity and are inexpensive and that all patients starting GCS should also take a calcium and vitamin D supplement prophylactically. Therefore, in addition to any effect of vitamin D on asthma parameters, adequate serum 25(OH)D may prove to be beneficial for bone health and mitigate the effects of long term anti-asthmatic therapy. However, further research is required among asthmatics to determine the effect, if any, of vitamin D therapy on bone health in asthmatics.

4. Conclusions

It is clear that vitamin D influences diverse influences immunoregulatory and anti-inflammatory. To better understand the relationship between vitamin D and asthma, data from human studies is required. The second part of this two-part review summarizes the existing epidemiological, case-control, cross-sectional, prospective and intervention studies regarding asthma and vitamin D [127].

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Author contributions

- CK made substantial contributions to review design and manuscript collection and interpretation of data; has drafted the submitted article; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- BE revised the submitted article critically for important intellectual content; has provided final approval of the version to be published.
- JF revised the submitted article critically for important intellectual content; has provided final approval of the version to be published.
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