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CME Review

Vitamin D and Asthma in Children

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SUMMARY

Vitamin D deficiency and insufficiency are increasingly being recognized in the general population, and have been largely attributed to lifestyle changes (reduced exposure to sunshine due to working indoors or the use of protective clothing and sunscreen; changes in diet) over the last few decades. The musculoskeletal consequences of severe vitamin D deficiency are well established, however, a number of other disorders have now been linked to vitamin D insufficiency, including asthma.

There is growing appreciation of the likely importance of vitamin D as a pleiotrophic mediator that contributes to pulmonary health. Children with asthma appear to be at increased risk of vitamin D insufficiency. Epidemiologic data suggest that low serum vitamin D in children with asthma is associated with more symptoms, exacerbations, reduced lung function, increased medication usage and severe disease. *In vitro* studies have demonstrated that vitamin D enhances steroid responsiveness in adult asthmatics. Vitamin D may play an important role in pulmonary health by inhibiting inflammation, in part through maintaining regulatory T cells, and direct induction of innate antimicrobial mechanisms.

More research is required to fully understand the role of vitamin D in the maintenance of airway homeostasis and address the diagnostic and therapeutic implications vitamin D may have in the future of asthma management. This review summarises the current understanding and uncertainties regarding the effect of vitamin D deficiency and insufficiency in children with asthma.

INTRODUCTION

Asthma is a common disease, affecting an estimated 300 million individuals worldwide, and has a significant social and financial burden on the individuals and families affected.[1,2] Factors such as genetic predisposition, early allergen exposure, infections, diet, tobacco smoke exposure, pollution, and vitamin D status are all proposed to influence the development and severity of asthma.[3–5]

SEARCH STRATEGY

References were identified by searches of MEDLINE (from January 1951 to January 2011), CINAHL (from January 1982 to January 2011), EMBASE (from January 1974 to January 2011) and online Cochrane databases (2010) for the subject headings wheeze or asthma and vitamin D. Manuscripts only published in English were included. Articles were chosen according to their relevance for this review and their bibliographies were also searched their bibliographies for references. Articles from our personal archives were also included.

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WHAT ARE THE SOURCES OF VITAMIN D?

Vitamin D comes from two sources: skin exposure to ultraviolet B (UVB) rays and dietary intake. Dietary sources include fish oil, fish, liver, egg yolk and dietary supplements.[6,7] As very few foods contain vitamin D, sunlight exposure is the primary determinant of vitamin D status in humans. In a fair skinned person, 20 to 30 minutes of sunlight exposure on the face and forearms at midday is estimated to generate the equivalent of around 2000 IU of vitamin D. Two or three such sunlight exposures a week are sufficient to achieve healthy vitamin D levels in summer in the UK.[8] In the absence of adequate sun exposure, at least 800–1000 IU (20–25 μg) vitamin D per day may be needed to achieve this.[9]

VITAMIN D METABOLISM

Vitamin D synthesis is initiated in the skin by solar UVB radiation (wavelength 290 to 315 nm), activating the precursor 7-dehydrocholesterol, which then circulates in the bloodstream to the liver, where it is converted into its main metabolite, 25-hydroxyvitamin D (25[OH]D), which has blood levels about 1000 times higher than the active metabolite, 1,25-dihydroxyvitamin D (1,25-[OH]2D. Until recently, it was thought that the conversion to 1,25-(OH)2D occurred only in the kidneys, but increasing evidence indicates that the cells of most organs have the vitamin D receptor

(VDR) and the capacity to synthesize 1,25-(OH)2D locally.[7] This synthesis of 1,25-(OH)2D is dependent on serum 25(OH)D levels, the primary circulating form of vitamin D.[7]

DEFINITION OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

Serum 25[OH]D is the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake and sun exposure, as well as the conversion of vitamin D from adipose stores in the liver. There are no consensus guidelines available on optimal levels of serum 25[OH]D. Vitamin D deficiency is defined by most experts as a 25[OH]D level of less than 50 nmol/L (20 ng per millilitre).[7,10–13] 25[OH]D levels are inversely related to parathyroid hormone levels until the former reach 75 to 100 nmol/L (30–40 ng per millilitre), at which point parathyroid hormone levels begin to level off (at their nadir).[13–15] Intestinal calcium transport increases by 45 to 65% when 25[OH]D levels increase from an average of 50 to 80 nmol/L (20 to 32 ng per millilitre).[16] 25[OH]D levels between 50–75 nmol/L (20–30 ng per millilitre) are considered indicative of vitamin D insufficiency on the basis of the above data and their association with health outcomes.[17,18] 25[OH]D levels of 75 nmol/L (30 ng per millilitre) to 100 nmol/L, are indicative of normal vitamin D levels.[17,19] Excessive levels or vitamin D intoxication are rare.[7,20]

PREVALENCE OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

Vitamin D deficiency is one of the most common medical conditions worldwide with more than 1 billion children and adults at risk.[21] A recent survey of adults in the United Kingdom showed 60% had serum 25(OH)D concentrations below 75 nmol/L (30 ng per millilitre) in the summer months and 87% were insufficient in the winter.[22] This survey also demonstrated a gradient of prevalence across the UK, with highest rates of insufficiency in Scotland, northern England, and Northern Ireland.[22] People living at higher latitudes are known to be at greater risk for vitamin D deficiency.[23] Depending on the levels used to define vitamin D deficiency, 57% to 93% of the general hospital inpatient population is deficient[13] and a recent meta-analysis concluded that use of vitamin D supplements is associated with decrease in total all-cause mortality rates.[24]

Children and young adults are also potentially at high risk of vitamin D deficiency; 12% of infants and toddlers from Boston,[25] 52% of Black and Hispanic adolescents from Boston[26] and 48% of white pre-adolescent girls in a study in Maine[27] had 25(OH)D concentrations below 50 nmol/L (20 ng per millilitre). A recent large observational, cross-sectional survey (National Health and Nutrition Examination Survey from 2001-2004) showed that 61% of children aged 1 to 21 years had insufficient levels of vitamin D.[28]

The prevalence of vitamin D deficiency is also reflected in the several hundred children with rickets treated each year in the UK.[29] However, these children represent a small proportion of all individuals with suboptimal vitamin D levels in the UK population.[22,30]

WHO IS AT RISK OF VITAMIN D DEFICIENCY AND INSUFFICIENCY (TABLE 1)

Many factors influence the amount of vitamin D that can be synthesized in the skin driven by UVB: the use of sunscreen (for example, use of sun protection factor (SPF) 8 reduces vitamin D production by 92.5% and SPF 15 by 99%),[7] darker skin pigmentation, clothing that completely covers the skin or spending the majority of time indoors all limit the amount of light that penetrates the skin.[9]

Table 1
Risk factors for Vitamin D Deficiency/Insufficiency

- Lack of sunlight exposure (Very little Vitamin D is produced in areas at beyond a latitude of 35° from October to March)
- Non-white ethnicity (pigmented skin)
- Concealed clothing (for example use of veil, headscarf)
- Use of sun screen
- Obesity
- Elderly
- Institutionalized individuals who spend relatively large amount of time indoors.
- Multiple, short spaced pregnancies
- Liver disease
- Malabsorption, short bowel
- Drugs (for example rifampicin, glucocorticoids, anticonvulsants)

THE ANTI-INFLAMMATORY PROPERTIES OF VITAMIN D: RELEVANCE TO ASTHMA

The scope of vitamin D's biologic actions is far beyond just calcium and phosphate homeostasis and bone metabolism. VDRs have been found in organs that are not typically involved in bone metabolism, including the immune system (such as activated T and B cells, monocytes, antigen presenting cells (APCs) including macrophages and dendritic cells).[31,32] Immune cells also have the enzymatic machinery required to activate 1,25(OH)2D. 1,25(OH)2D is able to traverse the cell membrane and act within the cell by binding to VDR in the nucleus.[7]

Asthma is classically driven by enhanced activity of Th2 cells, which induce IgE production, and promote eosinophilic airway inflammation and airway hyperresponsiveness.[33,34] Recent research has shown that vitamin D has multiple cytokine-modulating effects through several different cells of the immune system (Table 2). *In vitro*, T cells have been shown to be direct targets for 1,25(OH)2D,[35] and a five-fold increase in VDR expression has been reported after activation of quiescent CD4+ cells[31]. Essentially all studies using mouse or human cells agree on the capacity of vitamin D to inhibit T cell proliferation and Th1 responses. More recently vitamin D has been shown to inhibit Th17 responses,[36] which may be important in steroid refractory airway disease.[37] However there are contradictory reports of the effects of vitamin D on Th2 responses (recently reviewed by Lange et al[38]). Treatment with vitamin D resulted in reduced interleukin (IL)-4 concentrations in bronchoalveolar lavage fluid, and an attenuated inflammatory response *in vivo* in a Th2 dependent murine model of allergic airways disease.[39] It has also been shown to impair recruitment of eosinophils and reduce levels of IL-5 in a murine model of eosinophilic inflammation.[40] Taher et al demonstrated a beneficial effect of vitamin D administration to mice post allergic sensitization, but prior to allergen challenge by aerosol, when delivered together with a regimen of allergen immunotherapy.[41] A role for the immunoregulatory cytokines IL-10 and TGFβ was proposed. However other studies have shown that 1,25[OH]D3 administration to mice had no effect on the severity of allergic airway disease induced by OVA, and that VDR knockout mice failed to develop allergic airway disease leading the authors to conclude that vitamin D was required for the generation of Th2-driven inflammation in the airways.[42] Subsequent studies now suggest that vitamin D deficiency may alter the structure of the lungs leading to impaired function,[43] which may be relevant to this earlier observation. *In vitro* studies suggest that dosage effects may occur. For example whilst 1,25[OH]D3 inhibited both Th1 and Th2 cytokine production in cultures of human CD4+ T cells, very high concentrations of 1,25[OH]D3 failed to inhibit[44] or even enhanced Th2 responses.[45] A counterpart to this exists *in vivo* in humans. Hypponen et al[20] recently showed that "a significant, but nonlinear relationship" exists between serum 25[OH]D and IgE, with both a

Table 2
Response of various target cells to vitamin D

Target Cells of vitamin D	Effector function of vitamin D
T cells	Inhibit T cell proliferation[35]
Th1	Inhibit Th1 cytokine release[107,108]
Th2	Conflicting evidence for enhancement [108] and inhibition[109] of Th2 responses, which may pertain to dose.[44]
Th17	Inhibit Th17 cytokine release[36,110]
B cells	Nonlinear association between serum vitamin D levels and IgE[20] Enhanced production of immunomodulatory cytokine IL-10[47]
Regulatory T cells	Induces IL-10 synthesis[44,46,90] Enhance forkhead box P3 (FoxP3) cells[89] Enhance transforming growth factor (TGF) β synthesis[41]
Dendritic cells	Renders monocyte derived dendritic cells more immature and tolerogenic[111] Induces IL-10 synthesis[111]
Lung bronchial smooth muscle cells	Inhibit cytokine synthesis and release[39] Decrease lung inflammation[31,108] Inhibit bronchial smooth muscle cell proliferation and remodeling (eg, matrix metalloproteinase-9 [MMP-9])[60,62,63]
Mast cells	Inhibit the differentiation, maturation, and homing of mast cells to allergic airways[112]

very high and very low serum 25[OH]D associated with higher levels of IgE.

Vitamin D also enhances the production of the anti-inflammatory cytokine IL-10 by human T cells *in vitro* and *in vivo* both directly[44] and in concert with glucocorticoids.[46] Enhancement of IL-10 synthesis by B cells[47] by vitamin D has also been reported. There is further evidence for the capacity of vitamin D to promote mouse and human regulatory T cell populations, both directly and through effects on antigen presenting cells, an area that has recently been reviewed elsewhere.[48,49]

In innate cells vitamin D is generally believed to promote antimicrobial pathways,[50] and impair antigen presenting cell function.[32] Studies by Adorini and colleagues demonstrate the capacity of vitamin D to induce IL-10 production by dendritic cells,[51] and a tolerogenic phenotype in these cells that promotes regulatory T cells.[49,52]

MOLECULAR EVIDENCE FOR A LINK BETWEEN VITAMIN D LEVELS AND ASTHMA

Several genetic studies have reported associations between VDR and asthma. Genome scans for asthma have identified possible linkages on 17 different chromosomes, including chromosome 12, region q13-23. Because the VDR is mapped to chromosome 12q, some geneticists have postulated an association between VDR polymorphisms and genetic susceptibility for asthma.[53–55] Further evidence for a link between vitamin D and inflammatory airway diseases is provided by the interaction with vitamin D binding protein (VDBP).[56] VDBP is a serum protein, which has immunomodulatory functions relevant in the lungs, predominantly relating to macrophage activation and neutrophil chemotaxis.[57]

Respiratory epithelial cells can also constitutively convert inactive 25(OH)D to 1,25(OH)2D, enabling high local concentrations of active vitamin D to increase the expression of vitamin D-regulated genes with important innate immune functions.[58]

VITAMIN D AND AIRWAY REMODELLING

Airway remodelling is an important feature of asthma, which has been linked to steroid resistance in adults.[59] *In vitro* studies have shown that vitamin D may influence airway remodelling by a direct inhibitory effect on passively sensitized airway smooth muscle cell movement, by affecting growth and contractility and inhibiting TGFβ and matrix metalloproteinases (MMPs) as well as fibroblast proliferation.[60–62] Moreover, Bosse et al[63] have shown *in vitro* that vitamin D increases glucocorticoid bioavailability in bronchial smooth muscle cells suggesting a further beneficial role for vitamin D in the prevention and treatment of asthma.[64] These data suggest that lower vitamin D levels could lead to bronchial smooth muscle proliferation, cytokine release, and thus airway remodeling.[60–63]

VITAMIN D AND WHEEZING (TABLE 3)

Prenatal vitamin D status is thought to affect the development of the fetal lung and immune systems.[43,65] Thus it is possible that vitamin D deficiency/insufficiency early in life predisposes individuals to pre-school wheezing. In a New Zealand birth cohort, low serum 25(OH)D levels in cord blood was associated with increased risk of childhood wheezing.[66] Children born to women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for recurrent wheeze at 3 years of age.[67] An inverse association between maternal intakes of vitamin D during pregnancy and early childhood wheezing has been reported.[67,68] A birth cohort in Scotland showed children of mothers who had lower vitamin D intake had an increased risk of recurrent wheeze at age 5 years. However, there was no association with spirometry or exhaled nitric oxide concentration.[68] In an epidemiological study of mother-child pairs, the maternal intake of each additional 100 IU vitamin D in the first and second trimester was associated with a lower childhood risk of wheezing and asthma.[67] Another study has shown an inverse relationship between maternal vitamin D intake during pregnancy and the development of asthma and allergic rhinitis in children 5 years of age.[69] A limiting factor to all these studies was the use of food frequency questionnaires and not serum levels of vitamin D.

Children with a diagnosis of wheezy illness had more than two-and-a-half times the incidence of rickets than age matched controls and a 10 times higher incidence of wheezy illness when severe rickets was present.[70] Chest wall compliance allowing more dynamic airway collapse might have contributed to wheezy illness.

In summary, in utero and early life vitamin D deficiency/insufficiency is associated with an increased risk of wheezing. However, association does not prove causation, further evaluation needs to be undertaken to clarify the exact role of vitamin D in the pathogenesis of wheeze.

VITAMIN D AND ASTHMA

Epidemiological evidence of a link between vitamin D levels and asthma (Table 4)

A high prevalence of vitamin D deficiency (54%) and insufficiency (86%) was noted in a recent cross sectional case control

Table 3
Epidemiological studies: Vitamin D and wheeze in preschool children

Effect of vitamin D	Age group	Study type	Investigator
Low serum vitamin D is associated with increased risk of viral co-infection in wheezing children	Preschool children	Epidemiologic study Substudy of the VINKU project, Finland	Jartti et al[113]
Cord blood levels of vitamin D are inversely associated with risk of respiratory infections and childhood wheezing but no association with asthma at 5 years.	5 years of age	New Zealand birth cohort Population based cohort studies	Camargo et al[114]
Mothers in highest quartile of vitamin D intake had lower risk for recurrent wheeze in child at age 3 years	1194 children aged 3	Mother-child pre-birth cohort	Camargo et al[67]
Mothers in highest quintile of vitamin D intake had lower risk for child at age 5 years to have ever wheezed, wheezing in the previous year, and persistent wheezing. No association of vitamin D levels with asthma, spirometry, or atopic sensitization	1335, aged 2 years 1212, aged 5 years	Mother-child pre-birth cohort	Devereux et al[68]
Maternal 25-hydroxyvitamin D concentrations >30 ng/mL associated with an increased risk of eczema at 9 months and increased risk of asthma at 9 years	440 children aged 9 months 178 children aged 9 years	Mother-child pre-birth cohort	Gale et al[81]
Maternal vitamin D intake from foods during pregnancy is negatively associated with risk of asthma and allergic rhinitis	1669 children, aged 5 years	Finnish birth cohort study	Erkkola et al[69]
Atopic manifestations were more prevalent in the group with higher intake of vitamin D	123 children, aged 6 years	Postal questionnaire	Back et al[115]

study of inner-city African-American children with asthma. Significantly lower vitamin D levels were noted in asthmatic children compared to healthy controls.[71] Large cross sectional studies have shown that low serum vitamin D levels are associated with reduced lung function in adolescents[72,73] and adults.[74] A study of 616 Costa Rican asthmatic children between the ages of 6 and 14 years showed an inverse association between vitamin D levels and total IgE levels, and eosinophil counts.[75] More recently, a high frequency of vitamin D insufficiency (35%) in 1024 North American children with mild-to-moderate asthma has also been reported. In addition, vitamin D insufficiency was associated with a lower mean forced expiratory volume in one second (FEV_1) compared with children with sufficient levels.[76] This study was limited by the absence of repeated vitamin D measurements over time, an issue that limits our ability to understand the extent to which fluctuations in vitamin D levels over time (because of demographic and lifestyle variables) might be relevant to the observed effect[76].

Recently, Searing et al[77] have shown the prevalence of vitamin D insufficiency was 47% in children with asthma who were primarily from latitudes above 35 N, and 17% of asthmatic children were vitamin D deficient. These percentages were higher than those in the equatorial population from Costa Rica, in which 28% of asthmatic children were vitamin D insufficient.[75] The differences between these studies support the association of an increased risk of vitamin D deficiency in populations living at higher, northern latitudes. Searing et al[77] also found that low levels of vitamin D were positively correlated with FEV_1 percent predicted and the FEV_1/forced vital capacity (FVC) ratio.[77] Total IgE and the number of positive aeroallergen skin prick test responses showed a significant inverse correlation with vitamin D levels. More recently a positive association between vitamin D levels and asthma control (assessed by childhood asthma control test [ACT]) and negative association with exercise induced bronchoconstriction has also been shown in Italian asthmatic children.[78]

Although these studies suggested a role for vitamin D in asthma control, some authors have also suggested that vitamin D may promote, rather than ameliorate the asthmatic phenotype.[79] Regular vitamin D supplementation (2000 IU/day) in the first year of life increased the risk of developing atopy, allergic rhinitis, and asthma when assessed at age 31 years.[80] However, this study was limited by the absence of data on maternal intake of vitamin D and assessment of childhood asthma or atopy. Mothers reported the frequency and dose of vitamin D supplementation and daily dose was calculated based on this information. Furthermore, this finding may be related to the very high dose of vitamin D supplementation.[20] Another study from the United Kingdom has shown that pregnant women with higher levels of vitamin D have offspring with an increased risk of eczema at 9 months and asthma at 9 years of age,[81] however, this study also has important

Table 4
Epidemiological studies: Vitamin D and asthma in children and adults

Effect of vitamin D	Population studied	Children / adults	Study type	Investigator
Log10 ↑in serum vitamin D level associated with ↓ hospitalizations, ↓ anti-inflammatory medication, and ↓ markers of allergy	Costa Rica	616 children, aged 6-14	Cross sectional	Brehm et al[75]
Vitamin D insufficiency is common in children with mild-to-moderate asthma and is associated with higher odds of severe exacerbation over a 4-year period	North American	1024 Children	Sub study of Childhood Asthma Management Program (CAMP) study	Brehm et al[76]
Vitamin D insufficiency is associated with reduced asthma control	Italian	Children (5-11yrs)	Cross sectional	Chinellato et al[116]
Lower serum Vitamin D levels associated with reduced lung function and increased airway reactivity to exercise	Italian	Children (5-11yrs)	Cross sectional	Chinellato et al[78]
↑ FEV1 and ↑ FVC in subjects (US civilian population) whose serum vitamin D level was in the highest quintile	NHANES database	14,076 adults	Cross-sectional survey	Black et al[74]
Regular vitamin D supplementation (2000IU/day) in the first year of life increased the risk of developing atopy, allergic rhinitis, and asthma by age 31 years	Finland	7648 adults	Birth cohort study	Hypponen et al [80]
Vitamin D deficiency associated with decreased lung function in newly diagnosed asthmatics?	Chinese	Adults	Cross sectional	Li et al[117]

limitations (30% follow-up at age 9 years and small numbers). There was no association between cord blood 25(OH)D and risk of current asthma at age 5 years in the New Zealand birth cohort.[66] These variable results may be secondary to differences in the absolute amount of vitamin D exposure, the baseline vitamin D status (vitamin D deficiency versus insufficiency versus sufficiency) and the timing of exposure (naive immune cells versus mature cell lines).

The observational nature of these studies precludes an assessment of cause and effect. Epidemiological observational studies suggest an association but do not prove causality; and no interventional trials on individuals with low serum vitamin D have evaluated the effect of supplementation on asthma exacerbations, asthma control, or lung function. Such studies are urgently needed since it remains difficult to ascertain from cross-sectional investigations whether vitamin D deficiency is responsible for reduced lung function in asthmatics or whether asthma associated lifestyles, such as less outdoor exercise and thus decreased exposure to sunlight or decreased dietary intake are responsible for lower serum vitamin D levels. More longitudinal and interventional studies in children and adults are needed to elucidate any relationship more clearly.

VITAMIN D & STEROID RESISTANCE IN ASTHMA

Airway inflammation is a key component of asthma and inhaled glucocorticoids are the most effective anti-inflammatory treatments available. However, glucocorticoid resistance or insensitivity in some patients with asthma represents an important barrier to effective treatment and accounts for significant health-care costs.[82]

The molecular mechanisms of glucocorticoid resistance in children are unclear and there is no accepted definition of steroid resistance. Congenital steroid resistance from mutations in the corticosteroid receptor is rare.[83] Acquired steroid resistance is a spectrum and can be overcome by high doses, albeit at the risk of increased side-effects. There are many potential mechanisms of steroid resistance,[84–86] but these have been studied mostly in adults and the relevance in children is not clear. Regulatory T cells (Tregs) suppress the activation of the immune response that causes airway inflammation and airway hyperresponsiveness. Dendritic cells present allergens and activate Th2 cells. Tregs express the immunomodulatory cytokines IL-10 and TGFβ to suppress Th2 cells directly or indirectly via dendritic cells. Reduction in Tregs has been linked with glucocorticoid resistance.[48,87] Vitamin D has been shown to increase the production of Tregs[44,46,49,88–90] and in the absence of vitamin D the number and function of Tregs are reduced.[49,91] Glucocorticoids *in vitro* induce IL-10 synthesis and CD4+ T cells stimulated in the presence of glucocorticoids show a dose dependent induction of IL-10 synthesis.[91] Moreover, CD4+ T cells from steroid resistant adult asthmatics fail to demonstrate increased IL-10 synthesis following *in vitro* stimulation in the presence of the glucocorticoids,[91] suggesting that induction of IL-10 is an important part of the anti-inflammatory effect of glucocorticoids. This steroid-induced IL-10 synthesis was overcome by the addition of vitamin D to the T cell culture and more strikingly, in a small a pilot study, ingestion of vitamin D by three steroid resistant adult asthmatic patients enhanced their response to dexamethasone for the induction of IL-10 *in vitro*.[46] Thus vitamin D could potentially increase the therapeutic response to glucocorticoids in steroid-resistant asthmatics.

Sutherland et al[92] have reported an association between lower vitamin D concentrations and impaired lung function, increased airway hyperresponsiveness, and decreased *in vitro* steroid response in a small cohort of adults with mild or moderate asthma, whilst higher serum vitamin D concentrations associated with enhanced dexamethasone-induced expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) by peripheral blood mononuclear cells (PBMCs) in an apparently IL-10–independent fashion.[92] Future studies in children need to address whether this apparent enhancing of steroid responsiveness by vitamin D with respect to IL-10 synthesis equates with any clinical benefit to the patient.

Another mechanism of glucocorticoid resistance involves the ability to regulate inflammatory gene expression and glucocorticoid receptors. *In vitro*, physiologic concentrations of vitamin D 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 for steroid response by more than 10-fold.[77] This relationship was stronger in patients who were steroid naïve.[77]

A study in 616 Costa Rican asthmatic children showed an inverse association between vitamin D levels and the use of anti-inflammatory medication (either inhaled corticosteroids or leukotriene inhibitors) [75] and Searing et al[77] also found that low levels of vitamin D were significantly associated with inhaled and oral steroid use and total steroid dose[77] in children with asthma. These epidemiological and *in vitro* studies suggest that insufficient vitamin D might increase asthma severity, thus requiring increased treatment, or that down-regulation of glucocorticoid pathways due to insufficient vitamin D leads to a need for increased steroid doses. Vitamin D supplementation might potentiate the anti-inflammatory function of corticosteroids in asthmatic patients.[77]

Interventional trials with Vitamin D will identify whether experimental *in vitro* evidence suggesting a steroid enhancing function in steroid refractory asthma will correlate with clinical benefit.

VITAMIN D & ASTHMA EXACERBATIONS: INDUCTION OF INNATE ANTIMICROBIAL MECHANISMS

Vitamin D appears to act on innate immune cells to inhibit their inflammatory activity and capacity to prime adaptive immune responses, whilst also promoting direct antimicrobial functions.[48] Viral respiratory infections are a common cause of asthma exacerbations in children and adults.[93] Increasing evidence has suggested that viruses cause more than simple respiratory infections. Rhinoviruses have been shown to enhance allergic airway inflammation in mouse models.[94] In humans, rhinovirus infection induces airway inflammation, increases asthma exacerbation severity, and results in more severe infections in asthmatics when compared to normal subjects.[93,95] There is emerging evidence that low serum vitamin D levels are associated with more respiratory infections, especially among patients with asthma,[96] and with increased asthma severity.[75] A prospective cohort study that measured serial concentrations of vitamin D in 198 healthy adults observed that individuals with a 25(OH)D concentrations $>$ 95 nmol/L (38 ng/ml) had a twofold reduced risk of acute viral respiratory tract infections.[97]

Emerging evidence indicates that vitamin D mediated effects on innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), is important in host defence against respiratory tract pathogens.[98–101] In particular, hCAP-18 enhances microbial killing and acts as a chemoattractant for neutrophils and monocytes. Other antimicrobial products regulated by vitamin D are the cationic peptides and defensin-β 2 and 4. *In vitro*, the induction of hCAP-18 in respiratory epithelial cells by vitamin D enhances antimicrobial activity against respiratory pathogens.[101,102]

The association of vitamin D with asthma exacerbations triggered by acute respiratory infections is supported by intervention trials demonstrating decreased respiratory tract infections

in children receiving vitamin D supplementation.[103–105] Majak et al[105] in a recent double blind, placebo controlled clinical study assessed the effect of vitamin D supplementation in the time period from September to July on asthma symptom score, lung function and the number of exacerbations in children (aged 5-18 yrs) with newly diagnosed asthma.[105] Despite the lack of any significant differences between the study groups as far as the absolute changes of vitamin D levels were concerned, the number of children with decreased 25(OH)D levels were significantly lower in the group treated with vitamin D (500 IU cholecalciferol) in addition to inhaled corticosteroids than in the control group treated with inhaled corticosteroids alone. Vitamin D supplementation decreased the number of asthma exacerbations triggered by acute respiratory tract infections. Even though the dose of vitamin D was inadequate to increase serum 25(OH)D levels, significant clinical benefits were observed. In another multi-centre, randomised, double blind placebo-controlled clinical trial in Japanese school children, vitamin D supplementation appeared to have a stronger effect in the sub-cohort with underlying asthma. Vitamin D supplements (1200 IU daily for 4 months) led to a relative risk reduction in asthma exacerbations of 93% compared with children given placebo.[103] These observations are supported by a study by Brehm et al in 1,024 children with mild to moderate asthma in which vitamin D insufficiency was associated with higher odds of any hospitalization or emergency department visit (odds ratio 1.5)[76] and a Costa Rican study which showed that asthmatic children with higher vitamin D levels had fewer hospitalizations in the previous year (odds ratio =0.05, 95% confidence interval =0.004-0.71, P=0.03).[75] The potential for vitamin D to increase pulmonary defence against respiratory infections may reduce the triggering of asthma exacerbations caused by respiratory tract infections.[106]

A large, long-term, multicentre randomised trial is warranted to examine the effects of different doses of vitamin D on asthma control and exacerbations. Vitamin D supplementation cannot currently be recommended for the purpose of reducing the risk or severity of asthma.

FUTURE DIRECTIONS

1. Investigation of the use of vitamin D supplementation as a potential steroid-sparing agent in children with severe, persistent asthma
2. Evaluation of vitamin D requirements during pregnancy
3. Interventional studies examining the efficacy of vitamin D supplementation on incidence and severity of specific viral infections, including influenza, in the general population and in subpopulations with asthma

SUMMARY

Vitamin D is now known to have a complex role in the immune system and its regulation of various aspects of immunity has led to speculation on its potential role in asthma.

Vitamin D may play an important role in lung health and specifically in asthma by inhibiting inflammation, in part through maintaining regulatory T cells, and direct induction of innate antimicrobial mechanisms. Recent evidence has demonstrated associations between vitamin D and lung function, markers of inflammation and modulation in response to steroids. However, proof of concept that vitamin D insufficiency causes or worsens preschool wheeze or asthma or steroid resistance requires interventional trials.

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TRUE OR FALSE

1. The development and severity of asthma is influenced by early allergen exposure, infections, diet, tobacco smoke exposure, pollution, and vitamin D status.
2. Chicken is good source of vitamin D
3. Serum 25-hydroxyvitamin D (25[OH]D) is the best indicator of overall vitamin D status
4. Vitamin D intoxication is common in children and adults.
5. Sunscreen promotes vitamin D production
6. Vitamin D receptors are present in most organs including the immune system (such as activated T and B cells, monocytes, antigen presenting cells (APCs) including macrophages and dendritic cells
7. Vitamin D enhances the production of the anti-inflammatory cytokine IL-10 both in vitro and in vivo both directly and in concert with glucocorticoids.
8. Randomised control trials (RCTs) have shown that low serum vitamin D levels are associated with reduced lung function.
9. Vitamin D deficiency / insufficiency are more common in populations living at higher, northern latitudes.
10. Vitamin D mediated effects on innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), is important in host defense against respiratory tract pathogens.
11. The association of vitamin D with asthma exacerbations triggered by acute respiratory infections is supported by intervention trials demonstrating decreased respiratory tract infections in children receiving vitamin D supplementation.
12. Vitamin D may play an important role in lung health and specifically in asthma by inhibiting inflammation, in part through maintaining regulatory T cells, and direct induction of innate antimicrobial mechanisms.
13. Vitamin D deficiency is more common in obese children and adults.
14. Vitamin D insufficiency is associated with more asthma related symptoms & good asthma control.
15. Regulatory T cells (Tregs) express the immunomodulatory cytokines IL-10 and TGFβ to suppress Th2 cells directly or indirectly via dendritic cells. Vitamin D has been shown to increase the production of Tregs and in the absence of vitamin D the number and function of Tregs are reduced.
16. Vitamin D supplementation in adults is associated with an increase in total all-cause mortality rates.
17. The conversion of 25-hydroxyvitamin D (25[OH]D) to its active metabolite, 1,25-dihydroxyvitamin D (1,25-[OH]2D occurs only in the kidneys.
18. Vitamin D binding protein (VDBP) is a serum protein, which has immunomodulatory functions relevant to the lungs, predominantly relating to macrophage activation and neutrophil chemotaxis.
19. Low serum vitamin D levels are associated with increased use of anti-inflammatory medication in children with asthma.
20. Vitamin D increases pulmonary inflammation.