

Vitamin D, Respiratory Infections, and Asthma

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Over the past decade, interest has grown in the role of vitamin D in many nonskeletal medical conditions, including respiratory infection. Emerging evidence indicates that vitamin D–mediated innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), is important in host defenses against respiratory tract pathogens. Observational studies suggest that vitamin D deficiency increases risk of respiratory infections. This increased risk may contribute to incident wheezing illness in children and adults and cause asthma exacerbations. Although unproven, the increased risk of specific respiratory infections in susceptible hosts may contribute to some cases of incident asthma. Vitamin D also modulates regulatory T-cell function and interleukin-10 production, which may increase the therapeutic response to glucocorticoids in steroid-resistant asthma. Future laboratory, epidemiologic, and randomized interventional studies are needed to better understand vitamin D's effects on respiratory infection and asthma.

Introduction

Asthma is a common chronic medical condition associated with high morbidity and health care use [1,2]. Viral and atypical bacterial infections are common triggers of asthma exacerbations [3,4]. Additionally, chronic infection may play a role in lung inflammation and corticosteroid resistance in asthma [5]. Emerging evidence indicates that vitamin D–mediated innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), is important in host defenses against respiratory tract pathogens

[6,7••,8,9•,10]. Vitamin D insufficiency is widespread and is associated with increased incidence of respiratory tract infections in preliminary studies [11–13,14••]. This association may be particularly important for individuals with asthma, for whom respiratory tract infections often trigger asthma exacerbation and may increase the frequency, severity, and duration of lower respiratory tract symptoms [15]. The interaction of vitamin D, innate immunity, and respiratory infection, particularly in individuals with asthma, is supported by promising basic science and epidemiologic studies. In this review, we summarize the existing literature on this novel area of study and explore avenues for future research.

Vitamin D: Physiology and Epidemiology

Until recently, many health care professionals believed that the major health problems resulting from vitamin D insufficiency were limited to bone health, including rickets, osteomalacia, and osteoporosis [16••]. However, over the past decade, interest has grown in the role of vitamin D in many nonskeletal medical conditions. Vitamin D is involved in the regulation of 1000 human genes [17] and has been associated with increases in cardiovascular disease, cancer, autoimmune disease, and infection [16••]. Vitamin D supplementation appears to mitigate incidence of (and adverse outcomes from) these diseases and may reduce all-cause mortality [18,19].

Vitamin D comes from two sources: skin exposure to UVB rays and dietary intake (including supplements). Because few foods contain vitamin D, sunlight exposure is the primary determinant of vitamin D status in humans. During the late fall and winter months (ie, November–March in the Northern Hemisphere), there are insufficient ultraviolet UVB rays to produce vitamin D [16••]. Vitamin D synthesis is initiated in the skin by UVB radiation from the sun activating its precursor 7-dehydrocholesterol, which then circulates in the blood 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 and, along with this, the capacity to synthesize 1,25-(OH)₂D locally. This autocrine and paracrine synthesis of 1,25-(OH)₂D is dependent on serum 25(OH)D levels, the primary circulating form of vitamin D [16••].

Until recently, serum 25(OH)D levels of at least 25 to 50 nmol/L appeared to be adequate, based on the absence of rickets and improved skeletal outcomes, but increasing evidence suggests that levels of at least 75 nmol/L are required for good health [20•]. In a recent analysis of the National Health and Nutrition Examination Survey (NHANES), we found that the prevalence of serum 25(OH)D levels less than 75 nmol/L has increased from 55% to 77% of the US population over the past two decades (Ginde et al., unpublished data). Although successful campaigns for sun avoidance and sunscreen use have reduced the incidence of skin cancers, these efforts, in addition to the decreased outdoor activity and increased obesity in the US population, likely have contributed to the epidemic levels of vitamin D insufficiency [21].

Mechanisms of Vitamin D–Mediated Innate Immunity

Vitamin D recently has been shown to have an important role in the innate immune system, which helps to prevent infection without the need for immunologic memory from previous exposure to the pathogen [22•]. Innate immunity includes the production of antimicrobial peptides that are capable of killing viruses, bacteria, and fungi. These peptides, which include β-defensins and cathelicidins (eg, hCAP-18 or LL-37), are produced on epithelial surfaces and within circulating leukocytes [22•].

In particular, the only human cathelicidin, hCAP-18, enhances microbial killing in phagocytic vacuoles, acts as a chemoattractant for neutrophils and monocytes, and has a defined vitamin D–dependent mechanism [6,7••,8,9•,10]. Pathogenic antigens interact with Toll-like receptors on macrophages to upregulate the expression of genes that code for the vitamin D receptor and for the 1α-hydroxylase enzyme that converts 25(OH)D into the biologically active 1,25-(OH)₂D [7••]. In turn, 1,25-(OH)₂D interacts with the promoter on the cathelicidin gene and enhances hCAP-18 production—a mechanism demonstrated in myeloid cells [6], bronchial epithelial cells [9•], and keratinocytes [10]. Furthermore, Weber and colleagues [10] found that 25(OH)D could induce intracellular hCAP-18 through the autocrine induction of the 1α-hydroxylase enzyme.

Vitamin D and Respiratory Infection Tuberculosis

The important connections between vitamin D and innate immunity have translated to clinical studies that

have found an association between vitamin D status and risk of developing tuberculosis (TB). From a historical perspective, Niels Ryberg Finsen was awarded the 1903 Nobel Prize in Physiology and Medicine in recognition of his innovative work showing that concentrated light radiation could effectively treat lupus vulgaris (skin TB). For much of the 20th century, sunlight exposure (and presumably vitamin D production) was used to treat TB.

Emerging evidence linking vitamin D to cathelicidin provides one explanation for the extensively described link between sun exposure, vitamin D, and TB [23]. In a landmark study, Liu and colleagues [7••] reported that in *Mycobacterium tuberculosis*–infected macrophages, there was a 30-fold increased cathelicidin expression in 1,25(OH)₂D-treated cells compared with controls, which corresponded to a 50% reduction in *M. tuberculosis* viability at 3 days. The individuals with serum 25(OH)D levels less than approximately 25 nmol/L had the least efficient cathelicidin expression, and those with serum 25(OH)D levels above approximately 75 nmol/L had the highest induction of cathelicidin mRNA. Furthermore, black individuals, known to have increased susceptibility to TB infection, had low serum 25(OH)D levels and inefficient cathelicidin mRNA induction, but supplementation of 25(OH)D to normal range enhanced cathelicidin induction fivefold, to levels similar to those in the white patients.

Liu and colleagues [7••] extended these findings to provide further evidence that cathelicidin is the mechanism that enhances vitamin D–mediated antimicrobial activity against *M. tuberculosis* [8]. In these experiments, a short, interfering RNA was used specifically to block cathelicidin mRNA and protein expression, which eliminated vitamin D–mediated enhanced intracellular killing of *M. tuberculosis* that was observed in controls.

In the clinical arena, investigators also have linked vitamin D more directly to TB [23]. For example, a hospital-based case-control study in London found that vitamin D deficiency was associated with an odds ratio (OR) of 2.9 (95% CI, 1.3–6.5) for having active TB [24]. Susceptibility to TB has been linked to vitamin D receptor polymorphisms, with the presence of FokI F allele protecting against TB infection, and the TaqI t allele protecting against active disease but not infection [25]. Martineau and colleagues [26] recently found that a single dose of 2.5 mg (100,000 IU) of vitamin D (ergocalciferol) enhanced immunity to *M. tuberculosis*.

Early epidemiologic studies

In addition to TB, cathelicidins display antimicrobial activity against a broad range of other viral and bacterial respiratory pathogens [27]. Many studies have reported that children with rickets commonly present to hospitals with respiratory infections [22•]. Although 25(OH)D levels of at least 25 nmol/L are known to prevent rickets, the relationship of higher levels of 25(OH)D to respira-

tory infection is of greater public health interest. Recent clinical studies have demonstrated a consistent association between vitamin D insufficiency—at nonrachitic levels—and respiratory infections [11–13,14••].

For example, a Finnish cohort study found that young male soldiers with serum 25(OH)D levels less than 40 nmol/L at baseline had a 63% increased risk of absence from duty due to respiratory infection over the following 6 months than soldiers with levels ≥ 40 nmol/L ($P = 0.004$) [11]. A case-control study in India demonstrated that children 2 to 60 months old with serum 25(OH)D levels less than 50 nmol/L had 12.5-fold higher odds of acquiring severe acute lower respiratory infection [12]. Additionally, a Turkish case-control study found that serum 25(OH)D levels were lower in neonatal cases of acute lower respiratory infection (9.12 ng/mL, or 22.8 nmol/L) than in age-matched controls (16.33 ng/mL, or 40.8 nmol/L) [13]. Although a recent Canadian case-control study of children 1 to 25 months old found no difference in mean serum 25(OH)D levels between patients with acute lower respiratory tract infection (77.0 nmol/L) and hospital controls (77.2 nmol/L), the average vitamin D status of these individuals was greater than 75 nmol/L, as “virtually all of the infants ... consumed vitamin D” through fortified infant formula or supplements [28].

Recent epidemiologic studies

In a recent study of NHANES data, we found that lower serum 25(OH)D levels were associated with an increased adjusted OR of recent upper respiratory tract infection (compared with ≥ 75 nmol/L: OR, 1.36 for < 25 nmol/L and 1.24 for 25–74 nmol/L groups) [29]. We also found that the association between serum 25(OH)D levels less than 25 nmol/L and upper respiratory tract infection was much stronger among individuals with asthma (OR, 5.67) than those without asthma (OR, 1.24; P for interaction = 0.007).

Camargo and colleagues [30•] have established an important relationship between vitamin D status and incident wheezing in two separate birth cohorts: one in Massachusetts and one from New Zealand [14••]. In the Massachusetts cohort, they found that lower maternal intake of vitamin D during pregnancy was associated with increased risk of recurrent wheezing [30•], a finding that was subsequently replicated in an independent cohort by Devereux and colleagues [31] from Scotland.

In the New Zealand birth cohort, Camargo and colleagues [14••] were able to examine the association between low levels of 25(OH)D in cord blood and subsequent risk of respiratory infections and childhood wheezing. In this seemingly healthy cohort, 20% of children had a cord blood 25(OH)D level less than 25 nmol/L, and 73% (cumulative) had a 25(OH)D level less than 75 nmol/L. Cord blood 25(OH)D level had a statistically and clinically significant inverse association with risk of wheezing illness at ages 15 months, 3 years, and

5 years (all $P < 0.05$). Moreover, cord blood 25(OH)D was inversely associated with risk of respiratory infection by age 3 months; children with 25(OH)D levels less than 25 nmol/L were at a twofold higher risk than those with levels ≥ 75 nmol/L. These results were independent of season and other potential confounders. As a follow-up to this epidemiologic work, the team recently discovered a significant correlation ($r = 0.23$; $P = 0.002$) between cord blood levels of 25(OH)D and hCAP-18 (Camargo et al., unpublished data). These epidemiologic studies demonstrate a potential mechanism for the association between vitamin D insufficiency, respiratory infections, and childhood wheezing illnesses.

Preliminary evidence from interventional trials

Although there have been few interventional trials to date, the preliminary evidence on vitamin D supplementation and respiratory infection is promising. For example, two interventional cohort studies with 600 to 700 IU of vitamin D daily from cod liver oil/multivitamin supplementation [32] and 60,000 IU weekly from a vitamin D/calcium supplement [33] noted a decrease in respiratory infections in children receiving supplementation. One randomized, controlled trial of bone loss in postmenopausal black women found that 7.7% of women randomized to vitamin D, 800 to 2000 IU/d, reported respiratory symptoms over the 3-year follow-up, compared with 25.0% in the control group [34]. Another substudy of a randomized, controlled trial for fracture prevention found a non-statistically significant reduction in wintertime infection in participants randomized to vitamin D, 800 IU/d (adjusted OR, 0.90 [95% CI, 0.76–1.07]) [35]. Although promising, these studies were post hoc analyses of adverse events reported in skeletal health trials. Moreover, they were limited by the relatively low dose of vitamin D supplementation used; the impact of elevating 25(OH)D levels to greater than 75 nmol/L (or even > 100 nmol/L) merits investigation.

Vitamin D and Asthma

Asthma pathogenesis

The exact role of vitamin D in the pathogenesis of asthma remains unclear. As discussed by Camargo and colleagues [30•], ecological data suggest a possible association between vitamin D insufficiency and the asthma epidemic. The prevalence of both conditions is higher in racial/ethnic minorities, obese individuals, and westernized populations [1,21]. Furthermore, large cross-sectional studies of adolescents and adults have found that vitamin D insufficiency is correlated with lower pulmonary function, including forced expiratory volume in 1 second and forced vital capacity [36,37]. Of course, the causal nature of these cross-sectional associations is uncertain. Although it is possible that low levels of vitamin D cause asthma, it is also possible that individuals with asthma exercise outdoors less often

and that simple lifestyle differences could create vitamin D insufficiency. Likewise, some children with asthma historically have avoided milk intake (an important dietary source of vitamin D in US children [30•]), and this food avoidance also could create a spurious inverse association between vitamin D intake and asthma. Prospective studies (especially randomized trials) could help investigators to address these important methodologic concerns.

The hypothesis that low vitamin D may cause asthma—and that sunlight exposure and supplements may prevent asthma—is disputed by Wjst [38], who believes that vitamin D supplementation is an important *cause* of asthma. The strongest support for this hypothesis comes from a birth cohort in northern Finland [39]. In this study, Hypponen and colleagues [39] reported that regular vitamin D supplementation (≥ 2000 IU/d) in the first year of life increased the risks of developing atopy, allergic rhinitis, and asthma by age 31 years. However, this finding may be related to the very high dose of vitamin D supplementation (ie, that there are dose-specific effects). The Finnish study was also limited by the absence of data on maternal intake of vitamin D and the inability to control for major confounders. Furthermore, recall bias may have affected the ascertainment of early-life asthma and allergies. Another recent study from the United Kingdom also raises the possibility that vitamin D may cause atopy and asthma [40]. Unfortunately, this study also has important methodologic limitations (eg, small numbers, 30% follow-up at age 9 years).

In contrast to these two European studies, other evidence suggests that vitamin D has no association with incident asthma or may even have a modest protective effect. For example, preliminary evidence from two family-based studies demonstrated that gene polymorphisms on the vitamin D receptor were associated with childhood and adult asthma [41,42], but these results have not been confirmed in subsequent studies [43,44]. Two epidemiologic studies that have examined the issue have reported an inverse association between milk intake and risk of asthma in young children [45,46]. Additionally, the Boston [30•] and Scottish [31] birth cohorts found an association between maternal intake of vitamin D and recurrent wheezing in early childhood. The Scottish study also reported no association between maternal intake of vitamin D and doctor-diagnosed asthma at age 5 years [31]. Both studies were limited, however, by lack of serum 25(OH)D measurement. The unique contribution of the New Zealand birth cohort is the concurrent demonstration that low serum 25(OH)D levels in cord blood were associated with increased risk of respiratory infections and childhood wheezing, but there was no association between cord blood 25(OH)D and risk of current asthma at age 5 years [14••].

We hypothesize that if a modest association exists between vitamin D insufficiency and incident asthma that it may be mediated through increased risk of respiratory

infection in early life. In a recent study from the CoAST (Childhood Origins of Asthma) birth cohort in Wisconsin, Jackson and colleagues [47•] found that wheezing rhinovirus illness during infancy predicted development of asthma at 6 years of age. Linking these rhinovirus data and the aforementioned birth cohort data, we hypothesize that vitamin D insufficiency may contribute to the seasonal nature of the infectious respiratory infant disease bronchiolitis [48]. Early viral respiratory infections in a genetically susceptible host may induce subsequent asthma development, and if vitamin D mediates part of this pathway, there will be a new potential strategy for preventing asthma.

Asthma control

Among individuals with asthma, steroid resistance can be a vexing clinical problem. Xystrakis and colleagues [49••] administered vitamin D to a small group of healthy individuals and steroid-resistant asthmatic patients in London and found that the intervention enhanced subsequent responsiveness to dexamethasone due to induction of interleukin (IL)-10. The authors concluded that vitamin D could potentially increase the therapeutic response to glucocorticoids in steroid-resistant asthma patients. The role of regulatory T cells and IL-10 in the balance of the T-helper type 1 (Th1)-type and Th2-type cytokines and asthma phenotype was recently reviewed [50].

Although many laboratory studies suggest that vitamin D induces a shift in the balance between Th1- and Th2-type cytokines toward Th2 dominance [22•], Pichler and colleagues [51] found that in CD4⁺ and CD8⁺ human cord blood cells, vitamin D inhibits not only IL-12–generated interferon production (Th1 type) but also suppresses IL-4 and IL-4–induced expression of IL-13 (Th2 type). In theory, this balanced Th1–Th2 regulation may modulate asthma and other allergic diseases. Thus, the differences between the studies on the Th1–Th2 dominance may lie in the timing of exposure of the cells to vitamin D (ie, prenatal vs postnatal); the response of naïve T cells to vitamin D exposure may differ from that of mature cells when exposed to vitamin D. Another possibility is that the association depends on the vitamin D status of the individual. In other words, lower vitamin D intakes (eg, to correct a deficiency state) may have different consequences than relatively high-dose supplementation, in which an excess of vitamin D may have adverse effects. These hypotheses merit further investigation.

Asthma exacerbation

Viral respiratory infections, particularly rhinovirus, are associated with 50% to 85% of asthma exacerbations [3,4]. Most adults experience two to four upper respiratory infections per year (children, 6–10) [52]; individuals with asthma may be more susceptible to respiratory infection and have increased frequency of lower respiratory tract symptoms of higher severity and duration [15]. The

emerging role of vitamin D in innate immune responses may explain predisposition to infection and asthma exacerbation in certain populations.

As presented earlier in this review, there are persuasive epidemiologic associations between vitamin D and respiratory infection in the general population [11–13,14••,32–35]. However, there are only sparse data on the association in asthmatic individuals. In a recent analysis of NHANES data [29], we found that the association between serum 25(OH)D levels less than 25 nmol/L and upper respiratory infection was much stronger among individuals with asthma (OR, 5.67) compared with those without asthma (OR, 1.24; *P* for interaction = 0.007). Additionally, the association of lower cord blood 25(OH)D levels with increased respiratory infection, increased wheezing, and decreased hCAP-18 levels further implicates an association between vitamin D and recurrent wheezing in susceptible hosts (Camargo et al., unpublished data). However, it remains unclear what subgroup of asthma, if any, is caused by the role of vitamin D in the immune system to prevent respiratory infection. Our group has an active research agenda on the role of vitamin D in the incidence, severity, and duration of wheezing illnesses, including asthma and bronchiolitis.

Future Research on Vitamin D, Respiratory Infections, and Asthma

Although the preliminary data presented in this review are promising, many scientific gaps remain. The direct role of vitamin D–mediated innate immunity and protection from respiratory infection in asthmatic individuals has not been well characterized. An initial step is to further describe the association between vitamin D and respiratory infection as it relates to the development of asthma, chronic asthma control, and risk for asthma exacerbations. In these epidemiologic studies, the issue of reverse causation should be addressed, particularly in cross-sectional studies. Because the presence of asthma, decreased chronic asthma control, and increased asthma exacerbations likely contribute to decreased time outdoors (and, therefore, decreased sunlight exposure), the presence of vitamin D insufficiency may actually follow the outcomes measured.

Longitudinal cohort designs and outcomes that span a shorter duration than the 2- to 3-week half-life of serum 25(OH)D [16••] will help to address this important issue. Additionally, measurement of immune markers, including hCAP-18, regulatory T cells, IL-10, and other markers of the Th1–Th2 balance, may help to elucidate the mechanisms of the observed associations and provide additional face validity. Animal models in which these relevant pathways can be manipulated or knocked out will provide additional support and rationale for the associations between vitamin D and asthma. However, animal models should be selected with care. For example, it appears that

only primates have the vitamin D response element on the promoter of the cathelicidin gene. Accordingly, mouse, rat, and dog cell lines do not appear to require vitamin D for cathelicidin expression and thus have been unsuccessful in evaluating this vitamin D–mediated pathway [6].

Ultimately, large randomized, controlled trials of vitamin D supplementation will be needed to confirm the ability to reverse the suboptimal outcomes associated with vitamin D insufficiency. In these studies, higher doses of supplementation (at least 1000–2000 IU/d and probably higher in high-risk populations during winter months) may be required to maximize potential benefit. Current national recommendations for vitamin D supplementation (200–600 IU/d, depending on age) are unlikely to achieve the serum 25(OH)D levels (ie, ≥ 75 –100 nmol/L) that appear necessary for good general health, including prevention of respiratory infections. Many experts already argue that current recommended doses of vitamin D supplementation are woefully inadequate to meet the need for higher serum 25(OH)D levels [16••,20•]. For example, to raise serum 25(OH)D from 50 to 80 nmol/L requires an additional 1700 IU of vitamin D per day [53].

Consideration to adequate dosage in future trials and measurement of pre- and postsupplementation serum 25(OH)D levels will help to optimize trial conditions. Additionally, as the relative importance of vitamin D in different age and racial/ethnic groups is unknown, diverse study participants or multiple studies of different demographic subgroups will help us to understand this potential interaction.

Conclusions

Substantial evidence now indicates that vitamin D may enhance the innate immune response and protect against respiratory infection. The human cathelicidin hCAP-18 appears to have a particularly important role in the vitamin D–mediated mechanism against infection. Additionally, early evidence suggests that vitamin D modulates regulatory T-cell activity and IL-10 production, which are critical to the Th1–Th2 balance. These findings may be particularly important in the pathogenesis, control, and severity of asthma. However, much of these data are in cell culture or observational clinical studies, and the observed inverse associations may be due to residual confounding, such as from outdoor physical activity [21]. Future laboratory and clinical studies, with a special focus on children and adults with asthma, will help to clarify the vitamin D–asthma association. Randomized, controlled trials of higher-dose vitamin D supplementation (≥ 1000 IU/d), particularly in the winter season at higher latitudes, will help to clarify vitamin D supplementation's role in reducing respiratory infection. In turn, these insights may prove helpful in preventing asthma exacerbations and in the achievement of chronic asthma control.

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Disclosures

No potential conflicts of interest relevant to this article were reported.

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