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 active 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-