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CME Review

Vitamin D as an anti-microbial and anti-inflammatory therapy for Cystic Fibrosis

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EDUCATIONAL AIMS

AFTER READING THIS REVIEW, READERS WILL BE ABLE TO:

1) Describe the normal metabolism of vitamin D in healthy individuals and identify possible points that may be abnormal in CF
2) Describe molecular mechanisms of vitamin D immune modulating activity
3) Discuss important points to consider in developing a vitamin D supplementation trial for CF, including study design, selection of patient cohorts and deciding on an appropriate form and dose of vitamin D for supplementation

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SUMMARY

Cystic fibrosis (CF) is characterized by chronic infection and inflammation in the airways that lead to progressive lung damage and early death. Current anti-inflammatory therapies are limited by extensive adverse effects or insufficient efficacy. There is a large body of studies indicating beneficial anti-microbial and anti-inflammatory properties of vitamin D. Since most patients with CF present with vitamin D deficiency, and serum vitamin D levels demonstrate a positive correlation with lung function and negative correlation with airway inflammation and infection, correcting vitamin D deficiency may be an attractive therapeutic strategy in CF. The function of vitamin D is intricately tied to its metabolism, which may be impaired at multiple steps in patients with CF, with a potential to limit the efficacy of vitamin D supplementation. It is likely that the aforementioned beneficial properties of vitamin D require supplementation with doses of vitamin D markedly higher than those recommended to maintain proper bone function. This review will illustrate the potential for supplementation with vitamin D or its metabolites to modulate inflammation and improve defence against chronic infection in CF lung, as well as appropriate vitamin D supplementation strategies for improving lung function in CF.

INTRODUCTION

Cystic fibrosis (CF), the most frequently-occurring lethal autosomal recessive disorder among Caucasians [1], is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. CFTR encodes for a protein that functions as a chloride ion channel. The primary cause of CF morbidity and mortality is lung disease [2]. The consensus concerning the link between CFTR mutations and lung disease is that impaired chloride and water transport across the airway epithelium leads to increased mucus viscosity, defective mucociliary clearance, enhanced bacterial survival in the airways, and heightened inflammation [3]. A vicious cycle develops [4], such that infection with opportunistic pathogens (e.g., *Pseudomonas aeruginosa* [5] and *Burkholderia cepacia* complex [6]) persists in the lungs, provoking a heightened inflammatory state typified by elevated airway production of interleukin-8 (IL-8) and a subsequent influx of neutrophils [7,8]. Airway inflammation in CF may be intrinsically exaggerated due to CFTR mutations by currently poorly understood mechanisms [3]. Hyperinflammation causes airway damage and a progressive decline in pulmonary function in CF patients [9–12].

The negative impact of lung inflammation on disease progression (defined by annual loss of pulmonary function) was highlighted by beneficial effects of anti-inflammatory therapies such as high-dose ibuprofen [13] and oral corticosteroids [14]. However, since current drugs targeting airway inflammation in CF present concerns of serious adverse effects [15], there is a need for novel and safer anti-inflammatory therapies directly targeting

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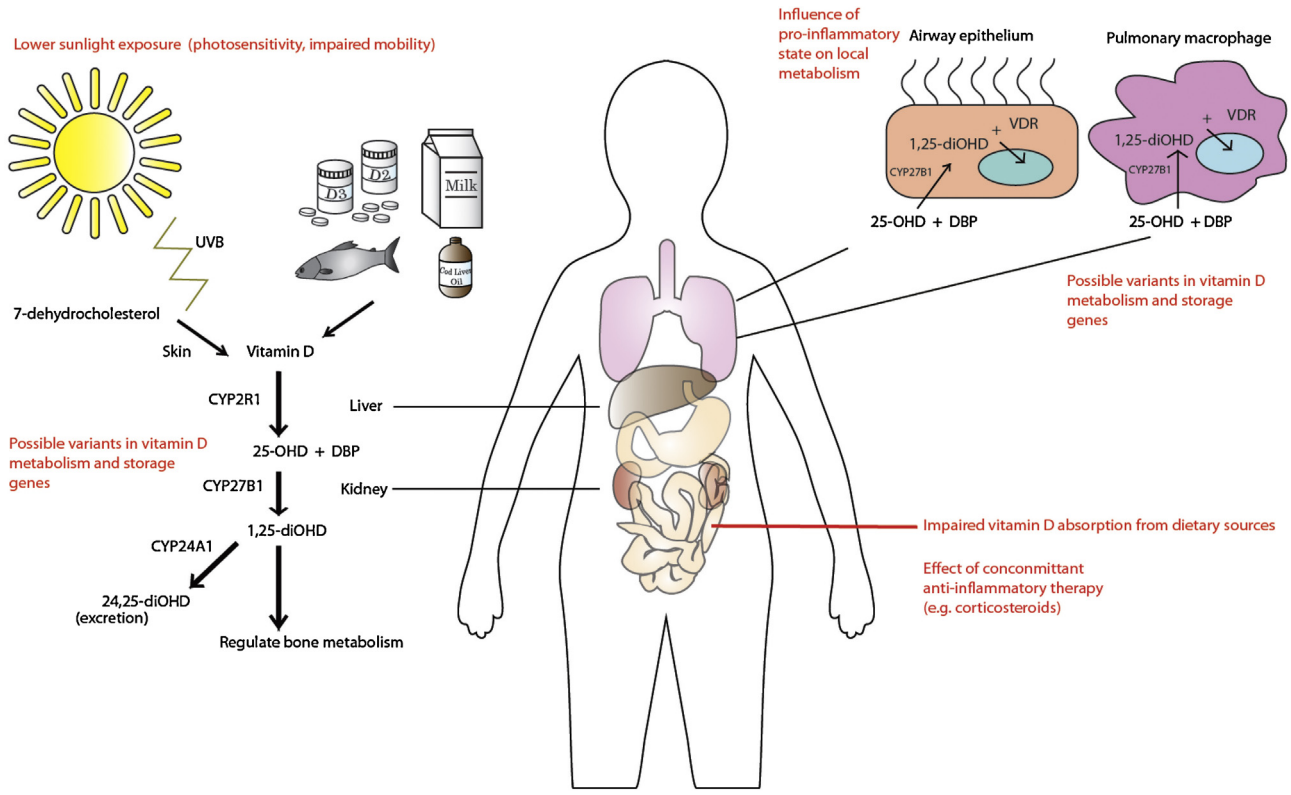

Figure 1. Metabolism of vitamin D via the classical pathway and in the airways: potential abnormalities in CF. Depicted here is how vitamin D is classically metabolized to regulate bone health, as well as how it is locally synthesized in the airways for anti-inflammatory and anti-microbial effects. Text in red indicates possible points in the pathway that may be affected in CF.

components of CF pathophysiology that may contribute to lung inflammation.

In addition to promoting bone health, there is a large body of non-CF studies indicating beneficial anti-microbial and anti-inflammatory properties of vitamin D, including enhancement of immunity by stimulation of anti-microbial peptide production [16], and suppression of pro-inflammatory cytokines [17]. We have shown that up to 95% of individuals with CF present with suboptimal vitamin D levels [18]. Considering the anti-inflammatory functions of vitamin D, restoring vitamin D levels may therefore reduce inflammation and decrease lung damage in CF patients. This review will illustrate the potential for supplementation with vitamin D or its metabolites to modulate inflammation, improve defence against chronic infection in the lung, and slow CF disease progression caused by the exaggerated inflammatory response.

VITAMIN D METABOLISM IN HEALTH

Vitamin D is primarily (~80%) [19] acquired through synthesis from 7-dehydrocholesterol in the skin after exposure to UVB in sunlight [20] (Figure 1). Vitamin D can also be acquired through oral supplementation, either as animal-derived vitamin D_3 (cholecalciferol) or plant-derived vitamin D_2 (ergocalciferol), or through dietary sources such as fortified milk, fish, and cod-liver oil. Both vitamin D_3 and D_2 undergo several hydroxylation steps by enzymes of the cytochrome P450 (CYP) family. First, vitamin D is converted into the major circulating vitamin D metabolite, 25-hydroxyvitamin D (25-OHD) by 25-hydroxylase (encoded by CYP2R1) in the liver. 25-OHD is used to clinically assess an individual's vitamin D status [20]. 25-OHD must bind to vitamin D binding protein (DBP) to remain stable in the systemic circulation and reach the target tissues [21]. 25-OHD is further hydroxylated in the kidneys by 1-α-hydroxylase (encoded by CYP27B1) to form 1,25-diOHD, the active metabolite [20]. More recently, extrarenal expression of CYP27B1 has been documented in multiple tissues, including alveolar macrophages and airway epithelial cells [22].

25-OHD has a half-life of approximately 2 weeks, whereas 1,25-diOHD lasts about 4 – 6 hours in the systemic circulation [23]. Despite high prevalence of suboptimal 25-OHD levels, serum concentrations of 1,25-diOHD are not significantly different between individuals with or without CF [24]. Due to the short half-life of 1,25-diOHD, its systemic levels are unlikely to significantly impact peripheral tissues, such as the airways. Rather, local tissue synthesis of 1,25-diOHD and its autocrine/paracrine action may be important for downstream functions of vitamin D.

To exhibit its effects intracellularly, 1,25-diOHD associates with vitamin D receptor (VDR). The 1,25-diOHD/VDR complex heterodimerizes with retinoid X receptors, and binds to specific sequences, known as Vitamin D Response Elements (VDRE), within promoters of many genes, leading to either repression or activation of target gene transcription [16]. Amongst the genes regulated by 1,25-diOHD is 25-hydroxyvitamin D-24-hydroxylase (encoded by CYP24), which catabolizes both 25-OHD and 1,25-diOHD, rendering them biologically inactive [20], and targeting them for excretion by the kidney [25].

There also exists a putative membrane bound VDR that mediates rapid, non-genomic effects, such as modulation of cell signalling. These rapid effects result in a cross-talk with and modulation of the genomic responses to 1,25-diOHD [26].

VITAMIN D DEFICIENCY AND CF

Since patients with CF are now living into adulthood, the prevalence of co-morbidities, such as osteoporosis, are increasing and require attention. Vitamin D deficiency partially accounts for