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Original Article

Vitamin D deficiency and its treatment in cystic fibrosis

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ABSTRACT

Vitamin D deficiency is a common finding in individuals with cystic fibrosis (CF), despite routine supplementation. Hypovitaminosis D is often the result of fat malabsorption, but other contributors include increased latitude, poor nutritional intake, decreased sun exposure, impaired hydroxylation of vitamin D, and non-adherence to the prescribed vitamin D regimen. Vitamin D is critical for calcium homeostasis and optimal skeletal health, and vitamin D deficiency in CF can lead to skeletal complications of osteopenia and osteoporosis. Over time, our understanding of treatment regimens for vitamin D deficiency in CF has evolved, leading to recommendations for higher doses of vitamin D to achieve target levels of circulating 25-hydroxyvitamin D. There is also some evidence that vitamin D deficiency may have non-skeletal consequences such as an increase in pulmonary exacerbations. The exact mechanisms involved in the non-skeletal complications of vitamin D deficiency are not clearly understood, but may involve the innate immune system. Future clinical studies are needed to help address whether vitamin D has a role in CF beyond skeletal health.

1. Background

Vitamin D deficiency is a common finding in children and adults with cystic fibrosis (CF) [1–6] and largely arises from fat malabsorption that accompanies the pancreatic exocrine insufficiency of CF. Vitamin D deficiency is associated with lower bone density at the hip and spine in adults [7]. This may manifest as fractures to trabecular bone such as vertebral bodies or the rib cage, which can compromise lung function and lead to a reduced quality of life [8,9]. The clinical presentation of vitamin D deficiency in an individual with CF does not typically involve features of rickets or osteomalacia [10]. This review will explore contributors to vitamin D deficiency in CF, recommendations for maintaining goal levels of vitamin D and explore the skeletal and non- skeletal benefits of vitamin D.

2. Definition of vitamin D deficiency

Vitamin D deficiency is a global health problem that impacts adults and children [11]. It is estimated that 1 billion people worldwide are deficient in vitamin D [12]. Populations at risk include anyone with increased melanin, malabsorption, obese children and adults, and individuals who practice abstinence from direct sunlight [11].

There is significant debate among professional societies regarding an optimal serum level of 25-hydroxyvitamin D (25(OH)D) [12,13]. The Institute of Medicine (IOM) and the Endocrine Society created guidelines designed to classify vitamin D deficiency; however, both professional groups differ on their criteria for defining deficiency. It appears that one of the main differences between IOM and Endocrine society guidelines is their target population. IOM's guidelines focus on a generally healthy populations [14]. Half of the population targeted by IOM met their daily requirements of vitamin D when 25OHD levels were 16 ng/ml (40 nmol/l) and 97.5% of their requirements met with good skeletal outcomes when levels measured 20 ng/ml (50 nmol/l) [15]. On the other hand, the Endocrine Society generated guidelines based on data gathered from individuals who were at higher risk for vitamin D deficiency [14]. One of the main criticisms of the Endocrine Society guidelines is the increased burden of screening individuals who may not be necessarily at risk for

Abbreviations: CF, cystic fibrosis; 25(OH)D, 25-hydroxyvitaminD; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; CFF, Cystic Fibrosis Foundation; PTH, parathyroid hormone; DBP, vitamin D binding protein

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Table 1
Vitamin D Status in Cystic Fibrosis Classification of 25(OH)D levels adapted from Norman et al publication and Tangpricha et al . Classification of sufficiency, insufficiency, and deficiency for assessing vitamin D status. Reference concentrations represent the sum concentration of 25(OH)D_2 and 25(OH)D_3

	US Reference range	SI Unit
Deficient	<20 ng/mL	<50 nmol/L
Insufficient	21-29 ng/mL	50 to 75 nmol/L
Sufficient	>30 ng/mL	>75 nmol/L

Norman, A.W., From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr, 2008. 88(2): p. 491S-499S.
Tangpricha, V., et al., An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab, 2012. 97(4): p. 1082-93.

vitamin D deficiency. This is cited as an unnecessary escalation of cost and a burden to an already inefficient healthcare system [16].

The American Academy of Pediatrics (AAP) [17] adopted the IOM guidelines. AAP and IOM suggest that individuals are sufficient if 25 (OH)D levels are >20 ng/ml(>50 nmol/l) [15]. The Endocrine Society, on the other hand, state that individuals with 25(OH)D < 20 ng/ml (<50 nmol/l) are deficient, 21–29 ng/ml (50–75 nmol/l) are insufficient, and levels >30 ng/ml (>75 nmol/l) are sufficient [11,18] (Table 1). The Cystic Fibrosis Foundation (CFF) currently accepts the Endocrine's Society's criteria for diagnosing vitamin D deficiency.

In 2012, the CFF released recommendations for the management of vitamin D. They recommend using 25-hydroxy vitamin D to measure vitamin D status [13]. Individuals with 25(OH)D < 20 ng/ml (<50 nmol/l) are considered deficient, and levels >30 ng/ml (>75 nmol/l) are sufficient [2,13] (Table 1). Goal 25(OH)D levels are 30-50 ng/ml (75–125 nmol/l) and levels should not exceed 100 mg/ml (250 nmol/l) [13].

3. Pathophysiology of vitamin D metabolism

Vitamin D_3 is a secosteroid that is endogenously produced in the skin. The precursor of vitamin D is 7-dehydrocholesterol, which is converted to pre-vitamin D_3 by UVB radiation (wavelength 290–315 nm) [19] and then undergoes thermal isomerization to vitamin D_3 [20,21]. Vitamin D_2 is produced by ultraviolet irradiation of ergosterol contained in fungi or yeast [22].

Cutaneous synthesis of vitamin D_3 is believed to be the major source for most people even though sun exposure can be limited by a variety of factors [12,17,20,21,23–25]. During summer months, adults with lighter skin pigment will require 10–15 min of full body sun exposure to generate 10,000–20,000 IU of vitamin D_3. Darker adults require 25–35 min of sun exposure to generate a similar amount of vitamin D_3 [17].

After vitamin D_3 is formed in the skin, it is translocated to the plasma but due to its lipophilic nature, vitamin D_3 must bind to a carrier protein like vitamin D binding protein (DBP) [21]. Vitamin D-DBP complex travels to the liver where it undergoes conversion to 25(OH) D by the hepatic 25-hydroxylase [21]. The blood levels of 25(OH)D increase in proportion to the dietary vitamin D_2 or D_3 intake or cutaneous production of vitamin D_3 in skin by UVB [21]. As a result, total 25(OH)D serves as the best indicator of vitamin D status [21].

After 25 hydroxylation occurs in the liver, the second step of vitamin D activation occurs mainly in the kidney [21]. The circulating 25 (OH)D undergoes 1α hydroxylation to yield 1α,25-dihydroxyvitamin D (1,25$(OH)_2D_3$) [25]. Once in its active form, 1,25$(OH)_2D_3$ circulates to its target organs. Most of the biological activities of 1,25$(OH)_2D_3$ are mediated by a high affinity receptor, the vitamin D receptor (VDR) [25]. The principal regulator of 1,25$(OH)_2D_3$ is the hormone itself and it functions to downregulate its own production. Parathyroid hormone(PTH), fibroblast growth factor 23 (FGF23), serum concentrations of calcium and phosphate also regulate 1,25$(OH)_2D_3$ [25] (Fig. 1).

Classic vitamin D responsive tissues are the kidney, bone, parathyroid gland, and intestine. One of the main roles of vitamin D is to assist with the active intestinal uptake of calcium and phosphorous. Without the presence of vitamin D, approximately 10% of dietary calcium is absorbed as opposed to 30–50% in a vitamin D replete state [12,21]. There are other tissues that have 1-α-hydroxylase activity include the prostate, breast, colon, lung, pancreatic β cells, and immune cells [26]. The extrarenal 1-α-hydroxylase is thought to be important for local 1,25$(OH)_2$D

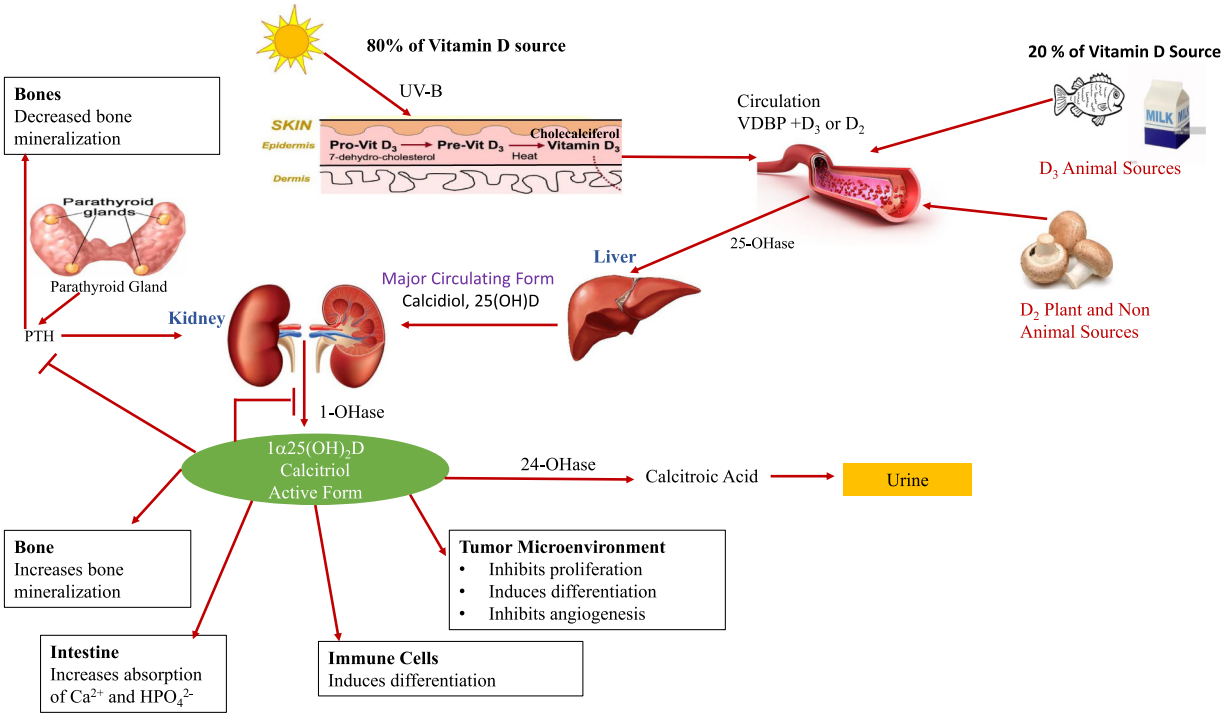

Fig. 1. Overview of vitamin D Metabolism. Cholesterol is metabolized to cholecalciferol in the skin. In the liver it is hydroxylated to calcidiol and in the kidney it is hydroxylated further to calcitriol.
VDBP vitamin D Binding Protein, PTH Parathyroid Hormone, 25(OH) D 25-hydroxyvitamin D, 1a25$(OH)_2$D, 1,25-dihydroxyvitamin D.

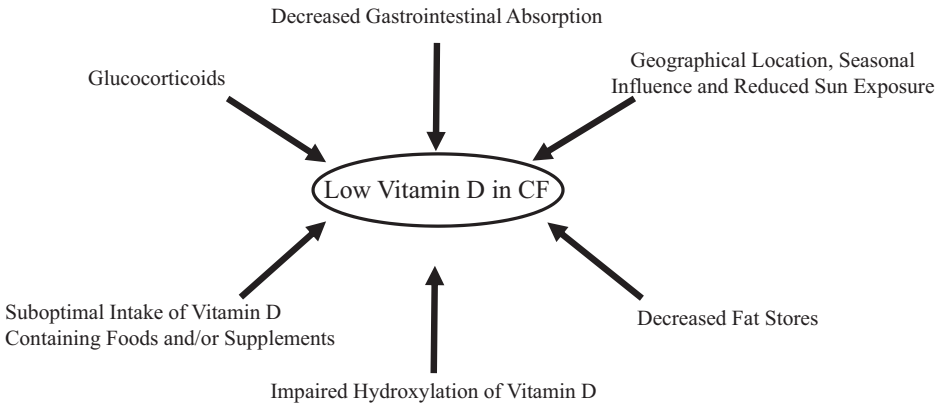

Fig. 2. Contributors to vitamin D Insufficiency and vitamin D Deficiency in Cystic Fibrosis.

production to be used in an autocrine/paracrine fashion [21,25,27]. Directly or indirectly $1,25(OH)_2D$ controls 100–1250 genes [12,28].

4. Prevalence vitamin D deficiency in CF

Approximately 90% of individuals with CF have exocrine pancreatic insufficiency (PI) which is a sign of exocrine pancreatic dysfunction [1,3,6,29]. Patients with CF with pancreatic insufficiency require additional supplementation of fat-soluble vitamins (A, D, E, and K). However, even with supplementing standard fat soluble multivitamin regimens, many individuals remain vitamin D deficient [29] (Table 1). Deficiencies in fat soluble vitamins have been reported across the age continuum with the earliest reports in infants younger than 3 months of age [6]. One study found that despite routine supplementation, 7% of PI-CF patients had vitamin D deficiency (25(OH)D < 11 ng/ml) and 90% had vitamin D insufficiency (25(OH)D < 30 ng/ml) [29]. Compared to healthy controls, patients with CF had a 20% increased risk of vitamin D insufficiency, but the extent to which this difference is due to variable intestinal absorbance or inadequate vitamin D doses to achieve goal levels of 25(OH)D could not be addressed [29]. Other studies found that despite increasing vitamin D supplementation by >450%, about half of the individuals with CF failed to reach target levels of 25(OH)D > 30 ng/ml [30].

The prevalence of vitamin D deficiency/insufficiency ranges from 23% to as high as 95% [5,6,30,31]. The literature is sparse in documenting the prevalence of vitamin D status in pancreatic sufficient individuals with CF. The existing data is rather variable with a United Kingdom (UK) group reporting a prevalence rate at 87% (25(OH)D < 30 ng/ml) and an Australian group reporting rates of 3%(25(OH)D < 20 ng/ml) [6,30]. Besides decreased intestinal absorption, poor nutritional intake, and poor compliance, other factors that contribute to vitamin D deficiency in CF include decreased outdoor activity and sunlight exposure, glucocorticoids, impaired hydroxylation, decreased fat stores and increased latitude (Fig. 2).

Geographic location and changes in season also play a role in determining vitamin D status due to the influence of UVB on the cutaneous production of pre-vitamin D_3 [12,20,21,24,25]. Seasonal changes in UVB penetration from the sun explain the difference in vitamin D production in the winter as compared to the summer and fall [6,24,29,32,33]. Individuals living in northern latitudes are at increased risk for vitamin D deficiency due to decreased exposure to UVB radiation [24,29]. In the UK and similar latitudes, very little cutaneous synthesis of vitamin D_3 occurs from the end of September to early March [23], thus highlighting the contribution that northern latitude has on low levels of vitamin D.

5. Diagnostic work up

The CFF recommends evaluating vitamin D status annually at the end of winter [13,34]. Vitamin D status is assessed by measuring 25 (OH)D levels in the serum [2]. Evaluation of $1,25(OH_2)D$ levels, is typically not useful in the assessment of vitamin D status due to its short circulating half-life and inability to accurately reflect vitamin D stores [1,13]. When evaluating a patient with CF for vitamin D deficiency, special consideration should occur if there is an underlying history of liver disease or chronic kidney disease. Both conditions can confound the clinical picture and lead to difficulty in maintaining adequate vitamin D levels [35,36]. For example, individuals with end stage liver disease can have significant derangements in 25(OH)D levels, which typically resolves following liver transplantation [35]. Patients with renal disease can have a high prevalence of vitamin D insufficiency or deficiency. In addition, they can also have elevated parathyroid hormone (PTH) levels, decreased bone mineral density and increased risk for mortality [36]. The recommendation for checking vitamin D status in liver or kidney failure is annually, which consistent with CFF recommendations [35,36].

6. Clinical impact of vitamin D deficiency in CF

6.1. Skeletal

6.1.1. Bone health

CF related bone disease (CFBD) can be impacted by many other conditions occurring in CF including CF related liver disease, CF related diabetes, hypogonadism, chronic corticosteroid use, and recurrent inflammation [26]. Insufficient levels of vitamin D also contribute to CFBD [37]. The prevalence of vitamin D deficiency tends to increase during adolescence [37] which is unfortunately during a time of peak growth velocity and bone mineral density accrual [38]. Inadequate levels of serum 25(OH)D may impact peak bone mass in CF young adults [29,38,39] and subsequently result in an increased fracture rate in this population [9,40–42]. Of particular concern is the acquisition of fractures to the vertebral spine and ribs [8,39]. This trauma can cause chronic pain [1,37] and skeletal deformities like kyphosis that may manifest as a decline in lung function, ineffective cough and airway clearance, limitations in chest physiotherapy, and potentially increased frequency of pulmonary exacerbations [1,9,39,40].

At the cellular level, osteoblastic activity is decreased in CF due to a decrease in osteoblast number. By contrast, osteoclast activity is increased with an overall increase in osteoclast number [38]. The imbalance between bone resorption and new bone formation leads to low bone mineral density [9,38]. In CF adults supplemented with vitamin D and calcium, one study found the rate of bone turnover

decreased and was one of the first studies to describe the effect of vitamin D and calcium supplementation on bone density in CF [43]. Vitamin D deficiency also leads to an increase in parathyroid hormone, termed secondary hyperparathyroidism, that can result in increased bone resorption [29]. In effect, inadequate levels of vitamin D can result in insufficient bone formation and increased bone resorption in patients with CFBD [1].

The literature suggests an association between low BMD and low 25(OH)D levels; therefore, sufficient levels of 25(OH)D may be integral in optimizing bone health [37]. Through a multipronged approach, the European Cystic Fibrosis Society provided recommendations that included optimizing nutritional interventions with attention paid to vitamin D supplementation [44,45].

6.2. Extraskeletal

6.2.1. Antibacterial and anti-inflammatory effects

Vitamin D may have anti-microbial and anti-inflammatory properties [46–50]. In its active form, $1,25(OH)_2D$ can act as a potent immunomodulator [12,50]. Monocytes and macrophages exposed to a lipopolysaccharide will up regulate the $1,25(OH)_2D$ gene and its receptor. Individuals who are vitamin D deficient (25(OH)D < 20 ng/ml), can have difficulty mounting an innate immune response [12,51]. In CF, the progression of lung disease is largely due to persistent inflammatory responses which play a central role in lung damage [52]. The discovery that the vitamin D receptor (VDR) and 1-α-hydroxylase (CYP27B1) are expressed in cells that control immune function led to the observation that $1,25(OH)_2D$ may be capable of controlling immune function at various levels [53].

The COPD and asthma literature explore vitamin D's role in decreasing inflammation in the lungs. Like CF, $1,25(OH)_2D$ plays a role as an immune system modulator in asthma through the suppression of dendritic cell maturation and IL-12 production. Treatment with $1,25(OH)_2D$ is effective in reducing asthma exacerbations due to increases in cathelicidin antimicrobial peptide (CAMP) expression and cytokine modification [53]. Vitamin D also modulates innate immunity by increasing the phagocytic ability of immune cells [53]. Asthmatic children with low levels of $25(OH)_2D$ tend to have hyper responsive airways, decreased lung function, and overall worse asthma control [54].

Anti-microbial effects of vitamin D have been postulated to come from the decrease in bacterial burden in the airways. In bronchial epithelial cells treated with $1,25(OH)_2D$ there is a decrease in the bacterial load of *P.aeruginosa*. The bactericidal activity of $1,25(OH)_2D$ is thought to originate from an upregulation of LL-37 (cathelicidin a peptide that is capable of destroying an infectious agent [22]) and defensin β2, antimicrobial peptides whose gene promoters contain vitamin D-responsive elements (VDRE) [47]. Vitamin D_3 metabolites can down regulate pro-inflammatory cytokines and chemokines that are elevated in the CF lung and promote the secretion of anti-inflammatory cytokines such as IL-10 [47]. Treatment of primary human monocytes with 25(OH)D suppressed mRNA expression of pro-inflammatory cytokines IL-6 and TNF-α [47,49,55]. CF respiratory epithelial cells incubated with $1,25(OH)_2D$ show a significant downregulation in the neutrophil-attracting chemokine, IL-8 [47,49]. Dauletbaev and colleagues found that IL-8 downregulation by vitamin D metabolites was achievable only with hyperinflammatory monocyte derived macrophages and in high concentrations of vitamin D [46].

In a Scandinavian CF cross-sectional study, there was a reported inverse relationship between 25(OH)D and IgG [56]. In a CF randomized control trial of vitamin D supplementation during a pulmonary exacerbation, there was a reduction in TNF-α and IL-6, but not the other cytokines evaluated [48]. Pincikova found that high doses of vitamin D_2 or D_3 (35,000 IU <16 yrs., 50,000 IU >16 yrs) in individuals with CF, have significant immunological effects and may decrease immune activation in a dose dependent manner [52]. Finally, vitamin D may alter the gut microbiome which may decrease intestinal and systemic inflammation. Kanhere et al. performed a randomized controlled trial of vitamin D supplementation in adults with CF and found that vitamin D supplementation resulted in enrichment of bacteria thought to be beneficial for intestinal health whereas placebo treatment resulted in enrichment of bacteria thought to be pathogenic [57].

6.2.2. Pulmonary complications

Pulmonary exacerbations in CF play an important role in determining disease progression [58] and are associated with reduced lung function [59]. CF patients with liver disease, diabetes or low FEV_1, are at increased risk for pulmonary exacerbations [58]. Pre-exacerbation lung function is not recovered in 15–25% of CF patients following an exacerbation [58]. Due to vitamin D's proposed anti-inflammatory properties, many have questioned if a clinically significant relationship between vitamin D status and pulmonary exacerbation exists. Unfortunately, the literature is mixed with regard to vitamin D deficiency and the increased risk for pulmonary exacerbation [32].

Simoneau examined youth ages 6–12 years with a positive Pseudomonas culture and found they were more likely to be vitamin D insufficient, although there was not much difference between vitamin D insufficient and sufficient subjects (29.6 vs. 33.2 ng/ml, $P = .047$) [60]. McCauley and Vanstone describe an association of low vitamin D status and increase frequency of pulmonary exacerbations [51,61]. In a small pilot study, a large dose of cholecalciferol, 250,000 IU, given within 48 h of an admission for a pulmonary exacerbation was examined. The intervention arm with vitamin D had more hospital free days compared to placebo arm and improved 1 year survival [62]. Extension of this intervention into a larger multi-center trial found no difference between vitamin D and control in the primary endpoint of time to next pulmonary exacerbation [63]. Some potential reasons why the vitamin D intervention did not improve risk to next pulmonary exacerbation included many subjects were already on vitamin D supplementation, the timing of vitamin D may have been too late to have any impact on the pulmonary exacerbation, and the subjects all received concurrent therapies to the pulmonary exacerbation which may have obscured the impact of vitamin D [64]. Overall, there is a paucity of randomized controlled trials that demonstrate positive outcomes when investigating the role of vitamin D supplementation during a pulmonary exacerbation. An increase in randomized controlled trials for CF individuals could provide further evidence to support or dissuade the potential benefit of vitamin D in CF during an acute illness.

The relationship of vitamin D deficiency to FEV_1 is less clear. In retrospective studies exploring this relationship, there is some suggestion that low vitamin D levels may be a predictor for low FEV_1 [10,61]. However, other studies find no predictive value of vitamin D status and low FEV_1 [56,64] (Supplementary Table 1).

6.2.3. Cystic fibrosis related diabetes

For over a decade, several studies have proposed a link between diabetes and vitamin D deficiency [14,65]. In CF, the relationship between glucose intolerance and vitamin D deficiency is not well documented. One study observed a reduction in bone mineral acquisition in individuals with CF related diabetes (CFRD) and impaired glucose tolerance [66]. Unfortunately, vitamin D status was not part of the sub-analysis for the study. The data between glucose intolerance, vitamin D deficiency and CFBD is sparse and future investigations exploring this relationship are warranted.

7. Routine management of vitamin D deficiency in CF

7.1. Sources of vitamin D

Vitamin D is not naturally abundant in the many foods [20,21] but can be found in fatty fish like tuna and mackerel, egg yolks, mushrooms and some fortified foods like milk and cereals [20].

Table 2
Adapted Cystic Fibrosis Foundation Guidelines for Screening, Diagnosis and Treatment of Vitamin D Deficiency in Cystic Fibrosis

Recommendations
4A. Assessment of Vitamin D Status, Target Treatment Goals and Strategy
1. Annually assess vitamin D status, preferably at the end of winter
2. Treat with vitamin D_3 (cholecalciferol) to achieve and maintain serum 25(OH)D levels of at least 30 ng/ml (≥75 nmol/liter).
3. Check serum 25(OH)D levels 3 months after the dose of vitamin D_3 has been changed.
4. Avoid using $1a25(OH)_2D$ as a marker of vitamin D status
5. Take once-daily vitamin D_3 therapy or its weekly equivalent to maintain serum 25(OH)D levels of at least 30 ng/ml (≥75 nmol/liter).
6. Difficult to treat vitamin D deficiency can be treated with calcitriol, doxercalciferol, or paricalcitol only in consultation with a specialist with expertise in vitamin D therapy.
4B. Treatment of Infants Birth to 12 months
1. Initial dose of 400–500 IU vitamin D_3 per day.
2. 25(OH)D levels less than 10 ng/ml (<25 nmol/liter) assess for rickets and manage urgently in consultation with a specialist with expertise in vitamin D therapy.
3. 25(OH)D levels that are at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and adherence to the prescribed regimen confirmed, increase the dose of vitamin D_3 to 800–1,000 IU per day.
4. 25(OH)D levels less than 20 ng/ml (<50 nmol/liter) or persistent serum 25(OH)D levels of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and there is confirmed adherence, increase vitamin D_3 to a maximum of 2,000 IU per day.
5. If unable to achieve a serum 25(OH)D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 2,000 IU vitamin D_3 per day, and confirmed adherence, consult a specialist with expertise in vitamin D therapy.
4C. Treatment of Children Older than 12 Months to 10 yr of age
1. Initial dose of 800–1,000 IU vitamin D_3 per day.
2. Serum 25(OH)D levels that are at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and confirmed adherence, adjust vitamin D_3 to 1,600–3,000 IU per day.
3. Serum 25(OH)D levels less than 20 ng/ml (<50 nmol/liter) or the patient has a persistent serum 25(OH)D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and confirmed adherence, increase vitamin D_3 to a maximum of 4,000 IU per day.
4. If unable to achieve a serum 25(OH)D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 4,000 IU vitamin D_3 per day, and confirmed adherence, consult a specialist with expertise in vitamin D therapy.
4D. Treatment of Children Above 10 yr of Age and Adults
1. Initial dose of 800–2,000 IU vitamin D_3 per day.
2. 25(OH)D levels that are at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and confirmed adherence, increase vitamin D_3 to 1,600–6,000 IU per day.
3. Serum 25(OH)D levels less than 20 ng/ml (<50 nmol/liter) or persistent serum 25(OH)D level of at least 20 ng/ml (≥50 nmol/liter) but less than 30 ng/ml (<75 nmol/liter), and confirmed adherence, increase vitamin D_3 to a maximum of 10,000 IU per day.
4. If unable to achieve a serum 25(OH)D level of at least 30 ng/ml (≥75 nmol/liter) after treatment with 10,000 IU vitamin D_3 per day, and confirmed adherence, consult a specialist with expertise in vitamin D therapy.
4E. Use of UV lamps
1. There are no recommendations for or against the use of UV lamps in the management of vitamin D deficiency.

Guidelines adapted from: Tangpricha, V., et al., An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab, 2012. 97(4): p. 1082-93. The strength of evidence is predominantly described as "Low - Consensus recommendation".

Cholecalciferol is the main animal source of vitamin D, whereas ergocalciferol is found in fungi and yeast [20]. In an effort to address the public health concern of vitamin D deficiency, many foods are fortified with both forms of vitamin D [21].

7.2. Different forms of exogenous vitamin D

7.2.1. Oral supplementation

Vitamin D exists in different forms which include cholecalciferol (D3), ergocalciferol (D2), and 25-hydyroxyvitamin D. For many years, vitamin D_2 and vitamin D_3 were thought to be equally effective in maintaining 25(OH)D levels (Supplementary Table 2). Several research studies in CF individuals, has since revealed that cholecalciferol is superior to ergocalciferol in the management of vitamin D deficiency [67–69]. In the CF population, one of the earliest studies to raise concern about ergocalciferol supplementation tested effectiveness of a high dose repletion protocol with ergocalciferol (400,000 IU of oral D_2 over 2 months) and found that most adult participants had 25(OH)D levels below the goal of 30 ng/ml. Only 8% of the subjects responded to the intervention with 25(OH)D levels >30 ng/ml. A subset completed a second course of 800,000 IU of D_2 and none attained 25(OH)D levels above 30 ng/ml. These findings led investigators to question the role of ergocalciferol in maintaining optimal vitamin D status in CF [68]. Green and colleagues conducted a similar study in the pediatric CF population with the goal of trying to determine the efficacy of various high dose vitamin D regimens. They administered 50,000 IU of ergocalciferol three times per week for 8 weeks in children with CF. Despite high doses of ergocalciferol, many children were still unable to reach target levels of 25(OH)D > 30 ng/ml [70]. Lark found that on average, patients with CF absorbed only 45% of the amount of D_2 that control subjects absorb [67]. Taken all together, these studies all contributed to the decision of making cholecalciferol the preferred calciferol to use in the CF population.

Vitamin D delivery can occur through different vehicles such as oils, powders and ethanol. In patients who don't have malabsorptive issues, the type of vehicle used for vitamin D supplements, oil vs powder, appears to be equally effective in improving 25(OH)D levels [71]. In patients with CF, a vitamin D supplement in a lipid based vehicle may not be as effective in increasing 25(OH)D levels due to their underlying problem of fat malabsorption [71]. Hermes and colleagues found that cholecalciferol was more efficiently absorbed in a powder rather than an oil vehicle in CF patients [72].

7.2.2. UVB therapy

Therapy with UVB lamps is another treatment modality explored in the CF population. In patients who use UVB lamps as directed, it can be an effective tool to increase 25(OH)D levels [73]. Khazai explored the relative efficacy of ergocalciferol, cholecalciferol, or UVB radiation in improving vitamin D levels in a CF population. The UVB group demonstrated problems with adherence [69]. However, after accounting for poor adherence, UVB was just as effective asD_2 in improving serum 25(OH)D levels. However, D_3 demonstrated a larger increase in 25(OH)D levels as compared to D_2 and UVB [69].

7.3. Goals of treatment

The goal of vitamin D supplementation is to optimize serum 25(OH)D concentrations to improve bone health and decrease the risk of osteopenia or osteoporosis. Researchers have evaluated different vitamin D regimens with the primary objective of maintaining

the balance of adequate levels of serum 25(OH)D to maintain serum PTH levels in the normal range while avoiding excess amounts which can lead to hypercalcemia, hypercalcuria and nephrolithiasis [27].

Shepard et al. investigated the safety and efficacy of a single oral high dose of vitamin D_3 followed by maintenance doses in a pediatric population [74]. Dosing was stratified by age and baseline 25(OH)D levels and ranged from 100,000–600,000 IU. Stoss therapy (high dose vitamin D therapy) followed by maintenance increased 25(OH)D levels above 30 ng/mL and this was sustained over a 12 month period [74]. Simoneau evaluated the bioavailability of vitamin D_2 vs vitamin D_3 in the pediatric population. In a prospective study, participants received oral vitamin D_3 50,000 IU weekly compared to oral vitamin D_2 50,000 IU twice weekly. They found that vitamin D_3 was more effective in achieving target 25(OH)D levels, as twice the dose of D_2 was required to achieve the same 25(OH)D levels [75].

For individuals unable to achieve serum 25(OH)D goals, Brown and colleagues suggest that there may be a role for $1,25(OH)_2D$ therapy. Adult subjects with and without CF received 2 weeks of oral calcitriol 0.5 μg twice daily. They found an increase in fractional calcium absorption, an increase in urinary calcium to creatinine ratios and suppression of PTH levels with no changes in serum ionized calcium. [76].

The European Cystic Fibrosis Society recommends starting infants on D_2 or D_3 at a dose of 1000–2000 IU per day. In children older than 1 year and adults, they recommend a dose of 1000–5000 IU per day of D_2 or D_3 [44]. The 2012 CFF recommendations for the management of vitamin D deficiency in the CF population are summarized in Table 2. It should be noted that the strength of evidence is predominantly described as "Low-Consensus Recommendation". The multidisciplinary task force advised against using $1,25(OH)_2D$ because its levels are not a good reflection of vitamin D status. The CFF recommends using cholecalciferol to treat vitamin D deficiency (Table 2) and to check serum 25(OH)D levels approxiamately12 weeks after making a change to the regimen [13].

UV lamps could be considered in some individuals with CF but there are problems with adherence, duration of exposure and amount of skin exposure needed to make dose effective [13]. In the CF population there are no studies linking UV lamps to skin cancer. However, it should be noted that there is epidemiological evidence in the general population linking UVB radiation to skin cancer, immune suppression, and oxidative stress [77]. UVA can have the same unintentional outcomes as UVB, but the adverse outcomes with UVA are not as significant as those seen with UVB [77]. In many of the UV lamp studies for patients with CF, skin erythema is documented as a common adverse reaction [73,78]. It should also be noted that certain antibiotics (fluoroquinolones, tetracyclines, sulfa drugs) commonly used in CF, can increase photosensitivity and therefore UV therapy should be approached with caution when on any of these antibiotics [13].

7.4. Complications of treatment

High circulating levels of 25(OH)D may lead to hypercalciuria and potentially nephrolithiasis [3]. Some have described the rate of nephrolithiasis to be approximately three-fold higher in the CF population. It should be noted that hyperoxaluria may serve as the main contributor to nephrolithiasis [79]. Nonetheless, when on very high doses of vitamin D supplementation, patients with CF should have serum 25(OH)D measured at least once yearly to ensure that the levels are not in a toxic range and be queried for signs and symptoms of nephrolithiasis [3]. Toxicity ensues when doses >50,000 IU per day are ingested or 25(OH)D levels exceed 150 ng/ml [12].

8. Potential impact of CFTR modulation

CFTR modulators open a new era in CF research through correction and restoration of mutant CFTR [80]. In the field of endocrinology, there are only a few studies that look at the introduction of CFTR modulators and its impact on endocrinopathies. To date, there are no trials investigating the impact of CFTR modulators on vitamin D status. Preliminary research with triple therapy (VX-659-tezacaftor-ivacaftor) demonstrates some improvement in FEV_1 and CFTR activity [81]. Other studies propose that CFTR modulators could improve nutritional status [82], which suggests that absorption of fat soluble vitamins may also improve. Beyond improving vitamin D status, CFTR modulators could also have a significant impact on bone health (such as decreasing fracture risk, attaining peak bone mass, normal bone mineral density). Sermet-Gaudelus and colleagues showed a positive relationship between the introduction of Ivacaftor and improvement in CFBD [83]. Improved vitamin D levels as a result of CFTR modulators, may mitigate some of the issues surrounding vitamin D status and the sequelae associated with deficiency of vitamin D.

9. Potential clinical trials and endpoints

CFTR modulator therapy and vitamin D status is an unchartered area in CF research. A randomized controlled trial interrogating clinically useful endpoints as it relates to vitamin D status such as bone mineral density, fracture prevention, and inflammation, could enhance our understanding of CFTR modulators and vitamin D status in CF. Modulators are currently at the forefront in CF research, but some very basic questions around the role of vitamin D in CF and inflammation remains unanswered. Ongoing research in this area, can assist with understanding the non-skeletal benefits of vitamin D supplementation for the CF population. Data generated could then determine if there is a role for vitamin D in delaying or preventing pulmonary exacerbations.

10. Future directions

Over the years, numerous studies highlight the importance of vitamin D in CF. However, many of the questions regarding vitamin D's benefit for the CF population remain insufficiently answered. The precise role of vitamin D in improving skeletal health such as preventing fractures and improving bone mineral density need further exploration through rigorous randomized controlled trials. In addition, future studies that explore the non-skeletal advantages of optimal vitamin D levels needed to prevent pulmonary exacerbation is of interest to CF clinicians and researchers. Newer areas of interest in vitamin D research investigate the complex interactions surrounding host-gut microbiome [84] and small molecules [33]. By studying these relationships, researchers are equipped to dissect the complex relationship between diet, malabsorption and the sequelae of vitamin D deficiency.

Clinical practice points

- Measure 25(OH)D annually
- Goal of therapy: keep levels >30 ng/ml (≥75 nmol/l).
- Ensure that patients are taking cholecalciferol (D_3) as prescribed
- The type of vehicle used to administer vitamin D can contribute to insufficient levels. If unable to achieve sufficient status with an oil-based vehicle, transition patient to a water or powder-based vehicle.
- If levels are insufficient or deficient, the clinician must rule out poor adherence to the prescribed regimen as the etiology of the deficiency. Consult endocrinology if there is continued difficulty with maintaining levels above 30 ng/ml (≥75 nmol/l) and there is confirmed adherence to the prescribed regimen.

11. Summary

Vitamin D deficiency is a common finding in CF. Despite supplementation, individuals remain at risk for vitamin D deficiency due to malabsorption and other factors related to CF. Screening for vitamin

D deficiency and appropriate vitamin D supplementation ensures adequate vitamin D status, which has been positively associated with higher bone density in children and adults with CF. The role of vitamin D as an anti-inflammatory agent in CF lung disease is less clear. More studies are needed that optimize vitamin D dosing, explore non-skeletal health outcomes associated with vitamin D deficiency, and decrease the disease burden for individuals living with CF.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

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