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Treatment of Vitamin D Deficiency in Cystic Fibrosis

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Abstract

Vitamin D deficiency occurs frequently in patients with cystic fibrosis (CF). Vitamin D is important for optimal mineralization of bone and may be important for other comorbidities commonly occurring in patients with CF. Vitamin D deficiency in patients with CF can arise from various causes including pancreatic exocrine insufficiency, lack of outdoor activity, and alterations of vitamin D metabolism. Due to fat malabsorption stemming from pancreatic insufficiency, higher oral doses of vitamin D are necessary to correct and maintain optimal vitamin D status in patients with CF. Recent studies have demonstrated that higher vitamin D status is associated with better lung function and that vitamin D therapy may help recovery from pulmonary exacerbations of CF. The mechanisms by which vitamin D may exert its beneficial actions in CF are unclear but likely related to the role vitamin D has in modulating the adaptive and innate immune response. Large randomized clinical studies to evaluate the potential role of vitamin D as adjunctive therapy in CF that goes beyond bone are necessary.

Background

Cystic fibrosis (CF) is one of the most common lethal autosomal recessive diseases among Caucasians in the United States. There are about 30,000 patients with CF in United States and approximately 70,000 patients worldwide with an incidence of 1 out of every 3,200 live births (1, 2). Cystic fibrosis results from a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. There have been more than 1,600 mutations that have been described with the most common mutation of the CFTR being a deletion of the amino acid phenylalanine at the 508 position (F508del) (3). The CFTR is a chloride and bicarbonate membrane transporter located on the apical surface of epithelial cells. Mutations in the CFTR gene result in an absent or dysfunctional CFTR protein, leading to defects in chloride transport across the apical epithelial membrane(4). Defects in chloride transport

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Conflicts of Interest

The authors declare no conflicts of interest

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result in dysfunction in fluid transport on epithelial membranes and thickened secretions lining epithelial surfaces, including the lung, pancreas, and colon.

The major co-morbidity and cause for mortality in patients with CF is chronic lung infection resulting in progressive respiratory decline. The CFTR dysfunction causes mucous stasis resulting in a susceptible environment for bacterial colonization for pathogenic bacteria such as *Pseudomonas aeruginosa*, chronic lung infection by other pathogenic bacteria, and chronic lung inflammation which can progress to end stage lung disease (4). In the pancreas of patients with CF, stasis of mucous, reduction of pancreatic fluid flow and increased concentration of protein results in pancreatic fibrosis, destruction and eventual insufficiency, leading to malabsorption of fat and fat-soluble vitamins, including vitamin D(5, 6). Other endocrine abnormalities can occur in patients with CF(7). Cystic fibrosis related diabetes (CFRD), delayed puberty and impaired fertility are also commonly occurring endocrine comorbidities in patients with CF(7).

Vitamin D Insufficiency and Deficiency in CF

The prevalence of vitamin D insufficiency (serum 25-hydroxyvitamin D (25(OH)D < 30 ng/mL) and deficiency (serum 25(OH)D < 20 ng/mL) in CF is high. Recent studies demonstrate that prevalence of vitamin D insufficiency in the CF population is up to 90% (8, 9). The etiologies of vitamin D insufficiency and deficiency are multifactorial in patients with CF. Pancreatic insufficiency is one major causes for vitamin D insufficiency; however, there other factors including reduced sunlight exposure, reduction of body fat and vitamin D binding protein, and impairment of hepatic hydroxylation of vitamin D(10). As in the general population, the serum 25-hydroxyvitamin D (25(OH)D) is used to determine vitamin D status. The Cystic Fibrosis Foundation recommends that the serum 25(OH)D concentration be checked annually preferably at the end of winter and should be maintained above 30 ng/mL (75nmol/L)year round(11).

Potential Role of Vitamin D in CF

Skeletal Health

Vitamin D plays a crucial role in maintaining proper bone mineralization in both the healthy and CF population. Sub-optimal concentrations of serum 25(OH)D results in secondary hyperparathyroidism potentially leading to a decrease in bone mineralization and eventually increasing the risk of osteopenia, osteoporosis and fracture (12). Early studies found that vitamin D deficiency (25(OH)D < 10 ng/mL) in adults with advanced CF was associated with lower bone mineral density at the hip and spine compared to adults with CF with higher serum 25(OH)D concentrations(13). Studies in children with CF have demonstrated that serum 25(OH)D positively correlated with Z-score at the femoral neck and lumbar spine(14, 15).

According to the 2013 CF Foundation patient registry, 21% of young adults with CF have osteopenia(16). Moreover, a systematic review and meta-analysis from 12 studies in the CF population have shown that the prevalence of osteopenia, osteoporosis vertebral and non-vertebra fractures are 38% and 23.5%, 14 % and 19.7 % respectively(17). Although vitamin

D deficiency is likely a major contributor to CF bone disease, there are many factors that contribute to bone disease in CF patients such as malnutrition, sex hormone deficiency, glucocorticoid usage and chronic inflammation (18).

Lung Function

Vitamin D may have a role in preserving lung function in the CF population(19). According to the Third National Health and Nutrition Examination Survey (NHANES III), there was a positive correlation between vitamin D status and lung function as assessed by the forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) (20). One retrospective cohort found that vitamin D status was positively associated with FEV1 in patients with CF(8). Other studies in CF populations have demonstrated that higher vitamin D status has been associated with better lung function and lower rates of pulmonary exacerbation(8, 21–23). The potential mechanisms by which vitamin D may preserve lung function based on studies in cystic fibrosis and other chronic lung disease include improved airway remodeling in response to injury, decreased airway inflammation, and decreased airway bacterial colonization (19).

Pulmonary Exacerbations and Infections

Patients with CF are at increased risk for lung infections and frequently require hospitalization for treatment with intravenous antibiotics. Vitamin D has been established to enhance the innate immune system by up-regulating antimicrobial peptides such as human cathelicidin (hCAP18 or its cleaved protein LL-37)(24). Invading microorganisms can bind to toll-like receptors on alveolar macrophages which result in up-regulation of the 1α -hydroxylase and increased production of the active form of vitamin D ($1,25(\text{OH})_2\text{D}$) and the vitamin D receptor (VDR)(25). The locally produced $1,25(\text{OH})_2\text{D}$ can induce expression of cathelicidin by macrophages and monocytes to clear the infection by the invading microorganisms (24, 25). Specific to CF, locally produced $1,25(\text{OH})_2\text{D}$ can potentially enhance airway concentrations of LL-37 to decrease colonization of airway pathogens such as *Pseudomonas aeruginosa* and *Bordetella bronchiseptica*(26). Vitamin D can also down regulate pro-inflammatory cytokine in macrophages and may also reduce the inflammation in the CF airway(27). Vitamin D may also have beneficial effects on induction of reactive nitrogen and oxygen intermediates and induction of autophagy to help clear infections (28).

High dose vitamin D given during the time of pulmonary exacerbation may improve outcomes in adults with CF who are hospitalized with a pulmonary exacerbation. In a randomized controlled double blind placebo controlled trial, 30 adults with CF hospitalized with a pulmonary exacerbation were randomized to receive a one-time oral dose of 250,000 IU cholecalciferol (vitamin D₃) or placebo. Subjects who received the vitamin D had better antibiotic therapy-free days, hospital-free days and 1 year survival compared to placebo group(29). In addition, inflammatory markers including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) were significantly reduced in high dose vitamin D group (29, 30). This pilot clinical study suggests that high dose vitamin D in patients with CF may be a beneficial adjunctive therapy during acute respiratory infection. These results are currently being confirmed with a follow-up larger multi-center study funded by the CF Foundation(31).

Treatment of Vitamin D Deficiency in CF

Previous guidelines on vitamin D for patients with CF recommended ergocalciferol (vitamin D₂) for treatment of vitamin D deficiency.(18). However, only 8 % of patients with CF achieved optimal vitamin D using these former guidelines(32). Despite doses of ergocalciferol that were higher than what was recommended by the previous guidelines, the success rate of treatment with ergocalciferol was still inadequate(33). Moreover, the absorption of ergocalciferol may be sub-optimal in patients with CF due to the oil based vehicle of the commercially available capsule of ergocalciferol(11, 34, 35). In contrast, studies have indicated success with the use of cholecalciferol in improving vitamin D status in patients with CF(23). In addition, a prospective randomized study in adults with CF demonstrated that cholecalciferol was superior to ergocalciferol in raising serum 25(OH) D concentrations (36). Therefore, the Cystic Fibrosis Foundation recommends that all CF patients with vitamin D deficiency should be preferably treated with cholecalciferol rather than ergocalciferol(11).

Vitamin D can be prescribed as a daily or weekly supplement in patients with CF to prevent and treat vitamin D deficiency and insufficiency(11). The dose of vitamin D supplementation depends on the age and vitamin D status. For both adults and children with CF should be initially treated with vitamin D₃ 800-2,000 IU/day and the dose should be titrated until a serum 25(OH)D concentration is greater than 30 ng/mL, with maximum dose of 4,000 IU/day in children and 10,000 IU/day in adults(11).In general, vitamin D from diet is insufficient to maintain optimal vitamin D status in CF. Sunlight exposure is another important source of vitamin D. A retrospective study in the CF population shows that there is seasonal variation in serum 25(OH)D in high UV exposure months (May to October) compared to low UV exposure months (November to April) (37). Sun exposure and outdoor activities should be encouraged in CF patients as well.

Conclusions

Vitamin D insufficiency and deficiency are very common in patients with CF due to multiple factors, including pancreatic exocrine insufficiency. Vitamin D deficiency is one of the major contributors to increased risk of fractures, osteopenia and osteoporosis in CF patients. Moreover, preliminary data suggest that vitamin D deficiency may contribute to the decline in lung function associated with CF. Vitamin D therapy may enhance anti-microbial peptide production and decrease pro-inflammatory cytokines which could result in improved clinical outcomes. Preventing vitamin D deficiency in patients with CF seems prudent until the results from large randomized controlled studies in CF are available.

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Highlights

- Vitamin D insufficiency is common in patients with cystic fibrosis.
- Vitamin D status is important for bone health, lung and immune function in patients with cystic fibrosis.
- Treatment of vitamin D insufficiency in patients with cystic fibrosis requires high dose cholecalciferol or ergocalciferol.
- Randomized, double blind, placebo controlled, large scale clinical trials are underway to evaluate the role of vitamin D as an adjunctive treatment in patients with cystic fibrosis.