

Vitamin - mineral and other supplementation

Vitamin D supplementation

Code: 041

Updated: February 28, 2024

Background

Vitamin D (mainly, vitamin D₃ = [cholecalciferol](#) and vitamin D₂ = [ergocalciferol](#), whose metabolite 25(OH)D is measured in serum), deficiency is common in CF patients, mainly in those with pancreatic insufficiency because of a lot of causes including malabsorption, decreased fat mass, reduced 25-hydroxylation of the vitamin, reduced exposure to sunlight, decreased vitaminD binding protein and exposure to drugs that increase metabolism.

Vitamin D deficiency is one of the several factors that contributes to reduced bone mineral density in people with CF, because its activity in the intestinal calcium absorption

A significant vitamin role in immunity has been, also, recognized ([Pincikova T.2017](#)), as it seems to be an essential component in the modulation of inflammatory response and in the promotion of antibacterial activity in the airways ([Douros K.2016](#)). In particular it has been speculated that vitamin D metabolites moderately down-regulate IL-8 in hyperinflammatory macrophages ([Daunletbaev n.2015](#)), inhibits pro-inflammatory cytokines in the airways of cystic fibrosis patients infected by *Pseudomonas aeruginosa* ([Olszowiec-Chlebna M. 2019](#)) and represses rhinovirus replication in cystic fibrosis cells ([Schögler A.2016](#)). Moreover its supplementation might decrease *Aspergillus fumigatus* specific Th2 responses in patients with aspergillus sensitization ([Nguyen NL.2015](#)).

Although this issue is still debated ([Thrusfield RM. 2018](#)), results of a retrospective study ([McCauley LA. 2014](#)), confirmed by a more recent one ([Ongaratto R. 2018](#)), has shown that higher 25(OH)D levels in children with CF are associated with lower rates of pulmonary exacerbations. Another study ([Sexauer WP. 2015](#)), about 597 CF patients, had demonstrated that serum 25(OH)D is an independent predictor of lung function parameters even if it has not been confirmed in another more recent one, about CF infants and pre-schoolers ([Oliveira MS. 2019](#)).

Finally, it has been hypothesized that vitamin D status is related to a lot of other effects, as glucose metabolism ([Pincikova T. 2011](#)), gut microbiota composition ([Kanhere M. 2016](#)), depressive symptoms ([Smith BA. 2014](#)) and presence of nasal polyps ([Konstantinidis I. 2017](#)).

Published International Consensus Guidelines ([Tangpricha V 2012](#)), revised in 2019 ([Abu-Fraiha Y. 2019](#)), and more recently by the Cystic Fibrosis Foundation ([Wood C. 2021](#)) recommend yearly screening for vitamin D status, preferably at the end of winter, using serum 25-OHD measurement, with a minimal 25-OHD concentration of 20- 30 ng/ml (50-75 nmol/liter) considered as normal value. Recommendations take into consideration age, clinical status, dietary intake and sunlight exposure of the individual patient.

A recent study ([Bright WA. 2022](#)) has suggested that CFTR modulator ELX/TEZ/IVA may improve vitamin absorption, specifically vitamin D and that, on this basis, it could be necessary to adjust vitamin supplementation in patient receiving CFTR modulator therapy.

Issues

Vitamin D supplementation beneficial effect on bone metabolism.

Vitamin D supplementation beneficial effect on lung infection and other CF-linked pathological aspects.

Optimal supplementation scheme.

Adverse events associated with supplementation.

What is known

One Cochrane review, updated May 2014 ([Ferguson JH.2014](#)) has included three RCT (69 CF people), not directly comparable because of differences in supplementation, outcome reporting and participants characteristics. In patients receiving vitamin D supplementation, 25-OHD levels were significantly higher, but there was no evidence of clinical benefit, also about bone mineral density status. No adverse events at the studied treatment regimens, have been described.

More recently ([Juhasz MF. 2020](#)) a systematic review e meta-analysis showed that , while a higher vitamin D dose elevates serum 25OHD, it does not seem to influence clinical outcomes.

A randomized controlled trial ([Simoneau T. 2016](#)) of vitamin D replacement strategies in CF patients 6-21 years old, has showed that vitamin D₂ administered as 50,000 IU twice weekly is as effective as vitamin D₃ 50,000 IU weekly for 8 weeks in patients with vitamin D insufficiency, even if only 66% of the studied patients achieved the desired 25-OHD concentration.

A RCT published in 2017 ([Pincichova T. 2017](#)) demonstrated that vitamin D supplementation may contribute to reduce inflammation, in terms of IL-8 plasma reduction and to improve lung function and quality of life.

A RCT, published in 2017([Hermes WA. 2017](#)) showed that, in adult patients, vitamin D₃ is more efficiently absorbed in a powder than

in an oil vehicle.

A RCT ([Kanhare M. 2018](#)) suggested that a bolus weekly vitamin D3 supplementation can impact gut and airway microbiota composition.

In february 2019 a study ([Tangpricha v. 2019](#)) has examined the impact, on future recurrence of pulmonary exacerbations, of a single high-dose bolus of vitamin D3 followed by maintenance treatment in adults with CF during an acute pulmonary exacerbation. No differences between the vitamin D3 and placebo groups in time to next pulmonary exacerbation or death at 1 year have been shown.

One secondary analysis of a multicenter, double-blind, randomized, placebo-controlled study ([Sivapiromrat AK. 2024](#)) investigated Vitamin D for glycemic control in adults with cystic fibrosis. Within 72 hours of hospital admission, participants were randomly assigned to a single dose of oral vitamin D (3) (250,000 IU) or placebo, and subsequently, received 50,000 IU of vitamin D (3) or placebo every other week, beginning at month 3 and ending on month 12. Glycemic control was assessed by hemoglobin A1c (HbA1c) and fasting blood glucose levels before and 12 months after the study intervention. 50/91 participants in the parent study were eligible for the secondary analysis. There were no differences in 12-month changes in HbA1c or fasting blood glucose in patients randomized to vitamin D or placebo. A high-dose bolus of vitamin D (3) followed by maintenance vitamin D (3) supplementation did not improve glycemic control in patients with CF.

Unresolved questions

Efficacy and adverse events associated with vitamin D supplementation strategies.

Impact of pubertal stage, latitude, season, lung disease severity and enzyme replacement on vitamin D bioavailability.

Impact of vitamin D supplementation on lung disease and on CF clinical complication

Some RCTs are ongoing, namely:

- A phase 1 study to define 25(OH)D3 catabolism in CF patients matched with control subjects in order to provide the first comprehensive characterization of vitamin D metabolism in CF patients and promote novel hypotheses for subsequent studies. ([NCT03104855](#))
- A phase 4 study will assess if administration of high-dose vitamin D and a commonly used prebiotic (inulin) is effective to reduce gastrointestinal dysbiosis and to improve critical intestinal functions in Cystic Fibrosis. ([NCT04118010](#))
- A phase 4 study to evaluate efficacy of intensive cholecalciferol monitoring and supplementation on serum vitD levels in pediatric patients ([NCT05276960](#)) Hospital Infantil de Mexico Federico Gomez
- A randomized, double blind study phase 3, to investigate maximum recommended doses of vitamin D given over two years to children able to normalize bone metabolism parameters and improve bone density and skeletal muscle force (<https://www.clinicaltrials.gov/ct2/show/study?term=Vitamin+D+supplementation+in+children&rank=1>)

Keywords

Bone Diseases; Malabsorption; Malnutrition; Nutrition Disorders; Osteoporosis; Vitamin D Deficiency; Supplementation; Vitamins;