Vitamin - mineral and other supplementation

Vitamin D supplementation

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Background

Vitamin D (mainly, vitamin D_3 = cholecalciferol and vitamin D_2 = ergocalciferol, whose metabolite 25(OH)D is measured in serum), deficiency is common in CF patients, mainly in those with pancreatic insufficiency due to 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

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 (Olszovwiec-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 CDSR (Ferguson JH,2014) has included three RCT (69 CF people), not directly comparable because of differences in supplementation, outcome reporting and partecipants 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.

A systematic review e meta-analysis (Juhasz MF, 2020) showed that, while a higher vitamin D dose elevates serum 25OHD, it does not seem to influnce 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 D_2 administered as 50,000 IU twice weekly is as effective as vitamin D_3 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 (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 (Hermes WA, 2017) showed that, in adult patients, vitamin D_3 is more efficiently absorbed as a powder than in an oil vehicle.

A RCT (Kanhere M, 2018) suggested that a bolus weekly vitamin D3 supplementation can impact gut and airway

microbiota composition.

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.

A a cross-sectional study (Mackenzie C Bergagnini-Kolev, 2023) compared measures of vitamin D metabolism among individuals with CF (n=83) and healthy control subjects (n=82). Participants with CF had similar mean (SD) total 25(OH)D concentrations as control subjects (26.7 [12.3] vs. 27.7 [9.9] ng/mL) and had higher vitamin D supplement use (53% vs. 22%). However, participants with CF had lower total 1?,25$(OH)_2$D (43.6 [12.7] vs. 50.7 [13.0] pg/mL), 4?,25$(OH)_2D_3$ (52.1 [38.9] vs. 79.9 [60.2] pg/mL), and 25$(OH)D_3$-S (17.7 [11.6] vs. 30.1 [12.3] ng/mL) ($p < 0.001$ for all). The pharmacokinetics of d_6-25$(OH)D_3$ and d_6-24,25$(OH)D_3$ did not differ between groups. In summary, although 25(OH)D concentrations were comparable, participants with CF had lower 1?,25$(OH)_2$D, 4?,25$(OH)_2D_3$, and 25$(OH)D_3$-S concentrations than healthy controls. Neither 25$(OH)D_3$ clearance, nor formation of 24,25$(OH)_2D_3$, appears to account for these differences and alternative mechanisms for low 25(OH)D in CF (i.e., decreased formation, altered enterohepatic recirculation) should be explored.

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 D3 (250,000 IU) or placebo, and subsequently, received 50,000 IU of vitamin D3 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 D3 followed by maintenance vitamin D3 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 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) was completed
- A phase 4 study to evaluate efficacy of intensive cholecalfiferol monitoring and supplementation on serum vitamin D levels in pediatric patients (NCT05276960) Hospital Infantil de Mexico Federico Gomez
- A randomized, double blind study phase 3, to investigate maximum raccommended 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.cl
- A randomized, double blind study phase III.b to perform the comprehensive assessment of the musculoskeletal health in children with cystic fibrosis – on the search for means of improvement (CTIS-2024-517886-18-00)

Keywords

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