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), has a key role in bone mineralization because its activity in the intestinal calcium absorption and Vitamin D deficiency is one of the several factors that contributes to reduced bone mineral density in people with CF.

A significant role of this vitamin 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 (Dourots K, 2016). In particular it has been speculated that vitamin D metabolites moderately down-regulate IL-8 in hyperinflammatory macrophages (Daunletbaev n, 2015) and inhibit pro-inflammatory cytokines in the airways of cystic fibrosis patients infected by Pseudomonas aeruginosa (Olszowiec-Chlebna M, 2019). Moreover, Vitamin D represses rhinovirus replication in cystic fibrosis cells (Schöler A, 2016) and its supplementation decreases 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 and that high-dose vitamin D assumption may have an anti-catabolic effect in adults with CF experiencing a pulmonary exacerbation (Alvarez JA, 2017). Another study (Sexauer WP, 2015), on 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).

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

Cystic fibrosis patients, mainly those with pancreatic insufficiency, are at great risk of developing vitamin D deficiency. This condition is due to malabsorption, chronic illness, medications, reduced activity, and, perhaps, as a review has suggested (Mailhot G, 2012), also to impaired vitamin D bioavailability. About 20% of patients have been described (Norton L, 2015) to have Vitamin D levels below normal values, above all the older patients and those with the lower percentage of forced expiratory volume in 1 second.

Published International Consensus Guidelines (Tangpricha V, 2012), more recently revised (Abu-Fraiha Y, 2019), 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. However it has been suggested (Timmers NKLM, 2019) that guidelines, have to be adjusted, because, to maintain adequate levels of serum 25(OH)D, vitamin D supplementation should increase with increasing body weight.

A recent approach (Regalado Lam Chew Tun R, 2018), based on high oral Vitamin D3 supplementation has demonstrated to be able to achieve optimal levels of serum 25-OHD in 70% of treated CF adults.

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.

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 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 D$_3$ is more efficiently absorbed in a powder than in an oil vehicle.

A RCT (Kanhere M, 2018) suggested that a bolus weekly vitamin D$_3$ 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 D$_3$ followed by maintenance treatment in adults with CF during an acute pulmonary exacerbation. No differences between the vitamin D$_3$ and placebo groups in time to next pulmonary exacerbation or death at 1 year have been shown.

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 complications.

Some RCTs are ongoing, namely:

- A pilot study evaluating single, high-dose pharmacokinetics/pharmacodynamics of Vitamin D$_3$ in Cystic Fibrosis (NCT03734744)
- Safety, efficacy, and feasibility of high-dose vitamin D$_3$ in pediatric patients with Cystic Fibrosis (NCT02613884)
- Clearance of 25-hydroxyvitamin D in Cystic Fibrosis (NCT03104855)
- Administration of Vitamin D and Prebiotics for intestinal Health in Cystic Fibrosis (NCT04118010)

Keywords

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