Vitamin - mineral and other supplementation

A, E, K vitamins supplementation

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Background

CF patients with pancreatic insufficiency are at risk of fat-soluble vitamin deficiency, mainly because of fat malabsorption and it has been affirmed (Siwamogsatham O, 2014) that, despite a near doubling of recorded fat-soluble vitamin supplementation over the past 5 years, there was no parallel increase in blood concentrations of these vitamins, probably because of suboptimal dosages, low adherence, or ongoing issues with malabsorption. CF patients with CF liver disease (CFLD) are at increased risk for vitamin deficiencies (Sherwood J, 2021)

Vitamin A is a group of unsaturated nutritional organic compounds that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids (most notably beta-carotene). Vitamin A is present in animal food sources and in a lot of vegetables. Vitamin A deficiency mainly causes eye and skin troubles, is essential for respiratory, urinary and intestinal epithelia and vitamin A intake influences gut microbiota variations (Li L, 2017). On the contrary, excessive vitamin A serum levels may determine respiratory, skeletal, and liver problems. Serum concentration < 0.70 ?mol/L (or 20 ?g/dl) is defined as vitamin A deficiency. CF patients, above all those with pancreatic insufficiency, are at risk of fat-soluble vitamin deficiency, because of fat malabsorption, but also because chronic lung inflammation causes increased turnover of nutrient antioxidants, such as vitamin E and vitamin A. It has been hypothesized (Rivas-Crespo

Vitamin E refers to a group of eight fat-soluble compounds that include both tocopherols and tocotrienols. There are many different forms of natural vitamin E, of which ?-tocopherol can be found in corn oil, soybean oil, and margarine, and ?-Tocopherol, the most biologically active form, can be found most abundantly in wheat germ oil, sunflower and other oilseeds.

Vit E deficiency may cause peripheral neuropathy, eye problems, cognitive impairment and hemolytic anemia. Up to now, it has not been stated whether to use plasma/serum a-tocopherol levels or serum a-tocopherol/cholesterol ratio as a biomarker for assessment of vitamin E status.

Even if Vitamin E is considered to have a important role in CF patients, above all because of its antioxidant effect, a study (Woestenenk JW, 2015), about long-term vitamin E intake and its effects in paediatric CF patients during a 7-year follow-up period, has shown that serum ?-tocopherol deficiency was rare and no evidence there is that higher serum ?-tocopherol levels have protective effects on pulmonary function. The same results have been reported in a more recent study (Loukou J, 2020)

Even when administered at high doses, no adverse events have been demonstrated.

Nutritional therapeutic guidelines usually recommend vitamin E as sole supplement or in combination with other vitamins. Because bile acids are essential for absorption of vitamin E, patients with cholestasis will need to use a water-soluble preparation. (Turck D, 2016).

Vitamin K deficiency occurs mainly in CF patients with pancreatic insufficiency, because of fat- malabsorption and, also, because of long-term use of antibiotics, bowel resection and liver dysfunction.

Vitamin K is an essential factor for blood coagulation (prothrombin, factors VII, IX, and X) and bone metabolism (undercarboxylated osteocalcin and matrix Gla-protein). Therefore, vitamin K deficiency may cause bleeding and reduced bone formation.

Vitamin K is present in green vegetables and is produced in human gut by bacteria. It can be administered orally or by intramuscular or intravenous injections. There are no routinely used biochemical indicators of vitamin K status. It can be evaluated by measuring serum concentrations of vitamin K, PIVKA-II (protein induced by vitamin K absence) and under carboxylated osteocalcin, but these markers are not usually measured in routine clinical practice due to cost. Prothrombin time can be measured but is insensitive, only becoming elevated in severe deficiency. In a study (Rana M,2014) about fat-soluble vitamin deficiency in Australian CF children, it was demonstrated that vitamin K deficiency was present in 29% of patients with a prevalence of prolonged prothrombin time of 22.62%. Vit K is deficient in all patients with CF-related liver disease (Krzyzanowska P, 2017) and the risk of developing vitamin K coagulopathy is higher in infants that are exclusively breast fed due to low vitamin K levels in breast milk (Cottam ST, 2015). Vitamin K toxicity seems not to be a concern, as there are no known adverse effects of supplementation. A recently published (Gavioli EM, 2021) retrospective evaluation of vitamin K for hemoptysis in adult Cf patients, showed that evidence for the use of vitamin K therapy in the setting of CF-related hemoptysis remain unclear

Guidelines about vitamin K supplementation have been published (Turck D, 2016).

Issues

Vitamin A

Short- and long-term beneficial effects of vitamin A therapy, including improvement of clinical and laboratory parameters possibly linked to oxidative stress condition.

Short- and long-term toxicity of vitamin A therapy

Vitamin E s

Short- and long-term beneficial effects of vitamin E therapy, also considering improvement of clinical and laboratory parameters linked to oxidative stress condition.

Vitamin K

Vitamin K supplementation efficacy in correcting coagulopathy and bone mineral metabolism markers.

Short- and long-term beneficial effects of vitamin K therapy, including clinical outcomes related to coagulopathy, bone mineral density, and quality of life.

Short- and long-term vitamin K therapy toxicity.

What is known

Vitamin A

A Cochrane Review, (jV de Vries, 2018) did not identify randomised or quasi?randomised controlled studies on retinoid supplementation, and no conclusions on the supplementation of vitamin A in people with CF have been drawn. It has been stated that until further data are available, country? or region?specific guidelines regarding these practices should be followed.

Vitamin E

One recent Cochrane Review (Okebukola PO, 2020), investigated the effects of any level of vitamin E supplementation on the frequency of vitamin E deficiency disorders. According to the data from 4 studies with a total of 141 partecipants (two studies in children aged 6 months to 14,5 years)Vitamin E supplementation showed to increase E levels, but no clinical benefit emerged.

Vitamin K

One recent Cochrane Review (Jagannath, 2020), is available. Three trials (total 70 participants, aged 8 to 46 years) have been included. Authors conclusions stated that there is very low quality evidence of any effect of vitamin K in people with cystic fibrosis, even if there is no evidence of harm and that ongoing recommendations by national CF guidelines should be followed.

Unresolved questions

Vitamin A

- Clinical advantages of vitamin a supplementation.
- Optimal dose required to achieve any clinical effectiveness

No clinical trials are ongoing about this issue

Vitamin E

- Clinical advantages of vitamin E supplementation
- Optimal dose required to achieve any clinical effectiveness

One phase 2 investigational trial is ongoing about the effect, on vascular endothelial function at rest and during exercise, of an antioxidant cocktail (Vitamin C, Vitamin E and Alpha Lipoic Acid) compared with BH4 (a cofactor for the production of nitric oxide, which is involved in vasodilation and improves systematic blood flow). NCT02690064

Vitamin K

- Clinical advantages of vitamin E supplementation
- Optimal dose required to achieve any clinical effectiveness

No clinical trials are ongoing about this issue

Keywords

Malabsorption; Malnutrition; Nutrition Disorders; Vitamin A Deficiency; Vitamin deficiencies; Supplementation; Vitamins;