Vitamin - mineral and other supplementation

Omega-3 fatty acids, zinc and probiotics supplements in cystic fibrosis

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Background

In humans, the polyunsaturated fatty acids (PUFA) linoleic acid (18:2 omega-6, or n-6) and alpha-linolenic (18:3 omega-3, or n-3) are ‘essential’ for normal growth and function; they can be introduced only with diet. Research into the omega-3 series of essential polyunsaturated fatty acids stems from the observation that the native Inuit (Eskimo) of Greenland (who consume a traditional diet rich in fish oils) have a very low incidence of some of the chronic inflammatory immune-based disorders commonly found in Europeans and North Americans. Omega-3 fatty acids have been shown to play an important role on the integrity of cellular membranes, where they exert anti-inflammatory response. Essential fatty acid deficiency may contribute to the development of the respiratory disease in infants with CF, even before clinical signs become apparent.

Fish oils are the richest dietary source of the metabolically active omega-3 fatty acid derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Some of the beneficial effects of the omega-3 fatty acids on inflammatory disease can be explained by a decrease in the production of pro-inflammatory metabolites from the omega-6 fatty acid family and an increase in the biologically less-active omega-3 and their metabolites.

Several studies provide that EPA and DHA can exert anti-inflammatory effects which may benefit a range of chronic inflammatory diseases, including CF.

A recent review discussed different aspects of disturbances in lipid metabolism seen in CF (Strandvik B et al, 2011). These include increased release of arachidonic acid (AA)(which is recognized as pro-inflammatory) from cell membrane phospholipids and a low status of linoleic and docosahexaenoic acids in CF. Recent research has explored more complicated lipid associations. Disturbances in annexins and ceramides might act in concert to explain the impact on inflammation and AA release. Animal models suggest that phenotypic changes in the CF-affected organs such as the lungs, pancreas and intestine may be due to a defect in essential polyunsaturated fatty acid metabolism.

Zinc (Zn) has significant anti-oxidant and anti-inflammatory activity. Zn deficiency can occur in subsets of patients with CF, especially those with malabsorption and impaired growth. Although supplemental Zn has significantly reduced infections in various disorders, its efficacy has not been thoroughly investigated in CF.

Probiotics are live bacteria that are administered orally and may decrease the severity and duration of childhood gastroenteritis, as well they prevent relapses of chronic inflammatory bowel diseases when given in adjunct to standard therapy. Some studies have postulated a beneficial effect of probiotics in CF.

Issues

- To determine whether there is evidence of benefit in using omega-3 polyunsaturated fatty acids supplementation in people with CF to reduce morbidity and mortality.
- To determine the effect of zinc supplementation and probiotics supplementation on reducing morbidity in CF.
- To identify any adverse events associated to these supplementations.

What is known

1 CDSR protocol (Coffey M et al, 2018) is ongoing to assess efficacy of any oral probiotic formulation (any strain(s), dose or formulation, with or without a prebiotic) compared to any other probiotic formulation, placebo or no treatment control in children and adults with CF including RCT and quasi-RCT. Primary outcomes will be pulmonary exacerbations, inflammatory biomarkers and adverse events.

1 CDSR (Oliver C et al, 2016) is available on omega-3 fatty acids to determine whether omega-3 polyunsaturated fatty acid supplementation reduce morbidity and mortality and to identify any adverse event associated with supplementation. RCTs that compared omega-3 fatty acid supplements with placebo in subjects with CF were evaluated.

15 studies were identified: four studies with 91 participants (children and adults) were included; duration of studies ranged from six weeks to six months. Five studies were judged to have a risk of bias.

Two studies compared the effect of omega-3 fatty acids to olive oil for six weeks. One study compared a liquid dietary supplement containing omega-3 fatty acids to one without for six months. One study compared omega-3 fatty acids and omega-6 fatty acids to a control group (capsules with customised fatty acid blends) for three months. One short-term study (19 participants) comparing omega-3 to placebo reported a significant improvement in lung function and Schwachman score and a reduction in sputum volume in the treated group. Another study (43 participants) showed a significant increase in serum phospholipid essential fatty acid content and a significant
drop in the n-6/n-3 fatty acid ratio following omega-3 fatty acid supplementation compared to control. The longer-term study (17 participants) demonstrated a significant increase in essential fatty acid content in neutrophil membranes and a significant decrease in the leukotriene B4 to leukotriene B5 ratio in participants taking omega-3 supplements compared to placebo.

Regular omega-3 supplements may provide some benefits for people with CF with relatively few adverse effects, but there is little evidence to recommend dietary intake of fish oil. No risk is documented related to its supplementation.

It would be recommended to increase pancreatic enzymes during supplementation with fatty acid supplements.

1 clinical trial (NCT00221546) has been completed: a Phase II trial to evaluate the influence of DHA-rich supplement vs placebo on DHA-status and health evolution of patients with CF (17 patients enrolled in Belgium). No data are published.

One Italian multicentre trial performed in thirty-four patients with CF did not show any improvement of respiratory function, nutritional status and inflammatory cytokines (Alicandro G et al, 2013) over a one year DHA supplementation.

1 clinical trial (NCT00530244) has been completed in USA on the use of formula fortified with DHA in infants with CF.

1 clinical trial has been completed (Hanssen L et al, 2014). Clinical status, exercise tolerance, inflammatory parameters, and erythrocyte fatty acid profile were evaluated in fifteen ?F508-homozygous patients with CF undergoing chronic azithromycin randomized to receive 1 year of oral omega-3 supplementation at a dose of 60mg/Kg/day or placebo. The number of pulmonary exacerbations decreased at 12 months (1.7 vs. 3.0, p<0.01), as did the duration of antibiotic therapy (26.5 days vs. 60.0 days, p<0.025), in comparison with the previous year, in the supplemented group. Supplementation significantly increased the levels of EPA and DHA as early as <3 months of administration, with concomitant decreases in AA levels.

One randomized double blind, cross-over clinical trial (NCT02690857) has been completed for evaluation of daily administration of DHA (Pro-Mind) to 10 patients, 5mg/kg for 2 weeks, then 10mg/kg for the next 2 weeks compared to placebo (sunflower oil) capsules. Biomarkers of lipid peroxidation and vitamin E levels have been measured. Plasma and platelet lipid compositions have been determined.

A randomized double-blind study (NCT02518672, PREMDIC project) has been terminated with the aim to evaluate whether daily supplementation monoglyceride of DHA will reduce lung inflammation and improve pulmonary function.

No CDSR is available on the potential role of zinc in CF.

One double blind placebo controlled pilot study (Abdelhamid I et al, 2008) showed that oral intake of 30mg/day of Zn reduced the number of days of oral antibiotics used to treat acute respiratory infections. A higher daily Zn dose may be needed to decrease acute infections and modify immune responses.

A Turkish observational study (Turk J et al, 2014) was performed to evaluate the effect of supplementary zinc on BMI, FEV1 and the number of hospitalizations in 30 children with CF. Supplementary zinc of 2mg/kg/day was administered to all patients. Serum level of zinc, alkaline phosphatase, and albumin as well as BMI, FEV1, and number of hospitalizations were compared before and after zinc administration. Height (p<0.001), weight (p=0.001) and BMI (p=0.001) were significantly increased after zinc, while the number of hospitalizations was significantly decreased (p=0.023). In contrast to patients with normal pulmonary function tests who received supplement therapy, BMI was not increased in those with abnormal pulmonary function after supplementary zinc.

Recently (Marguerettaz M et al, 2014) it has been postulated that CczRS, the zinc cadmium-specific two-component system, is not only involved in metal resistance, but also in virulence and carbapenam antibiotic resistance in Pseudomonas aeruginosa (PA). As zinc levels have been demonstrated in the sputum of CF patients a valuable strategy to modulate Zn levels may modify the increasing burden of PA infections in CF patients.

An Indian double-blind randomized placebo-controlled trial (Sharma G et al, 2016) was conducted among children with CF to assess the effect of zinc supplementation administered daily for 12 months for reducing the need for antibiotics by 50%. Any significant difference in the need for antibiotics, pulmonary function tests, hospitalization, colonization with Pseudomonas, was found for children with CF receiving zinc supplementation of 30mg/day.

1 review (Anderson JL et al, 2017) is available on the role of probiotics in CF. Primary outcomes were pulmonary exacerbations, duration of hospitalization and antibiotics, and all-cause mortality. Secondary outcomes included gastrointestinal symptoms, markers of gut inflammation, and intestinal microbial balance.

Nine studies (RCTs, 6, non-RCTs, 3; N=275) were included in the review. The pooled estimate showed significant reduction in the rate of pulmonary exacerbation (fixed effects model, two parallel group RCTs and one cross-over trial: relative risk (RR) 0.25 (95% CI 0.15; 0.41); p < 0.00001; level of evidence: low) and decrease in fecal calprotectin (FCLP) levels (fixed effect model, three RCTs: mean difference (MD) -16.71, 95% CI -27.30; -6.13; p = 0.002; level of evidence: low) after probiotic supplementation. Probiotic supplementation significantly improved gastrointestinal symptoms (one RCT, one non-RCT) and gut microbial balance (decreased Proteobacteria, increased Firmicutes, and Bacteroides in one RCT, one non-RCT).

Details of some studies included in the analysis are reported below.

A prospective randomized, double-blind, placebo-controlled study enrolling 61 patients with CF with mild-to-moderate lung disease has been performed showing that Lactobacillus Reuteri (LR) has beneficial effects on the rate of respiratory exacerbations and infections of both upper respiratory and gastrointestinal tracts (Di Nardo G et al, 2014).

A prospective, randomized, controlled iranian clinical trial (Jafari SA et al, 2013) investigated the effects of probiotics on the quality of life and pulmonary exacerbations in 37 CF patients (2-12 years old) that were randomly assigned to “probiotic group” or placebo group. 20 patients in the probiotic group took probiotics (2×10^9 CFU/d) for one month while 17 patients in the control group took placebo capsules. Quality of life was determined using PedsQL™4.0 questionnaire at the beginning, then three and six months after completing the treatment period. Rate of pulmonary exacerbations in probiotic group patients was also evaluated during three months after intervention and compared to the same three months of the previous year. Significant improvement was observed in the mean total
score of parent reported quality of life among probiotic group patients in comparison with placebo group after three months (p=0.01), but this was not significant after six months of probiotic treatment. Rate of pulmonary exacerbation was significantly reduced among probiotic group (p<0.01).

A prospective cross-over randomized study showed that probiotics reduce incidence of pulmonary exacerbations and hospital admissions in CF (Bruzzese E et al, 2007). The same group (Bruzzese E et al, 2014) investigated both the composition of intestinal microbiota in children with CF and analyzed its relationship with intestinal inflammation and the microflora structure before and after Lactobacillus GG (LGG) administration in children with CF with and without antibiotic treatment. The main results demonstrated that the levels of *Eubacterium rectale*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Bifidobacterium adolescentis*, *Bifidobacterium catenulatum*, and *Faecalibacterium prausnitzii* were reduced in children with CF. A similar but more extreme pattern was observed in children with CF who were taking antibiotics. LGG administration reduced fecal calprotectin and partially restored intestinal microbiota. There was a significant correlation between reduced microbial richness and intestinal inflammation. These data suggest that qualitative and quantitative changes in intestinal microbiota of subjects with CF may be restored by probiotics, supporting the efficacy of probiotics in reducing intestinal inflammation and pulmonary exacerbations. In a phase III randomised double-blind clinical trial in children with CF (Lactobacillus GG 6x10^9 CFU/day vs placebo) for 12 months no significant difference was found for body mass index and FEV1 (Bruzzese E et al, 2017).

An Iranian RCT study (Fallahi G et al, 2013) showed that in about two-thirds of forty-seven patients with CF (divided into two groups - one group received probiotic powder and another received placebo for four weeks) with abnormal fecal calprotectin levels (>50 mg/g) probiotic administration decreased calprotectin concentrations and subsequently intestinal inflammation in CF patients.

An RCT (de Freitas MB et al, 2017) explored the effect of synbiotic supplementation versus placebo in children and adolescents with cystic fibrosis. Markers evaluated before and after 90-day of supplementation with a synbiotic were: FEV1, nutritional status, IL-12, TNF-alpha, IL-10, IL-6, IL-1beta, IL-8, myeloperoxidase (MPO), nitric oxide metabolites (NOx). Results showed that NOx diminished significantly after supplementation in the synbiotic CF group (p = 0.030). In the synbiotic CF group with positive bacteriology, reductions were found in IL-6 (p = 0.033) and IL-8 (p = 0.009) after supplementation.

Finally, a systematic review (Anderson JL, 2017) conducted by an electronic search with the aim to evaluate the effect of probiotics on respiratory, gastrointestinal and nutritional outcomes detected five databases and three trial databases. Results suggest that probiotics may improve respiratory and gastrointestinal outcomes in a stable CF clinic population, but there is inadequate evidence to recommend a specific species, strain or dose of probiotic as likely to be of significant benefit.

3 systemic reviews (Nikniaz Z, 2017; Van Biervliet S, 2017; Anderson JL, 2017) and one double-blind cross-over study (Van Biervliet S, 2018) showed that there is insufficient evidence to support the use of probiotics to treat CF pulmonary exacerbations and intestinal inflammation even if no side effects are reported and some beneficial effects are described (improvement of gut permeability).

### Unresolved questions

A RCT study (NCT01837355) is recruiting pediatric CF patients with the purpose to modulate the effect of lactobacillus rhamnosus as diet supplementation on intestinal and pulmonary inflammation evaluated by change from baseline at week 12 and week 24 in fecal calprotectin levels and change from baseline at week 12 and week 24 in pulmonary calprotectin levels.

A RCT study from Brasil (RBR-5byrsc, 2016) is recruiting children and adolescents with CF for evaluating the effect of supplementation with a synbiotic (fructooligosaccharides, Lactobacillus paracasei, Lactobacillus rhamnosus, Lactobacillus acidophilus and Bifidobacterium lactis) for 90 days on markers of the inflammatory response.

Well designed, adequately powered, long-term, multicentre, randomized, controlled studies are needed in order to define dosage and duration of treatment and to assess influence of omega-3 fatty acids, zinc and probiotics supplements on disease severity in CF.

### Keywords

Minerals; Omega-3; Omega-6; Supplementation;