Vitamin - mineral and other supplementation

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

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Background

Polyunsaturated fatty acids

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 European and North American people.

Fish oils are the richest dietary source of the metabolically active omega-3 fatty acid derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids have been shown to play an important role on the integrity of cellular membranes, where they exert anti-inflammatory response. 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 metabolities. Several studies provide that EPA and DHA can exert anti-inflammatory effects which may benefit a range of chronic inflammatory diseases, including CF. Animal models suggest that phenotypic changes in the CF-affected organs such as lungs, pancreas and intestine may be due to a defect in essential polyunsaturated fatty acid metabolism.

Different aspects of disturbances in lipid metabolism have been seen in CF (Strandvik B et al, 2022). These include increased release of arachidonic acid (AA),which is recognized as a pro-inflammatory agent, from cell membrane phospholipids and a low status of linoleic and docosahexaenoic acids. 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.

Endogenous specialized pro-resolving lipid mediators (SPMs) as lipoxins, resolvins, protectins, and maresins derived from polyunsaturated fatty acids are locally produced in inflammatory loci to restrain this innate response, prevent further damages to the host, and permit return to homeostasis, thus limiting excessive leukocyte infiltration and pro-inflammatory signals, stimulating innate microbial killing, and enhancing resolution. In CF non-resolving inflammation is one of the mechanism involved in morbidity and mortality. Essential fatty acid deficiency may contribute to the development of the respiratory disease, even before clinical signs become apparent. The potential role of SPMs derived from polyunsaturaed acids as protective against inflammation and infections has been recently reviewed, underlining proofs of principle for their exploitation as innovative, non-immunosuppressive drugs to address inflammation and infections in CF (Recchiuti a et al, 2019).

Zinc

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. Several years ago (Marquerettaz M et al, 2014) it has been postulated that CzcRS, the zinc and cadmium-specific two-component system, is not only involved in metal resistance, but also in virulence and carbapenem antibiotic resistance in Pseudomonas aeruginosa (PA). As different 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.

Probiotics

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.

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
- To determine the effect of probiotics supplementation on reducing morbidity in CF.
- To identify any adverse events associated to these supplementations.

What is known

One CDSR (Williams N, 2023) attempted to include trials using both single and combined fibre?prebiotic interventions of inulin, FOS and GOS, but did not identify any relevant trials for inclusion in this review whose aim was to compare any oral fibre?prebiotic (inulin,

FOS and GOS, dose or formulation, without a probiotic) to any other prebiotic formulation, probiotic or synbiotic, or placebo or no control treatment. This review did not find any evidence for the use of prebiotics in people with CF. Until such evidence is available, it is reasonable for clinicians to follow any local guidelines and to discuss the use of dietary prebiotics with their patients. Large and robust RCTs assessing the dietary prebiotics of inulin or galacto?oligosaccharides or fructo?oligosaccharides, or any combination of these, are needed. Such studies should be of at least 12 months in duration and assess outcomes such as growth and nutrition, gastrointestinal symptoms, pulmonary exacerbations, lung function, inflammatory biomarkers, hospitalisations, intestinal microbial profiling, and faecal short?chain fatty acids. Trials should include both children and adults and aim to be adequately powered to allow for subgroup analysis by age.

A systematic review (Sohouli MH, 2023) evaluated the impact of omega-3 supplementation on children and adolescents patients with CF. A meta-analysis of 12 of the eligible studies showed that omega-3 supplementation significantly increased the levels of docosahexaenoic acid (weighted mean [WMD]: 2.06%, 95% confidence interval [CI]: 1.29, 2.82, p?<?0.001) and eicosapentaenoic acid (WMD: 0.32%, 95% CI: 0.15, 0.48, p?<?0.001) as well as decreased arachidonic acid (WMD: -0.78%, 95% CI: -1.50, -0.05, p?=?0.035) and C-receptive protein (CRP) (WMD: -3.76?mg/L, 95% CI: -7.42, -0.10, p?=?0.044) especially when used in higher doses and for a longer period of time compared to the control group. However, no significant effect was observed on other factors including FEV1, FVC as well as anthropometric parameters. In addition, high heterogeneity was reported for all fatty acids, but heterogeneity was low and not significant for other variables. In pediatric patients with CF, omega-3 supplementation showed benefits only in plasma fatty acid profile and serum CRP.

One CDSR (Oliver C, 2020) investigated omega?3 fatty acid supplementation in people with CF, of any age and severity. 5 RCTs were included. This review found that regular omega?3 supplements may provide some limited benefits for people with CF with relatively few adverse effects: however, the quality of the evidence across all outcomes was very low.

1 CDSR (Oliver C et al, 2016) determined whether omega-3 polyunsaturated fatty acid supplementation reduces 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.

1 RCT (López-Neyra A, 2020) investigated a long-term docosahexaenoic acid (DHA) supplementation in pwCF (96 CF patients (age >2 months) 44 female, age 14.6±11.9 years (48 DHA and 48 placebo)). Patients were randomized to receive a seaweed DHA oil solution (50 mg/Kg/day) or matching placebo for 48 weeks. There were no differences in all primary outcomes [serum-IL-8 (p=0.909), respiratory-IL-8 (p=0.384) or fecal calprotectin (p=0.948)], all secondary inflammatory biomarkers, or in any of the clinical outcomes evaluated. There were few adverse events, with similar incidence in both study groups. In conclusion in this study, long-term DHA supplementation in CF patients was safe, but did not offer any benefit on inflammatory biomarkers, or in clinical outcomes compared with placebo.

One Phase II clinical trial (NCT00221546) has been completed in order 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 has been completed (Hanssens L et al, 2016). Clinical status, exercise tolerance, inflammatory parameters, and erythrocyte fatty acid profile were evaluated in fiftheen ?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 in 2019 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. No published data are available.

A randomized double-blind study (NCT02518672)(PREMDIC project) has been terminated in 2017 with the aim to evaluate whether daily supplementation monoglyceride of DHA may reduce lung inflammation and improve pulmonary function. No published data are available.

A controlled study (Ayats-Vidal R et al, 2023) was performed in order to characterize the fatty acid profiles in the erythrocyte membrane of pediatric pwCF receiving highly concentrated docosahexaenoic acid (DHA) supplementation (Tridocosahexanoin-AOX® 70%) at 50 mg/kg/day (n = 11) or matching placebo (n = 11) for 12 months. The mean age was 11.7 years. The DHA group showed a statistically significant improvement in n-3 polyunsaturated fatty acids (PUFAs), which was observed as early as 6 months and further increased at 12 months. Among the n-3 PUFAs, there was a significant increase in DHA and eicosapentaenoic acid (EPA). Additionally, a statistically significant decrease in n-6 PUFAs was found, primarily due to a decrease in arachidonic acid (AA) levels and elongase 5 activity. No change in linoleic acid levels was observed. The administration of DHA over one year was safe and well tolerated. The administration of a high-rich DHA supplement at a dose of 50 mg/kg/day for one year can correct erythrocyte AA/DHA imbalance and reduce fatty acid inflammatory markers, although this treatment did not fully normalized PUFA concentration.

dne RCT (Ayats-Vidal R, 2024) investigated the impact of 1-year supplementation with high-rich Docosahexaenoic acid (DHA) (Tridocosahexanoin-AOX(®) 70%) at 50 mg/kg/day on clinical variables and inflammatory biomarkers in pediatric cystic fibrosis patients (n=22; 11 in the treatment group and 11 in the placebo group; mean age=11.7 years). In the DHA group, there was a significant increase in FVC (p = 0.004) and FVE(1) expressed in liters (p = 0.044) as compared with placebo, and a lower median number of exacerbations (1 vs 2). Differences in sputum cellularity (predominantly neutrophilic), neutrophilic elastase, and sputum and serum concentrations of resolvin D1 (RvD1), interleukin (IL)-8 (IL-8), and tumor necrosis factor alpha (TNF-?) between the study groups were not found. Significant increases in weight and height were also observed among DHA-supplemented patients. The administration of the study product was safe and well tolerated. In conclusion the use of a highly concentrated DHA supplement for 1 year as compared with placebo improved pulmonary function and reduced exacerbations in pediatric CF.

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

Recently (Bauer SE, 2021) a longitudinal study has been performed in order to determine the prevalence of low serum Zn (sZn) and its relationship with growth in the first 3 years of life in children with CF. A total of 106 sZn measurements from 53 infants were evaluated. Seventeen infants (32%) had intermittent Zn insufficiency, defined as at least one sZn <70 mcg/dl in their first 3 years of life. Cross-sectional and longitudinal analyses revealed discrepant associations between sZn and growth. Therefore, prospective studies are needed to understand the role of Zn in growth in CF.

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 in 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.

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.

PROBIOTICS

1 CDSR (Coffey MJ, 2020) was performed to evaluate the effect of probiotics in CF, including 12 RCTs (11 completed and one trial protocol ? this trial was terminated early) (464 children and adult CF patients). Probiotics significantly reduce faecal calprotectin (a marker of intestinal inflammation) in children and adults with CF, however the clinical implications of this require further investigation. Probiotics may make little or no difference to pulmonary exacerbation rates, however, further evidence is required before firm conclusions can be made.

A previous systematic review (Neri LCL et al, 2019) aimed to categorize current evidence regarding the effects of probiotics supplements in CF patients on gastrointestinal and respiratory outcomes according to the type of intervention, as reported by Cochrane Collaboration recommendations. Studies were categorized by probiotic strain (Lactobacillus reuteri; Lactobacillus rhamnosus GG or a mix of strains); dosage (low dosage if <10 CFU or high dosage if >10 CFU); and duration of intervention (1, 3, 6, or 12 months). Among a total of 205 identified studies only 9 met the criteria for meta-analysis inclusion. 4 of 5 studies reported a positive result for intestinal inflammation, and other 4 studies reported a positive result for pulmonary exacerbation frequency, regardless of the treatment approach. Despite data indicated as useful probiotic use in CF, studies of standardized therapeutic interventions are needed to confirm these data.

1 CDSR trial protocol (Coffey M et al, 2018) including RCT and quasi-RCT was performed 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 primary outomes as pulmonary exacerbations, inflammatory biomarkers and adverse events was early terminated.

One multi-center, double-blind, randomized placebo-controlled trial (Ray KJ, 2022) investigated the association of gut Bifidobacteria enrichment following oral Lactobacillus-supplementation (daily Lactobacillus rhamnosus strain GG (LGG) probiotic supplementation over a 12-month period) with clinical improvements in children with CF. Resilts showed that Bifidobacteria-dominated fecal microbiota were more likely to arise in LGG-treated children with CF (P?=?0.04). Children with Bifidobacteria-dominated gut microbiota had a reduced rate of pulmonary exacerbations (IRR?=?0.55; 95% CI 0.25 to 0.82; P?=?0.01), improved pulmonary function (+?20.00% of predicted value FEV(1); 95% CI 8.05 to 31.92; P?=?0.001), lower intestinal inflammation (Calprotectin; Coef?=??-?16.53 ?g g(-1) feces; 95% CI?-?26.80 to?-?6.26; P?=?0.002) and required fewer antibiotics (IRR?=?0.43; 95% CI 0.22 to 0.69; P?=?0.04) compared to children with Bacteroides-dominated microbiota who were less likely to have received LGG. In conclusion the majority of pediatric CF patients in this study possessed a Bacteroides- or Bifidobacteria-dominated gut microbiota. Bifidobacteria-dominated gut microbiota were more likely to be associated with LGG-supplementation and with better clinical outcomes.

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.

Other 2 systematic reviews (Nikniaz Z, 2017 ; Van Biervliet S, 2017) and one double-blind cross-over study (Van Biervliet S, 2018) showed that there is insufficient evidence to support the use of probiotics for treatment of CF pulmonary exacerbations and intestinal inflammation, although no side effects are reported and some beneficial effects are described (improvement of gut permability). 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 showed 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 suggested 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 6x109CFU/day vs placebo) for 12 months no significant difference was found for body mass index and FEV1 (Bruzzese E et al, 2017) .

SYNBIOTICS

1 RCT (N Bilan, et al., 2020) investigated the effects of synbiotic supplementation on the pulmonary manifestations and anthropometric measurements in 40 children with cystic fibrosis. Children were assigned to receive either two synbiotic supplements or placebo each day for 6 months. Results showed that there were no significant differences in the number of pulmonary exacerbation (P?=?0.92), duration and number of hospitalization (P?=?0.91 and P?=?0.98, respectively) between groups during the intervention. The synbiotic also did not have a significant effect on forced expiratory volume in one second (FEV1, P?=?0.22) and BMI z-score (P?=?0.77). Authors cocnluded that the synbiotic had no significant effect on pulmonary and anthropometric outcomes in children with CF. Further studies are necessary to confirm these findings.

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.

Unresolved questions

One CDSR protocol (Williams N, 2022) is ongoing and will include trials using both single and combined fibre?prebiotic interventions of inulin, FOS and GOS. Authors will exclude candidate fibre prebiotics of resistant starch, polydextrose, xylo?oligosaccharide, imalto?oligosaccharide and isomalto?oligosaccharide due to the lack of evidence to accepted them as qualified prebiotics; candidate non?fibre prebiotics polyphenolics, and polyunsaturated fatty acids. In vitro trials or trials examining the effect of probiotics alone or synbiotics (without adequate description on dose of prebiotic and type of prebiotic used) will be excluded. No restrictions for CF participants (childrene and adults) in terms of age, gender, genotype, pancreatic exocrine sufficiency status, disease severity, comorbidities, antibiotic use or CFTR modulator therapy. Primary outcomes: 1) Growth and nutrition (mean change from baseline and post?treatment absolute mean): height, weight, BMI. 2) GI symptoms measured using the multimodal questionnaire for the assessment of abdominal symptoms in people with cystic fibrosis (CFAbd Score). 3) Adverse events. Secondary outcomes: pulmonary exacerbations, lung function (mean change from baseline and post?treatment absolute mean), inflammatory biomarkers, hospitalisations (all causes), Health?related quality of life (HRQoL) measured using a validated questionnaire (e.g. Cystic Fibrosis Questionnaire – Revised (CFQ?R); Quittner 2009).

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. The current evidence is insufficient to draw firm conclusions or recommend routine use of omega-3 acids supplements in people with CF. A large, long?term, multicentre, randomised controlled study is needed to determine any significant therapeutic effect and to assess the influence of disease severity, dosage and duration of treatment. Future researchers should note the need for additional pancreatic enzymes when providing omega?3 supplementation or olive oil placebo capsules. More research is required to determine the exact dose of pancreatic enzyme required. No risk is documented related to its supplementation.

Probiotics are associated with a small number of adverse events including vomiting, diarrhoea and allergic reactions. In children and adults with CF, probiotics may be considered by patients and their healthcare providers. Given the variability of probiotic composition

and dosage, further adequately?powered multicentre RCTs of at least 12 months duration are required to best assess the efficacy and safety of probiotics for children and adults with CF.

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;