Vitamin - mineral and other supplementation

Antioxidants in cystic fibrosis

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Background

Current literature, including cellular and animal models and clinical studies, suggests a relationship between CFTR dysfunction, oxidative status and lung function (Moliteo E et al, 2022).

In CF, the source of oxidative stress is two-fold the infectious agent and the host inflammatory immune response. Many factors predispose CF patients to oxidative stress. An increased oxidant burden results from activated neutrophils that colonize the infected lungs and from an increased metabolic rate.

Reactive oxygen species (ROS) are generated by products of cellular metabolism, primarily in the mitochondria. Small (physiological) amounts of ROS are required in the cellular environment, as they are involved in signaling pathways that induce and regulate a variety of cellular activities, including cytokine secretion, growth, differentiation and gene expression, and protection against invading pathogens. Under physiological conditions, there is a well-managed balance between production and neutralization of ROS by antioxidants systems that scavenge or eliminate them. In CF oxidative stress can occur either when ROS production is accelerated or when the mechanisms involved in maintaining the normal reductive cellular milieu are impaired. Increased production of ROS is thought to occur more frequently than diminished antioxidant defence, and it has been postulated to play a role in the pathogenesis of the disease. However, it is not clear whether oxidative stress is the cause or the consequence of the primary CFTR dysfunction (Cohen TS et al, 2012).

The CF lung suffers from a systemic redox imbalance caused by the inability of cells bearing mutations in their CFTR to efflux glutathione, the most abundant cellular antioxidant, into the extracellular environment. Glutathione (GSH) is synthesised and maintained at 300–800 ?M in the airway surface liquid of healthy lung, but it is depleted to less than 10% of that concentration in the airway surface liquid of CF patients, possibly as a result of the combined effect of infection and ROS reactions. Glutathione has been shown to disrupt pyocyanin-mediated virulence by interrupting ROS production. Additional oxidants are released by inflammatory neutrophils at lung infection sites, contributing further to the imbalance. In P. aeruginosa biofilms, the metabolite pyocyanin intercalates with and strengthens the eDNA crosslinks within the matrix (Manos J, 2021).

The potential involvement of ROS in the pathogenesis of CF suggests that free-radical scavengers and antioxidants might have therapeutic uses. Although there is a significant experimental evidence demonstrating the protective effects of antioxidants, the clinical evidence for such protection is relatively scarce and/or controversial.

Antioxidant micronutrients may be a worthwhile addition to current treatment in CF. They may offset oxidant damage in the lungs resulting from persistent infection. Since people with CF have insufficient fat absorption and a diminished bile acid pool, they have low levels mainly of two fat soluble antioxidants, as vitamin E and beta-carotene.

Micronutrients as vitamin E, vitamin C, ß-carotene and selenium, referred to as free radical scavengers, may help in maintaining the oxidant-antioxidant balance.

Alternatively, the activity of glutathione peroxidase may be diminished during times of increased oxidative stress, for example after treatment of an acute infection, further contributing to decreased antioxidant defenses inducing decreased levels of GSH.

Oral N-acetilcystein (NAC) and reduced glutathione have been postulated to exert antioxidant properties (Guerini M et al, 2022).

Recently ((Laselva O, 2021)Dimethyl fumarate (DMF), that is an approved anti-inflammatory and anti-oxidant drug for auto-immune and inflammatory diseases, has been investigated as a potential anti-inflammatory molecule to ameliorate lung inflammation in CF and improve the CFTR modulators efficacy. In particular, DMF reduced the inflammatory response to LPS stimulation in both CF and non-CF bronchial epithelial cells evaluated as CF-related cytokines expression, and ROS measurements, and restoring LPS-mediated decrease of Trikafta™ in CF cells bearing the most common mutation F508del.

Issues

1. To evaluate differently the safety and efficacy of vitamin C, vitamin E, ß-carotene and selenium as a potential therapeutic approach, respectively;
2. to evaluate the efficacy and safety of oral/inhaled thiol derivatives as antioxidants through modulation of inflammatory and oxidative stress markers.

What is known

1 CDSR (Ciofu O, 2019) included one quasi-randomized and 19 randomized controlled studies of all people of either gender with a confirmed CF diagnosis and all degrees of severity (n= 924 children and adults), including those who have undergone lung transplant who were supplemented with oral or inhaled antioxidants such as vitamin C, vitamin E, beta-carotene, selenium and glutathione. The

Authors concluded that regarding to micronutrients, there does not appear to be a positive treatment effect of antioxidant micronutrients on clinical end?points; however, oral supplementation with glutathione showed some benefit to lung function and nutritional status. Based on the available evidence, inhaled and oral glutathione appear to improve lung function, while oral administration decreases oxidative stress; however, due to the very intensive antibiotic treatment and other concurrent treatments that people with CF take, the beneficial effect of antioxidants remains difficult to assess in those with chronic infection without a very large population sample and a long?term study period.

1 CDSR (Ciofu O et al, 2014) evaluated one quasi-randomized and nine randomized controlled studies, including a total of 436 subjects aged from six months to 32.9 years. Eight studies compared oral supplementation with antioxidants to placebo and two compared inhaled antioxidants supplements to placebo. While one study (n=46) of an oral combined supplement did not demonstrate a significant difference in FEV1% after two weeks, a further study (n=41) of oral supplementation with glutathione showed a significant improvement in FEV1 and FVC after six months from the beginning of the treatment, a positive effect on the nutritional status (body mass index %) of the patients, with a mean difference of 17.20 (95% CI 12.17; 22.23). In two studies when 83 people with CF were supplemented with vitamin E, an improvement after two months in the blood levels of vitamin E was detected with a mean difference of 11.78 ?M/L (95% CI 0.14; 13.42). In one of the two studies evaluating the effect of inhaled glutathione supplementation, there was an improvement in FEV1% after three and six months (n = 153), mean difference 2.57 (95% CI 2.24; 2.90) and 0.97 (95% CI 0.65; 1.29) respectively.

Data from a multicenter, randomized, double-blind, controlled clinical trial (NCT01859390) recruiting 73 subjects with CF and pancreatic insufficiency 10 years of age and older with an FEV1 between 40% and 100% predicted was published. Patients were randomized to 16 weeks of an antioxidant-enriched multivitamin ((AquADEKs-2) compared to a control group with multivitamin without antioxidant enrichment. Endpoints included systemic antioxidant concentrations, markers of inflammation and oxidative stress, clinical outcomes (pulmonary exacerbations, anthropometric measures, pulmonary function), safety, and tolerability. Main results demonstrated that a ntioxidant supplementation was safe and well tolerated, resulting in increased systemic antioxidant concentrations while a modest reduction in systemic inflammation after 4 weeks was registered. Antioxidant treatment was also associated with a lower risk of the first pulmonary exacerbation (Sagel SD et al, 2018).

The benefit of antioxidants in people with CF who receive CFTR modulators therapies should also be assessed in the future. Recently (Sommerburg O, 2021) it has been investigated the course of plasma vitamin A and E in patients with CF under LUM/IVA therapy. Clinical outcomes including pulmonary function status, body mass index (BMI), and clinical chemistry as well as fat-soluble vitamins were examined in patients with CF from annual reports before and during LUM/IVA therapy. Main results showed that patients with CF receiving LUM/IVA improved pulmonary inflammation, associated with a decrease in blood immunoglobulin G (IgG) from 9.4 to 8.2 g/L after two years ($p < 0.001$), while during the same time, plasma vitamin A increased significantly from 1.2 to 1.6 µmol/L ($p < 0.05$), In contrast, plasma vitamin E as vitamin E/cholesterol ratio decreased moderately over the same time from 6.2 to 5.5 µmol/L ($p < 0.01$).

N-acetylcysteine (NAC).

1 CDSR (Nash Edward F et al, 2013) evaluated the role of thiol derivatives either nebulized or oral to loosen sputum, improved lung function and reduced frequency of chest infections. Nine out of 23 trials were selected. Three trials on nebulized thiol derivatives were identified (one compared 20% NAC to 2% NAC; one compared sodium-2-mercaptoethane sulphonate to 7% hypertonic saline; and the third compared glutathione to 4% hypertonic saline). Although generally well-tolerated with no significant adverse effects, no evidence of significant clinical benefit was detected in primary outcomes in participants receiving these treatments. Five studies of oral thiol derivatives were identified. Three studies compared NAC to placebo; one compared NAC, ambroxol and placebo; and one compared carbocysteine to ambroxol. Oral thiol derivatives were generally well-tolerated with no significant adverse effects, but no evidence of significant clinical benefit in primary outcomes was documented. No outcomes were included for evaluation of thiols as antioxidants.

A multicenter, phase IIb, randomized, placebo-controlled, double-blind study of the effects of NAC on redox changes and lung inflammation in CF patients (NCT00809094) has been completed. Changes in the level of human neutrophil elastase activity (HNE) measured in sputum and in concentration of IL-8 measured in sputum and plasma, as well as change in concentration of GSH measured in whole blood, and change in the neutrophil count measured in sputum were evaluated as primary and secondary outcomes. As main published results (Conrad C et al, 2015) NAC recipients maintained their lung function while placebo recipients declined (24 week FEV1 treatment effect=150 mL, p<0.02). No effect on HNE activity and other selected biomarkers of neutrophilic inflammation were detected.

Glutathione.

Glutathione has been shown to disrupt pyocyanin-mediated virulence by interrupting ROS production. Glutathione is synthesised and maintained at 300–800 ?M in the airway surface liquid of healthy lung, but is depleted to less than 10% of that concentration in the airway surface liquid of CF patients, possibly as a result of the combined effect of infection and ROS reactions (Manos J, 2021).

In the light of these findings, studies have sought to evaluate whether exogenously added glutathione can overcome the effect of pyocyanin and ROS and restore depleted intracellular levels of glutathione. A previous observational study (Grey V, 2003) showed that dietary supplementation with a whey-based product can increase glutathione levels in CF, suggesting that a nutritional approach may be useful in maintaining optimal levels of GSH and counteract the deleterious effects of oxidative stress in CF lungs.

Glutathione (administered either orally or by inhalation) appears to improve lung function in some cases and decrease oxidative stress. Few trials evaluated the potential role of oral and/or inhaled glutathione as antioxidants.

A European randomized, placebo-controlled, double-blinded study has been performed to investigate the safety and efficacy of a 24-week inhaled glutathione treatment on lung function in CF patients (NCT00506688). Results of this study showed that inhaled glutathione in the administered dose did not demonstrate clinically relevant improvement in lung function, pulmonary exacerbation frequency and patient-reported outcomes. Glutathione delivery to the airways was not associated with changes in markers of oxidation, proteolysis or inflammation (Griese M, 2013). A multicenter Italian 12 months single blind RCT has been performed to evaluate the effect of inhaled glutathione on lung functions (Calabrese C et al, 2015). Main results show that a twelve month treatment with inhaled GSH did not achieve the predetermined primary outcome measure of 15% improvement in FEV1%. Only in patients with moderate lung disease, 3, 6 and 9 months treatment with GSH resulted in a statistically significant increase of FEV1 values from the baseline.

Moreover GSH therapy improved 6-minute walking test in the pediatric population. GSH was well tolerated by all patients.

A placebo-controlled, randomized, double-blind clinical trial has been completed to evaluate the effect of oral glutathione (65mg/Kg) on growth failure through 6 months in 44 pediatric subjects with CF 18 months ages to 10 years (Visca A et al. 2015). Oral reduced L-GSH significantly improved measures of growth status and gut inflammation in CF. No side effects were registered.

A multi-center, randomized, placebo-controlled, double-blind, Phase II clinical trial (Bozic M. 2020) recruited 58 patients with CF between the ages of 2-10 years. Patients received reduced glutathione or placebo orally daily for 24 weeks. No significant differences were seen between glutathione (n?=?30) and placebo (n?=?28) groups in the 6 month change in weight-for-age z-score (-0.08; 95% CI: -0.22, 0.06; p?=?0.25); absolute change in weight (kg) (-0.18; 95% CI: -0.55, 0.20; p?=?0.35); or absolute change in BMI kg/m (-0.06; 95% CI: -0.37, 0.25; p?=?0.69). There were no significant differences in other secondary endpoints. Overall, glutathione was safe and well tolerated. In conclusion, oral glutathione supplementation did not impact growth or change serum or fecal inflammatory markers in pancreatic insufficient children with CF when compared to placebo.

A multicentre double-blind RCT (Devereux G. 2020) investigated the efficacy of oral cysteamine as an adjunct treatment in cystic fibrosis pulmonary exacerbations. Eighty nine adult CF patients from 15 US and EU centres were randomized equally to a concomitant 14-day course of placebo, or one of 5 dosing regimens of cysteamine. 78 subjects completed the 14-day treatment period. Cysteamine had no significant effect on sputum bacterial load, however technical difficulties limited interpretation. The most consistent findings were for cysteamine 450 mg twice daily that had effects additional to that observed with placebo, with improved symptoms, Chronic Respiratory Infection Symptom Score (CRISS) additional 9.85 points (95% CI 0.02, 19.7) p = 0.05, reduced blood leukocyte count by 2.46x109 /l (95% CI 0.11, 4.80), p = 0.041 and reduced CRP by geometric mean 2.57 nmol/l (95% CI 0.15, 0.99), p = 0.049. In this exploratory study cysteamine appeared to be safe and well-tolerated. Future pivotal trials investigating the utility of cysteamine in pulmonary exacerbations of CF need to include the cysteamine 450mg doses and CRISS and blood leukocyte count as outcome measures.

A natural compound, as caffeic acid phenethyl ester (CAPE) derived from propolis extracts that has antioxidant and anti-inflammatory activities has been proposed as a promising strategy to assist in the treatment of the disease (Soares VEM. 2022)

Unresolved questions

One ongoing RCT (IRCT20221229056976N1) aims to evaluate the effects of curcumin-piperine in reducing Pseudomonas infection and improving clinical outcome in patients with cystic fibrosisis. Target sample size: 138 (age >5years). The intervention group are cystic fibrosis patients with pseudomonas infection who are treated with curcumin-piperine in addition to the usual treatments for CF. The duration of the treatment period will be 3 months. Curcumin-piperine is prepared in the form of 500 mg capsules with 5 mg of piperine as an absorption enhancer (Sami Labs Ltd., India) and is given to CF patients along with the usual treatment. The control group are patients with CF who are treated with placebo in addition to the usual treatments of CF. Placebo tablets contain microcrystalline cellulose matched in size, shape and color to the curcuminoids tablets. Main outome measures: clinical symptoms, pulmonary symptoms, Pseudomonas pulmonary infection, weight, height, BMI, quality of life.

Data on the efficacy of antioxidant supplementation appear to be conflicting.

Data from in vivo and in vitro experimental models suggest that antioxidants could potentially become an attractive therapeutic target for CF. However, clinical trials have shown limited evidence. An optimal dose and timing of antioxidant supplementation has yet to be determined. Multiple doses were used across studies, making comparisons and grouping based on dose impossible, similarly for the optimal duration of supplementation.

When a significant damage to macromolecules and tissue injury have already occurred antioxidant therapy can only rescue undamaged macromolecules and surviving cells, an effect that might not be sufficient to attenuate the symptoms. It is therefore important to begin antioxidant therapy at an early stage of the disease. Moreover clinicians cannot yet determine which individuals might get benefit from which antioxidant therapy, neither which optimum daily doses have to be considered. In addition, some subgroups of individuals might react negatively to particular antioxidants. Therefore, clinicians will need a means of determining both the type of antioxidant supplementation appropriate for a specific individual, and the responsiveness of each patient to the prescribed treatment. Furthermore, it should be indicated which panels of oxidative biomarkers could reflect the severity of the oxidative stress in patients undergoing clinical trials, as clinical endpoints indicators allow to point out the success (or the failure) of a specific treatment.

Currently, there is insufficient evidence to answer these unresolved questions. Larger trials looking at important clinical effects are needed.

Further studies, especially in very young children, using outcome measures such as lung clearance index and the bronchiectasis scores derived from chest scans, with improved focus on study design variables (such as dose levels and timing), and elucidating clear biological pathways by which oxidative stress is involved in CF, are necessary before a firm conclusion regarding effects of antioxidants supplementation can be drawn.

Keywords

Antioxidants; Supplementation; Thiols;