Diet

Calorie supplements in cystic fibrosis

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Background

In CF it is well known that a good nutritional status and its continuous monitoring favorably influence lung disease and the prognosis in general. Numerous studies have documented how lung disease and survival in children and adults correlated inversely with the degree of nutrition. The onset of malnutrition in CF is certainly multifactorial: low calorie intake, higher energy expenditure, increased turnover of essential fatty acids, exocrine and endocrine pancreatic insufficiency, intestinal inflammation, altered microbiota pattern, intestinal inflammation and the reduced secretion of bicarbonates are the main conditions that predispose to the state of malnutrition. Already 2012 Kalnins and Wilschanski (Kalnins D et al, 2012) underlined the relevance of maintaining a good nutritional status, thanks also to the intervention of an expert dietitian in the context of the multidisciplinary team dedicated to CF. In particular, adequate assessment of nutritional status at all ages, supplementation with fat-soluble vitamins at recommended doses, replacement therapy with pancreatic enzymes in subjects with pancreatic insufficiency at fixed doses and surveillance of nutritional intake in some complex clinical conditions (recurring abdominal pain, diabetes, decreased bone mineral density, lung transplant management, pregnancy) can contribute to maintaining a good nutritional status.

In 2018, the European Cystic Fibrosis Society (Castellani C et al, 2018) underlined how individualized behavioral modifications or motivational interviews to parents and/or patients are essential to improve adherence to diet, sodium intake and pancreatic enzymes in order to maintain adequate nutritional status. In particular a 2019 review (Colombo C et al, 2019) reiterated how the energy imbalance deriving from an incorrect composition of the diet, as well as non-adherence to nutritional recommendations, and the correct administration of pancreatic enzymes affect the adequacy of the caloric intake. Regular surveillance, including expert advice, age-specific, difficult clinical situations (for example, patient with severe lung disease awaiting lung transplantation), and nutritional support of a dedicated dietitian as part of the care team, are an integral part of the care of individuals with CF. These recommendations were subsequently updated by a group of Australian experts (van der Haak N et al, 2020). and reaffirmed in a recent review (Mariotti Zani E et al, 2023).

As recently reported (Bass R et al, 2021)(Southern KW et al, 2023) the advent of new drugs aimed at correcting the CFTR protein defect has contributed to improving the nutritional status of CF patients, and their anthropometric parameters, as well as the control of specific factors, including metabolism of bile acids, pancreatic function, energy expenditure, intestinal dysbiosis, small intestinal pH, and intestinal inflammation. Literature data support to early initiate CFTR modulators, since their use in elegible younger patients corrects the growth curve and partially restores pancreatic insufficiency. On the other hand, the early use of modulators could reduce the need for salt and fat-soluble vitamin supplementation.

Issues

1. Oral caloric supplements

To establish whether there is evidence of benefit in using oral caloric supplements in terms of:

- increase in daily caloric intake
- improvement in nutritional intake
- improvement in nutritional indices
- improvement in lung function
- improvement in survival and quality of life

and to identify any adverse effect associated with using these supplements.

1. Enteral nutrition

To evaluate whether enteral tube feeding, when indicated:

- improves nutritional status
- improves respiratory function
- improves quality of life
- is not related to adverse effects

1. Parenteral nutrition (PN)

To evaluate whether PN, when indicated:

- improves nutritional status
- improves respiratory function
- improves quality of life
- is not related to adverse effects

What is known

A historical meta-analysis (Woestenenk JW, 2013) was conducted on treatment approaches to malnutrition in CF to compare the effect of oral supplementation, enteral nutrition, parenteral nutrition and behavioral intervention on weight gain before and after treatment. All interventions were effective in producing weight gain in patients with CF. Behavioral intervention appeared to be as effective in improving weight gain in patients with CF as a more invasive medical procedure.

1. *Oral caloric supplements*

1 CDSR (Francis Damian K et al, 2015) evaluated the effect of oral protein calorie supplements in children with CF in three studies, but results were unable to draw any conclusions based on the limited data extracted. In children with CF who are moderately malnourished the use of dietary advice and monitoring alone could be an appropriate approach to management. Nutritional supplements may be used, but should not be regarded as an essential part of care.

1 CDSR (Smith Rosalind L, 2017) evaluated the effect of oral supplementations in children and adults with CF. The following outcome measures were evaluated: change in activity (% 24 hours); change in BMI (kg/m2); change in BMI centile (percentile points); change in lung function parameters; change in auxologic parameters; change in Kcal/day from supplement; change in mid-upper arm circumference (cm); change in total fat (g/day); change in total Kcal/day; change in total protein (g/day); change in weight (kg); change in weight centile (percentile points); change in weight for height (%). Three randomized controlled trials out of 21 trials, including 131 moderately malnourished patients aged between 2 and 15 years, were analyzed comparing use of oral calorie supplements for at least one month to increase calorie intake with no specific intervention or additional nutritional advice. Only one trial reported that people taking supplements consumed significantly more calories at 12 months than people receiving dietary advice alone. There were no significant differences between people receiving supplements or dietary advice alone for any nutritional or growth measurements as weight, height, body mass index, z-score or other indices of nutrition or growth, as well as for lung function, adverse effects on the digestive system or levels of activity.

Oral caloric supplementations, usually in the form of either fortified milk or juice drinks or simple energy sources, are used to increase total daily calorie intake and improve weight gain. However, they are expensive and there are concerns they may reduce the amount of food eaten and not improve overall energy intake. Oral supplements should be used as additional calories in a time-limited trial or temporarily as meal replacement for ill patients with moderate malnutrition, as suggested by the European Cystic Fibrosis Society Standards of Care (Castellani C et al, 2018).

In the era of ETI therapy a prospective observational study (Hevilla F et al, 2024) aimed to evaluate changes in nutritional and morphofunctional assessments, as well as anxiety, depression symptoms, and quality of life, in pwCF before and after 12 months ETI therapy. In a total of 31pwCF significant improvements were observed in respiratory function and quality of life, alongside an average weight increase of approximately 5 kg measured by body composition (fat mass [FM] and fat-free mass [FFM]) using bioelectrical impedance analysis (BIA) and skinfold thickness measurements (60% FM and 40% FFM). The prevalence of malnutrition, based on BMI and the FFM index, decreased significantly, while the rate of overweight/obesity increased. Biomarker analysis indicated better nutrient absorption and reduced intestinal inflammation, as evidenced by significant changes in faecal calprotectin, nitrogen, and fat levels, as well as blood lipid and vitamin profiles. Despite a reduction in caloric intake, an increase in weight was observed one year after initiating ETI. This increase was attributed to gains in both FM and FFM, suggesting improved metabolic efficiency and nutrient absorption. These findings indicate the need to modify the nutritional approach, focusing on the quality rather than the quantity of intake.

A recent real world multicenter prospective study (Enaud R al, 2025) (NCT06072365) aimed to assess changes in nutritional status and dietary intake assessed via 3-day food diaries collected at baseline (M0) and one year after ETI treatment in 62 pwCF (36 children, 26 adults). Over the first year of ETI treatment, Body Mass Index (BMI) significantly increased with a median BMI Z-score gain of 0.2 (IQR: 0.7) for children and median BMI gain of 1.0 kg/m^2 (IQR: 1.8) for adults. These gains occurred without a significant increase in median daily caloric intake (2216 kcal (IQR: 750) at M0 vs. 2266 (IQR: 733) kcal at M12). Pancreatic enzyme requirements and calprotectin decreased significantly with ETI ($p < 0.001$ and $p < 0.01$, respectively), indicating improved pancreatic function and intestinal inflammation in some patients. Seven patients became overweight after one year of ETI. ETI therapy enhances nutritional status in pwCF, independently of increased caloric intake. These resuts suggest to refine dietary recommendations under ETI treatment, aiming to prevent overweight and obesity.

1. *Enteral nutrition*

1 CDSR (Conway S et al, 2015) included thirty-eight trials; however, no studies were eligible for inclusion in this review, because of small number of enrolled participants, study design and incomplete data regarding primary and secondary outcomes.

One observational retrospective study (Shabbir S et al, 2014) was performed in Manchester (UK) to compare changes in weight and FEV1 in 53 CF adult patients receiving one of 3 interventions in order to prevent weight loss at 6 and 12 months: i) Percutaneous Endoscopic Gastrostomy (PEG), ii) oral steroid therapy (megestrol acetate- MA) or iii) nasogastric (NG) tube feeding. All 3 interventions were equally effective in improving nutritional status as measured by weight gain, and possibly to stabilize lung function. The small sample size and the lack of a control group cannot lead to strong conclusions.

One retrospective case-control study (Khalaf RT, 2018) comparing CF patients who received Percutaneous Endoscopic Gastrostomy (PEG) (n=20) and a control group who did not receive PEG (n=40) concluded that lung function trajectory showed a trend towards preservation among patients with CF who receive PEG despite lack of significant difference in BMI. There may be a favorable effect of PEG on lung function independent of changes in BMI.

No conclusions can be met regarding the role of this method on nutritional status. However, a few studies reported an increase in total energy intake resulting in significant improvements in body weight, height and height velocity, respiratory function (in particular, one study reported a slower rate of decline in respiratory function and reductions in the number of infections leading to fewer hospital admissions), and quality of life (all studies reported improvement in physical activity, but a negative impact about body image). Few

adverse effects were registered as transient nausea, vomiting (mainly associated with coughing), early morning fullness with loss of appetite, abdominal pain, loose stools, irritation of the nose and throat (in case of nasogastric feeding) and irritation of the gastrostomy site.

Enteral nutrition is routinely used in many CF centres by enteral tube feeding in different situations as weight for height percentage less than 85%, weight loss for longer than a two-month period or when no weight gain for two to three months (under five years old) or for six months (over five years old) has been registered. Temporary nasogastric (NG)/nasojejunal (NJ) feeds may be useful in individuals with moderate malnutrition.

In general, the papers report that both nasogastric and gastrostomy tube feeding are well-tolerated by people with CF.

1. *Parenteral nutrition (PN)*

No randomized controlled stadies are available on this topic.

Short term PN intervention may increase body weight, triceps skinfold thickness, and mid-arm muscle circumference. The effects of PN with high content of lipids and aminoacids were inconclusive regarding its impact on respiratory function, exercise tolerance, or recurrent infections. However, PN is recommended in severe malnourished patients with CF.

Unresolved questions

1. *Oral caloric supplements*

No studies reported outcomes measured daily, weekly or over some other time interval. No study reported outcome measures of eating behaviour.

Oral protein energy supplements in the short-term management of people with CF and acute weight loss should be assessed in prospective RCTs. It would be also defined the effect of oral caloric intake for the long-term nutritional management of adults with cystic fibrosis and/or advanced lung disease.

1. *Enteral nutrition*

Clinicians must balance possible potential benefit against the invasive nature and cost of procedures and products involved for each individual.

1. *Parenteral nutrition*

Indication for PN is based on anedoctal experiences of PN on short term. No conclusions can be made about the effect of PN on the long term intervention.

Keywords

Failure to Thrive; Nutrition Disorders; Caloric Intake; Supplementation;