MediDrink CF

MEDIFOOD

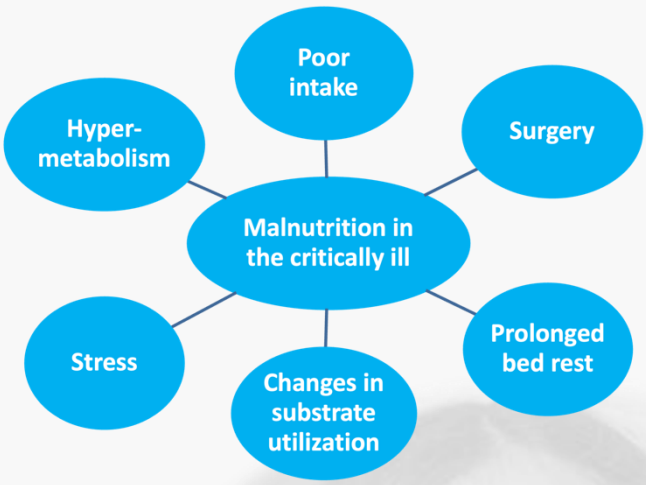
PRODUCT MONOGRAPH

FOOD FOR SPECIAL MEDICAL PURPOSES FOR THE DIETARY MANAGEMENT OF CYSTIC FIBROSIS

1. Malnutrition

Malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients. One type of malnutrition is undernutrition, which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals). Malnutrition affects people in every country. Around 1.9 billion adults worldwide are overweight, while 462 million are underweight. An estimated 41 million children under the age of 5 years are overweight or obese, while some 159 million are stunted and 50 million are wasted (WHO 2016).

Malnutrition is as much a cause as a consequence of ill health: a poor food intake, especially for a prolonged period, makes patients more prone to illness and injury that can lead to a reduced appetite through a wide variety of mechanisms – which results in poor food intake. Thus, it is a vicious cycle which often requires medical help to stop.



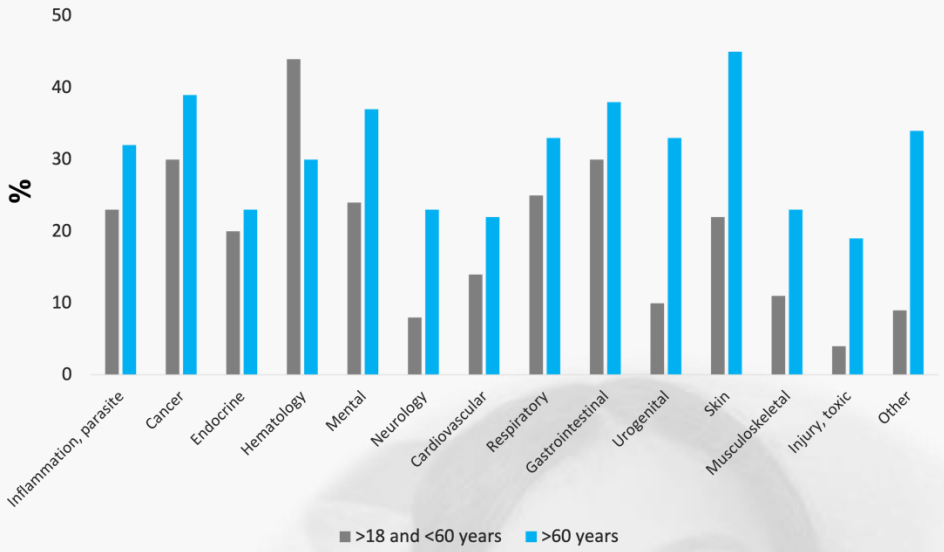
Factors contributing to the development of malnutrition

2. Disease-related malnutrition

Disease-related malnutrition (malnutrition caused by the changes of the body metabolism which increases the daily nutritional needs due to illness) has been an important and under-recognized problem for many years, and it continues to be a growing major public health problem with an aging population (Correia et al. 2003, Meijers et al. 2009). Since disease-related malnutrition inversely affects different organs and systems of the body and leads to severe physical and psycho-social consequences, all health care settings need to develop ways for the early diagnosis and the treatment / prevention of this condition. Surveys from the United Kingdom (UK) suggest that the majority of persons affected by or at risk of malnutrition are not those being treated in the hospital. Of the estimated 3 million people affected by malnutrition in the UK, only 2% are in hospitals, 93% live in the community, largely in their homes, 2-3% in sheltered housing, and 5% in care homes (Pryke et al. 2013). In the European Union countries, about 20 million patients are affected by disease-related malnutrition. This number is as high as 33 million patients when all countries of Europe are considered. Annual treatment costs of disease-related malnutrition reach € 120 billion in the European Union, and about € 170 billion in Europe (Ljungqvist et al. 2009, Ljungqvist et al. 2010). In Germany, UK, and Ireland, the annual costs of disease-related malnutrition on a national level have been calculated: € 9 billion in 2006, and € 15 billion in 2007 (Freijer et al. 2014a, Freijer et al. 2014b).

Nutritional depletion in Western countries is usually caused by the joint action of an underlying disease (e.g. cancer, chronic obstructive pulmonary disease [COPD], inflammatory bowel disease [IBD], cognitive impairment of the elderly, Alzheimer disease) and dietary deficiency (Naber et al. 1997). As a consequence, treatment should focus not only on the disease itself, but also on nutritional intervention. The most common diseases that can cause malnutrition include oncological diseases such as cancer, pulmonary diseases such as chronic obstructive pulmonary disease or cystic fibrosis, and gastroenterological diseases such as inflammatory bowel disease. Certain treatments of these diseases, such as chemotherapy or radiation therapy, can also have a negative impact on nutrition.

Disease-related malnutrition is present in a wide range of diseases, e.g. in infectious and parasitic diseases, oncologic, endocrine, gastrointestinal, pulmonary, hematologic, psychiatric, urogenital, and neurological disorders. The problem is known worldwide, affecting about 20 million patients with the cost of 120 billion Euros in the EU countries (Freijer et al. 2013).



Frequency of malnutrition in different diseases (Freijer et al. 2013)

For patients with a variety of diagnoses, reports indicate that up to 62% may be considered at risk of malnutrition or frankly malnourished on admission to hospital with rates of up to 12.5% in the community. Studies specifically in general medical patients indicate a possible prevalence rate of up to 56% on admission to hospital (Stratton et al. 2003).

The consequences of malnutrition, if left untreated, are serious, causing a marked decline in physical and psychological health and function. Malnutrition has a negative effect on recovery from disease, treatment efficacy, wound healing, frequency of complications (e.g. infection, decubitus), prognosis, mortality, tolerance of treatment, quality of life, and healthcare use (e.g. general practitioners visits, number and length of hospital stay) (Martyn et al. 1998, Löser C. 2010). Weight loss during an illness is a red flag for even the most inexperienced clinician, but malnutrition in the absence of manifest illness is rarely recognized as a modifiable risk factor for development of chronic diseases. The social determinants influencing food intake and hence malnutrition, e.g. loneliness and isolation, poverty, poorly fitting dentures, inaccessible food outlets, difficulty in cooking, or in supporting oneself to eat and drink, may be in operation long before associated comorbidities appear. Moreover, treatment and amelioration of these factors may delay or even prevent the onset of disease (Pryke et al. 2013).

For such a widespread significant problem, malnutrition has so far attracted very little attention in primary care. One factor of this phenomenon may be nutrition's notable absence from most medical school curricula and postgraduate training, resulting in poor awareness, large knowledge gaps, and a deficit of nutrition-related competencies. Lack of ownership among clinicians is another factor, because malnutrition, like other processes such as pain, inflammation and obesity, cuts across traditional clinical specialty boundaries instead of falling neatly within one or other. Reflecting this collective uncertainty and patchy knowledge, a host of unhelpful nutritional myths have also propagated and stabilized within our culture and have normalized nutritional problems. It would be timely to debunk the perception that weight loss is an inevitable part of ageing or that lower energy "healthy foods" are appropriate for everyone (Pryke et al. 2013).

There is ongoing debate in the literature about the merits of oral nutritional supplements (ONS) compared to first-line dietary advice ("food first": information on food fortification, snacks, food choices). Skepticism regarding ONS relate to its largely hospital-focused evidence base. Issues around palatability, taste fatigue (particularly in the chronically ill requiring long-term supplementation), patient preference for "normal food", and psychological factors were regarded as factors that might all impact the effectiveness of therapy. Thus, skeptics suggest to prefer dietary advice versus ONS. Conversely, superficial dietary advice runs the risk of at-risk patients simply increasing calories without addressing essential protein and micronutrient requirements, and it is unfeasible for a "food first" approach to address nutritional deficits in some patients, particularly those with anorexia and/or early satiety. Although dietary fortification and counselling can improve nutritional intake, the evidence base is weak for improved outcomes relative to the evidence for ONS, questioning whether "food first" can replicate the combination of nutrients found in ONS (Pryke et al. 2013). These results indicate that compared to dietary counseling, the use of ONS are based on more evidence in the treatment and prevention of malnutrition. Numerous clinical studies investigated the effect of nutritional therapy on disease-related malnutrition. Meta-analyses on treatment of disease-related malnutrition with medical nutrition show a reduction in complications and mortality, improvement of wound healing, and increase of quality of life (Elia et al. 2021, Elia et al. 2005, Stratton RJ. 2005).

2.1. Malnutrition in cystic fibrosis

Many different factors contribute to nutritional abnormalities and muscle dysfunction in chronic respiratory diseases. Nutritional abnormalities are frequent in different chronic respiratory diseases such as COPD, bronchiectasis, cystic fibrosis (CF), interstitial fibrosis and lung cancer, having important clinical consequences. However, nutritional abnormalities often remain underdiagnosed due to the relative lack of awareness of health professionals. Therefore, systematic anthropometry or even better, assessment of body composition, should be performed in all patients with chronic respiratory conditions, especially following exacerbation periods when malnutrition becomes more accentuated (Gea et al. 2018).

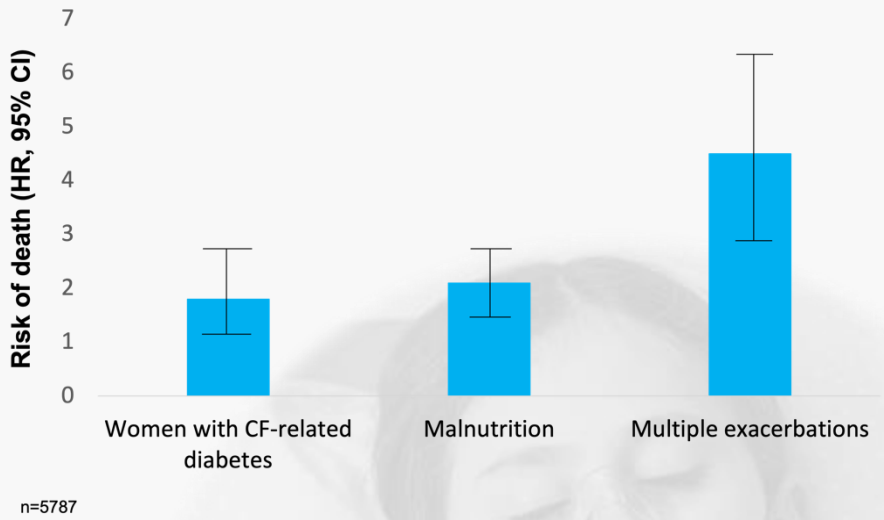
Multiple studies have shown that nutritional status is a strong predictor of morbidity and mortality in patients with CF. Since CF is characterized by progressive lung disease, it could be argued that the underlying lung disease is what determines the nutritional failure seen in most patients. Longitudinal studies with sufficiently large follow-up times have demonstrated that young underweight patients have worst pulmonary function outcomes. More importantly, these studies concur that the yearly change in growth parameters has a significant effect on the rate at which pulmonary function develops. Although the mechanisms behind this important association are yet unclear, there is some suggestion from interventional studies that the accrual of lean body mass is the factor that is involved in the preservation of lung function (Milla et al. 2004).

Data obtained in 8,178 infants with CF showed that moderate malnutrition (z-score ≤-2) is still present in the year after diagnosis, and that their weight and height was significantly lower than that of their healthy counterparts (p<0.001) (Hoch et al. 2018).

It is hypothesized that the severity of lung disease would be associated with increased protein catabolism and systemic inflammatory status in clinically stable patients. In a study of 40 adults with CF and 22 healthy controls, urinary pseudouridine excretion, a marker of protein breakdown, was significantly increased in CF patients (p=0.019). Excretion of cross-linked N-telopeptides of type I collagen (NTx), a marker of bone connective tissue breakdown was also significantly increased in CF patients (p<0.01). Both markers were inversely associated with forced expiratory volume 1s (FEV_1) (p=0.001 and p<0.01 respectively). Serum levels of inflammatory markers such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and their soluble receptors were significantly higher in CF patients than healthy controls (Ionescu et al. 2002).

Nutritional status strongly influences pulmonary health among CF patients. Therefore, aggressive nutritional support aiming at achieving normal growth patterns should lead to adequate development of lung function and maintenance of pulmonary health (Milla et al. 2004).

A Canadian registry study of 5,787 individuals with CF showed that malnourished patients (HR=2.1, 95% CI 1.6-2.8), those with multiple exacerbations (HR=4.5, 95% CI 3.2-6.4) and women with CF-related diabetes (HR=1.8, 95% CI 1.2-2.7) were at increased risk of death (Stephenson et al. 2014).



Malnutrition, multiple exacerbations, and CF-related diabetes increase risk of death in patients with CF (Stephenson et al. 2014)

2.2. Summary

Malnutrition and cachexia are common complications in patients with chronic respiratory diseases such as CF. Since nutritional status, and presence of cachexia have a deleterious effect on disease outcomes and quality of life in these patients, the early diagnosis and treatment with oral nutritional supplements are extremely important for the adequate therapy of patients suffering from these chronic conditions.

3. Nutritional needs in cystic fibrosis

3.1. Energy and protein intake

Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). From an energy point of view, an increased weight loss may be related to a decrease in thermodynamic efficiency. Variable thermodynamic efficiency in metabolic systems is related not only to differences in weight but also may confer metabolic advantages or drawbacks. At present, it is widely held that elevated resting energy expenditure (REE) is a major determinant in the development of malnutrition in cachectic patients. Resting energy metabolism represents the combustion of fuel sources needed to provide energy for metabolic processes involved in maintaining the function and integrity of cells and body organs and for the mechanical processes involved in keeping the body alive. It is appropriate, therefore, to presume that abnormalities in carbohydrate, lipid and protein metabolism are major biochemical bases of elevated REE (Hyltander et al. 1991, Argiles et al. 2014).

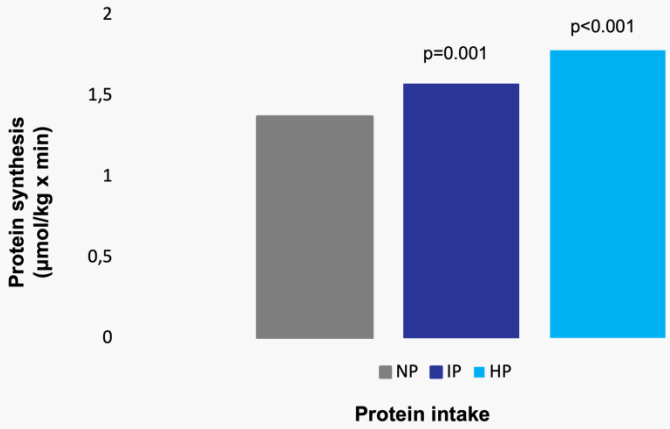
Treatment for cachexia has concentrated on increasing food intake, although that alone is unable to reverse the metabolic changes (Tisdale et al. 2004). Due to the hypercatabolic state and increased protein breakdown seen in malnourished / cachectic patients, increased energy and protein intake is vital in slowing down / stabilizing or even reversing weight loss and lean body mass / muscle wasting in cachectic patients (Cawood et al. 2012, Broekhuizen et al. 2005a, Guagnozzi et al. 2012).

The importance of high energy intake to counter the increased catabolic processes is very well recognized in CF patients. The Cystic Fibrosis Foundation (CFF) recommends energy intakes greater than the standard for the general population to support weight maintenance in adults and weight gain at an age-appropriate rate in children. Improved weight status has been found at intakes 110-200% of energy needs for the healthy population of similar age, sex, and size. For children with growth deficits and adults with weight deficits, the CFF recommends the use of nutritional supplements (oral and enteral) in addition to usual dietary intake to improve the rate of weight gain (Stallings et al. 2008).

Several recent publications indicate that the maximum stimulation of muscle protein fractional synthetic rate occurs with intake of 20-30 g protein. This finding has led to the concept that there is a maximal anabolic response to protein intake with a meal, and that the normal amount of protein eaten with dinner will generally exceed the maximally-effective intake of protein. However, protein breakdown has not been taken into account when evaluating the anabolic response to protein intake. Protein anabolism occurs only when protein synthesis exceeds protein breakdown. Higher protein intakes when protein synthesis is maximized is characterized by suppressed protein breakdown and via that mechanism leads to a greater anabolic response. This explains why when net protein synthesis is measured, the relationship between amino acid availability and net gain remains linear, without any apparent plateau of effect at higher levels of availability. It may be concluded that there is no practical upper limit to the anabolic response to protein or amino acid intake in the context of a meal (Deutz et al. 2013).

Low values for fat-free mass (FFM) have been found in 25–38% of CF adults and 14–20% of CF children with normal or elevated body mass index (BMI). Low FFM was undetectable by BMI in 58% of the CF adults and children. Low FFM was related to lung function impairment in CF adults and associated with impaired lung function and bone mineral loss independent of loss of fat mass in CF children. Although BMI has improved in the past decades, the prevalence of FFM loss is still high in CF. Nutritional care in CF should therefore aim at improving muscle mass instead of focusing only on increasing body weight or BMI (Engelen et al. 2014).

Due to increased losses with malabsorption, and increased needs with acute exacerbations, it is recommended that 20% of calories should come from proteins in the diet of CF patients (Matel et al. 2012). In a study of 8 pediatric CF patients, 3 randomly allocated isocaloric diets with normal (NP), intermediate (IP), and high (HP) amounts of protein (1.5, 3, and 5 g/kg/day, respectively) were administered by continuous drip feeding during a 4-day period at 6-week intervals. A dose-response effect on protein synthesis was observed in stunted children with stable CF. Protein synthesis was 30% higher in the high compared to the normal-protein group which resulted in more protein anabolism (Geukers et al. 2005).



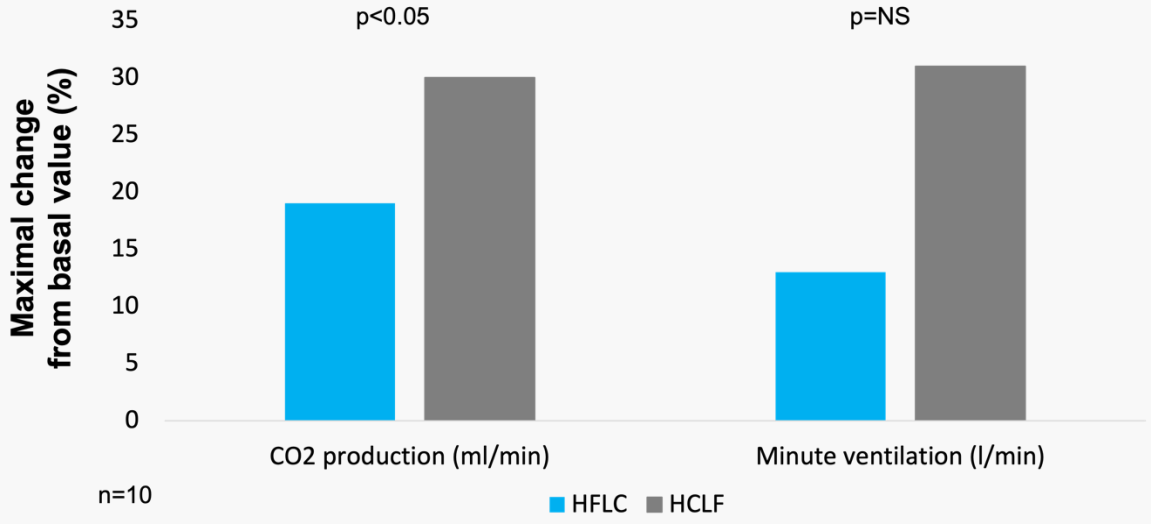
High protein intake results in higher protein synthesis in CF patients (Geukers et al. 2005)

3.2. Tailored composition of enteral nutrition

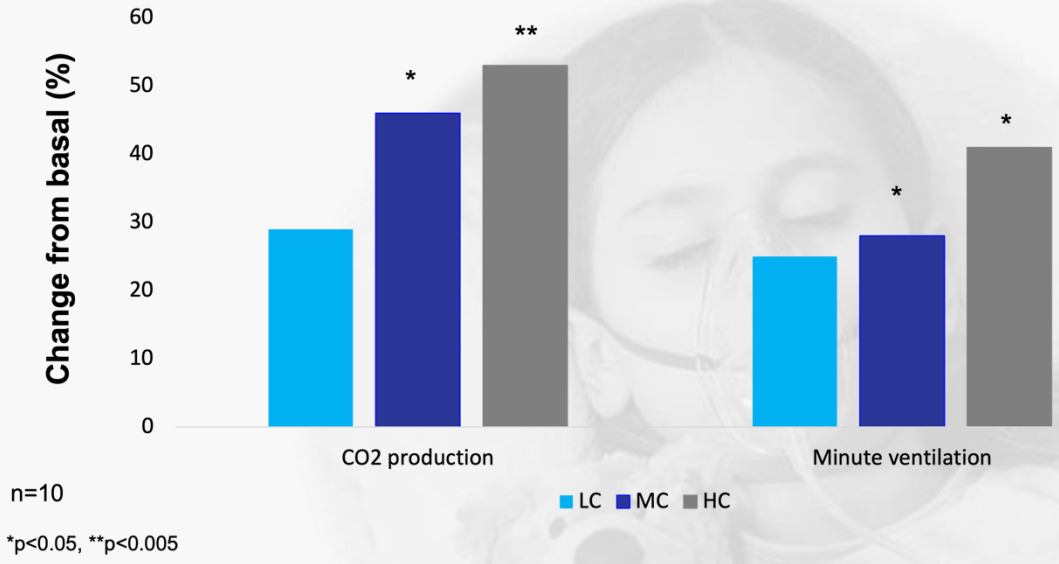
3.2.1. Main energy source in cystic fibrosis

For CF patients, the dietary recommendation is to have at least 40% of the consumed energy to come from fats (Braga et al. 2013). In a study of 10 malnourished CF patients, the influence of a higher-fat-lower-carbohydrate-energy (HFLC: 16.7% protein, 28.1% carbohydrate, 58.2% fat) and a higher-carbohydrate-lower-fat-energy (HCLF: 21% protein, 51% carbohydrate, 27% fat) oral nutritional supplements on the energy and pulmonary metabolism was compared. The patients' basal energy expenditure (BEE) before ingesting the supplements was 120% of that predicted by the Harris-Benedict equation. The CO_2 production (VCO_2) increased 9-19% for the 3 h after ingesting 500 kcal/m^2 of the HFLC, and 25-30% after ingesting HCLF ($p<0.05$). The respiratory quotient (RQ) was significantly greater for HCLF than HFLC. The minute ventilation (VE) rose 10-13% for the 3 h after ingesting HFLC, versus 27-31% after ingesting HCLF, but the difference was not significant (Kane et al. 1991).

In another study, 10 CF patients aged 17 to 24 years (mean 21.4 years) received 1000 kcal/m^2 of a low-carbohydrate (LC: 28.1 energy% carbohydrate), a medium-carbohydrate (MC: 53.9 energy% carbohydrate), and a high-carbohydrate (HC: 84.4 energy% carbohydrate) formula in random order. BEE without feedings averaged 120% of that predicted by the Harris-Benedict equation. Oxygen consumption (VO_2) increased 21-27% during nighttime feedings with no difference between formulas. VCO_2 increased 29% for LC, 46% with MC, and 53% with HC. The increase in VCO_2 with LC was significantly less than with MC ($p<0.05$) and with HC ($p<0.005$). The respiratory quotient (RQ) for LC (0.88) was the same as the BEE, but increased with MC (1.00), and with HC (1.08). The 41% increase in minute ventilation with HC was greater than the 25-28% increase observed for LC and MC ($p<0.05$) (Kane et al. 1990).



A higher-fat-lower-carbohydrate ONS induces less CO_2 production and a lower increase in minute ventilation than a higher-carbohydrate-lower-fat ONS (Kane et al. 1991)



Medium- or high-carbohydrate ONS significantly increase CO_2 production and minute ventilation in CF patients compared to a low-carbohydrate ONS (Kane et al. 1990)

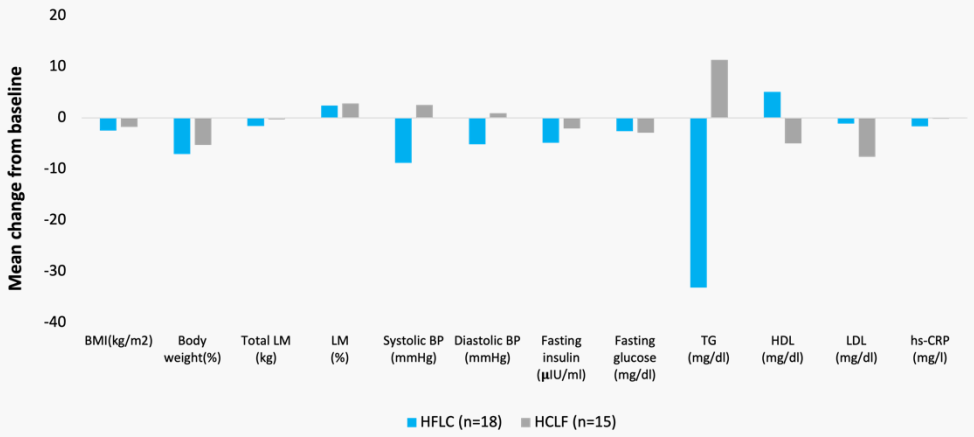
3.2.2. Main energy source in cystic fibrosis – medium chain triglycerides

Fats constitute the most significant nutritional source of energy. Their proper use by the body conditions a number of complex mechanisms of digestion, absorption, distribution, and metabolism. These mechanisms are facilitated by fats made of medium chain fatty acids (MCT). Hydrolysis of MCT (which is faster than long-chain fatty acids / LCT hydrolysis anyway) does not require bile and lipase. Without hydrolysis, they may also be absorbed by the enterocytes and they do not require re-esterification. From enterocytes they are directly absorbed into the portal vein and then transported mainly to the liver. Thus, absorption of MCT is faster than that of LCT. Their metabolism is facilitated as well because they are metabolised by the liver almost completely (only when the liver's metabolic abilities are exceeded the process is taken over by peripheral tissues) with energy release, regardless of the presence of carnitine (which is necessary for the transport of LCT through the mitochondrial membrane). Thanks to this, the availability of medium-chain fatty acids for mitochondrial oxidation is better. This means that MCT are an easy and quick source of energy (Los-Rycharska et al. 2016).

Unlike LCT, MCT do not affect the release of cholecystokinin or the emptying of the gallbladder and they do not increase the secretion of pancreatic enzymes. An increased supply of MCT is particularly important in patients with disturbances of digestion and absorption, who suffer from energy deficiency and disturbed absorption of fats. These are patients with disturbed bile secretion (cholestasis, disturbances in hepatic-intestinal circulation of bile acids, intestinal dysbacteriosis), or pancreatic lipase secretion (for example, in pancreatic failure in the course of CF), since MCT do not have to be emulsified in the digestive tract or undergo the process of lipolysis (Los-Rycharska et al. 2016).

3.2.3. Main energy source in cystic fibrosis – safety of a low-carbohydrate-high-fat diet

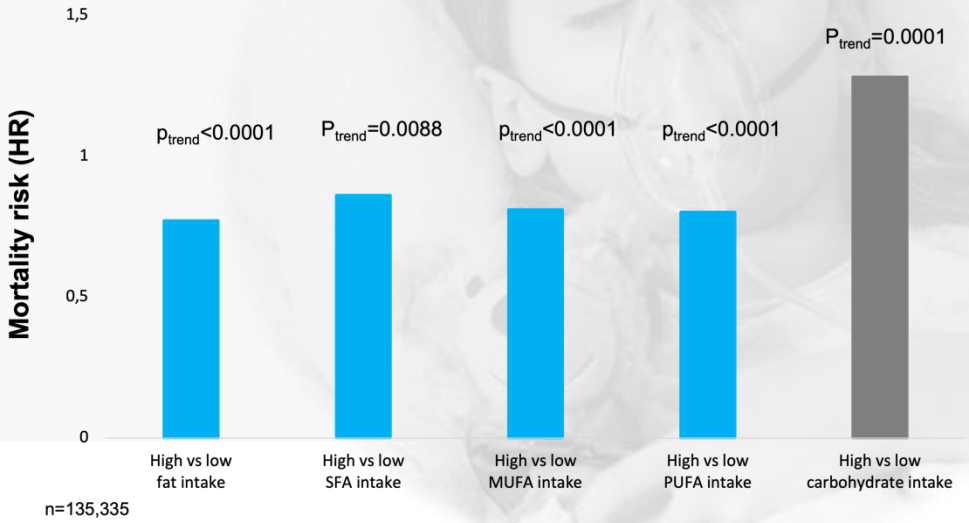
Larosa et al. were the first to demonstrate in 1980 (and confirmed by others many times since) that low-carbohydrate diets (30-130 g/day) do not necessarily require higher fat or protein intake, and a spontaneous decrease in overall calorie consumption frequently results in little protein or fat added back for the carbohydrate removed (Larosa et al. 1980). This causes the phenomenon that a very low carbohydrate diet ameliorates all the investigated anthropometric laboratory parameters (BMI, abdominal fat, triglycerides, HDL, triglycerides/HDL ratio, ApoB/ApoA1 ratio, small LDL, blood glucose, plasma insulin, saturated fatty acid) of patients with atherogenic dyslipidemia (Hite et al. 2011). In a study, which randomized obese subjects (29.0-44.6 kg/m2) recruited from Boston Medical Center to a hypocaloric high-carbohydrate-low-fat / HCLF (n=26) or low-carbohydrate-high-fat / LCHF (n=29) diet for 12 weeks, the LCHF group had greater improvements in blood lipids and systemic inflammation with similar changes in body weight and composition, relative to the HCLF group (Ruth et al. 2013).



BMI: body mass index, LM: lean mass, BP: blood pressure, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, hs-CRP: serum high sensitivity C-reactive protein

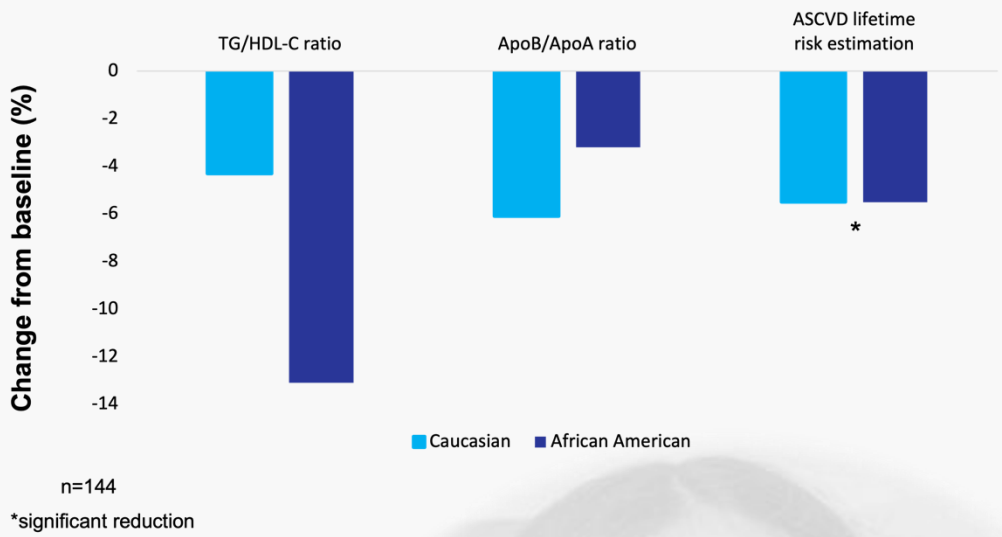
Beneficial effects of a low-carbohydrate diet (Ruth et al. 2013)

In a large, epidemiological cohort study of individuals aged 35–70 years in 18 countries with a median follow-up of 7.4 years (IQR 5.3-9.3), dietary intake of 135,335 individuals was recorded using validated food frequency questionnaires. Participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on percentage of energy provided by nutrients. During follow-up, 5,796 deaths and 4,784 major cardiovascular disease events were documented. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] *vs* lowest quintile [quintile 1] category, HR=1.28 [95% CI 1.12-1.46], p_{trend}=0.0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 *vs* quintile 1, total fat: HR=0.77 [95% CI 0.67-0.87], p_{trend}<0.0001; saturated fat (SFA): HR=0.86 [0.76-0.99], p_{trend}=0.0088; monounsaturated fat (MUFA): HR=0.81 [95% CI 0.71-0.92], p_{trend}<0.0001; and polyunsaturated fat (PUFA): HR=0.80 [95% CI 0.71-0.89], p_{trend}<0.0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 *vs* quintile 1, HR=0.79 [95% CI 0.64-0.98], p_{trend}=0.0498). Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality. Based on these results, the authors suggest the reconsideration of global dietary guidelines (Dehghan et al. 2017).



High carbohydrate intake is associated with higher risk of total mortality, whereas total fat and individual types of fat are related to lower total mortality (Dehghan et al. 2017).

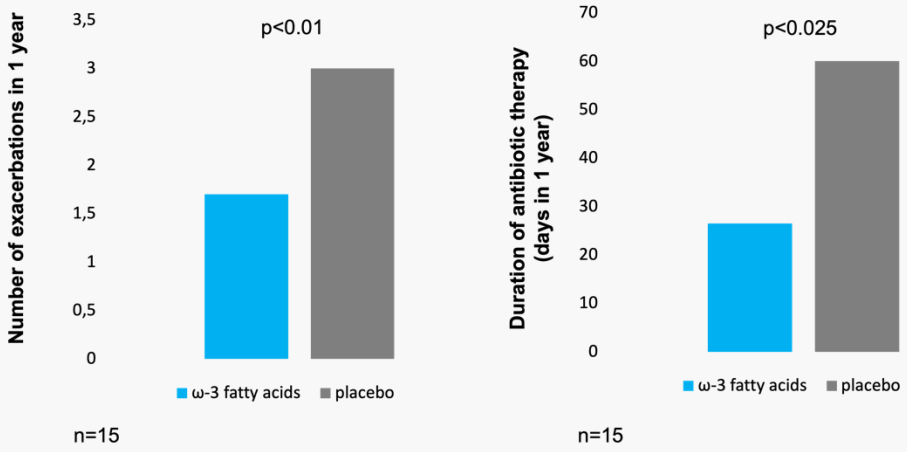
A study recruited 144 premenopausal women of age 21-50 years with class I/II obesity (BMI 30-39.9 kg/m^2) to keep a balanced high-fat diet (50% fat, 30% carbohydrate, 15% protein, with a balanced fat content – 1/3 saturated fatty acids, 1/3 monounsaturated fatty acids, 1/3 polyunsaturated fatty acids) for 16 weeks. In order to control the effects of high simple carbohydrate intake, total carbohydrate was maintained as 50% sugars (mono- and disaccharides) and 50% starches. Results in European American and African American participants were analyzed separately. Consuming the balanced high-fat diet significantly reduced cardiovascular risk by 5.5% (increased HDL particle size, increased the number of large HDL particle size, and increased apolipoprotein AI level) in both groups. In addition, European American women had significant reductions in fasting insulin levels (by 24.8%) and in HOMA-insulin resistance (by 29%). In the group of European American women, the most significant improvements occurred in VLDL particle size, apolipoprotein B levels, serum triglyceride, number of plasma LDL particles, and serum LDL cholesterol (Niswender et al. 2018).



High-fat balanced diet improves atherosclerotic cardiovascular disease (ASCVD) risk in obese premenopausal women (Niswender et al. 2018)

3.2.4. Anti-inflammatory nutrition in cystic fibrosis

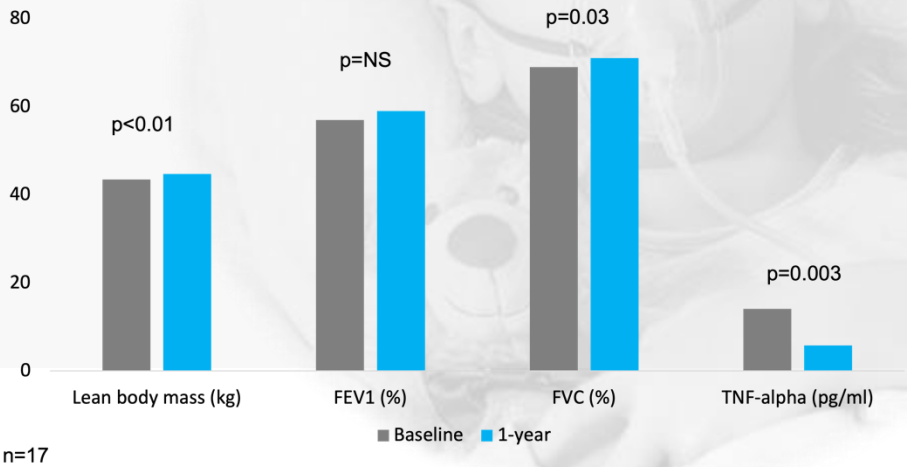
In a study of 15 ΔF508-homozygous CF patients undergoing chronic azithromycin treatment, patients were randomized to receive ω-3 fatty acid supplementation at a dose of 60 mg/kg/day or placebo. In comparison with the previous year, in the supplemented group, the number of pulmonary exacerbations decreased 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, $p<0.025$). This pilot study concluded that long-term ω-3 fatty acid supplementation offers several clinical benefits as to the number of exacerbations and duration of antibiotic therapy in CF patients (Hanssens et al. 2016).



Long-term ω-3 supplementation decreases the number of exacerbations and duration of antibiotic therapy in CF patients (Hanssens et al. 2016)

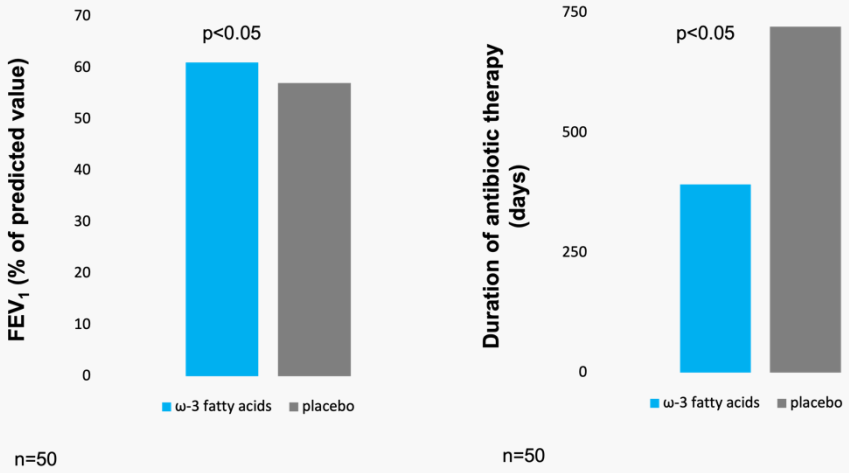
A placebo-controlled trial of eicosapentaenoic acid (EPA, 2.7 g daily for 6 weeks) assessed its effects on markers of clinical state, peripheral neutrophil function, and lung inflammation in 16 patients with cystic fibrosis colonized with *P. aeruginosa*. EPA was well tolerated and resulted in a significant reduction in sputum volume (median change with EPA -10 ml/day, placebo 0; p=0.015), and improvements in Schwachman score (EPA 5%, placebo 0; p=0.034), FEV_1 (EPA 0.25 l, placebo -0.1 l; p = 0.006), and vital capacity (EPA 0.6 l, placebo 0; p=0.011). The authors postulated that in chronic inflammatory disease, in which there is a sustained overproduction of leukotriene (LT)-B4, supplementation with 3 g daily EPA improves the LTB4-induced chemotactic defect by correction of suppressed LTB4 receptors. A simultaneous inhibitory post-receptor effect could explain why neutrophil chemotaxis improved significantly but did not reach normal values in EPA-treated CF patients (Lawrence et al. 1993).

In another study, 17 adult subjects with CF received 324 mg of EPA, 216 mg of docosahexaenoic acid (DHA), 480 mg of linoleic and 258 mg of gamma-linolenic acid (γ-LA) daily for 1 year. At the end of the treatment period, TNF-α levels fell significantly. Lean body mass and spirometry (FEV_1 and forced vital capacity / FVC) improved significantly as well. Annual respiratory exacerbations and days of antibiotic treatment fell significantly. The quality of life also improved, but the difference was not significant (Oliveira et al. 2010).



ω-3 supplementation increases lean body mass, forced vital capacity, and decreases inflammation in adult CF patients (Oliveira et al. 2010)

In a prospective study involving 30 CF patients and 20 control subjects, ω-3 fatty acid supplementation (EPA 1.28 g/day and DHA 0.93 g/day) resulted in a significant decrease of serum immunoglobulin G (IgG) and of α-1 antitrypsin ($p<0.05$) concentrations. Pulmonary function testing showed mild but significant improvement of FEV_1 from 61% ± 19% to 57% ± 19% of predicted values ($p<0.05$). The number of days of antibiotic therapy during the study period was markedly lower compared with the preceding 8-month period (392 vs 721 days; $p<0.05$) (De Vizia et al. 2003).

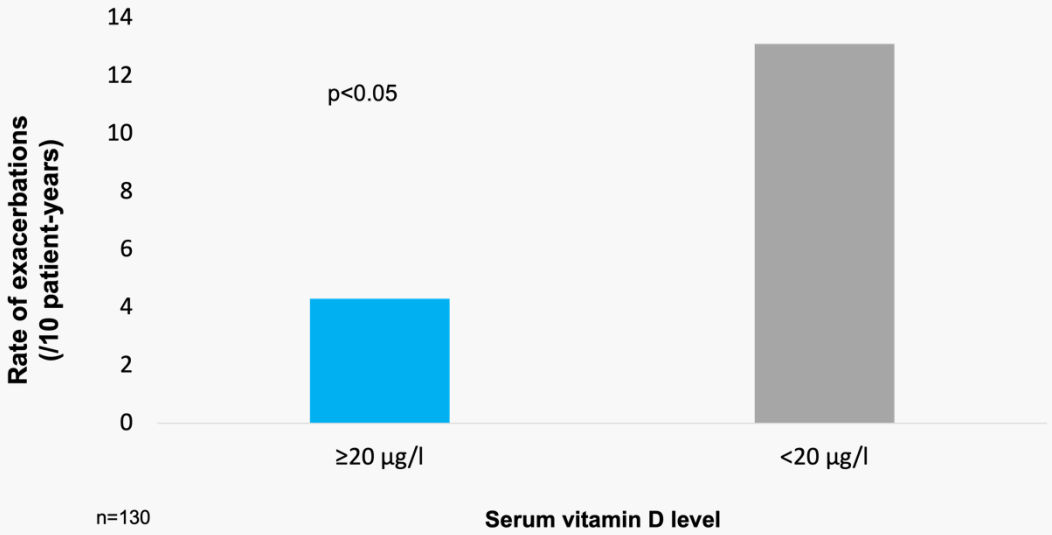


Long-term ω-3 supplementation improves respiratory parameters in adult CF patients (De Vizia et al. 2003)

3.2.5. Antioxidant micronutrients in cystic fibrosis

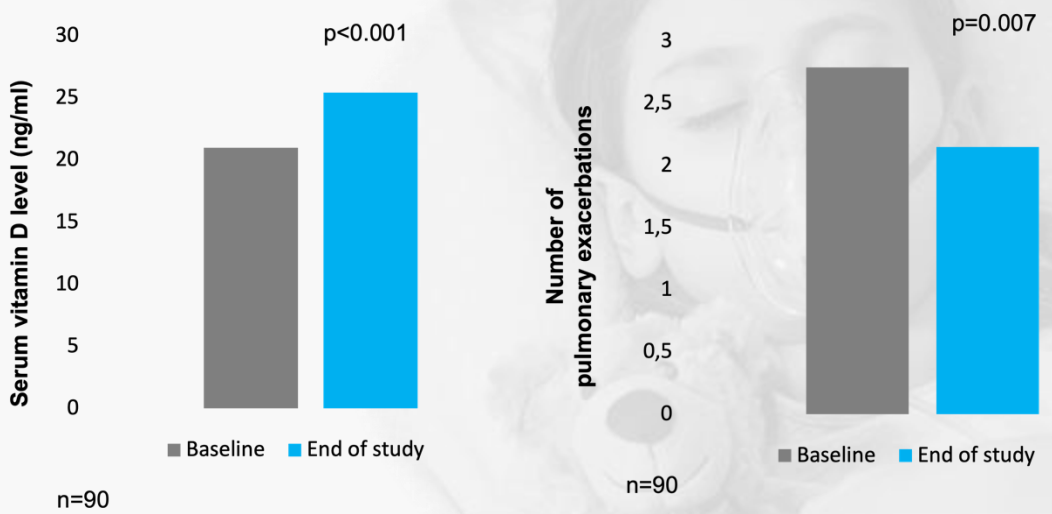
Approximately 85% to 90% of people with CF do not produce enough enzymes in their pancreas and are not able to absorb fat when digesting food. These individuals are also likely to have problems absorbing the fat-soluble vitamins A, D, E, and K. If levels of vitamin E are too low, this may cause nervous system, memory and thinking skills, and blood disorders. Oral and parenteral multivitamin and vitamin E supplements have previously been used to ameliorate vitamin E deficiencies. In CF, this supplementation is usually oral and used in conjunction with pancreatic enzyme replacement therapy. Treatment is usually begun as soon as the serum vitamin E levels are investigated and is often life-long. Even in large doses, treatment has few adverse effects (Okebukola et al. 2017).

It is suggested that vitamin D plays an important role in the prevention of diseases coexisting with CF. The right dosage of vitamin D allows to maintain a better lung function and prevent chronic pulmonary infections. A retrospective longitudinal study of 130 children aged 6 to 18 years between 2000 and 2012 examined 25-OHD levels classed in three vitamin D groups: sufficient (≥30 µg/l), insufficient (20-29 µg/l), and deficient (<20 µg/L). The prevalence of vitamin D deficiency and insufficiency increased slowly through adolescence. The rate of exacerbations for the deficient vitamin D group, aged 15 to 18 years, was 13.1 per 10 patient-years, significantly higher than 4.3 per 10 patient-years for the insufficient and sufficient vitamin D groups ($p<0.05$), which were not significantly different. There were no differences between vitamin D groups in pulmonary function or incidence of first *P. aeruginosa* infection, which was about 2 per 10 patient-years. Higher 25-OHD levels in children with CF were associated with lower rates of pulmonary exacerbations and, in adolescents, higher FEV_1 (McCauley et al. 2014).



Sufficient vitamin D level significantly decreases the rate of exacerbations in children with CF (McCauley et al. 2014)

In a 1-year study of 90 patients from The CF Clinic at Hadassah Mount-Scopus Hospital, vitamin D dosage was increased to the dosage according to the North American Cystic Fibrosis Foundation guidelines. The mean serum concentration of vitamin D increased significantly from 20.97 ng/ml (52.34 nmol/l) at baseline to 25.41 ng/ml (63.42 nmol/l) at the end of follow-up ($p < 0.001$). The number of pulmonary exacerbations decreased significantly from 2.79 ± 3.96 to 2.15 ± 2.91 ($p = 0.007$). The change in vitamin D levels was correlated with a decrease in pulmonary exacerbations (correlation coefficient = -0.318, $p = 0.002$) (Abu-Fraiha et al. 2018).

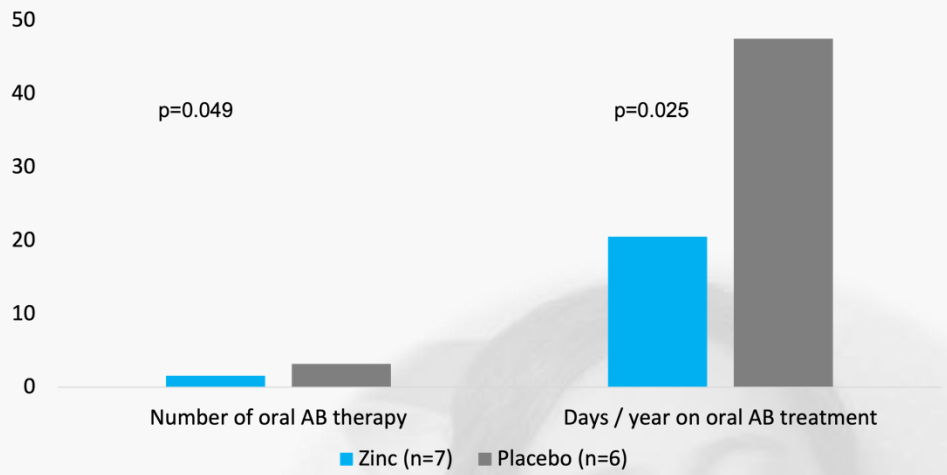


Increase of serum vitamin D level decreases the number of pulmonary exacerbations in CF patients (Abu-Fraiha et al. 2018)

Moreover, results of a pilot trial with the participation of 16 CF patients indicated that vitamin D supplementation may modulate immune activation in CF in a complex manner (Pincikova et al. 2017).

Vitamin C status and possible associations with the disease process in CF patients were also investigated. In a study of patients from 2 different mid-European populations (Swiss n=62; Austrian n=60) taking no or low-dose vitamin C from multivitamin supplements, in patients with vitamin C concentrations <40 µmol/L, all indexes of inflammation were relatively high, whereas those with concentrations >80 µmol/L (upper quartile of control subjects) showed clearly lower values. These results are consistent with the hypothesis that by scavenging oxygen free radicals, vitamin C interacts with an inflammation-amplifying cycle of activation of alveolar macrophages and neutrophils, release of proinflammatory cytokines and oxygen free radicals, and inactivation of antiproteases (Winklhofer-Roob et al. 1997).

In a double blind placebo controlled pilot study, oral intake of 30 mg/day of zinc for 1 year reduced the number of days on oral antibiotics used to treat respiratory tract infections in children (aged 7-18 years) with CF (Abdulhamid et al. 2008).



Zinc supplementation decreases the use of antibiotics used to treat respiratory tract infections in zinc-depleted CF patients (Abdulhamid et al, 2008)

3.3. Summary

Malnutrition and cachexia are developed in a wide range of chronic diseases including CF. Since nutritional status has a significant effect on the outcome of the disease and the quality of life of patients, enteral nutrition with high calorie and protein content is extremely important in the nutritional therapy of these patients. Due to the deleterious effects of a high carbohydrate content in patients with CF, nutritional supplementation with a low carbohydrate and high fat content is more beneficial for these patients than the enteral nutritional supplements with high carbohydrate and lower fat content. Moreover, low-carbohydrate diets lead to greater improvements in blood lipids and systemic inflammation compared to high-carbohydrate diets. Among fats, medium chain triglycerides provide an easy and quick source of energy for patients, who suffer from energy deficiency and disturbed absorption of fats (e.g. CF patients). Long-term ω-3 supplementation has been shown to decrease the number of exacerbations and duration of antibiotic therapy, and inflammation, and to ameliorate respiratory functions in CF patients. Low vitamin C levels have been shown to inversely correlate to the serum levels of inflammatory markers in CF patients. Low vitamin D levels increase the rate of exacerbations, while increasing vitamin D serum level to the values recommended by CF guidelines decreases the rate of exacerbations in children with CF. Moreover, results of a pilot trial indicated that vitamin D supplementation may modulate immune activation in CF in a complex manner. Zinc supplementation has been shown to decrease the use of antibiotics used to treat pulmonary exacerbations in zinc-depleted CF patients. Therefore, clinical nutrition with elevated vitamins C, E, and D, and zinc contents may be beneficial in CF patients.

4. MediDrink CF

4.1. Product description

MediDrink CF is a nutritionally complete, 2.0 kcal/ml, ready-to-consume food for special medical purposes (as per the EU regulation 128/2016) for the dietary management of cystic fibrosis.

MediDrink CF must be used under medical supervision.

MediDrink CF is suitable as a sole source of nourishment or as a supplemental nutrition.

4.2. Target groups

MediDrink CF is indicated for enteral feeding to enhance the energy, protein, and micronutrient intake of CF patients and children above 3 years of age. MediDrink CF is suitable for all patients with a functional gastrointestinal tract who are unable to meet the nutritional requirements with oral nutrition alone.

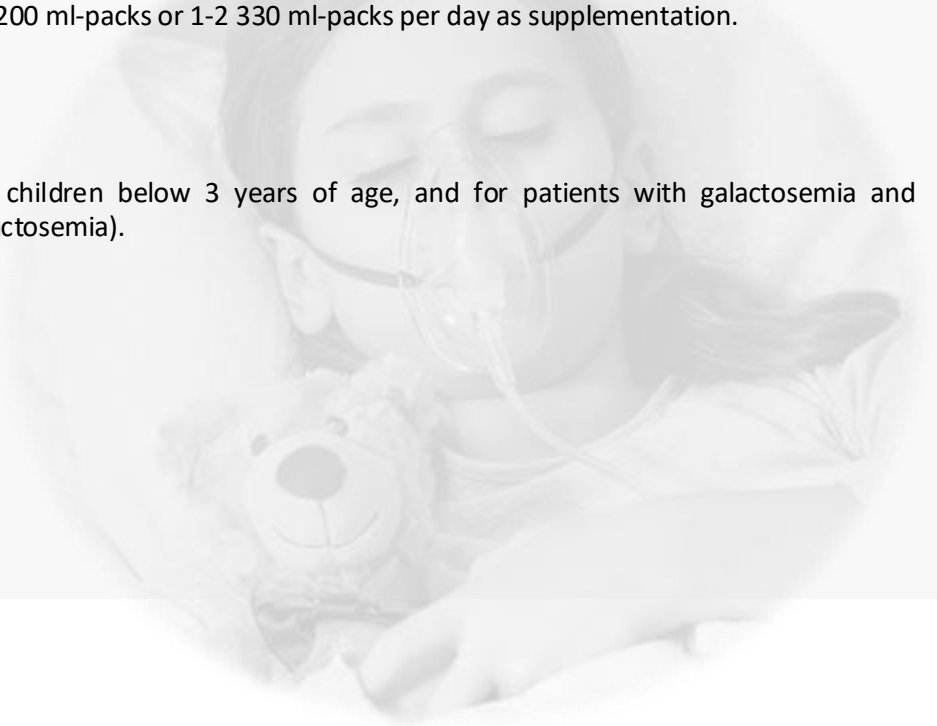
MediDrink CF is lactose-free (contains lactose ≤0.1 g / 100 g), and is gluten-free, therefore, can be administered to patients with lactose- or gluten-intolerance.

4.3. Recommended dosage

The dosage of MediDrink CF administered should be decided by a physician and varies from patient to patient according to individual needs and whether MediDrink CF is used as supplemental nutrition or as the sole source of nourishment. The recommended daily allowance is 5-6 200 ml-packs or 3-4 330 ml-packs per day for adults as a sole source of nutrition or 1-3 200 ml-packs or 1-2 330 ml-packs per day as supplementation.

4.4. Precautions

MediDrink CF is not suitable for children below 3 years of age, and for patients with galactosemia and hereditary fructose intolerance (fructosemia).



5. MediDrink CF in the dietary management of cystic fibrosis

Based on the data in the literature, we can extrapolate that due to its high energy and high protein content, MediDrink CF is able to attenuate the deterioration of the nutritional status, to improve weight, to decrease the rate of complications, and to influence the modulators of the catabolic response in patients with cystic fibrosis. The high energy and protein content of MediDrink CF has a sparing effect on protein utilization in order to favor restoration of lean body mass and can improve these patients' status and consequently their quality of life as well.

Since high intake of carbohydrates increase CO_2 production and may precipitate respiratory failure in patients with severe lung disease, due to its lower carbohydrate and higher fat content, MediDrink CF results in less CO_2, and thus may permit a reduced level of pulmonary strain caused by nutritional intake in patients with compromised respiratory function, such as CF patients.

Due to its medium chain triglycerides content, MediDrink CF provides an easy and quick source of energy for CF patients.

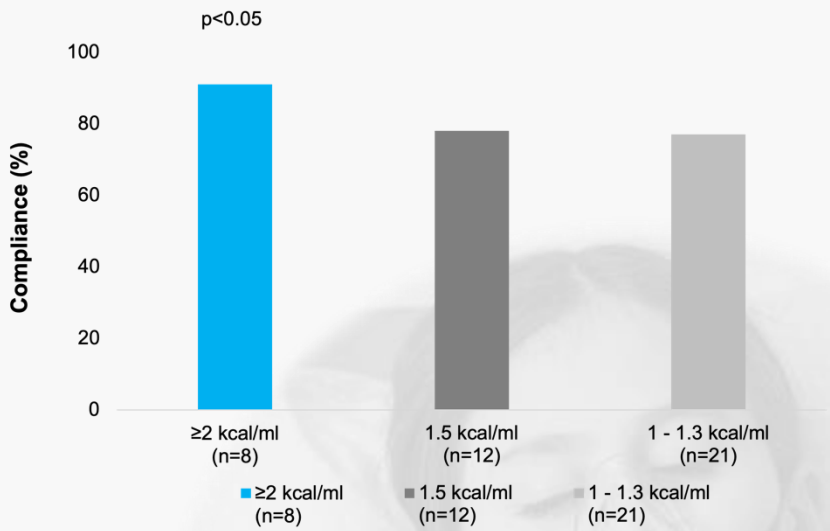
Long-term ω-3 supplementation has been shown to decrease the number of exacerbations and duration of antibiotic therapy, and inflammation, and to ameliorate respiratory functions in CF patients. Thus, we can extrapolate that the high ω-3 fatty acids content of MediDrink CF has a beneficial effect on the outcomes and quality of life of CF patients due to its ability to diminish the chronic inflammatory processes.

The elevated vitamin C, E, and D content of MediDrink CF, together with its zinc content, may help decrease the rate of exacerbations and the duration of antibiotic treatments in CF patients.

6. Safety and tolerability

6.1. Compliance

According to the data from a meta-analysis, the overall compliance to oral nutritional supplementation is good, especially with higher energy-density ONS, resulting in improvements in patients' total energy intakes that have been linked to clinical benefits. A range of ONS-related attributes have been associated with compliance. Recent comparisons suggest significantly greater compliance and energy intakes with the use of small volume, energy dense ONS compared to standard 1.5 kcal/ml ONS. Therefore, in patients who struggle to ingest the prescribed volume of ONS, a change to a higher energy density ONS could increase total energy intake and reduce wastage. This strategy could be employed in the nutritional management of malnourished individuals (Hubbard et al. 2012).

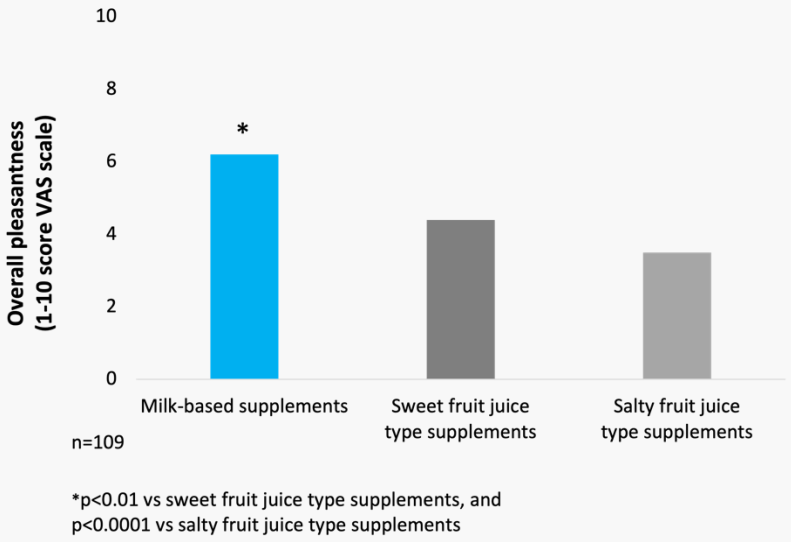


Compliance is greater with higher energy-density ONS (Hubbard et al. 2012)

A randomized controlled interventional trial of 77 elderly nursing home residents with high functional impairment showed that a low-volume, nutrient- and energy-dense ONS was well accepted and resulted in significant improvements of nutritional status and, thus, was effective to support treatment of malnutrition (Stange et al. 2013).

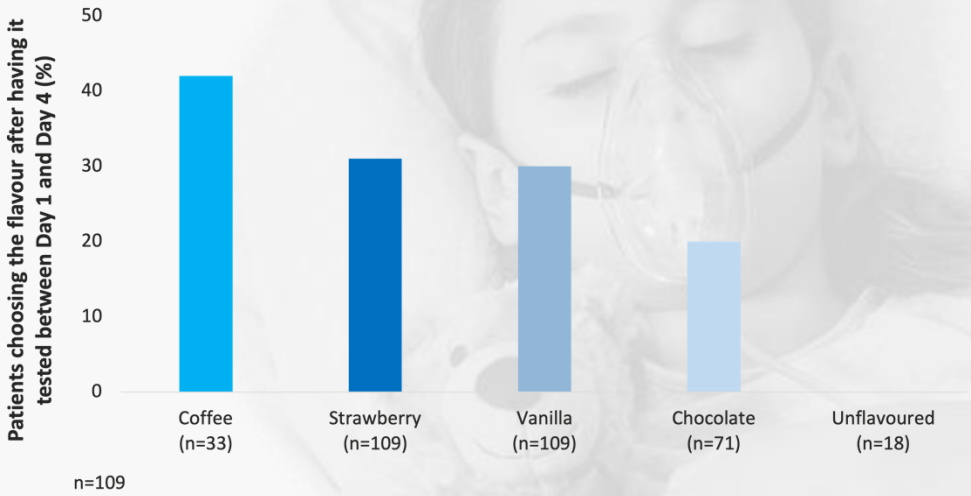
6.2. Taste

The investigation of taste preferences of milk-based and fruit juice-type supplements in malnourished in-patients showed that the overall pleasantness is significantly better for milk-based supplements than for sweet and salty fruit juice-type products (Darmon et al. 2008).



Pleasantness of milk-based ONS is significantly better than that of sweet and salty fruit juice-type products (Darmon et al. 2008)

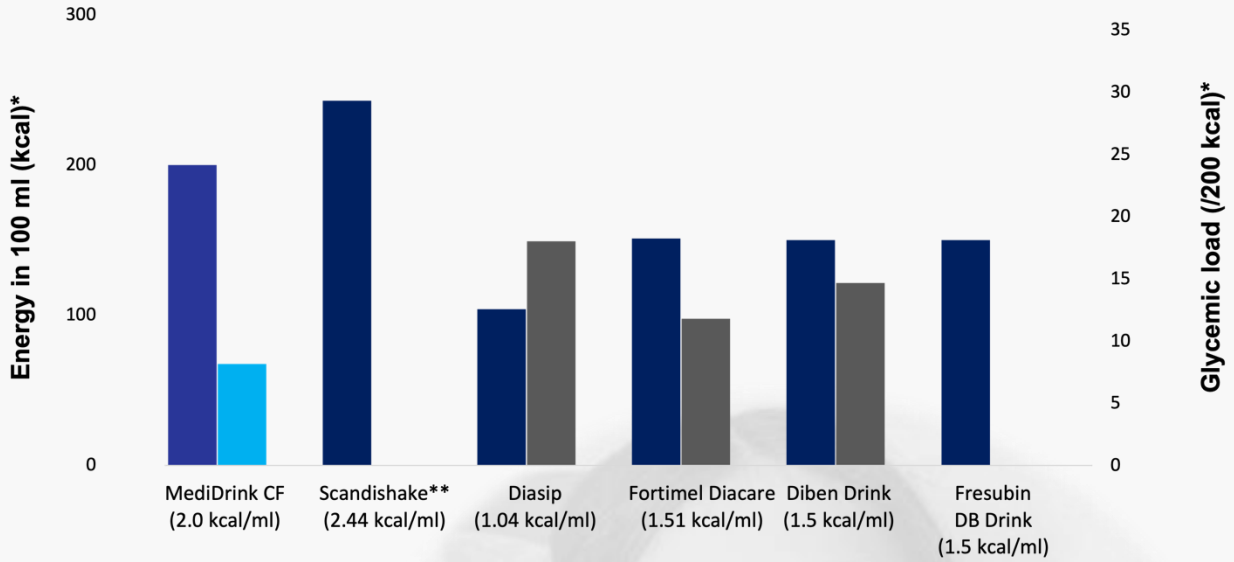
Among milk-based ONS, coffee, strawberry, vanilla, and chocolate are the most preferred flavours (Darmon et al. 2008).



Coffee, strawberry, vanilla, and chocolate are the most preferred flavours among milk-based ONS (Darmon et al. 2008)

6.3. Glycemic load

The concept of glycemic load has been introduced by Walter Willett at the Harvard School of Public Health in 2004. While glycemic index (GI) ranks the different sources of carbohydrates according to their blood sugar-raising capacity, the glycemic load (GL) takes also into account the quantity of food / carbohydrates consumed. GL is calculated by multiplying the GI of the carbohydrates by the quantity of the carbohydrates taken in. Therefore, the GL of a certain food depends not only on the GI but also the quantity consumed (Venn et al. 2007, Fajcsák & Lelovics. 2006). Based on the calculation of GL, MediDrink CF has the lowest glycemic load and therefore the lowest strain on the metabolism of the patients among the different ONS depicted below. Thus, MediDrink CF is suitable also for diabetic patients, since when consuming the same amounts of kilocalories, the GL of MediDrink CF is lower than that of the ONS specifically designed for the diabetic patients.



*Calculation based on publicly available data (missing values indicate the lack of publicly available data)
**Prepared according to the manufacturer instrictions

Energy content and glycemic load of several oral nutritional supplements

(Venn BJ. & Green TJ 2007, Fajcsák & Lelovics 2006, [Complete therapy with clinical nutrition] Nutricia 2016, Medifood data on file 2020, https://www.nutricia.nl/content/dam/sn/local/bnl/sn-hcp/website-assets/voedingstabellen/nl/sip-feed/Voedingstabel_Scandishake_Mix_032021.pdf, https://nutriciamedical.hu/termek/fortimel-diacare/, www.fresenius-kabi.co.uk, www.fresenius-kabi.ie, https://www.fresubin.be/wp-content/uploads/2015/09/DB-drink-technische-fiche.pdf

6.4. Tolerability

So far there are no tolerability study results available for MediDrink CF.

7. Summary

Malnutrition and cachexia are developed in a wide range of chronic diseases including CF. Since nutritional status has a significant effect on the outcome of the disease and the quality of life of patients, enteral nutrition with high calorie and protein content is extremely important in the nutritional therapy of these patients. Due to the deleterious effects of a high carbohydrate content in patients with CF, nutritional supplementation with a low carbohydrate and high fat content is more beneficial for these patients than the enteral nutritional supplements with high carbohydrate and lower fat content.

Cachexia is a metabolic syndrome with underlying chronic inflammatory processes, therefore, any nutritional supplement with high ω-3 fatty acid composition able to decrease the level of this chronic inflammation has an additional favorable effect on the disease in CF patients. Vitamins C, E, and D, and zinc help maintain the function of respiratory airways and decrease the antibiotics use in CF patients.

With its high energy, high protein (mainly casein), low carbohydrate energy, MCT, high ω-3 fatty acid, high vitamins C, E, and D, and zinc content, MediDrink CF is an ideal enteral nutritional supplement for patients suffering from CF.

MediDrink CF, a milk protein-based sip feed available also in the best-rated flavors of chocolate, strawberry, and vanilla, can be supposed to generate an overall good compliance in patients with CF.

Due to its low-volume, nutrient- and energy-dense content, nutrition with MediDrink CF should be well accepted and result in significant improvements of nutritional status and support for treatment of malnutrition.

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