Nutritional management in cystic fibrosis

By Malin Garemo and Birgitta Strandvik

ABSTRACT

Cystic fibrosis (CF) is the most common hereditary fatal disease but the survival rate has improved markedly over the past 30 years. The three main reasons include specialised knowledge by centralisation of medical treatment, improved treatment of the bacterial infections in the lungs and the increased awareness of the importance of nutrition. Different factors, which affect the nutritional status have to be considered when nutritional recommendations in cystic fibrosis are given. These factors are abnormal metabolism, malabsorption and a decreased intake. An ordinary diet with a high mixed fat content including essential fatty acids together with supplement of fat soluble vitamins in water dispersion, are the basic in the nutritional treatment of the disease.

Keywords: Cystic fibrosis, energy expenditure, essential fatty acids, nutritonal management, vitamins

Introduction

Cystic fibrosis (CF) is the most common hereditary fatal disease. It is caused by abnormalities in the cystic fibrosis transmembranous conductance regulator (CFTR), coded at a gene located on chromosome 7. There are currently more than 870 known mutations (1). In Sweden, the most common mutations are $\Delta F508$ and 394delTT (2). CF is a generalised disease, which mainly affects pancreas and the airways. As long as the disease can not be cured, general clinical treatment will be important for the patients' survival as well as quality of life. The improved survival rate over the past 30 years are due to a number of reasons. The three key ones include specialised knowledge by centralisation of medical treatment, improved treatment of the bacterial infections in the lungs and the increased awareness of the importance of nutrition.

In a recent consensus report, it was established that normal growth and nutritional status should be the goals of the nutritional treatment (3). Many recent reports indicate normal growth among patients, but there are also accounts of sub-optimal growth, in particular in newly diagnosed patients, during puberty or periods of severe lung disease (4,5). In spite of the fact that normal growth can be obtained, many patients have a different body composition with a lower than normal fat percentage (6,7). Moreover, it is indisputable that nutrition plays an important role for the lung function, for the patients' survival, self-esteem and quality of life (8,9).

It is of utmost importance that an aggressive nutritional treatment is dispensed in order to stop the vicious circuit of malnutrition and a deteriorating state of the disease. It is well known that malnutrition affects the immunological defence, thereby increasing the impact of the chronic infections. The successful rate of lung transplantation is considerably increased if patients have received adequate nutritional supplements before the transplantation.

A number of factors such as abnormal metabolism, malabsorption, infection and reduced intake will affect the nutritional status.

Factors affecting the nutritional status

Abnormal metabolism

Increased resting energy expenditure: The total as well as resting energy demand is increased in CF, but the causes are not fully understood. Increased respiratory work might explain the increased total energy expenditure, but reasons for the increased resting energy demand is more controversial (10-13). Some evidence has been presented that the energy expenditure is genetically determined and that patients with $\Delta F508$ so far have higher energy needs than those with milder mutations (14). In rats with essential fatty acid deficiency the energy expenditure is increased and this might be one contributing factor also in the CF patients (15). For many patients with a normal growth rate and well-controlled malabsorption, the energy demand equals that of Nordic Nutrition Recommendation (NNR) (16).

Essential fatty acid deficiency (EFAD): Essential fatty acid deficiency is characterised by low levels of linoleic acid (18:2 n-6), increased levels of palmitoleic (16:1 n-7), oleic (18:1 n-9), and eicosatrienoic

(20:3 n-9) acids resulting in a high 20:3 n-9/20:4 n-6 ratio. In severe deficiency low levels of arachidonic (20:4 n-6) and α -linolenic (18:3 n-3) acids may also be seen but in mild deficiency arachidonic acid is usually increased. Although a common finding in many patients (17,18), this abnormality has gained little attention in clinical practice. This is mainly explained by the fact that it has been considered to be secondary to impaired fat absorption related to the pancreatic insufficiency. It is however obvious that it also occurs in patients with normal pancreatic function (19). It is easy to overlook due to the unspecificity of the symptoms, the first one usually being growth retardation, which can have many other causes in CF. It commonly debuts in infancy or prepuberty, and is followed by deterioration in the lung function if not treated. In animals it is usually associated with increased metabolic rate (20), increased water permeability (21) and abnormal glucose homeostasis (22,23). The involvement of these factors in the symptoms of the CF-patient with EFAD is only partially defined. It has been shown to be associated with dermatological symptoms (24), renal dysfunction (25) and liver steatosis (26). Treatment of EFAD has also been shown to improve the lung function in these patients (27). The tendency to develop this deficiency seems to be genetically determined, most pronounced in patients with the $\Delta F508$ and 394delTT mutations, (*unpublished observation*). Since the EFA status decline during pregnancy in healthy women (28) it is even more important to make sure that CF-patients have a good EFA-status before and during pregnancy.

The metabolic factor behind the development of EFAD is not fully understood. An increased release of arachidonic acid has been shown in several studies (29-31) and an abnormal fatty acid turn-

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over has also been reported (32). Linoleic acid, the precursor of arachidonic acid, is an important constituent of all membranes, and a decreased level might contribute to the symptomatology also secondarily by influencing membrane functions, including membrane bound enzymes and transport proteins. The increased release of arachidonic acid also gives an increased synthesis of prostanoids (33,34) and leukotrienes (35), which further might contribute to the varying symptomatology of the CF disease.

Malabsorption

Pancreatic insufficiency: At the age of three, 80-85 percent of patients suffers from exocrine pancreatic insufficiency. This organ involvement has clearly been associated with the genotype (36,37). The impaired function is characterised by reduced secretory capacity of both bicarbonate and pancreatic enzymes, which affect the contents, frequency and amount of faeces. In general, the enzyme secretion must fall below 2% of normal values before clinical manifestations occur (38). With modern enzyme preparations the fat absorption can often be mainly normalised, but when the pancreatic enzyme supplements are sub-optimal, malabsorption can partially remain (39). When pancreatic enzymes have to be used enough information should be given to the patient about the dosage and administration of the enzymes, and this has to be followed up regularly.

Other reasons: There are a number of other potential causes of malabsorption, which have to be considered in patients with persistent malabsorption. Many patients have gastroesophageal reflux and there is scanty data about gastrointestinal motility, by some authors reported to be abnormal (40). The liver disease might also influence digestion by impaired biliary secretion (41), although many patients seem to have adequate bile acid duodenal concentration (42). Diabetes mellitus is a common finding (43) and may contribute to malabsorption. Food intolerance and celiac disease occur in a CF population as well as in a healthy population (44), and inflammatory bowel disease may even be a complication to the CF disease itself (45). Colonic wall thickening has been described also without relation to enzyme therapy (46).

Reduced intake

Gastrointestinal symptoms: A number of gastrointestinal symptoms (GI), some of them already mentioned, may negatively affect the intake (47,48). Gastroesophageal

Table 1. General nutrition recommendation to CF patients with indications for necessary supplementations (E%=energy percentage, NNR=Nordic Nutrition Recommendation, PUFA= Poly Unsaturated Fatty Acids).

	Recommendation from food	Supplementation additional to the food
Energy	Individually based Usually 100-150% of NNR	Try to keep the same composition of the energy as food
Fat ^a	40-50E% 10E% PUFA ^b	PUFA might be necessary as daily oil supplement or intravenous fat emulsions
Protein ^{a,c}	10-15E%	
Carbohydrate	35-50E% Sugar<10E% Fibre – as high as possible	
Vitamins	100% of NNR	A 100% of NNR D 100% of NNR E ≥100 mg K before surgery or when long term antibiotics C 100% of NNR
Minerals	100% of NNR	Multimineral preparation Higher doses of specific minerals might be considered
Pancreatic enzymes ^d		Determined on individual basis 500-4000 lipas units/gram fat and day (3)

a The recommendation is only relevant provided that the energy intake is sufficient

b From experience we know that 10E% is usually an adequate intake to avoid EFAD. However, we do not have a recommendation for the intake

c The intake might increase during long term infection periods

d Only for patients that are pancreatic insufficient

phagal reflux is common although often related to increased breathing, increased mucus and coughing (49,50). It is also clear that it may present as an early symptom before development of lung symptoms and contribute to the latter (51). It has been speculated that high prostaglandin levels may even reduce the oesophageal sphincter pressure. Nausea as a consequence of extensive production of tenacious mucus may also influence food intake negatively in several ways i.e. by the coughing and swallowed mucus filling up the stomach. CF-associated liver disease and biliary complication are common (52-56) and a different bile acid composition might also have an influence on the stomach emptying and intestinal motility (42,57). Constipation might be related to the secretions in the intestine and is sometimes a problem for older children and adults (58). Energy dense foods, often recommended to the patients, are also low in fibres. Distal intestinal obstruction syndrome (DIOS), the equivalent of meconium ileus in the new-born, might occur recurrently at all ages and by obstruction and pain influence the appetite (58,59). Inadequate amounts of enzyme replacement may present with abdominal pain as well.

Psychological factors: Since food is an important part of the treatment especially parents may come under a great deal of pressure (60). The negative behaviour on their part, have been shown to affect children's eating habits, by affecting intake (61). The young patient can also reduce the intake as an objection against recurrent medical treatment, which is more difficult to reject to. Furthermore, the western fashion of extreme slenderness of the teenagers is not beneficial to the health of these patients.

Infections: Loss of appetite is often the first indication of an impending infection, especially in infants and small children. It occurs often as a symptom before the colour and the volume of the sputum is changed or specific lung symptoms can be shown. A loss in weight of 0.5-1.5 kilo is not uncommon during infection, and weight retardation might even be the first indication for treatment of an exacerbation. The weight is usually quickly recuperated as soon as the treatment with antibiotics is started (62,63). Sometimes treatment with antibiotics can result in diarrhoea, which may affect the intake as well. In those cases where the treatment with antibiotics does not result in an

Figure 1. Suggested relations between different causes to the increased/abnormal energy requirements in CF.

improved appetite, fat emulsions have to be considered as an intravenous supplement during the last days of the treatment of the exacerbation.

Recommendations

Table 1 shows recommendations for energy, nutrient and pancreatic enzymes.

Energy

Factors affecting the energy demand of CF patients include the characteristics of the mutation, the functionality of the pancreas, the degree of malabsorption, the infections and the impairment of lung function, the current nutritional status and need of a catch-up growth (Figure 1). The level of physical activity also influences the energy demand. In patients with severely impaired lung function the energy demand

may be remarkably increased to more than twice the NNR. The energy need of CF patients generally accounts to 100-150 percent of the NNR, which also is the current guideline for nutritional treatment (3,64-67). However, instead of applying general guidelines, more modern approaches adapt the energy need to the individual and to the before mentioned factors.

Protein

In many countries, a high intake of protein is recommended (67) and several studies have reported a high protein intake expressed as gram protein per kilo body weight among CF patients (68-70). However, there are few, if any studies on what the actual protein requirement is in this disease. In infants, protein and energy malnutrition has been reported prior to the

diagnosis, but subsequent to catch-up growth no elevated requirement has been recorded. Malabsorption is caused by general exocrine pancreatic deficiency. However, the lack of protein enzymes is better compensated for than the lipase deficiency. It is well known that fever and acute infections increase the protein demand, but this does not imply that the NNR recommendations should be exceeded since these are well above the actual protein requirements for healthy individuals (71), especially if the energy intake is high. A high protein intake unnecessarily increases the workload on the kidneys and the liver. Therefore a protein intake according to NNR is usually enough.

Fat

Fat has a number of functions for the CF patients as well as for healthy people. Fat is the primary source of energy and enables the absorption of fat soluble vitamins. Fat also provides essential fatty acids and modulates pulmonary inflammation by influencing the immune defence.

Most caregivers today agree that the intake of fat should be high for CF patients and recommendations globally vary between 35 and 50 energy percent (65-67). A recent study has identified a correlation between total daily fat intake expressed in grams and the percentage of recommended daily intake (RDI) (72). Moreover, a correlation has been seen between %ideal weight for height and total fat intake (72,73). In the future, we think that the recommendation will be expressed as gram fat or gram PUFA per kilo body weight. The type of fat recommended will vary. Some consider MCT fat as an appropriate product. However, taken into account its lower energy content and the fact that it cannot compensate for the lack of essential fatty acids, it should not be generally recommended.

A high intake of polyunsaturated fat, in particular n-6 fatty acids is recommended to everyone with normal serum fatty acid values or minor deficiencies. Fat emulsions, should be given intravenously to patients with severe or recurrent deficiencies. So far we recommend a fat intake of 40 energy percentage providing that energy requirements are met. Patients with CF-related diabetes should follow the same recommendations. The appropriate level of PUFA intake is not known. However, based on experience, we know that an intake of 10 energy percentage usually is sufficient to avoid deficiencies provided that energy requirements are met. Recently a workshop suggested an adequate intake of different fatty acids for healthy adults (74) and the intake for CF individuals should probably exceed these.

Omega 3 fatty acids, usually supplied as eicosapentaenoic acid, has been demonstrated to be effective in reducing inflammation in rheumatoid arthritis and ulcerative colitis. Only a few studies on a small number of CF patients have been carried out (75,76). Before a general recommendation can be made further studies are necessary.

For patients with poor lung function, fat should be the primary source of energy since the resulting production of CO_2 is lower than in a diet with more carbohydrates.

Carbohydrates

The intake of carbohydrates will constitute 35-45 energy percent of the total intake. Complex carbohydrates are preferred to sugar even if the latter might be necessary. Since 20-40 percent of CF patients have an abnormal oral glucose tolerance (77,78), and the prevalence of diabetes in CF patients has been reported to be 15% (77), recommending glucose as the primary source of energy would be illogical. One study has shown that patients with relatively higher fibre intake suffer from less GI symptoms (79). If possible, an increase of the fibre content of the diet while maintaining the level of fat would be beneficial.

Vitamins

A high intake (200% of NNR) of vitamins are recommended in CF. This recommendation will be met by having a vitamin intake from the food according to NNR, giving the rest as supplements.

The literature offer many reports of clinical vitamin E deficiency (80-83) with severe manifestations like progressive neurological symptoms. Vitamin E is a powerful antioxidant that protects against oxidation of membrane lipids and the oxidative destruction of vitamin A. It is also involved in the prostaglandin synthesis, which indirectly affect the lung function. CF-patients have an increased oxidative capacity (84-85) and therefore vitamin E has to be given in high doses. It is usually further necessary to increase the supplementation of vitamin E parallel with an increased intake of polyunsaturated fatty acids or increased physical activity. Vitamin E can probably not be toxic (86).

Vitamin A deficiency is well known in CF-patients (80-82) and ophthalmological symptoms have been reported (87). Since vitamin A plays an essential role for the optimal maintenance and function of the immunological system and has various effects at the pulmonary level, it has to be monitored regularly. Patients with CF need higher supplementation than healthy individuals and the serum levels and the

Figure 2. The figure illustrates different modalities in which the CF patient can get its energy supply. After considering lung function, physical activity, degree of malabsorption, pancreatic supplementation, gastrointestinal symptoms, essential fatty acid pattern, appetite, the need of catch up, psychological status and possibility of compliance and adherence one modality is chosen.

The time axis will only illustrate that different modalities have to be used for different periods in the same patient. When patients get worse they usually go from left to right.

liver stores might decrease with age if not supplementation is provided in water soluble preparations. Vitamin A and E should be regularly monitored by serum levels, since both are usually low if not adequately supplemented. Occasionally vitamin A intoxication has been shown (88) but despite high supplementation we have not seen any patient presenting symptoms of vitamin A intoxication.

Beta carotene deficiency has been reported in CF (89,90) but has gained little attention generally. Supplementation should only be given with careful monitoring since high levels might have adverse effect (91).

Both normal and decreased levels of vitamin D has been reported (92-94). D vitamin is necessary for the calcium balance but it also has other hormonal effects. It needs to be supplemented especially where sun light exposure is low like in the Nordic countries.

Vitamin K has to be given parenterally or intramuscularly before surgical interventions. It is controversial if orally given supplement is required. However it is still given routinely at many CF centres (95).

Water soluble vitamins are well absorbed and there is no evidence of clinical significant deficiencies in well nourished patients. Malabsorption of vitamin B₁₂ has been shown (96), however deficiency is rare.

The intake of vitamin C should probably be high since it works also as an antioxidant and would contribute to balance the increased oxidative capacity of the patients. The recommendations should be above general as indicated by the few studies done in CF-patients (97).

Minerals

Many reports on trace element status in CF are conflicting but in well controlled patients our experience is that the patients seldom need mineral supplements. On the other hand the routine care usually includes the supplementation of a combination of vitamins and minerals. This might indicate that deficiency states could be hindered by a regular low supplementation of mixed minerals.

Studies have shown both normal and low serum or plasma levels of zinc (98-100). Plasma copper concentration has been shown to be normal or slightly increased and erythrocyte levels and urinary copper excretion has been observed to be increased (98,99). We have not found low levels of zinc in our patients.

Selenium has been reported decreased (98,99). To our experience it is extremely unusual in patients with adequate vitamin E supplementation. In a prospective study five years for we did not find low selenium levels in the CF-patients (*unpublished observation*). Magnesium deficiency has

been reported as an adverse event of aminoglycoside treatment (101), but is to our experience extremely rare.

Recent reports have shown that there is a high prevalence of osteopenia and osteoporosis in the CF population, even though they have normal serum levels of calcium, parathormone, vitamin D and calcitonin (102-104). Whether this is a result of a low calcium and/or D-vitamin intake or absorption or if other causes than the nutritional ones contribute is not clear. So far calcium has not been recommended as a general supplement.

Iron has been thought to be absorbed in excess amounts in CF-individuals since hemosiderosis has been reported in autopsy materials (105). In the nineties some reports have shown a high prevalence of iron deficiency in CF patients (106-107). Since iron stimulates bacteria growth it will not be given as a general supplementation but it has to be controlled and temporarily supplemented when indicated, especially at puberty.

Applying the recommendations

Nutritional guidelines have been published in USA (3), UK (65,66) and in Australia current approaches have been published (64).

The standard diet for CF-patients should consist of normal food with a high fat content, enriched by primarily polyunsaturated fat (18:2 n-6) from safflower oil, corn oil, sunflower oil, walnuts, peanuts, pecan nuts, etc. MCT-fat should only exceptionally be used (Figure 2).

Insufficient weight gains during periods of lung infections in a mild form of the disease can usually be remedied by intensified nutritional advice and the application of fat enrichment, extra meals, desserts etc. In addition, the amount, frequency and composition of faeces should be monitored as well as the pancreatic enzyme supplements. Oral supplements as energy drinks should be used restrictively i.e. only for snacks, since they have been shown to replace normal food intake as opposed to increasing the total energy intake. Adequate treatment of the infections in the lungs will also improve the efficiency of the nutritional treatment by reducing the overall energy requirement and increase the appetite. If the patient still doesn't gain weight sufficiently, EFAD or diseases such as diabetes, celiac disease and food intolerance need to be ruled out.

In cases of more deteriorated lung function and growth retardation, other nutritional approaches should be considered. Enteral nutrition is one of the opportunities (108-109). To ensure compliance, as well as not to unnecessarily affect the quality of life for the CF patient or the

family negatively, these actions have to be planned carefully. Initially, the resistance to receive nutrition by other means than through the mouth is often hard, but following adequate information and trial periods, many patients regret not having embarked on this path earlier. Self-confidence is greatly influenced by the appearance, and a healthy demeanour is important, also when having a severe lung disease. Gastrostomy is commonly recommended in order to avoid the displeasure caused by tubes in combination with phlegm and nausea. Moreover, although it can be used for shorter periods combined with intense pulmonary treatment, enteral nutrition is often a long-term treatment, which further emphasises that supplements should be based on gastrostomy. The objective of the enteral nutrition is to have the patient get as much energy as possible in the shortest time, preferably nightly, as a support to the oral intake at daytime. Hereby, a number of limitations exist including the viscosity, osmolarity and volume of the supplement. An energy dense solution containing 1.5 kcal/ml is usually used, given priority to high fat (not MCT) contents. Whether whole protein or a semi elementary diet is used is indifferent from an absorption perspective (110). Elementar diets give no advantages (111). Optimal fat absorption occurs if the pancreatic enzymes are taken before and during the enteral feeding.

Enteral nutrition can also be a temporary solution where the gastrostomy is eliminated once the target has been achieved and the patient can keep weight without using the gastrostomy during prolonged periods of time.

If proper attention is paid to the nutritional status, parenteral nutrition seldom has to be applied. Long-term total parenteral nutrition should be avoided or at least it should be restricted due to its well-known effect on the liver.

The beneficial nature of fat emulsions containing a high degree of polyunsaturated fatty acids, has been well documented (25-27,112). Since CF patients, who are chronically colonised by *Pseudomonas aeruginosa*, often receive antibiotics intravenously, the venous aders as a port-a-cath or CVK can be used for the fat emulsions as well. Towards the end of a ten-day treatment with antibiotics, patients, if they have or are at risk of developing EFAD, poor appetite or failure to thrive, are commonly treated during six hours with 10 ml/kg body weight of 10% fat emulsion. This treatment is repeated 3-4 nights every second to third week, usually for 3-6 months to achieve stable catch up or maintain normal serum essential fatty acid levels.

Conclusions

Even though the knowledge of nutritional needs in CF has improved during the last decades there are still many challenges in making the treatment better. For the general health of the patients an active and aggressive nutritional treatment from an early stage of life is of great importance. An ordinary diet with a high mixed fat content including essential fatty acids together with supplement of fat soluble vitamins in water dispersion, are the basic nutritional treatment of the disease. The role of the oxidative injury (85), which might also explain the increased risk of malignancy (113) in CF, has to be met by optimizing fat intake and antioxidants (114). It is very important to continue to refine and individualize dietary advice given in CF if the goal of normal growth and nutritional status for every individual is to be realised. The nutritional status has to be given enough consideration because it will not only improve the general status of the patient but also the survival and lung function and-of importance for adherence and coping-also improve the self-esteem of the patient by helping him/her look healthy.

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