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REVIEW

Maintenance of nutritional status in patients with cystic fibrosis: new and emerging therapies

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Daina Kalnins[1]
Michael Wilschanski[2]

[1]Clinical Dietetics, Respiratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada; [2]Pediatric Gastroenterology Unit, Hadassah University Hospitals, Jerusalem, Israel

Abstract: Poor clinical outcomes in cystic fibrosis are often associated with undernutrition. Normal growth and development should be achieved in cystic fibrosis, and nutritional counseling is paramount at all ages. Prevention and early detection of growth failure is the key to successful nutritional intervention. The advance in nutritional management is certainly one factor that has contributed to the improved survival in recent decades. This review outlines the major nutritional parameters in the management of the patient with cystic fibrosis, including recent advances in pancreatic enzyme replacement therapy and fat-soluble vitamin therapy. There are sections on complicated clinical situations which directly affect nutrition, for example, before and after lung transplantation, cystic fibrosis-related diabetes, and bone health.

Keywords: cystic fibrosis, nutrition, fat-soluble vitamins, pancreatic enzymes

Introduction

It is well known that malnutrition and lung disease are interrelated.[1–3] Care for cystic fibrosis involves attention to both nutritional status and lung function in order to promote the most favorable outcomes. A dietitian with experience in the area of cystic fibrosis plays an essential role in the care of patients and should be an integral part of the cystic fibrosis team. Further, it is recognized that a multidisciplinary team approach to cystic fibrosis care with routine visits and follow-up provides the best opportunity for addressing overall health care issues, including nutritional status.[4,5] We present the following areas of nutrition support that help to maintain normal nutritional status and assist in preventing malnutrition in patients with cystic fibrosis.

Nutritional intake

The emphasis on good nutritional status and its association with improved lung function parameters offers parents and patients with cystic fibrosis more motivation to adhere to prescribed nutritional therapies, such as enzymes, vitamins, and a balanced, high energy dietary intake.[6–11] Recommendations by the North American Cystic Fibrosis Foundation Consensus Committee on Nutrition include appropriate evaluation of nutritional status at all ages and a diet that is age-appropriate, with sufficient energy to meet needs for normal growth and weight gain.[4,12] A diet composed of 35%–40% calories from fat is recommended in order to meet the energy demands of those with cystic fibrosis.

A recent consensus on feeding guidelines for infants with cystic fibrosis has been published.[13] Breast milk continues to be recommended as a primary source of nutrition for the first year of life. Breastfeeding has been shown to be protective for the infant

Correspondence: Michael Wilschanski
Pediatric Gastroenterology Unit, Hadassah University Hospitals, Mount Scopus Campus, PO Box 24035, Jerusalem, Israel
Tel +1 972 2584 5039
Fax +1 972 2584 4697
Email michaelwil@hadassah.org.il

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with cystic fibrosis. Breastfed compared with formula-fed infants with cystic fibrosis had improved lung function and a reduced incidence of infections in the first 3 years of life in a recent study from Italy.[14] Breast milk can provide complete nutritional support for infants with cystic fibrosis for the first 4–6 months of age, though supplemental energy may sometimes be required by fortifying a portion of the breast milk feeds with formula, or by fortifying formulas to a more concentrated energy level for those infants on a combination of breast milk and formula, or on formula alone. Regular cow's milk-based infant formulas can be used if breastfeeding is not an option or if supplementation is required, and there is no need for a predigested formula in most instances.[15] Sodium supplementation is often recommended in warmer climates and if infants are reported to have a higher degree of loss in sweat.[12,13] Supplementation of milk or solids with table salt to provide 2–4 mmol/kg per day is recommended; however, due to the potential for errors in the accuracy of salt measurement, liquid mineral mix solutions prepared by hospital pharmacies are often advised. After 4–6 months, breast milk or formula is supplemented with solids, where additional fat may be added for increased energy. For the exclusively breastfed infant, meat may be recommended as the first food due to its increased energy content, and more importantly for its iron and zinc content. Whole milk is recommended after 12 months of age as the milk of choice unless breast milk continues to be offered.

Toddlers and children

In the preschool years, dietary intake and degree of physical activity vary. The addition of calorie-rich food is important at this stage. Children establish self-feeding skills, feeding habits, and food preferences. It is important that mealtimes are positive experiences. As children enter school, there may be conflicts with activities which will limit snacks and adherence to enzymes, so health care providers should provide parents with appropriate strategies to support compliance with enzyme therapy.

As children get older, they have higher nutrient requirements due to accelerated growth, but progression of lung disease may start to compromise nutritional status by increasing daily energy demands, interfering with appetite, and resulting in a decreased overall energy intake.[16] When oral intake alone is not enough to support expected growth or maintain nutritional status, aggressive nutritional support via enteral tube feeding may be required. While enteral tube feeding support in cystic fibrosis has been documented to improve poor nutritional status and decrease the deterioration in pulmonary status, this should not be advised until a thorough evaluation of nutritional failure is completed.[17–19] Behavioral and emotional issues, as well as noncompliance, and comorbid conditions such as gastroesophageal reflux, cystic fibrosis-related diabetes, and distal intestinal obstruction syndrome, must be addressed before this type of support is recommended. Enteral tube feeding support is best presented as a positive approach to help improve quality of life and health outcomes. Enteral tube feeding, usually delivered as overnight feeds with appropriate enzyme therapy, may provide approximately 30%–50% of estimated daily energy requirements. While guidelines defining deteriorating nutritional status may be used to determine when supplemental enteral nutrition is to be commenced, this is a decision which varies from individual to individual. Total parenteral nutrition is rarely used in the non-postsurgical situation because weight gain is not sustained once stopped. However, there are some centers that use intravenous lipids as an adjunct to enteral nutrition while a patient is hospitalized.

Quality assurance initiatives have been undertaken recently by many cystic fibrosis centers and can be successful in improving nutritional parameters in clinic populations.[8,11,20] Awareness by clinic staff about the overall nutritional status of their patient population allows for more focus on nutritional support when clinical indices fall below standards. Sharing these results with patients and their families provides an opportunity for team work and collaboration.

Fat-soluble vitamins

Fat-soluble vitamin supplements are required by pancreatic-insufficient patients with cystic fibrosis due to the ongoing mild to moderate fat malabsorption that occurs despite oral enzyme therapy.[21] While there is general consensus about the recommended need for additional fat-soluble vitamins, the recommended amount of supplementation of vitamin A and vitamin K differs between countries.[4,12] The European guidelines are similar to those of the United States, apart from a higher recommended vitamin A dose (4000–10,000 IU) and a higher starting dose of vitamin E and vitamin K (100 IU and 1 mg, respectively). This discrepancy is due to the lack of controlled studies that help define lower limits of intake that support normal serum levels. Those patients who are pancreatic-sufficient, ie, do not require pancreatic enzyme supplementation for normal growth and have normal serum vitamin blood levels, do not require vitamin supplementation. However, there is some evidence that supplementation of

fat-soluble vitamins in pancreatic-sufficient patients may be associated with a decreased incidence of pulmonary exacerbations possibly due to the antioxidant effect of these compounds.[22] The recommendations for vitamin supplementation in the United States are described in the Consensus Report on Nutrition for CF, and are shown in Table 1.[4] New guidelines from the North American CF Foundation Committee on vitamin D (presented at the annual North American CF Conference in Anaheim, 2011, not yet published) advise higher supplemental amounts of vitamin D than are found in the currently available vitamin supplements for cystic fibrosis in individuals with suboptimal serum 25-hydroxyvitamin D levels. Additional vitamin D supplements are therefore recommended. Yearly monitoring of serum vitamin levels is recommended for vitamin A, vitamin E, and vitamin D. Vitamin K is more difficult to monitor because the test used to assess serum levels, ie, PIVKA, is not routinely available at most hospital laboratories. Obtaining serum PIVKA or at least prothrombin levels is advised for patients with hemoptysis or hematemesis and in patients with liver disease. It is likely that the amount of vitamin K currently available in vitamin supplements marketed for patients with cystic fibrosis is not adequate to correct suboptimal vitamin K status, and more studies are needed in order to establish the minimum requirement.[23–25] Toxicity of fat-soluble vitamins is very rare in cystic fibrosis; there is one exception and this is post lung transplantation (see below).

Evaluating pancreatic function

The use of fecal pancreatic elastase-1 has now become a common diagnostic test for assessing pancreatic status.[26–30] The advantages and limitations of fecal elastase-1 in cystic fibrosis are presented in recent review articles.[31,32] The cutoff levels of fecal elastase for pancreatic insufficiency range between 100 and 200 μg/g stool, with the majority of centers using the upper level of 200 μg/g stool. However, the use of 200 μg/g stool weight may result in patients falsely identified as being pancreatic-insufficient. One center compared elastase values with 72-hour fecal fat in both known pancreatic-insufficient and pancreatic-sufficient patients, and found that an elastase value of 100 μg/g stool had a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal fecal fat finding.[26] Patients with pancreatic sufficiency on the basis of a normal fecal fat balance study were found to have fecal elastase values in the range of 100–200 μg/g stool.[33,34] Borowitz et al[35] compared the monoclonal and polyclonal elastase tests (two enzyme linked-immunosorbent assays, with the polyclonal method having a higher median value than the monoclonal method) in patients with cystic fibrosis and pancreatic insufficiency. Elastase levels were compared with the fecal fat test (coefficient of fat absorption). Whether pancreatic insufficiency was defined as a <93% or 90% coefficient of fat absorption, fecal elastase cutoff levels of <100 μg or <200 μg/g stool for either monoclonal or polyclonal methods were positive predictors of pancreatic function; however, they did not include patients with pancreatic sufficiency in this study population. Overall, these observations question the validity of defining the cutoff for pancreatic insufficiency as a fecal elastase value below 200 μg/g stool. In the majority of cases, the fecal elastase result will define clearly whether a patient is pancreatic-insufficient or pancreatic-sufficient, provided the test is done accurately. In situations where stool is more watery, such as in acute diarrhea, short gut, or stool from an ileostomy, a false negative result may be obtained, and it would be advisable to wait until the diarrhea resolves, or until a sample that is more formed is available. In those patients with more rare genetic variations, where there are no supportive clinical features of pancreatic insufficiency, fecal elastase values are often borderline, so may not provide a definitive answer on pancreatic status. In such cases, elastase can be used to monitor pancreatic status, in conjunction with ongoing evaluation of clinical and nutritional status.[36] It has also been suggested that a range of values may be advised versus one cutoff level to define pancreatic function.[30] In Table 2, the *CFTR* mutations associated with pancreatic

Table 1 Fat soluble vitamin recommendations in cystic fibrosis

	Individual vitamin daily supplementation			
	Vitamin A (IU)	**Vitamin E (IU)**	**Vitamin D (IU)**	**Vitamin K (mg)**
0–12 months	1500	40–50	400	0.3–0.5*
1–3 years	5000	80–150	400–800	0.3–0.5*
4–8 years	5000–10,000	100–200	400–800	0.3–0.5*
>8 years	10,000	200–400	400–800	0.3–0.5*

Note: *Ideal doses of vitamin K are not currently available in products.

Table 2 Genetics and pancreatic insufficiency/pancreatic sufficiency

Usually PI-associated mutations	Usually PS-associated mutations
Main *CFTR* mutations as related to pancreatic status	
F508del	R117H
G542X	R347P**
G551D	3849+10kbC -> T
N1303K	A455E
W1282X	R334W**
R553X	G178R
621+1G -> T	R352Q
1717–1G -> A	R117C
R1162X	3272–26A -> G
I507del	711+3A -> G
394delTT	D110H
G85E*	D565G
R560T	G576A
1078delT	D1152H
3659delC	L206W
1898+1G -> T	V232D
711+1G -> T	D1270N
2183 AA -> G	
3905insT	
S549N	
2184delA	
Y122X	
1898+5G -> T	
3120+1G -> A	
E822X	
2751+2T -> A	
296+1G -> C	
R1070Q-S466X*	
R1158X	
W496X	
2789+5G -> A*	
2184insA	
1811+1.6kbA -> G	
1898+1G -> A	
2143delT	
1811+1.6kbA -> G	
R1066C	
Q890X	
2869insG	
K710X	
1609delCA	

Notes: PS/PI classification is based on an apparent consensus from literature or from unpublished reports. *May also be associated with PS; **may also be associated with PI.
Abbreviations: PI, pancreatic insufficiency; PS, pancreatic sufficiency.

insufficiency and pancreatic sufficiency are presented.[37] This can aid the clinician in predicting pancreatic status.

Oral pancreatic enzyme replacement therapy

One of the most important contributions in maintaining adequate nutritional status in cystic fibrosis is pancreatic enzyme replacement therapy. Interestingly, pancreatic enzyme products were exempt from the Food, Drug, and Cosmetic Act of 1938 and therefore did not require approval of the Food and Drug Administration (FDA). Over the years, a plethora of products were made available to the public without the need for strict preclinical and clinical studies. The FDA mandated that all manufacturers of pancreatic enzyme products in the United States must seek approval of new drug applications by April 2010.

There are now three preparations which are currently approved, ie, Creon®, Zenpep®, and Pancreaze® (no published studies).[38-49] The study of Creon was a double-blind, randomized, placebo-controlled trial of 54 adult patients with chronic pancreatitis or postpancreatic surgery. A fixed dose of 72,000 lipase units with meals and 36,000 with snacks (Creon) were evaluated. The treatment arm showed a difference in coefficient of fat absorption of 19.3% over placebo (85.6 versus 66.3).

Nutrient absorption was similar between Creon and Zenpep at 83%–87% fat absorption. The dosages of these products are based on the lipase units contained in the product. The North American CF Foundation has published guidelines according to the age of the patient and according to the grams of fat ingested per day (Table 3).[44] It is now common for patients to change from one product to another using a 1:1 lipase ratio and then titrating for maximum efficacy.

A major concern has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious, but there is often difficulty in feeding the infant capsules or microspheres, however small they may be. Some centers continue to use the unprotected powder enzymes for infants until 1 year of age, and these enzymes may have some advantage over the enteric-coated versions for this patient population in certain situations. When providing unprotected powder enzymes to an infant, breastfeeding mothers should be instructed on proper infant

Table 3 Pancreatic enzyme replacement therapy: North American CF Foundation consensus statement

Infants (up to 12 months)	2000–4000 U lipase/120 mL formula or breast milk
12 months to 4 years	1000 U lipase/kg/meal initially, then titrate per response
Children >4 years and adults	500 U lipase/kg/meal initially, up to maximum of 2500 U lipase/kg/meal or 10,000 U lipase/kg/day or 4000 U lipase/g fat ingested per day
PLUS: one half the standard meal dose to be given with snacks	

mouth care after enzyme delivery. Using soft cotton swabs or a washcloth dipped in sterile water to wipe the inside of the infant's mouth and inside the gums will be sufficient to prevent nipple irritation in the mother as well as gum erosion in the infant. The efficacy of unprotected powder enzymes (in tablet or powder form) has not been directly compared with the enteric-coated version in infants, but infants treated with this approach do achieve growth and weight gain, confirming their efficacy.[15] For infants with meconium ileus requiring surgery or those with an ileostomy, the powder enzymes may provide the advantage of immediate release in the duodenum and theoretically improve nutrient digestion compared with the pH-sensitive, delayed-release, enteric-coated microsphere enzyme products. Tablets without a protective coating can be crushed if the powder version in capsules or in bottles is not readily available. In addition to their use in infants, unprotected powder enzymes are often used to help digest enteral tube feedings when oral administration of enzymes is not possible, or when jejunostomy feeds are required.

A recent advance has been the production of specially designed enzymes for the small child. A study of Creon for children has recently been published comparing spoon administration containing 5000 lipase units with the standard Creon 10,000 capsule.[45] This was a multicenter, crossover study in cystic fibrosis infants who were randomized to receive Creon for children or the regular enzyme for 2-week periods. The primary endpoint was parental preference. Over three-quarters of the parents preferred Creon for children over the standard preparation.

An enzyme preparation with added bicarbonate has also been available in the past, but at this time has still not yet received approval by the FDA. Theoretically, the addition of bicarbonate to enteric-coated enzyme preparations might raise the proximal intestinal pH and thereby optimize dissolution of the enteric coating and improve enzyme activity. There have been conflicting studies on its efficacy when compared with standard, pH-sensitive microsphere enzymes. One study demonstrated no improvement when compared with a standard enzyme preparation while another study showed improvement in fat absorption with the bicarbonate-containing enzyme.[46,47] However, in both studies, approximately 80% fat absorption was achieved using the bicarbonate-containing enzyme, and Kalnins et al found the same degree of fat absorption with the conventional enteric-coated enzyme product.

There are several other enzyme products in Phase II or III trials. One novel enzyme is liprotamase, which is a nonporcine pancreatic enzyme replacement therapy containing a biotechnologically derived formulation of crystalline lipase, protease, and amylase.[49] There are several advantages of using this type of designer drug enzyme. Other pancreatic enzyme replacement therapies are subject to possible viral contamination, and precise dose standardization is difficult in the porcine product, although the problem of overfill stability has been solved with the new FDA requirements. A preliminary Phase I study demonstrated good clinical activity and a multicenter Phase III study showed that there was significant improvement in the coefficient of fat absorption.[49] A long-term, 12-month, open-label tolerability and clinical activity study in a large number of patients has just been published.[50]

The three pancreatic enzyme replacement therapies currently approved by the FDA have demonstrated efficacy, but new formulations like liprotamase will allow for variety in the type of pancreatic enzyme replacement therapy available.

While enzyme therapy for those with pancreatic insufficiency does allow for normal growth and weight gain in most individuals with cystic fibrosis, they do not completely correct nutrient malabsorption, and this is an important factor for clinicians, cystic fibrosis patients, and families of those with cystic fibrosis to appreciate.[51] There are suggested reasons for incomplete nutrient digestion with currently available enzyme products.

First, a proportion of the unprotected powder enzymes or tablets may become inactivated by prolonged exposure to gastric acid, resulting in decreased duodenal active enzyme recovery. Second, enteric-coated microspheres, which dissolve at a pH >5.5, may only be released in the ileum if the duodenal milieu does not reach this pH, as occurs in cystic fibrosis.[52] Evidence from intubation studies confirms that release of enzymes from enteric-coated microspheres is delayed in cystic fibrosis, and thus they are delivered beyond the duodenum, even as far distal as the ileum.[52] As a result, nutrient digestion occurs in the more distal small intestine, not in the duodenum and proximal jejunum, as in health. Third, malabsorption and not just maldigestion contribute to the insufficient assimilation of nutrients. Studies suggest that fatty acid absorption as well as digestion of triglycerides is impaired in subjects with cystic fibrosis.[53,54] Factors contributing to nutrient malabsorption include incomplete lipid solubilization caused by a depleted bile salt pool and thick intestinal mucus, which may affect the unstirred water layer, reducing absorption of fatty acids into the small intestine epithelium. Clinicians can thus appreciate that achieving $>90\%$ nutrient digestion as evaluated by 72-hour fecal fat studies

is likely not to occur in the majority of patients with cystic fibrosis. A large center reported <80% fat absorption in approximately 30% of treated patients, so a degree of malabsorption is to be expected, and for the reasons mentioned.[51] An individualized approach to treatment is recommended with this understanding in mind. Awareness of these factors on the part of both clinicians and patients will help to guide a rational approach to enzyme therapy in cystic fibrosis.

Challenging nutritional situations

Infants requiring surgery

Infants requiring surgery for meconium ileus equivalent can present a challenge in the immediate period after surgery. There are no studies in cystic fibrosis that look at nutritional interventions for this group of patients, so guidelines for infants with cystic fibrosis can be used and adapted to individual needs. Total parenteral nutrition may be required initially, with subsequent and gradual slow introduction of enteral feeds. Unprotected powder enzymes can be added to breast milk or formula to "predigest" the nutrients in these milks and can be delivered via nasogastric or other enteral tube. In infants with an ileostomy, replacement of electrolytes (sodium) requires attention, and electrolytes in the ileostomy effluent can be measured and replaced (with addition of mineral mix solutions) to the milk of choice.[55] The amount of sodium required may be >2–4 mmol/kg/day depending on electrolyte content and degree of ostomy output.[13]

Bone health

A decrease in bone mineral density in patients with cystic fibrosis may begin at a young age.[56–58] There are many factors that influence bone health, both in healthy individuals and in patients with cystic fibrosis. These include nutritional status, calcium, vitamins D and K, pulmonary infection, exercise, glucocorticoids, and class of *CFTR* mutation.[59] The causes of poor bone mineral density, a reflection of bone health, are thus multifactorial. Efficacy of treatments for improving and maintaining bone health are lacking in cystic fibrosis; however, consensus guidelines have been established and a protocol is presented in Figure 1.[59] Newer guidelines are to be published in the near future. Monitoring of bone mineral density and ensuring factors related to bone health are addressed at routine visits are recommended.

Cystic fibrosis-related diabetes

Cystic fibrosis-related diabetes guidelines are present in the consensus report in 2010, and provide caregivers with an approach to evaluation and treatment.[60] The 2-hour oral glucose tolerance test is recommended yearly for patients 10 years of age and older and for those who demonstrate signs of suspected glucose intolerance. While an HbA_{1c} value >6.5% on its own cannot be used to diagnose cystic fibrosis-related diabetes, this elevated result warrants further investigation. Recent studies indicate that growth and nutritional status is already compromised in those diagnosed with cystic fibrosis-related diabetes in the years preceding the diagnosis when compared with those patients with cystic fibrosis without cystic fibrosis-related diabetes.[61,62] A recent study of a small group of patients with cystic fibrosis by a group in the Czech Republic showed that in patients with early-stage insulinopenia, low-dose insulin therapy improved nutritional status and resulted in a stabilization of lung function.[63] In an Australian study, once-daily insulin given to children and adolescents with early signs of impaired glucose metabolism improved nutritional status.[61] It remains to be determined if a more aggressive approach to treating impaired glucose tolerance before development of overt cystic fibrosis-related diabetes improves health outcomes. Randomized controlled trials are required in order to confirm these recent findings.

Growth hormone and appetite stimulants

The efficacy of growth hormone therapy in cystic fibrosis has been recently reviewed.[64] While growth parameters and pulmonary function do seem to improve in treated patients, the overall benefits to health cannot be determined from the moderate evidence available. One recent multicenter trial in which growth hormone was administered for 12 months to patients with reduced growth and bone age indicated its effectiveness in improving growth and lung volumes.[65] Larger trials are needed in order to establish safety and effectiveness, with appropriate patient selection.

Appetite stimulants are often requested by individuals with cystic fibrosis, or by parents of a child with cystic fibrosis, in anticipation of an enhanced appetite and increased energy intake to promote weight gain.[66] While megesterol acetate is one of the most studied appetite stimulants in cystic fibrosis, results are not conclusive on use of appetite stimulants in patients with cystic fibrosis at this time, and larger controlled studies are needed.

Pregnancy

Guidelines for the management of pregnancy in cystic fibrosis were recently presented.[67] In general, pregnancy in cystic fibrosis does not adversely affect the mother or child. However, women with greater lung severity, or more poorly

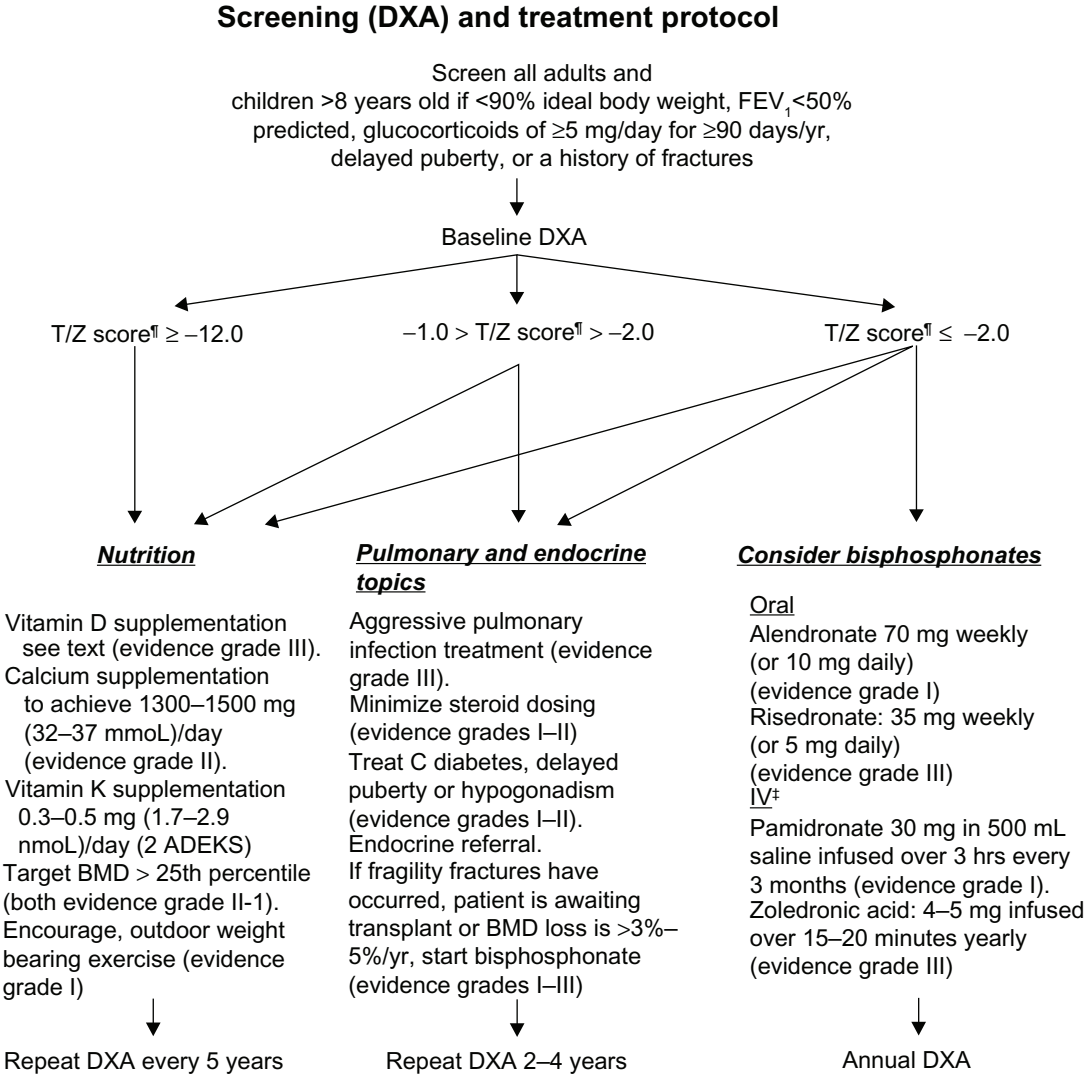

Figure 1 Improving bone health in cystic fibrosis.

Notes: Patients that have had a previous fragility fracture, a documented significant reduction in BMD (defined as >3% in the lumbar spine or >5%–6% in the proximal femur), or awaiting solid organ transplantation in which a significant reduction in BMD has been documented, should undergo a treatment plan equivalent to a T/Z score less than or equal to –2.0. ¶Use Z scores for children <18. T and Z scores are nearly equivalent over the ages 18–30. Use T scores for ages 30 and higher. Some experts and guidelines (WHO) would not initiate bisphosphonate treatment without additional risk factors until the T score is less than or equal to –2.5. ‡IV bisphosphonates have been associated with severe bone pain and should be used with caution. Evidence grades: I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence obtained from well-designed controlled trials without randomization. II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. "T/Z" indicates the scan results.

Abbreviations: ADEKS, vitamins A, D, E, and K; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FEV_1, forced expiratory volume in 1 second.

controlled disease, can have a poorer prognosis. The largest study was done in 2003, using the US database.[68] This study looked at 680 women with cystic fibrosis and found that median 10-year survival was 80% (after successful pregnancy). Pregnant women had a survival advantage (when compared with 3327 nonpregnant controls). Survival seemed to be better, or at least not worse, in those who became pregnant, with the exception of women <18 years of age. The guidelines state that the multidisciplinary cystic fibrosis team has an important role to play in supporting women with cystic fibrosis before, during, and after pregnancy.

Lung transplant

The patient with cystic fibrosis may present with added nutritional challenges before and after lung transplantation. Before transplant, energy intake is often affected and may be suboptimal, requiring enteral tube feeding support for increased nutritional support.[69] Reduced bone mineral density is a concern both before and after lung transplantation.[70,71] After transplant, appetite usually improves, and patients are often able to take in enough energy through the oral route alone, with less and eventually no dependence on enteral tube feeding support if in place. However, it is advisable to leave the enteral tube in

place for a period of about 6 months following transplant in the event that oral intake becomes insufficient to meet energy needs. Attention to electrolytes, such as magnesium and potassium, is required as a result of the medications used after transplant.[72] Further, the majority of patients become insulin-dependent due to the combination of steroid use and immune suppression, which increases insulin resistance and decreases insulin production, respectively.[73] Routine blood monitoring of levels of fat-soluble vitamins is suggested. Hypervitaminosis A has been reported following transplantation.[74,75] Although the etiology of this novel finding is unclear, possibilities include altered absorption, drug interactions, impaired retinol metabolism, or increased hepatic synthesis of retinol binding protein. Usual vitamin supplements may need to be altered due to the elevated vitamin A levels observed in patients with and without cystic fibrosis. Patients who respond well after transplant may require counseling on lower energy food options due to the increased appetite that many patients experience as a result of the effects of corticosteroids, and the associated decreased rate of growth in children. An exercise and rehabilitation plan that will benefit lung performance as well as nutritional status is recommended.[76]

Abdominal pain

Abdominal pain is a very common symptom in cystic fibrosis and may affect nutritional status as the patient fails to reach the required intake. Pancreatic insufficiency per se does not cause abdominal pain. While inadequate enzyme intake may indeed be a cause of abdominal discomfort due to increased intestinal gas produced via fermentation by gut flora of undigested nutrients, this is not the only cause of abdominal pain in patients with cystic fibrosis. However, it is often the common, but incorrect, practice by many health care providers to increase the dose of enzymes when a patient complains of abdominal pain. The most common causes of abdominal pain in cystic fibrosis are constipation and distal intestinal obstruction syndrome. Pancreatitis may also be a cause of abdominal pain, especially in pancreatic-sufficient patients.

The incidence of distal intestinal obstruction syndrome with complete intestinal obstruction was recently studied in children, and found to be between five and twelve episodes per 1000 patients per year throughout Europe.[77] Rates for incomplete obstruction, ie, impending distal intestinal obstruction syndrome, are likely to be higher; distal intestinal obstruction syndrome is seen more frequently in adult populations (35.5/1000 patient-years). The ESPGHAN working group established a consensus on definitions of distal intestinal obstruction syndrome and constipation, with a strict distinction between these two entities, which should simplify future studies on these manifestations of cystic fibrosis.[78]

Distal intestinal obstruction syndrome was described as an acute complete or incomplete obstruction, while constipation was described as a gradual fecal impaction in the total colon. Complete distal intestinal obstruction syndrome was defined as the combination of complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography with a fecal mass in the ileocecum and abdominal pain and/or distension. Incomplete distal intestinal obstruction syndrome was defined as the combination of history (usually days) of abdominal pain and/or distension and a fecal mass in the ileocecum, but without signs of complete obstruction.

Patients are at risk of recurrence of distal intestinal obstruction syndrome, especially those who had meconium ileus at birth. Therefore, the goal should be prevention through maintenance therapy. Several factors have been identified as predisposing to distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome is mainly seen in patients with a severe genotype, although it can be encountered in patients with a mild genotype. Indeed, the majority of patients with distal intestinal obstruction syndrome are pancreatic-insufficient, with less than 10% of distal intestinal obstruction syndrome patients being pancreatic-sufficient.

A previous history of meconium ileus is also a strong risk factor. Almost half of the distal intestinal obstruction syndrome patients in a large European study had presented with meconium ileus at birth, as opposed to a frequency of 15% in the general cystic fibrosis population. Given that both conditions probably share a similar pathophysiology, such as slow intestinal transit and impaired intestinal secretion, this association seems logical.

A previous distal intestinal obstruction syndrome episode will enhance the risk of subsequent episodes. The chance of having a further episode was found to be more than 10 times higher in patients who had experienced a previous episode of distal intestinal obstruction.

Patients with incomplete distal intestinal obstruction syndrome usually respond to oral rehydration combined with an osmotic laxative containing polyethylene glycol (PEG). Alternatively, sodium meglumine diatrizoate (Gastrografin®) can be administered orally or by nasogastric tube. Complete distal intestinal obstruction syndrome should be treated by nasogastric PEG, but if vomiting persists, hospitalization and

intravenous rehydration is required, and Gastrografin may be administered by enema. Prophylactic therapies to avoid further attacks include PEG, mineral oil, and lactulose.

Conclusion

The overall goal in cystic fibrosis is that every patient should achieve normal growth. This requires regular surveillance, including age-specific individualized expert advice, particularly in difficult clinical situations. Nutritional support, including a dedicated dietician as part of the cystic fibrosis team, is an integral part of the care of patients with cystic fibrosis, and adequate monitoring impacts favorably on disease progression. New high calorie formulas with anti-inflammatory properties would be welcomed.

Disclosure

The authors report no conflicts of interest in this work.

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