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NUTRITIONAL MANAGEMENT OF CYSTIC FIBROSIS

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GENERAL FEATURES OF CYSTIC FIBROSIS

Cystic fibrosis (CF) is an inherited disorder that affects children and young adults. It is inherited as an autosomal recessive trait; heterozygotes with one normal CF allele and one mutant allele are entirely asymptomatic and are considered to be carriers. A child born to two carriers has a one in four chance of being affected with CF by acquiring a mutation from each parent (7). Disease frequency varies considerably among ethnic groups; it is highest among people of northern European origin, where approximately one in 2,500 newborns is affected. It is hardly ever seen in people of mongoloid or negroid origin.

The predominant clinical feature of CF is respiratory tract involvement, where obstruction of airways by sticky mucus gives rise to infection, especially with *pseudomonas* species. Most patients experience gastrointestinal difficulties; 85% show pancreatic insufficiency due to obstruction in small pancreatic ducts, which in turn gives rise to pancreatic fibrosis and atrophy (27). In the newborn period, over 10% of affected patients present with bowel obstruction due to meconium ileus (37). Up to 5% of patients develop overt liver disease, frequently in adolescence or adulthood. Infertility in males is virtually universal (59). Undernutrition is a significant cause of morbidity in affected children, adolescents, and young adults (32, 39, 57, 67). This review addresses the pathogenesis of the various factors that contribute to an energy deficit and describes approaches to nutritional evaluation and therapy.

In 1989, following concerted efforts of a number of investigators throughout the world, the CF gene was identified by Lap-Chee Tsui and Jack Riordan of the University of Toronto in collaboration with Francis Collins of the University of Michigan (36, 53, 55). The CF gene comprises 27 exons spanning 230 kb of DNA. The gene product, named the cystic fibrosis transmembrane conductance regulator (CFTR), is a protein of 1,480 amino acids. The predominant mutation, which accounts for approximately 70% of all the CFTR genes worldwide, is a three base pair deletion in exon 10 of the candidate gene, which results in the loss of a single amino acid, phenylalanine, at codon 508 (Δ508). The remaining 30% appear to be rather heterogeneous. More than 170 mutations have already been described; some of them appear to be relatively infrequent, others are clearly private mutations.

It is not surprising to note that expression of the CF gene is largely restricted to epithelial cells (70). The highest mRNA levels have been found in the pancreas, salivary glands, sweat glands, intestine, and the reproductive tract, but in all affected tissue mRNA is transcribed at relatively low levels. Studies of CFTR expression in the human lung have indicated very low expression in the respiratory epithelium and higher expression within submucosal glands.

The predicted amino acids sequence of CFTR showed striking homology

to a family of proteins involved in active transport of cell membranes (44). This super family has several features in common, notably the presence of transmembrane domains and nucleotide-binding folds. CFTR also contains a unique domain that has been called the R (regulatory) domain. The function of CFTR has been the subject of intense scientific investigation. Data from electrophysiological studies and DNA transfection studies, together with reconstituting experiments in which purified CFTR is reinserted into lipid bilayers, now provide fairly conclusive evidence that CFTR itself can function as a cAMP-regulated chloride channel. The CFTR protein may carry out other important functions as well (3, 70). For example, intracellular organelles may be defectively acidified in patients with CF; this abnormality may in turn affect vital intracellular functions, including intracellular processing of proteins.

In 1989 Dr. Tsui initiated the coordination of an international effort, the Genetic Analysis Consortium. Pooling the research efforts of geneticists around the world provided an opportunity to identify further gene mutations and to determine the population frequencies of each possible CF gene mutation. The prevalence of Δ508 appears to vary considerably in different patient populations, the highest percentage occurring in northeast Europe and the lowest in southern Mediterranean countries and in the Middle East (18). For example, the predominant mutation Δ508 accounts for about 85% of the mutations in Denmark but for only 30% in Israel. Worldwide, the combination of all mutations discovered to date accounts for about 84% of all the CF chromosomes analyzed. Other mutations may be found with a high frequency in specific populations; for example, in Ashkenazic Jews, the mutation W1282X has a prevalence of 60%.

As information about the variety of CF mutations has accumulated, we have gained considerable insight into the genotype-phenotype relationships. From the clinical and nutritional point of view, mutations can be grouped into those that cause pancreatic insufficiency (PI) and those that cause pancreatic sufficiency (PS) (27). The term pancreatic sufficiency is an operational one, describing patients who almost always have pancreatic disease but retain sufficient pancreatic function to permit normal digestion and absorption of nutrients. Pancreatic-sufficient patients, who constitute approximately 15% of the population, have much milder disease expression. It is characterized by diagnosis at a later age (presumably due to milder symptoms), more slowly progressive lung disease, better growth, and a far superior survival rate than found in patients with pancreatic insufficiency. We have proposed that mutations in the CFTR gene can be divided into two classes, severe and mild, according to the status of pancreatic function (38). Our data show that patients with two severe mutations will develop pancreatic insufficiency, while those with one or two mild alleles have pancreatic sufficiency. Exceptions to this rule are few. It is interesting that when mild mutations are examined at the

molecular level, they all appear to be missense, single amino acid substitutions, whereas severe mutations are generally manifest as more severe defects at the gene level (40). To date, all other mutations classed as single amino acid deletions, stop/splice junction and frame shift mutations have been severe with regard to pancreatic function status.

OVERVIEW OF NUTRITIONAL PROBLEMS IN CYSTIC FIBROSIS

Chronic undernutrition with significant weight retardation and linear growth failure has long been recognized as a general problem among most CF patient populations. Some researchers thought that it was an inherent consequence of the disease, while others argued that it resulted from physiologic adaptation to advanced pulmonary disease. Some early studies of CF patients, however, showed a good correlation between the degree of malnutrition and the severity of pulmonary disease, which in turn adversely affected the survival rate (39, 67). It has been suggested that these two factors are causally associated, but it is not clear whether prevention of malnutrition and growth failure would slow the progression of lung disease and improve survival. The past decade has seen renewed interest in evaluating the multiple interdependent variables that give rise to chronic malnutrition and growth failure. In most CF centers around the world, nutritional support is now viewed as an integral part of the multidisciplinary care of patients with cystic fibrosis, and aggressive programs have been instituted to prevent malnutrition.

Growth retardation in CF patients is now viewed as the result of an unfavorable energy balance rather than as a factor inherent in the disease. Over ten years ago, in contrast to results of studies elsewhere, reports from Toronto indicated that most patients attending the CF clinic at The Hospital for Sick Children closely conformed to the normal distribution of growth in the general population (15, 32, 57). Cross-sectional data from the Toronto clinic showed a normal distribution of height percentiles in males and females (15). In females, however, particularly after adolescence, weight distribution was skewed toward the lower centiles, but weight retardation was far less evident than in reports from other centers. In a comparative study of two CF clinic populations of similar size and age distribution (Toronto and Boston), Corey et al (16) found a marked difference in median age of survival: 21 years in Boston versus 30 in Toronto (Table 1). Furthermore, after 10 years of age there was a dramatic separation in survival curves between the two centers. Pulmonary function was no different in the two clinic populations. Males and females attending the Toronto clinic, however, were taller than those in the Boston clinic, and males in Toronto were heavier. With the exception of nutritional management of their patients, the general approach to patient care,

Table 1 Characteristics of CF clinic populations in Boston and Toronto (1982)[a]

	Boston	Toronto
Number of patients	499	534
male/female (%)	57/43	58/42
Age: Mean ± SD (years)	15.9 ± 9.6	15.2 ± 8.3
Range (years)	0–45	0–43
Median survival (50%) in years	21	30

[a] Adapted from Corey et al (16).

particularly pulmonary care, was similar in the two clinics. It was suggested that the higher survival rate in the Toronto CF population could be attributed to superior nutritional status.

An examination of dietary practices in the two clinics revealed a striking difference in philosophy. The approach in Boston (63), which closely resembled that in most centers, was to prescribe a low-fat, carbohydrate-rich diet. It was reasoned that reduction in dietary fat would improve bowel symptoms and reduce stool bulk. Recognizing the problem of maldigestion and poor absorption of long-chain triglycerides, many centers advocated use of artificial diets with protein hydrolysates and substitution of long-chain fat with medium-chain triglycerides (MCT) (1). However, other reports showed no long-term benefits to growth when protein hydrolysates and MCT were used as supplements or substitutes (30). The effect was to provide CF patients with a restrictive, unpalatable diet and to exclude them from the many energy-rich foods that comprise some of the more tasty choices in a "normal" Western diet. Fortunately, these supplements are now rarely advocated for reasons of cost, poor compliance, and unpalatability. Chronic malnutrition from reduced energy intake appears to have been an unfortunate yet deliberate iatrogenic effect in most CF programs throughout the world.

Since the early 1970s, the Toronto group advocated a calorically enriched diet by encouraging rather than restricting dietary fat and recommending additional enzyme supplements to enhance digestion (17, 49). Because fat is the most energy-rich, economical, and appetizing energy source, patients were encouraged to eat larger portions than their peers, to add fat in the form of butter or untrimmed meat, and to eat high-calorie snacks between meals and before bed. Fat malabsorption occurred, but with additional pancreatic enzyme supplements, net absorbed energy improved and better growth resulted. In recent years it is gratifying to see that most CF caregivers have adopted a similar philosophy for the nutritional care of their patients. Coincidentally, it is generally accepted that the primary objective of nutritional management is to achieve normal nutrition and growth for children of all ages. This view is

reflected in the following statement from a Consensus Conference, organized by the United States Cystic Fibrosis Foundation, on Nutritional Assessment and Management in Cystic Fibrosis: "There is no reason to accept nutritional failure and/or impaired growth in any individual with CF" (51).

PATHOGENESIS OF ENERGY IMBALANCE

A variety of complex, related, and unrelated factors may give rise to energy imbalance in patients with cystic fibrosis. The net effect on growth potential varies considerably from patient to patient, according to marked differences in disease expression and with disease progression. In simple terms, an energy deficit results from an imbalance between energy needs and intake (Table 2) and is determined by three factors: energy losses, energy expenditure, and energy intake.

Energy Losses

Fecal nutrient losses from maldigestion/malabsorption are known to contribute to energy imbalance. Only 1 to 2% of residual pancreatic capacity for secreting digestive enzymes is required to prevent maldigestion (29), and yet in the majority of CF patients (approximately 85%) evidence of pancreatic failure is present at diagnosis. In those who exhibit maldigestion, very good correlations exist between residual pancreatic function (colipase secretion) and the severity of fat malabsorption (Figure 1). Patients with documented steatorrhea, therefore, have variable but very limited residual pancreatic function. This observation partially explains why some patients with pancreatic insufficiency digest nutrients better than others when given pancreatic enzyme supplements with meals. Despite improvements in the enzymatic potency and intestinal delivery of ingested pancreatic enzyme supplements,

Table 2 Energy imbalance in cystic fibrosis

Increased needs	Reduced intake
Increased intestinal losses	Reduced intake
Pancreatic insufficiency	Iatrogenic fat restriction
Bile salt metabolism	Anorexia
Hepatobiliary disease	Feeding disorders
Regurgitation from reflux	Depression
	Esophagitis
Increased urinary losses	
Diabetes mellitus	
Increased energy expenditure	
Pulmonary disease	
Primary defect?	

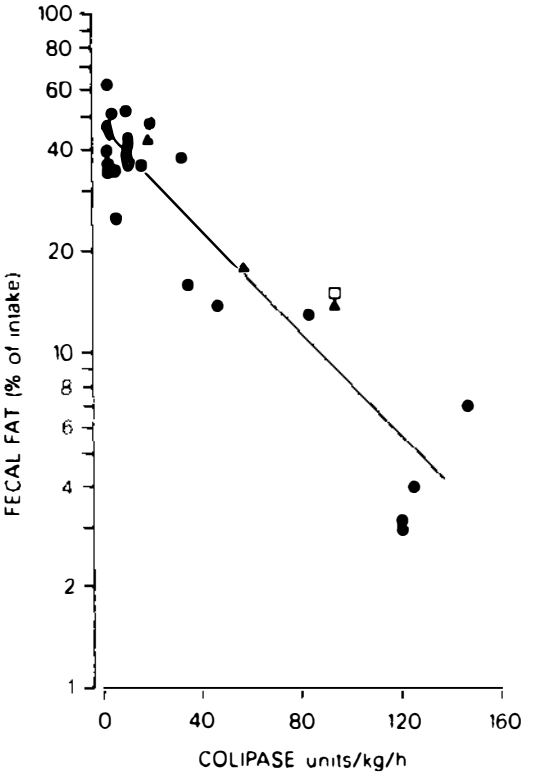

Figure 1 Comparison of fecal fat excretion (percent of fat intake) with pancreatic colipase secretion in 28 patients with steatorrhea due to pancreatic insufficiency. *Closed circles*: patients with cystic fibrosis. *Closed triangles*: patients with Shwachman syndrome. *Open square*: patient with congenital pancreatic hypoplasia. $r = -0.92$, p 0.001. From Gaskin et al (29).

many patients continue to have severe steatorrhea and azotorrhea, even when they receive adequate amounts of enzyme supplements.

In the absence of adequate pancreatic bicarbonate secretion (28), gastric acid entering the duodenum may lower intestinal pH until well into the jejunum. The acid-resistant coating of the newer enzyme preparations may not dissolve in the proximal intestine. Pancreatic lipase is readily denatured below pH 2, and even if not denatured, enzymatic activity is considerably reduced at a low pH. Bile acids are readily precipitated in an acid milieu (77), and duodenal bile acid concentration may fall below the critical micellar concentration, thereby exacerbating fat maldigestion. Precipitated bile salts also appear to be lost from the enterohepatic circulation in greater quantities, thus reducing the total bile salt pool and altering the glycocholate:taurocholate

ratio. Bile salt losses are exacerbated by the binding of salts to unabsorbed protein or neutral lipid. Oral taurine supplements have been reported to benefit some patients (5). Viscid, thick intestinal mucus, with altered physical properties, may have a deleterious effect on the thickness of the intestinal unstirred layer, further limiting nutrient absorption.

Two other factors, more prevalent in adolescents and adult patients with CF, may contribute to energy losses. Diabetes mellitus, if not adequately controlled, may increase caloric losses due to glycosuria. Advanced liver disease with multifocal biliary cirrhosis may result in inadequate bile salt secretion, which in turn results in severe fat malabsorption.

Energy Intake

Actual energy intakes in healthy patients with cystic fibrosis have been poorly documented. Nevertheless, it has been widely accepted that energy intake should exceed normal requirements, and crude estimates have suggested that patients may require 120–150% of the Recommended Daily Allowance (RDA) for age and sex (57). When we accurately evaluated nutrient intakes of a group of healthy adolescents, we were surprised to learn that energy intakes were close to the normal range for age, body weight, and sex (4). Patients with normal growth percentiles for height and weight did show higher energy intakes than those with growth retardation. Other CF centers, which have developed more liberal attitudes to dietary fat intake, have noted a corresponding improvement in energy intake and growth (19, 46). However, in most reports nutrient intakes were found to be close to the normal range.

Patients with cystic fibrosis are especially prone to complications that might limit oral intake. Esophagitis induced by acid reflux is quite common in patients with advanced pulmonary disease and is frequently associated with pain, anorexia, and vomiting following bouts of coughing (24, 58). The distal intestinal obstruction syndrome (meconium ileus equivalent), an unusual form of subacute obstruction within the distal ileum and proximal colon (56), is seen in some adolescents and adults with pancreatic failure; it frequently causes recurrent, crampy abdominal pain that is often aggravated by eating. Other abdominal symptoms, including extrahepatic biliary obstruction, cholangitis, advanced liver disease, and severe constipation, are less likely to be associated with a prolonged reduction in dietary intake.

Respiratory problems usually cause restricted oral intake due to anorexia, resulting in acute weight loss. With improvement in respiratory symptoms, patients with mild pulmonary disease usually show rapid catch-up in weight. However, in the terminal stages of pulmonary disease, chronic anorexia is a consistent feature. Further, patients with a severe chronic disease are prone to bouts of clinical depression, which in the adolescent or adult may lead to severe anorexia.

Over the past few years we have seen a number of younger children (infancy to 8 years of age) with behavioral feeding difficulties; their absorption and energy expenditure are within the normal range. Their treatment has proven difficult. In some, behavior management with oral supplements has been successful, but in others we have had to resort to the use of supplemental feeding with gastrostomy tubes to achieve satisfactory nutritional results. This nutrition support modality has reduced parental anxiety and facilitated the implementation of behavior modification feeding programs.

Energy Expenditure and Metabolism

In recent years, a number of studies have focused on examining the rates of energy expenditure in patients with cystic fibrosis. In 1984, Pencharz et al (48) evaluated the relationship between heart rate and energy expenditure, using an exercise cycle with graded workloads. Simultaneous measurements of oxygen consumption and carbon dioxide production were taken using a closed-circuit indirect calorimeter and heart-rate telemetry. The subjects were malnourished and had moderate to advanced pulmonary disease. The patients were receiving nutritional rehabilitation by continuous nasogastric tube feeding with a semielemental diet. Absorbed energy intake was calculated by subtracting stool energy content from the energy content of the feed. The energy needs of the patients were shown to be 25–80% higher than those of healthy persons of the same age, sex, and size. It was hypothesized that energy expenditure increased because of the increased work of breathing in patients with advanced lung disease. Consequently, a patient with advanced lung disease might not be able to ingest sufficient calories to meet energy needs, resulting in energy imbalance and weight loss. In a subsequent study, resting energy expenditure (REE) was measured by continuous computerized open-circuit indirect calorimetry in 71 patients (8.9 to 35.5 years) who were not suffering from an acute respiratory infection (74). Nutritional status and pulmonary function were studied simultaneously. Resting energy expenditure was found to be above normal (range 95% to 153%) of predicted values for age, sex, and weight and was negatively correlated with pulmonary function and nutritional status (percentage of body fat). In addition, in agreement with the observations of others (39), pulmonary function was positively correlated with nutritional status. These findings have since been confirmed by Buchdahl et al (9), who demonstrated that patients with cystic fibrosis had a resting energy expenditure of 9% above body weight and 7% above lean body mass, respectively, in comparison with healthy controls.

These two studies hinted at the possibility that the CF gene might have a direct effect on basal metabolism. Feigal & Shapiro (23) had earlier reported that mitochondria from cultured fibroblasts from CF homozygotes and heterozygotes had increased O_2 consumption associated with calcium trans-

port. Rates in the homozygote were two times as high and in the heterozygote 1.5 times as high as those in controls. In a subsequent study of CF nasal epithelium, oxygen consumption exceeded that of control tissue by two to three times (68). Shepherd et al (62) investigated total daily energy expenditure using the doubly labelled water method in clinically well, appropriately nourished CF infants without clinical evidence of lung disease, and data were compared with studies in healthy infants. This methodology permits measurement of total energy expenditure in unrestricted subjects. CF infants had rates of energy expenditure 25% higher than values obtained in healthy infants matched for age and body weight. We were concerned about some methodologic difficulties that were brought to the attention of the investigative group (50). Over the next two years, when additional subjects were evaluated, the differences between the infants with CF and the controls disappeared. When the gene responsible for CF was identified (55), it was suggested that the gene product might be directly involved in the regulation of ion transport across membranes (53), since CFTR shared structural similarity with several other transport systems with transmembrane regions and ATP-binding domains. Recent studies strongly suggest that CFTR is a cAMP-regulated chloride channel and provide further evidence that the genetic defect might have a direct effect on basal metabolism. Following this line of investigation, O'Rawe et al (44) reported preliminary results supporting the hypothesis that the genetic defect may have such an effect. Resting energy expenditure was increased by 25% in subjects homozygous for the most common CF mutation (ΔF508) and by 10% in those with ΔF508 on one chromosome and an undefined CF gene mutation on the other. However, their study did not control for lung function or nutritional status. This is important, because we had shown that lung function has a significant effect on REE (74). Further, we have also shown that undernutrition results in a decreased REE (71). We recently published the results of a study in which we controlled for these two confounding variables (26). Little if any increase in REE was seen in healthy, normally nourished CF males with good lung function. Furthermore, we were unable to demonstrate any difference in REE in patient groups with different genotypes. Thus, if there is a primary genetic cause for increased REE in patients with CF, its effects must be minimal. Conversely, lung function is a major determinant of an increase in REE. Once forced expiratory volume in one second (FEV_1) fell below 75% of predicted, the subject's REE rose in a curvilinear (quadratic) fashion (Figure 2). Thus, it appears that deteriorating lung function is the major factor associated with an increase in REE. Recently O'Rawe et al (45) published a full report of their study, in which they controlled for nutritional status but not for lung function. The FEV_1 data for their homozygous group (ΔF508/ΔF508) was 48–64% of predicted (mean 56%) and for their heterozygous group (ΔF508/other) was 52–74% of predicted

(mean 63). It is therefore not surprising, if the pulmonary function data shown in Figure 2 are considered, that the REE values in each group were increased to 121 and 109% of predicted, respectively. The authors did attempt to correct for the effects of lung function, using analysis of covariance; however, their data are open to the alternate explanation, namely, that the increased REE is secondary to reduced lung function.

Protein synthesis is thought to be responsible for up to 25% of REE (69). We therefore measured REE and whole-body protein synthesis in normal controls, in undernourished patients with CF, and in patients with anorexia nervosa matched to the CF patients by nutritional status (72). There were no differences in protein synthesis between the three groups. However, the patients with anorexia nervosa had reduced REE while the CF patients had increased REE compared with controls. Further, we measured protein synthesis and REE in CF patients during renourishment with nocturnal supplemental feedings. REE rose significantly with refeeding but no changes were seen in protein synthesis (71). The increase in REE with refeeding is evidence that the CF patient does adapt to a negative energy balance in the same manner as patients with self-imposed food restriction (75). Following refeeding, the patients with anorexia nervosa increased their REE in a similar pattern to the undernourished patients with CF (71, 75). Thus at least two factors appear to affect REE in the undernourished CF patient with impaired lung function. The first is a normal response to a negative energy balance, and the second appears to be related to the severity of lung function. The precise causes of

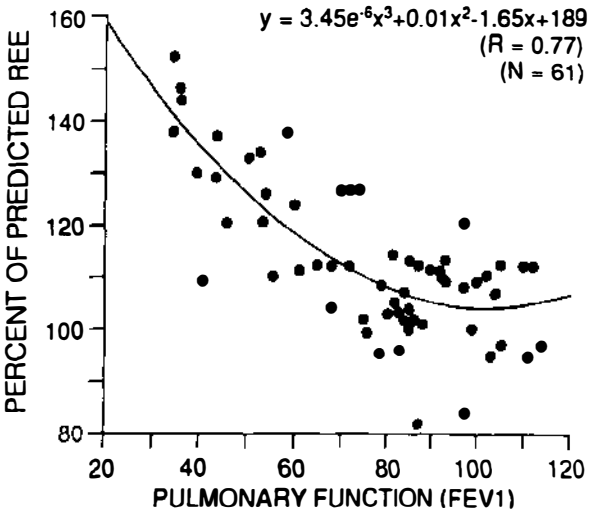

Figure 2 Resting energy expenditure (percent of predicted) versus pulmonary function in normally nourished males with cystic fibrosis. From Fried et al (26).

increased REE in CF patients with moderate to severe lung disease remain to be elucidated. However, the evidence is compelling that alterations in protein metabolism are not responsible (71, 72).

Resting energy expenditure can also be increased by drugs used in the management of CF lung disease. Prior to chest physiotherapy, for example, many patients use inhaled bronchodilators, usually symphomemetic amines. One of these, the β-agonist salbutamol, has been shown to be absorbed through the respiratory tree and to result in a significant increase in REE (approximately 10%) over a period of three hours (73).

In practical terms, energy requirements should be determined by assessing total daily energy expenditure (TDEE). A significant increase in TDEE probably would result in a negative energy balance, which if left untreated would lead to undernutrition. It is interesting that patients with moderate lung impairment adapt to an increased REE by reducing their activity levels, thereby maintaining TDEE at levels comparable to controls (66).

Pathogenesis of an Energy Deficit

We have proposed a model to explain the cause of the energy deficit in CF patients (Figure 3), which helps to define the web of interdependent variables giving rise to chronic malnutrition and growth failure in these patients. It must be reemphasized, however, that most patients with cystic fibrosis can maintain normal growth velocity and nutritional status by voluntary intake of calories, particularly when lung function remains relatively unimpaired (16). Expressed another way, most patients are capable of compensating for the various factors that may contribute to an energy deficit. We and others have speculated that

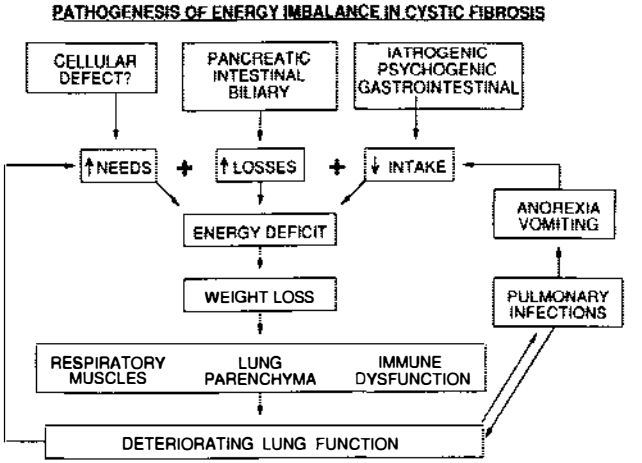

Figure 3 Interdependent factors that may give rise to progressive energy deficit and weight loss as lung function deteriorates. From Durie & Pencharz (21).

malnutrition and decline in pulmonary function are closely interrelated, but a cause-effect relationship remains to be proven. As lung disease worsens, most commonly in older adolescents and young adults, several factors come into play that might predispose the patient to an energy deficit. The frequency and severity of pulmonary infections may increase, inducing anorexia. Chest infections often give rise to vomiting, which may further reduce intake. These factors, in combination with the increase in REE that accompanies advancing lung disease, may lead to an energy deficit. Weight loss will result, initially producing a significant loss of adipose tissue but with time a loss of lean tissue along with muscle wasting. Respiratory muscle wasting would adversely affect respiratory motion and prevent effectuve coughing, thereby further contributing to the deterioration of lung function. Malnutrition is known to adversely affect lung elasticity and a variety of aspects of immune function (11). Taken together, these factors would appear to contribute to progressive deterioration of lung function. In essence, a vicious cycle is established, leading inevitably to end-stage pulmonary failure and death.

DEFICITS OF ESSENTIAL NUTRIENTS

Deficits of essential micronutrients can occur as a result of primary malnutrition or secondary features of the disease, such as pancreatic failure (12, 14). By way of example, CF patients with pancreatic insufficiency frequently malabsorb fat-soluble vitamins, and thus risk developing signs and symptoms of nutritional deficiency.

Water-Soluble Vitamins

With the exception of vitamin B_{12}, water-soluble vitamins are well absorbed, and there is no evidence of clinically significant deficiencies in well-nourished patients. In pancreatic-insufficient patients, vitamin B_{12} absorption can be normalized with adequate pancreatic enzyme replacement therapy. Vitamin B_{12} administration is not necessary, apart from patients with meconium ileus who have undergone extensive ileal resection and show biochemical evidence of B_{12} deficiency.

Fat-Soluble Vitamins

Deficiencies of vitamins A, D, E, and K have been demonstrated at diagnosis (12, 14, 64). Fat-soluble vitamin supplements are a necessary part of the nutritional care of CF patients with pancreatic insufficiency or severe liver disease. Vitamins A and E are of the greatest concern, particularly in patients with severe malabsorption or liver disease. Vitamin D deficiency is more of a concern with inadequate sunlight exposure (52) or with advanced cholestatic liver disease. Current recommendations for supplementation with fat-soluble

vitamins were provided in the proceedings of a recent consensus conference on nutrition assessment and management (51).

Trace Metal Deficiencies

No obvious defect of trace metal absorption or metabolism has been observed in cystic fibrosis. Plasma zinc levels, for example, appear to be low only in patients with moderate to severe malnutrition, and the levels correlate directly with plasma proteins, retinol-binding protein, and vitamin A (65). Plasma levels of copper and ceruloplasmin may be elevated in patients with cystic fibrosis, but usually in proportion to the severity of pulmonary disease, because ceruloplasmin is an acute-phase reactant (65). No reliable evidence supports the concept that selenium is of any clinical significance (10). Symptomatic hypomagnesemia, with evidence of a positive Trousseau sign, tremulousness, muscle cramps, and weakness, may develop in patients receiving aminoglycosides (31) and is reported to be a secondary complication in patients treated for distal intestinal obstruction syndrome with repeated oral doses of *N*-acetylcysteine.

Iron-deficiency anemia with low serum ferritin is frequently seen in patients with advanced pulmonary disease (12), but may also be seen in the stable patient (2). In patients with pulmonary insufficiency, polycythemia seems to occur less commonly than in other pulmonary disorders of comparable severity, suggesting that these patients have a relative anemia. However, hemoglobin values do respond to nutritional repletion of the undernourished patient (42). The precise mechanism of iron-deficiency anemia is poorly understood, since there is no evidence of a defect of iron absorption or metabolism. In fact, some reports demonstrated increased iron absorption in children with CF not receiving pancreatic extracts, but these studies may have been carried out in children with depleted iron stores (33).

Essential Fatty Acid Deficiency

In infancy, particularly before diagnosis, clinical features of essential fatty acid deficiency (EFAD) can occur with desquamating skin lesions, increased susceptibility to infection, poor wound healing, thrombocytopenia, and growth retardation. In older patients who are adequately treated, clinical evidence of EFAD is extremely rare. Most patients with pancreatic insufficiency, nevertheless, have biochemical abnormalities of blood and tissue lipids (22). Changes include decreased linoleic and increased palmitoleic, oleic, and eicosatrienoic acids. It has been suggested that these biochemical abnormalities reflect an underlying defect of fatty acid metabolism (54), while others have argued that the low plasma and tissue levels are due to increased metabolic usage in undernourished patients (35). In a survey of 32 patients, we found that low plasma essential fatty acid levels were confined to patients

with less than 5% of pancreatic function (25). Furthermore, Parsons et al (47) concluded that suboptimal caloric intake and undernutrition are important determinants in the development of EFAD. EFAD levels in tissues were restored by providing malnourished CF patients with caloric supplements via nasogastric tube feeding.

NUTRITIONAL EVALUATION AND THERAPY

Clinical

Nutritional support should be an integral part of the care of CF patients and requires close clinical evaluation, monitoring of growth rates, and appropriate dietary counseling. At diagnosis, height and weight (percentiles) should be carefully measured, and anthropometric measurements taken (skin folds, mid-arm circumference). During routine follow-up visits, growth should be carefully monitored, and where necessary, dietary counselling provided. When patients receive an adequate diet, normal growth can be expected until impeded by advanced respiratory disease. Patients who fail to grow at a normal rate deserve careful evaluation, particularly young children with little pulmonary disease.

Close involvement of a qualified, experienced dietitian is invaluable. Both energy intake and compliance with pancreatic enzyme supplements should be carefully evaluated; in addition, the adequacy of stool fat absorption (72-hr fecal fat) should be determined and fat and energy intake documented during administration of regular pancreatic enzyme supplements. The dose of enzymes may need to be adjusted with or without the judicious use of agents to inhibit or neutralize gastric acid secretion.

Patients with mild pulmonary disease will often lose weight following an acute respiratory infection but generally catch up after recovery. Those suffering from recurrent abdominal pain due to distal intestinal obstruction syndrome often reduce caloric intake to control their symptoms. In these cases, aggressive treatment may be necessary, and in our experience, is best achieved by intestinal lavage with a balanced electrolyte solution containing polyethylene glycol (13). Similarly, signs of esophageal reflux and esophagitis (24, 58) must be sought and aggressive treatment instituted because severe symptoms will reduce caloric intake. Generally, patients with hepatic disease will grow normally, except in rare instances of severe cholestasis or hepatic decompensation.

The diet must be calorically adequate for individual needs and should be as normal for age and peer group as possible. Actual energy requirements of patients with cystic fibrosis are extremely variable, for the reasons described earlier. Dietary intake may be affected by a patient's level of self-esteem and

general feeling of well-being. It is therefore essential that patients who have nutritional difficulties receive psychological support, especially in adolescence and adulthood. Exercise programs aimed at improving physical capacity are considered important. Improved muscle mass may lead to a sense of accomplishment and stimulate an interest in providing nutritional support for physical goals.

As a general rule, protein intakes of children with CF are more than adequate (4), but nitrogen balance may be particularly sensitive to insufficient total energy intake. Provided the latter is adequate, we recommend that protein intake equal the recommended daily allowance for age, sex, and weight. The use of fat as a source of energy, previously discussed in some detail, provides an excellent supply of palatable, energy-rich calories. The limited reserves of essential fatty acids in CF patients and the vulnerability of malnourished patients to essential fatty acid deficiency require specific attention. Although there is no evidence to suggest that biochemical essential fatty acid deficiency has any major clinical impact, we do recommend a diet that contains adequate quantities of linoleic acid to maintain normal or close to normal fatty acid profiles. There is no known defect in the transport of monosaccharides, and some investigators have even suggested enhanced glucose absorption. Complex carbohydrates are quite well tolerated and are good sources of energy. Supplemented doses of fat-soluble vitamins are indicated in patients with pancreatic insufficiency or severe hepatic-biliary disease; generally, two to three times normal intake is recommended.

Biochemical

Biochemical evaluation at diagnosis requires a careful assessment of pancreatic and nutritional status. To determine pancreatic status and the need for pancreatic enzymes, we recommend quantitative evaluation of fecal fat losses while accurately measuring fat intake. Alternatively, recent modifications to the oral bentiromide test (*N*-benzyl-tyrosyl-aminobenzoic acid) provide a less costly and time-consuming method of evaluating pancreatic function (76). Poor substitutes include documentation of fat on stool microscopy, stool trypsin or chymotrypsin activity, serum carotene, and vitamin A and E levels. Many of these tests are useful, however, for monitoring response to treatment on return visits. Serum levels of immunoreactive trypsinogen may be reduced in the patient with pancreatic insufficiency, but only after the age of 7–8 years (20). The most accurate method of assessing pancreatic function is the direct pancreatic stimulation test (29), but this invasive, difficult test should be reserved for evaluating patients with pancreatic sufficiency, in order to better define reserve exocrine function.

Routine laboratory studies of nutritional status in patients with CF were recently reviewed and a consensus report has been published (51). It was

recommended that a complete blood count, plasma retinol, and alpha-tocopherol be performed at diagnosis and yearly as a part of routine care. If low levels of retinol and/or alpha-tocopherol are detected, the patient needs a more complete evaluation of fat absorption and liver function, and an increase in the dose of vitamins A and E. If there is evidence of iron deficiency in routine hematologic studies, then iron status must be measured more accurately, i.e. serum iron, transferrin, and ferritin.

Electrolytes, acid-base status, and serum albumin should be measured at diagnosis. Subsequently, serum albumin is indicated only if there is weight loss, growth failure, or clinical deterioration. Electrolytes and acid-base measurements are indicated with prolonged fever or in the summer heat, particularly in breast-fed infants. Infants may well need a salt supplement on hot summer days. Shorter half-life proteins like transferrin, retinol-binding protein, and pre-albumin are unnecessary, since they offer no advantage over serum albumin combined with anthropometry.

Age-Related Nutritional Guidelines

Standard guidelines for the nutritional evaluation and support of patients with cystic fibrosis must be modified according to individual needs, the age of the patient, and specific complications of the disease.

We now approach these patients diagnostically from the perspective of energy balance. Key factors are energy intake, absorption, and expenditure. Intake is determined from diet records, usually over 3 to 5 days. Absorption is measured by 3-day stool collection combined with a 3-day food record; hence the coefficient of fat absorption can be calculated. Energy expenditure is measured using open-circuit indirect calorimetry (74). We recognize that most centers will not have access to indirect calorimetry; therefore, on the basis of our experience, we have suggested a way of estimating the REE of a patient with CF based on normal standards, lung function, age, and gender (51). Estimated REE enables the calculation of daily energy needs. The reader is referred to the recent consensus report for further details (51).

INFANCY TO TWO YEARS The majority of patients with CF are diagnosed in infancy because of meconium ileus or a nutritional disturbance. The time of diagnosis is a crucial period for instituting therapeutic interventions, dietary counselling, and nutrition education. Furthermore, this is a phase of rapid growth and high energy needs.

Newly diagnosed infants may be profoundly anorexic and indifferent to food. Those presenting with hypoalbuminemia, edema, and anemia of infancy require careful attention. In addition, during the neonatal period active nutritional management is imperative after surgery for meconium ileus. A short course of intravenous nutrition and/or enteral tube feeding may be the

only way to ensure adequate nutrition in the first few weeks of care. In general, patients improve rapidly with adequate attention to caloric requirements, vitamin needs, and pancreatic enzyme supplementation; routine oral feeding with a standard age-appropriate formula becomes possible very quickly. In some instances a formula with a higher caloric density may be needed. In many infants with CF, normal growth can be sustained on human milk, provided adequate attention is paid to their caloric needs and sodium requirements. Protein hydrolysates, medium-chain triglycerides, and polysaccharide supplements are rarely required. Infants who cannot maintain adequate growth with high-calorie standard nutrients hardly ever do better when given these supplements unless they are artificially delivered by enteric tubes.

TWO TO FIVE YEARS At this age, children develop some independent feeding habits, expressed through clear food preferences. Daily intake varies considerably. Since feeding habits are developing at this age, it is important to maintain close attention to energy balance and nutrient needs, using an organized system of guidance and dietary counselling.

SIX TO TWELVE YEARS Children in this age group are expected to develop a greater sense of personal responsibility for their treatment and daily activities. This, in turn, may cause difficulties with drug compliance (pancreatic enzymes and vitamins); in addition, peer pressure may have an impact on their choice of nutrients.

ADOLESCENT YEARS The period of adolescence is associated with an increase in energy requirements due to accelerated growth, pubertal development and, in many instances, a high level of physical activity. Poor growth and delayed development of puberty can create considerable emotional stress. Peer pressure may cause patients to deny their disease. Although the reasons have not been clearly defined, females with CF appear to be at the greatest risk of undernutrition and growth failure. During adolescence, patients with more advanced pulmonary disease are at greatest risk of suffering from the ill effects of energy imbalance.

ADULTHOOD If close attention is paid to energy needs and food intake, it is possible to maintain adequate energy balance for optimal growth to adulthood in most patients, especially when lung function is not severely impaired. A minority of affected adults, especially females, will suffer weight loss in association with advanced pulmonary disease. These patients have an energy imbalance since they seem unable to maintain adequate energy intake by voluntary means.

NUTRITIONAL INTERVENTION

A variety of approaches to artificial nutritional supplementation has been taken in patients who fail to respond to routine nutritional management. The hope is that restoration of nutritional status may result in easier control of chest infections, ameliorate the rate of decline in respiratory function, and extend survival. High-energy liquid dietary supplements are advocated, and although they are convenient to use and may be successful in the short term, no reliable information is available regarding long-term efficacy. It is our impression that many of these energy rich-supplements are at best substitutes for normal dietary habits and do not result in long-term improvement in nutritional status. Patients with growth failure or weight loss, particularly those with deteriorating pulmonary function, therefore may be considered candidates for more invasive, artificial forms of supplementary nutrition. We have critically reviewed the current literature on the subject.

Short-Term Studies

A variety of short-term parenteral and enteral feeding techniques has been used with malnourished CF patients. Shepherd et al (60) evaluated malnourished CF patients (mean age, 5.43 years) 6 months before and 6 months after a 3-week period of parenteral nutrition. During the pre-treatment period, while receiving "conventional" dietary management, the patients showed inadequate growth velocity, but 6 months after the short period of intravenous nutrition they appeared to exhibit continuing catch-up growth, fewer pulmonary infections, and a significant improvement in clinical score.

Other studies have failed to show lasting improvement following short-term nutritional support. The improved nutritional status in the patients in Shepherd's study could be explained by aggressive pulmonary management while the patients were hospitalized. In addition, the very young age of their patients suggests that closer attention to voluntary nutrition may well have prevented the problem at the outset. Mansell et al (43), who evaluated older malnourished CF patients (aged 10–17 years), also demonstrated improvement in nutritional status following a 1-month period of supplemental parenteral nutrition when patients were provided 120% of their energy needs. Immediately following supplementation, body weight, triceps skinfold thickness, and mid-arm muscle circumference increased significantly. Maximum inspiratory airway pressure also increased, suggesting improvement in respiratory muscle strength, but none of the indices of lung function improved. One month after parenteral nutrition, however, the patients were once again malnourished, falling back to levels similar to those seen before treatment. In a study from Montreal (6), supplemental feeding by nasogastric tube was instituted while patients were in hospital and was continued at home for 4 weeks. Patients

showed considerable weight gain, attributable to increased caloric intake, but the nutritional changes were transient and not accompanied by long-term improvement in growth. In a study from our center, Pencharz et al (48) evaluated body composition, nutritional status, and energy needs of six undernourished adolescents and adults with cystic fibrosis. Lean body mass was preserved but there was significant wasting of adipose tissue. Following a brief period of nasogastric feeding with a semi-elemental diet, the effects of refeeding on body composition were reassessed. After refeeding, body weight, body fat, and total body potassium increased significantly, but fat-free body mass and total body nitrogen did not change. None of the subjects was able to continue for longer than 2 to 3 months because of nasal irritation and coughing up the tube. Thus, nutritional benefits derived from brief periods of supplemental nutrition are short-lived and do not produce long-term improvement in growth or function. The failure of brief periods of supplemental feeding to effect long-term benefit is not surprising if the pathogenesis of the energy imbalance is considered (Figure 3), since the underlying causative factors are not reversed.

Long-Term Studies

Since the effects of brief periods of energy supplementation on chronically malnourished CF patients were transient, long-term approaches were clearly necessary to achieve and maintain normal nutrition in patients unable to meet their own energy needs. In addition, it was thought that reversal of malnutrition might have a favorable influence on the course of pulmonary disease and consequently on survival.

As shown in Table 3, three major studies have addressed the problem by using forms of nocturnal enteral supplements (8, 41, 61). In a study from Toronto (41), patients were given nocturnal supplemental feeding of a semi-elemental formula by gastrostomy tube for an average period of 1 year. The adolescent and adult patients were suffering from moderate to severe lung disease and all were markedly wasted or stunted. Gastrostomy tubes were placed endoscopically under local anesthesia. A contemporary group of patients with CF (matched for age, sex, nutritional status, and pulmonary function) drawn from the clinic's computerized data bank werte pair-matched to the study group. In a second Canadian study (8), 10 malnourished CF patients (mean age, 13.6 years) with moderate to severe lung disease were provided with nocturnal supplemental feeding of an intact formula by a needle jejunostomy tube for periods of 10 to 36 months. Pancreatic enzyme supplements were added to the formula. In the third study, from Australia, Shepherd et al (61) evaluated 10 undernourished CF patients (mean age, 8.9 years) who were unable to maintain normal growth by oral means. They were followed during a 1-year course of nutritional supplement with a balanced-

Table 3 Long-term enteral feeding of malnourished patients with cystic fibrosis[a]

Variable	Toronto	Ottawa	Brisbane
Study Design			
Patients (male/female)	14 (5/9)	10 (5/5)	10 (5/5)
Age: Mean (years)	12.9	13.6	8.9
Range (years)	5–22	6–21	3–13
Enteral route	Gastrostomy	Jejunostomy	Nasogastric/Gastrostomy
Supplement type	Semielemental	Intact	Semielemental
Duration (years)	1.1	1.6	1.0
Controls	Concurrent	Retrospective	Prospective
Patient characteristics			
Weight as % of height	82 ± 10	80 ± 9	No data[b]
FEV_1 (%)[c]	47 ± 15	No data	66 ± 16
FVC (%)[d]	53 ± 13	64 ± 18	84 ± 12

[a] Adapted from Durie & Pencharz (21).
[b] Expressed as Z-score.
[c] FEV_1 = forced expiratory volume in one second.
[d] FVC = forced vital capacity.

peptide or a semi-elemental formula given overnight by nasogastric or gastrostomy feeding. These patients were compared concurrently with patients receiving conventional nutritional therapy, and matched for height, sex, and pulmonary function. In all three studies, normal activity and regular meals were permitted during daytime hours.

In each study, long-term enteral supplemental feeding resulted in a significant improvement in catch-up growth and positive changes in body composition (Table 4). There appeared to be beneficial effects on pulmonary

Table 4 Effects of long-term enteral feeding in malnourished patients with cystic fibrosis[a]

Variable	Toronto	Ottawa	Brisbane
Nutritional status			
Δ Weight (kg)	↑	↑	↑
Δ Height (cm)	↑	↑	↑
Δ Weight as % of Height (%)	↑	↑	↑
Total body potassium (g)	↑	No data	No data
Body fat (%)	↑	No data	No data
Mid-arm muscle circumference	No data	↑	No date
Protein synthesis	No data	No data	↑
Respiratory function			
Patients	Unchanged	Unchanged[b]	Improved
Controls	Deteriorated	Deteriorated[b]	Deteriorated

[a] Adapted from Durie & Pencharz (21).
[b] Compared with year before intervention.

Table 5 Approach to nutritional treatment of patients with cystic fibrosis

Encourage good feeding habits early
In patients with growth failure, assess:
energy intake
absorptive function
for gastrointestinal complications that would reduce intake
energy expenditure
psychological/family dysfunction
Provide voluntary supplements and/or modify enzyme therapy
Consider invasive methods of nutritional supplementation before severe undernutrition occurs
Avoid invasive methods in patients with end-stage pulmonary failure, as these will only prolong the agony of dying

function, but the effect on survival remains unanswered. In the two Canadian studies (8, 41), nutritional supplements appeared to slow the rate of deterioration of pulmonary function. In Shepherd's study (61), respiratory function deteriorated in the control group but appeared to improve in the patient group; however, the patients were considerably younger than those in the two Canadian studies.

Following our initial publication of long-term gastrostomy supplemental feeding (41), we established a multidisciplinary approach to the evaluation and care of the failing patient (Table 5). This approach uses the services of dietitians, nutrition support nurses, social workers, and physicians. Patients identified as having an energy problem are seen first by the dietitian. If diet counselling and/or voluntary supplements are not effective, the patient is referred for assessment for long-term gastrostomy feeding. It involves both a family and social evaluation and a medical/nutritional assessment. Once all the factors for and against nutritional intervention are considered by the multidisciplinary team, the patient and family are brought into the decision-making process. Currently only 24 of the 550 patients attending our CF clinic are receiving supplementary gastrostomy feeds. Very few patients have been able to discontinue gastrostomy feeding, since their energy needs remain elevated. In the past 12 months we have moved from percutaneous, endoscopically-placed gastrostomy tubes to placement by an interventionist radiologist under diagnostic imaging control (34). This procedure is well tolerated, and patients are discharged about 3 days after gastrostomy insertion.

CONCLUSION

If close attention is paid to the individual patient's energy needs and nutritional status, undernutrition can be prevented or promptly treated. In the vast majority of patients, normal growth and nutrition can be achieved with the

rational use of a normal, high-energy diet. However, in a small group of patients, advanced lung disease causes a rise in energy expenditure, and energy imbalance may result. At this stage, long-term, invasive methods of nutritional support should be considered. In patients with more advanced lung disease who are candidates for a lung transplant, prior maintenance of nutritional status is an important prognostic factor. Aggressive nutritional therapy, however, is likely to be unsuccessful during the terminal stages when the patient is suffering from end-stage cardiopulmonary failure (42).

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