Clinical Nutrition (2000) **19(6)**: 387–394

doi:10.1054/clnu.1999.0079, available online at http://www.idealibrary.com on IDEAL®

REVIEW ARTICLE

Pathogenesis of malnutrition in cystic fibrosis, and its treatment

P. B. PENCHARZ*, P. R. DURIE†

Division of Gastroenterology and Nutrition, Department of Paediatrics and the Research Institute, The Hospital for Sick Children, and the †Departments of Paediatrics and Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada (Correspondence to PBP, Division of Gastroenterology and Nutrition, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1x8)

Abstract—Pathogenesis: We have developed a model of the pathogenesis of malnutrition in cystic fibrosis. It consists of the relationship between nutrient balance and nutrient requirement. The validation has been conducted with respect to energy, but the same general principals can be applied to any nutrient. A patient with CF either loses weight or fails to grow normally if their absorbed energy intake is less than their total daily energy expenditure. Multiple factors have the potential to contribute to reduced energy intake including, anorexia, gastroeosophageal (GE) reflux leading to vomiting and hence food loss, as well as maldigestion. Another more recently recognized source of energy loss, is glucosuria as a result of CF related diabetes (CFRD). Conversely, lung inflammation appears to be related to increases in resting metabolic rate (RMR). Acute exacerbations of the chronic lung disease increases RMR which returns to a basal level some weeks after the inflammation is treated. In clinically stable patients with CF, RMR rises in a quadratic fashion as lung function falls. When FEV_1 is $>85\%$ predicted RMR is not different from controls, but it rises in a curvilinear fashion as FEV_1 falls. Initially it appears that patients adapt to their increased RMR by reducing their activity so their total daily energy expenditure (TDEE) is often no higher than controls. But this is by no means always the case. Furthermore good lung care requires CF patients to be involved in aerobic activities, hence their TDEE would rise. Although there has been considerable interest as to whether the genetic defect has an energy wasting effect, it appears genetic factors have little or no effect on RMR.

Treatment: This starts with making an energy diagnosis. First, a 3 day faecal fat balance study is conducted. This provides information with regard to intake as well as to maldigestion. In addition a history of GE reflux is sought, since it can readily be treated with H_2-blockers. If significant fat malabsorption exists, efforts are made to improve pancreatic enzyme dose and function. The possibility of CFRD also needs to be considered. We measure the RMR of the patient using open circuit indirect calorimetry. Recommendations for diet therapy are based on estimated TDEE, which is determined from RMR taking into account faecal losses. Diet therapy places the emphasis on increasing the fat content of the diet. We have conducted a study to determine whether or not oral supplements help increase TDEE and they did not; they merely replaced food energy. Conversely, nocturnal gastrostomy supplemental feeding, while reducing voluntary food energy intake by about 20%, does result in a significant increase in total daily energy intake. Our target is to achieve a completely normal nutritional status. Long term follow-up of these patients has shown significantly better survival in patients who achieve normal nutritional status. The advent of lung transplantation has added another dimension. In our experience, following a successful lung transplant, most patients no longer need their supplemental gastrostomy feeding.

Summary: Our clinic policy is to encourage a high fat diet (35–40% total energy) and our patients grow normally in height and weight until their lung disease deteriorates significantly. Patients who develop a negative energy balance seldom if ever respond to diet therapy and hence are candidates for supplemental nocturnal gastrostomy feeds. Gastrostomy fed patients constitute 3 to 5% of our total CF population of approximately 590 patients. © 2000 Harcourt Publishers Ltd.

Key words: cystic fibrosis; malnutrition; energy needs, nutritional assessment

Overview of nutritional problems

Chronic undernutrition with significant weight retardation and linear growth failure has long been recognized as a general problem among cystic fibrosis (CF) patient populations. Some early studies of CF patients (1,2), showed a good correlation between the degree of malnutrition and the severity of pulmonary disease, which in turn adversely affected the survival rate. Although a causal association between these two factors has been postulated, it is not clear whether prevention of malnutrition and of growth failure would slow the progression of lung disease and improve survival rates. The past decade has seen renewed interest in evaluating the multiple interdependent variables that cause 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, and aggressive programs have been instituted to prevent malnutrition.

Growth retardation in CF patients is now recognized as being caused by an unfavorable energy balance rather than being inherent to the disease. Over 15 years ago, reports from Toronto (3, 4) indicated that most patients attending the CF clinic at The Hospital for Sick Children conformed to the normal distribution of growth in the general population. Cross-sectional data from the Toronto clinic (3) showed a normal distribution of height percentiles in males and females. Although weight distribution was skewed toward the lower centiles in females, particularly after adolescence, weight retardation was far less evident than that reported from other centers.

In a comparative study of two CF clinic populations of similar size and age distribution (Boston and Toronto in 1982), Corey et al. (5) found a marked difference in median ages of survival: 21 years in Boston vs 30 in Toronto. 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 Bostan clinic, and males in Toronto were heavier. With the exception of nutritional management, the general approach to patient care, 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 (6), which closely resembled that of most centers in the 1980s, was to prescribe a low-fat, carbohydrate-rich diet, the rationale being that reduction in dietary fat would improve bowel symptoms and reduce stool bulk. The effect was to provide CF patients with a restrictive, unpalatable diet and to exclude them from the many energy-rich foods that compose some of the tastier choices in the usual Western diet. Chronic malnutrition from reduced energy intake appears to have been an unfortunate 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 (7, 8). Fat is the most energy-rich, economical, and appetizing energy source, so 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 and more efficacious pancreatic enzyme supplements, net absorbed energy increased and better growth resulted. Coincidentally, the primary objective of nutritional management is considered to be achieving normal nutrition and growth in children and maintaining goal weight in adults. This view is reflected in this statement from a Consensus Conference (9) on Nutritional Assessment and Management in Cystic Fibrosis, organized by the United States Cystic Fibrosis Foundation: There is no reason to accept nutritional failure and/or impaired growth in any individual with CF.

Pathogenesis of energy imbalance

A variety of complex factors, both related and unrelated, 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 progression of the disease. In simple terms, an energy deficit results from an imbalance between energy needs and intake and it is determined by three factors: energy losses, energy expenditure, and energy intake (10, 11).

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 enzyme is required to prevent maldigestion (12); yet in most CF patients (approximately 85%), evidence of pancreatic failure is present at diagnosis. In those who exhibit maldigestion, strong correlations exist between residual pancreatic function (colipase secretion) and the severity of fat malabsorption (13). Patients with documented steatorrhea, therefore, have variable but very limited residual pancreatic function.

The observation only 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, many patients continue to have severe steatorrhea and azotorrhea, even when they receive what are considered to be adequate amounts of enzyme supplements; i.e. $\sim$1800 U lipase/g fat or 1000–3000 U lipase/kg/meal (14). In the absence of adequate pancreatic bicarbonate secretion (15), 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 (16), 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 aggravated by the binding of salts to unabsorbed protein or neutral lipid. Oral taurine supplements have been reported (17) to benefit some patients. Viscid, thick intestinal mucus, with altered physical properties, may have a harmful effect on the thickness of the intestinal unstirred layer, further limiting nutrient absorption.

Two additional factors, more prevalent in adolescents and adult patients with CF, may contribute to energy losses. CF-related diabetes, 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 causes severe fat malabsorption.

Energy intake

It has been widely accepted that energy intake should exceed normal requirements; it has been suggested (18) that patients may require 120–150% of the Recommended Daily Allowance (RDA) for age and sex. However, when we determined the nutrient intake of a group of healthy adolescents with CF, with minimal lung disease, we were surprised to learn that energy intakes were close to the normal range for age, body weight, and sex (19). Patients with normal growth percentiles for height and weight did show higher energy intakes than those whose growth was retarded. More recently, a study completed at our clinic (20) revealed that adolescent males and females with normal growth percentiles consumed 110% of the RDA. Other CF centers that have developed more liberal attitudes to fat consumption have noted a corresponding improvement in energy intake and growth (21, 22). Other reports (23) found nutrient intakes in CF patients to be close to the normal range.

CF patients are especially prone to complications that might limit oral intake. Esophagitis induced by acid reflux is common in patients with advanced pulmonary disease and is frequently associated with pain, anorexia, and vomiting after bouts of coughing (24, 25). Distal intestinal obstruction syndrome, an unusual form of subacute obstruction within the distal ileum and proximal colon, is seen in some adolescents and adults with pancreatic failure (26); it frequently causes recurrent, crampy abdominal pain that is often aggravated by eating. This syndrome may result from poor compliance with enzyme therapy. 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. Encouraging compliance with enzyme therapy and adequate fluid intake can sometimes help relieve these abdominal symptoms and prevent recurrence.

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 can be expected to show a rapid catch-up in weight. In the terminal stages of pulmonary disease, however, chronic anorexia is a consistent feature. Furthermore, patients with severe chronic disease are prone to bouts of clinical depression, which in the adolescent or adult may lead to severe anorexia.

Oral supplements are often prescribed for adolescents and adults with poor eating habits due to busy school or work schedules. However, their efficacy must be evaluated during treatment, as preliminary results from one study (27) indicate that oral supplements do not improve nutritional status. Gastrostomy or jejunostomy tubes have been used for supplemental enteral feedings, usually achieving satisfactory nutritional results. In some patients, this nutritional support method has reduced anxiety arising from poor weight gain; in others, however, poor compliance has resulted in less use and limited or no weight gain (see Nutritional support).

Energy expenditure and metabolism

Several studies have examined the rates of energy expenditure in patients with cystic fibrosis. In 1984, Pencharz and colleagues (28) 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 by means of a closed-circuit indirect calorimeter and heart-rate telemetry. The subjects were malnourished and had moderate to advanced pulmonary disease. They were receiving nutritional rehabilitation by continuous nasogastric tube feeding with a semi-elemental diet. Absorbed energy intake was calculated by subtracting stool energy content from the energy content of the food. The energy needs of the patients were shown to be 25–80% higher than that of healthy persons of the same age, sex, and size. It was hypothesized that energy expenditure was increased because of the increased work of breathing in patients with advanced lung disease. These patients might be unable to ingest sufficient calories to meet energy needs, resulting in energy imbalance and weight loss.

In a subsequent study (29), resting energy expenditure (REE) was measured by continuous computerized open-circuit indirect calorimetry in 71 patients (8.9–35.5-years-old) who were not suffering from an acute respiratory infection. Nutritional status and pulmonary function were studied simultaneously. REE was found to be above normal (range, 95–153% of predicted values) for age, sex, and weight, and was negatively correlated with pulmonary function and nutritional status (percentage of body fat). Consistent with the

observations of others (1), pulmonary function was positively correlated with nutritional status. These findings have since been confirmed by Buchdahl and colleagues (30), who demonstrated that CF patients had a resting energy expenditure of 9% above body weight and 7% above lean body mass respectively, compared with healthy controls.

These two studies (30, 29) hinted that the CF gene may have a direct effect on basal metabolism. Feigal and Shapiro (31) had earlier reported that mitochondria from fibroblasts cultured from CF homozygotes and heterozygotes had increased O_2 consumption associated with calcium transport. Rates of consumption in the homozygote were twice, and in the heterozygote one and one-half times, those of controls. In a subsequent study of CF nasal epithelium, oxygen consumption exceeded that found in control tissue by two to three times (32).

Shepherd et al. (33) investigated total daily energy expenditure by the double-labelled water method in clinically well, adequately nourished CF infancts without clinical evidence of lung disease, and compared the results with those in studies of healthy infants. This methodology permitted measurement of total energy expenditure in unrestricted subjects. CF infants were reported to have rates of energy expenditure 25% higher per kg of body weight than values obtained in healthy infants matched for age, but total daily energy expenditure was not increased (34). Over the next 2 years, when additional subjects were evaluated, even the differences per unit weight between the infants with CF and controls disappeared. When the gene responsible for CF was identified (35), it was speculated that the gene product might be directly involved in the regulation of ion transport across membranes (36), since CFTR shared structural similarity with several other transport systems involving transmembrane regions and ATP-binding domains.

O'Rawe and co-workers (37) reported preliminary results that supported the hypothesis that the genetic defect has such an effect. REE was increased by 25% in subjects homozygous for the most common CF mutation (DF508) and by 10% in those with DF508 on one chromosome and an undefined CF gene mutation on the other. However, their study did not control for lung function or nutritional status, which are both important determinants of REE (29). We have also shown that primary undernutrition results in a decreased REE (58). In a study (39) in which we controlled for both these confounding variables, we noted little if any increase in REE 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, once forced expiratory volume in 1 s (FEV_1) fell below 75% of predicted values, the subject's REE rose in a curvilinear (quadratic) fashion (39). Deteriorating lung function therefore appears to be the major factor associated with an increase in REE.

O'Rawe et al. (40) examined REE and patient genotype while controlling for nutritional status but not lung function. The FEV_1 data for their homozygous group (DF508/DF508) was 48–64% of that predicted (mean 56%); and for their heterozygous group (DF508/other), 52–74% (mean 63%). It is therefore not surprising, considering the pulmonary function versus REE data (39), that the REE data in each group were 121% and 109% of predicted values, respectively. The authors did attempt to correct for the effects of lung function, using analysis of covariance; however, their data are open to the alternative explanation, namely, that the increased REE is secondary to reduced lung function.

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; the second appears to be related to the severity of lung function impairment. The precise causes of 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 (38, 41).

REE can also be increased by drugs used in the management of CF lung disease. Before chest physiotherapy, for example, many patients use inhaled bronchodilators, usually sympathomimetic amines. One of these, the b-agonist salbutamol, has been shown to be absorbed through the respiratory tree and to cause a significant increase in REE (approximately 10%) over a period of 3 h (42).

In practical terms, energy requirements should be determined by assessing total daily energy expenditure. A significant increase would probably result in a negative energy balance, which, if left untreated, would lead to undernutrition. Patients with moderate lung impairment adapt to an increased REE by reducing their activity levels, thereby maintaining total daily energy expenditure at levels comparable to controls (43).

Pathogenesis of an energy deficit

We have proposed a model to explain the cause of the energy deficit in CF patients (Fig. 1). This model helps to define the web of interdependent variables giving rise to chronic malnutrition and growth failure in these patients. It must be re-emphasized, however, that most CF patients can maintain normal growth velocity and nutritional status by voluntary intake of calories, particularly when lung function remains relatively unimpaired (8). Expressed another way, most patients are capable of compensating for the factors that contribute to an energy deficit. We and others have speculated that malnutrition and decline in pulmonary

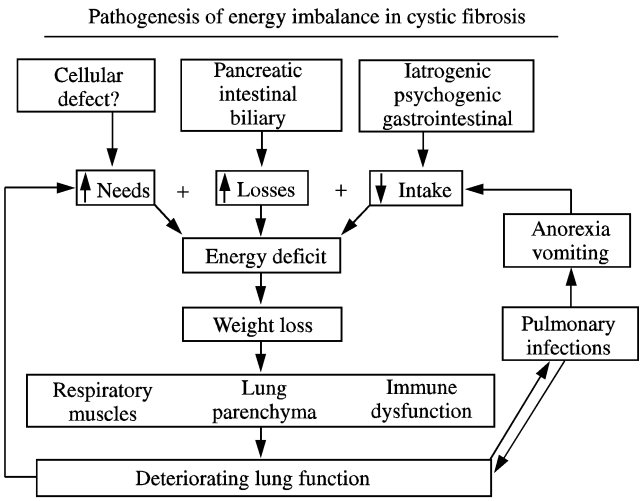

Fig 1. Interdependent factors that may give rise to progressive energy dificit and weight loss as lung function deteriorates. From Durie and Pencharz (10).

function are closely interrelated, but a cause-and-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 cause 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 causing a substantial loss of adipose tissue and, with time, a loss of lean tissue along with muscle wasting. Wasting of the respiratory muscles would adversely affect respiratory mechanics and reduce effectiveness, 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 (44). Taken together, these factors 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.

Standard nutrition and dietary supplementation

Standard guidelines for the nutritional evaluation and care of CF patients must be modified according to individual needs, the age and sex of the patient, and specific complications of the disease. Patients should be encouraged to follow what used to be considered a standard Western diet, with 35–40% of energy in the form of fat. Some patients are concerned because a lower-fat diet is recommended to prevent atherosclerosis; however, the main priority for patients with CF is prevention of a negative energy balance. As the proportion of dietary energy derived from fat falls, so does the total number of calories ingested. Clearly, this reduction in calories is inappropriate. If, however, a patient has pancreatic sufficiency and a family history of hyperlipidemia, blood lipid levels should be monitored.

Another potential problem is that of dietary fiber. Since some patients with CF become constipated, a moderate amount of dietary fiber is recommended, provided there is adequate fluid intake. However, a high-fiber diet can be low in energy and may exacerbate distal ileal obstructive syndrome (DIOS); therefore, diets high in fiber should be avoided.

With the patient who loses weight, we approach diagnosis from the perspective of energy balance. Key factors are energy intake, absorption, and expenditure. Energy and enzyme intake is determined from 3 day food records. Absorption is measured by 72 h stool collection combined with a 72 h food record, which will permit the coefficient of fat absorption to be calculated. Energy expenditure is measured by open-circuit indirect calorimetry (29). 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 (9). Estimated REE enables the calculation of daily energy needs. The reader is referred to Appendix A of the consensus report (9) for further details. Generally, a close estimate of energy requirements can be calculated using the basal metabolic rate X 1.1 (for malabsorption) X an activity factor (1.5 to 1.7) + 200–400 kcal/day.

The first step in managing the patient who has lost weight, after ensuring that enzyme therapy is optimized, is to augment the fat content of the diet and include snacks in the meal plan. The dietitian, using results of 3 day food records, can suggest ways to increase the energy value of the meal plan. Homemade milk shakes may be recommended for some patients, while others prefer to use commercially prepared high-energy beverages and foods. However, as reported earlier (8), we are concerned that oral supplementation may replace food intake and question their efficacy. Conversely, in gastrostomy-supplemented patients, although food intake was suppressed by 20%, total daily energy intake was increased and nutritional status was improved 41.

Nutritional support

In patients in whom dietary intervention and oral supplementation do not resolve their negative energy balance, a variety of nutritional support approaches have been tried, including nasogastric and enterostomy feeding and parenteral nutrition. The hope is that restoration of nutritional status may provide easier control of chest infections, ameliorate the rate of decline in respiratory function, and extend survival. We have critically reviewed the current literature on the subject.

Short-term studies

A variety of short-term parenteral and enteral feeding techniques have been used with malnourished CF patients. Shepherd et al. (45) evaluated malnourished CF patients (mean age, 5.43 years) 6 months before and after a 3 week period of parenteral nutrition. During the pretreatment period, while receiving 'conventional' dietary management, the patients showed inadequate growth velocity; but 6 months after the short period of intravenous nutrition, they exhibited continuing catch-up growth, suffered fewer pulmonary infections. and showed 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 the study by Shepherd and colleagues could be explained by aggressive pulmonary management during hospitalization. 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. (46), 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 with 120% of their energy needs. Immediately after this supplementation, their body weight, triceps skinfold thickness, and mid-arm muscle circumference increased significantly. Maximum inspiratory airway pressure also rose, 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 (47), supplemental feeding by nasogastric tube was instituted while patients were in hospital and was continued at home for 4 weeks. Patients showed substantial weight gain, attributable to increased caloric intake, but the nutritional changes were transient and not accompanied by long-term improvement in growth.

Pencharz et al. (28) 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. After a brief period of nasogastric feeding with a semi-elemental diet, the effects of refeeding on body composition were reassessed: 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 the feeding for longer than 2 to 3 months because of nasal irritation and coughing up the tube.

Thus, the benefits of brief periods of supplemental nutrition do not produce long-term improvement in growth or function. This result is not surprising when one considers the pathogenesis of the energy imbalance (Fig. 1), 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 favorably influence the course of pulmonary disease and consequently the rate of survival.

Several investigators have studied the effect of parenteral nutrition in patients with CF and malnutrition, delivered over periods varying from 4 months (48) to over 1 year (49). Once sufficient energy was delivered, all the patients improved their weight and nutritional status. However, no change was seen in their pulmonary status; and once TPN was discontinued, all patients progressively reverted to their former state of malnutrition (49, 48). In the longest-term study (49), central-line complications were significant and there was an increased need for intravenous antibiotics.

Three major studies (50–52) have addressed the problem by using forms of nocturnal enteral supplements. In a study from Toronto (51), 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 were pair-matched to the study group. In a second Canadian study (50), ten 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. (52) evaluated ten 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-peptide or a semi-elemental formula given overnight by nasogastric or gastrostomy feeding. These patients were compared with patients concurrently 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 produced a significant improvement in catch-up growth and positive changes in body composition. There

appeared to be beneficial effects on pulmonary function, but the effect on survival remains unanswered. In the two Canadian studies (50, 51), nutritional supplements appeared to slow the rate of deterioration of pulmonary function. In Shepherd and associates' study (52), 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 the results of long-term gastrostomy supplemental feeding (51), we established a multidisciplinary approach to the evaluation and care of the failing patient. 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 includes both a family and social evaluation and a medical/nutritional assessment. Once the multidisciplinary team has considered the factors for and against nutritional intervention, the patient and family are brought into the decision-making process.

Currently, only 3 to 5% of the approximately 590 patients attending the Toronto Clinics are receiving supplementary gastrostomy feeds. Since their energy needs remain elevated, few patients have been able to discontinue gastrostomy feeding completely; these have, however, been able to maintain an appropriate weight. Some have been able to decrease the frequency of feedings to 4–5 nights per week while maintaining an appropriate weight. In the past 4 to 5 years, we have shifted from percutaneous, endoscopically-placed gastrostomy tubes to placement by an interventional radiologist guided by diagnostic imaging (53). This procedure is well tolerated, and patients are discharged 3–5 days after gastrostomy insertion. A full description of our enterostomy program has been published (13).

Parenteral nutrition, as described earlier, can improve weight gain in the short term, but is not routinely used with our adult patients because it is expensive, yields minimal benefits, and poses higher risks of infection (49). In some situations, lipids alone may be used to help maintain or promote weight gain in hospitalized patients who are not able to meet their energy requirements with oral intake alone.

When close attention is paid to the individual's energy needs and nutritional status, undernutrition can be prevented or promptly treated. In the vast majority of patients, normal weight and nutrition can be attained with the rational use of a normal high-energy diet. However, in a small group of CF patients, advanced lung disease causes a rise in energy expenditure; 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. However, aggressive nutritional therapy should not be initiated during the terminal stages, when the patient is suffering from end-stage cardiopulmonary failure (54).

Our target is to achieve a completely normal nutritional status. Longer term follow-up of these patients, in our clinic, has shown significantly better survival in those patients who achieve normal nutritional status. The advent of lung transplantation has added another dimension. Our experience to date is that those patients who are successfully transplanted no longer need their supplemental gastrostomy feeding.

Conclusion

Our clinic policy is to encourage a high fat diet (35–40% total energy) to maintain energy balance. Using this approach most patients grow normally in height and weight until their lung disease deteriorates significantly. These patients develop a negative energy balance that seldom if ever responds to diet therapy and are hence candidates for supplemental nocturnal gastrostomy feeds.

Acknowledgement

Much of the work from our units referred to in this manuscript has been made possible through the generous support of the Canadian Cystic Fibrosis Foundation.

References

1. Kraemer R, Rüdeberg A, Hadorn B et al. Relative underweight in cystic fibrosis and its prognostic value. Acta Paediatr Scand 1978; 67: 33–37
2. Sproul A, Huang N. Growth patterns in children with cystic fibrosis. J Pediatr 1964; 65: 664–676
3. Corey M. Longitudinal studies in cystic fibrosis. In: Sturgess J M, ed. Perspectives in Cystic Fibrosis. Proceedings of the 8th International Congress on Cystic Fibrosis. Toronto, Canadian Cystic Firbrosis Foundation, 1980, pp 246–255
4. Gurwitz D, Corey M, Francis P W J et al. Perspectives in cystic fibrosis. Pediatr Clin North Am 1979; 26: 603–615
5. Corey M, McLaughlin F J, Williams M et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 1988; 41: 583–591
6. Shwachman H. Therapy of cystic fibrosis of the pancreas. Pediatrics 1960; 25: 155–163
7. Crozier D N. Cystic fibrosis. A not-so-fatal disease. Pediatr Clin North Am 1974; 21: 935–950
8. Pencharz P B. Energy intakes and low-fat diets in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 1983; 2: 400–402
9. Ramsey B W, Farrell P M, Pencharz P, and the Consensus Committee Nutritional assessment and management in cystic fibrosis: a consensus report. Am J Clin Nutr 1992; 55: 108–116
10. Durie P R, Pencharz P B, A rational approach to the nutritional care of patients with cystic fibrosis. J R Soc Med 1989; 82 (Suppl 16): 11–20
11. Pencharz P B, Durie P R. Nutritional management of cystic fibrosis. Ann Rev Nutr 1993; 13: 111–136
12. Gaskin K J, Durie P R, Lee L et al. Colipase and lipase secretion in childhood-onset pancreatic insufficiency. Delineation of patients

with steatorrhea secondary to relative colipase deficiency. Gastroenterology 1984; 86: 1–7
13. Grunow J, Chait P, Savoie S et al. Gastrostomy Feeding. In: David T J, ed. Recent Advances in Paediatrics. Edinburgh: Churchill Livingstone, 1993, pp 23–29
14. Kalnins D, Ellis L, Corey M, Pencharz P, Durie P R. Extreme variability of response to enzyme therapy in patients with CF, Pediatr Pulmonol 1997; (Suppl 14): 309
15. Gaskin K J, Durie P R, Corey M et al. Evidence for a primary defect of pancreatic HCO_3-secretion in cystic fibrosis. Pediatr Res 1982; 16: 554–557
16. Zentler-Munro P L, Fine D R, Batten J C et al. Effect of cimetidine on enzyme inactivation, bile acid precipitation, and lipid solubilisation in pancreatic steatorrhea due to cystic fibrosis. Gut 1985; 26: 892–901
17. Belli D C, Levy E, Darling P et al. Taurine improves the absorption of a fat meal in patients with cystic fibrosis. Pediatrics 1987; 80: 517–523
18. Roy C C, Darling P, Weber A M. A rational approach to meeting macro and micronutrient needs in cystic fibrosis. J Pediatr Gastroenterol Nutr 1984; 3 (Suppl 1): S154–S162
19. Bell L, Linton W, Corey M L et al. Nutrient intakes of adolescents with cystic fibrosis. J Can Diet Assoc 1981; 42: 62–71
20. Bentur L, Kalnins D, Levison H et al. Dietary intakes of adolescent males and females – is there a difference? J Pediatr Gastroenterol Nutr 1996; 22: 254–258
21. Daniels L, Davidson G P, Martin A J. Comparison of macronutrient intake of healthy controls and children with cystic fibrosis on low fat or nonrestricted fat diets. J Pediatr Gastroenterol Nutr 1987; 6: 381–386
22. Parsons H G, Beaudry P, Dumas A et al. Energy needs and growth in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 1983; 2: 44–49
23. MacDonald A, Holden C, Harris G. Nutritional strategies in cystic fibrosis: current issues. J Royal Soc Med 1991; 84 (Suppl 18): 28–35
24. Feigelson J, Girault F, Pecau Y. Gastro-oesophageal reflux and esophagitis in cystic fibrosis. Acta Paediatr Scand 1987; 76: 989–990
25. Scott R B, O'Laughlin E V, Gall D G. Gastroesophageal reflux in patients with cystic fibrosis. J Pediatr 1985; 106: 223–227
26. Rosenstein B J, Langbaum T S. Incidence of distal intestinal obstruction syndrome in cystic fibrosis. J Pediatr Gastroenterol Nutr 1983; 2: 299–301
27. Kalnins D, Durie P, Corey M, Ellis L, Pencharz P, Tullis E. Are oral dietary supplements effective in the nutritional management of adolescents and adults with CF? Pediatr Pulmonol, 1996; (Suppl 13): 314
28. Pencharz P, Hill R, Archibald E et al. Energy needs and nutritional rehabilitation in undernourished adolescents and young adult patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1984; 3 (Suppl 1): S147–S153
29. Vaisman N, Pencharz P B, Corey M et al. Energy expenditure of patients with cystic fibrosis. J Pediatr 1987; 111: 496–500
30. Buchdahl R M, Cox M, Fulleylove C et al. Increased resting energy expenditure in cystic fibrosis. J Appl Physiol 1988; 64: 1810–1816
31. Feigel R, Shapiro B L. Mitochondrial calcium uptake and oxygen consumption in cystic fibrosis. Nature 1979; 278: 276–277
32. Stutts M J, Knowles M R, Gatzy J T et al. Oxygen consumption and ouabain binding sites in cystic fibrosis nasal epithelium. Pediatr Res 1986; 20: 1316–1320
33. Shepherd R W, Holt T L, Vasques-Velasquez L et al. Increased energy expenditure in young children with cystic fibrosis. Lancet 1988; i: 1300–1303
34. Pencharz P B, Berall G, Vaisman N et al. Energy expenditure in children with cystic fibrosis. Lancet 1998; ii: 513–514
35. Rommens J M, Iannuzzi M C, Kerem B-S et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989; 245: 1059–1065
36. Riordan J R, Rommens J M, Kerem B-S et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989; 245: 1066–1073
37. O'Rawe A, Dodge J A, Redmond A O B et al. Gene/energy interaction in cystic fibrosis. Lancet 1990; 335: 552–553
38. Vaisman N, Clarke R, Pencharz P B. Nutritional rehabilitation increases resting energy expenditure without affecting protein turnover in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 13: 1991; 383–390
39. Fried M D, Durie P R, Tsui L-C et al. The cystic fibrosis gene and resting energy expenditure. J Pediatr 1991; 119: 913–916
40. O'Rawe A, McIntosh I, Dodge J A et al. Increased energy expenditure in cystic fibrosis is associated with specific mutations. Clin Sci 1992; 82: 71–76
41. Vaisman N, Clarke R, Rossi M et al. Protein turnover and resting energy expenditure in patients with undernutrition and chronic lung disease. Am J Clin Nutr 1992: 55; 63–69
42. Vaisman N, Levy L D, Pencharz P B et al. Effect of salbutamol on resting energy expenditure in patients with cystic fibrosis. J Pediatr 1987; 111: 137–139
43. Spicher V, Roulet M, Schutz Y. Assessment of total energy expenditure in free-living patients with cystic fibrosis. J Pediatr 1991; 118: 865–872
44. Chandra R K, Newberne P M Nutrition, Immunity and Infection: Mechanisms of Interaction. 1977, New York: Plenum Press
45. Shepherd R, Cooksley W G E, Domville Cooke W D. Improved growth and clinical, nutritional, and respiratory changes in response to nutritional therapy in cystic fibrosis. J Pediatr 1980; 97: 351–357
46. Mansell A L, Andersen J C, Muttart C R et al. Short-term pulmonary effects of total parenteral nutrition in children with cystic fibrosis. J Pediatr 1984; 104: 700–705
47. Bertrand J M, Morin C L, Lasalle R et al. Short-term clinical, nutritional, and functional effects of continuous elemental enteral alimentation in patients with cystic fibrosis. J Pediatr 1984; 104: 41–46
48. Kirvela O, Stern R C, Askanazi J et al. Long-term parenteral nutrition in cystic fibrosis, Nutrition 1993; 9: 119–126
49. Allen E D, Mick A B, Nicol J et al. Prolonged parenteral nutrition for cystic fibrosis patients. Nutr Clin Prac 1995; 10: 73–79
50. Boland M P, Stoski D S, MacDonald N E et al. Chronic jejunostomy feeding with a non-elemental formula in undernourished patients with cystic fibrosis. Lancet 1986; i: 232–234
51. Levy L D, Durie P R, Pencharz P B et al. Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis. J Pediatr 1985; 107: 225–230
52. Shepherd R W, Holt T L, Thomas B J et al. Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. Pediatr 1986; 109: 788–794
53. Ho C-S, Gray R R, Goldfinger M et al. Percutaneous gastrostomy for enteral feeding. Radiology 1985; 156: 349–351
54. Levy L, Durie P, Pencharz P et al. Prognostic factors associated with patient survival during nutritional rehabilitation in malnourished children and adolescents with cystic fibrosis. J Pediatr Gastroenterol Nutr 1986; 5: 97–102

Submission date: 11 October 1999 *Accepted:* 20 October 1999