Rationale of modern dietary recommendations in cystic fibrosis

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Introduction

Significant nutritional and growth problems affect many cystic fibrosis (CF) patients[1]. They have been reported to have suboptimal growth, poor weight for height[2] and delayed puberty[3], and the eventual size and nutritional state of those who survive to adulthood is commonly well below average[4].

The majority of CF individuals have severe intestinal malabsorption secondary to pancreatic insufficiency[5]. The secondary malnutrition and poor growth which follows untreated or inadequately treated malabsorption almost certainly has a deleterious effect on the patients' wellbeing and ability to combat infection and eventually on their ultimate survival[6-8].

There are a number of well recognized factors which contribute to the poor nutritional state of so many CF individuals. These include not only the severe and rarely completely controlled intestinal malabsorption, but also a poor nutritional intake related not least to the traditional advice to follow a low-fat diet. The increased energy requirement results not only from the malabsorption but also from the presence of repeated and chronic chest infection.

The dietary recommendations designed to combat these potential reasons for malnutrition have changed significantly over recent years in most clinics. In summary, the new dietary recommendations include the taking of a high-energy, high-protein diet, without any restriction of dietary fat, to achieve an energy intake of between 120% and 150% of the DHSS recommended daily allowance for age[9] (see Table 1).

Table 1. Reasons for malnutrition in cystic fibrosis

Problem	*Solution*
Poor energy intake	Dietitian's assessment Increase intake: more food no fat restriction energy/protein supplements nasogastric feeding intravenous feeding enterostomy feeding
Severe intestinal malabsorption	Measure severity - faecal fat Use microsphere pancreatic supplements Increase the dose Check effect - faecal fat H_2 blockers - rarely Gastrointestinal investigation
Increased energy expenditure	Control chest infection Control diabetes
Abnormal fat-soluble vitamin status	Give daily supplements: vitamin A 8000 units vitamin D 800 units vitamin E 100-200 mg Check plasma levels

Further re-emphasis and justification of the changes in dietary advice are appropriate, for a significant proportion of CF individuals of all ages referred to our regional CF unit for assessment have recently received advice at their referring hospital which involves the restriction of dietary fat intake. Other patients have self-restricted fat for health reasons. Furthermore, there is reluctance by many health professionals to recommend a normal diet without at least some fat restriction, so entrenched is the belief that CF patients should have low-fat diets.

The reasons for changing the traditional dietary recommendations have included the obvious poor nutritional state of so many CF individuals and also the increasing awareness of the importance of the patients' nutritional state both in CF and many other chronic disorders affecting children. In Toronto, where fat restriction had been abandoned in the early 1970s, the patients' better nutritional state appeared to result in a better prognosis[7]. Also there have been improved methods of increasing the energy intake by oral supplements, and if these fail, by enteral, parenteral and enterostomy feeding. Lastly, the availability of more effective pancreatic extracts - the microsphere preparations Creon and Pancrease - has been a major factor in permitting the introduction of a more liberal diet of large amounts of normal food without any deliberate restriction of dietary fat[10,11].

Structural abnormalities of the gastrointestinal tract

Anatomical abnormalities of the gastrointestinal (GI) tract in CF are well documented. Although there are histological changes throughout the GI tract, the severe pancreatic insufficiency is the most important single factor in the pathogenesis of the severe maldigestion and malabsorption, although other factors including disturbed bile salt metabolism and small intestinal mucosal dysfunction are of importance.

There are minor histological changes in the salivary glands and their secretions contain increased concentrations of protein and enzymes. In particular, lingual lipase is secreted in increased amounts by CF patients[12] and is responsible for increased gastric lipolytic activity[13]. Although this acid-resistant lipase is considered to be responsible for a significant proportion of the residual duodenal lipolytic activity in CF patients, it is nevertheless ineffectual in the majority for the control of the severe malabsorption which occurs so commonly in affected individuals[14].

The pancreas is usually histologically abnormal even at birth[15]. The characteristic histological changes include inspissation of secretions in the ducts and acini and an increase in fibrous connective tissue. Although in some patients the histological appearance may appear normal by routine methods, differentiation of CF from unaffected individuals is possible if the ratio of volume of the exocrine acinar tissue to the connective tissue is examined. The normal linear increase in this ratio around birth contrasts significantly with the progressive fall seen in CF infants[16,17]. The difficulties in interpretation of pancreatic histology in extremely immature low birth weight infants have recently been reported[18].

The severity of the pancreatic involvement progresses with age and this has been documented by serial pancreatic function studies[19]. The almost invariable increase in plasma immunoreactive trypsin present in the neonatal period[20] progressively falls through childhood as the pancreatic tissue becomes more damaged[21,22]. Also, the severity of the ultrasound changes increases with age[23]. The increasing glucose intolerance is also age-related; clinical diabetes rarely affects CF children, but no less than 20% eventually develop diabetes through adolescence and early adult life[24].

The small bowel, large bowel and appendix show characteristic histological abnormalities. The mucosal glands may contain variable inspissated secretions. There is usually normal or even tall small intestinal villous structure, both by light and electron microscopy[25]. Excessive mucus on the luminal surfaces is usually evident and has been suggested as a contibutory factor to the malabsorption. It has been suggested that this mechanical obstruction to absorption may account for the disproportionately low frequency of positive radio-allergosorbent tests to foods in atopic CF patients compared to those with asthma[26]; however, others have demonstrated increased permeability with sugar absorption tests[27].

Decreased activity of cytoplasmic peptide hydrolase in intestinal mucosa has been described and associated with reduced uptake of phenylalanine and cycloleucine when compared with controls[28]. Abnormalities of phenylalanine and glycine absorption have also been described[29]. Intestinal disaccharidase activity is now considered to be normal[30]; xylose absorption is either normal or increased[31].

Liver and gallbladder abnormalities occur in a significant proportion of CF patients[32], including steatosis, focal biliary cirrhosis and multilobular cirrhosis. Consequences of disturbed liver parenchymal function are usually not a major problem. However, portal hypertension and bleeding from oesophageal varices are an increasing and potentially serious problem as more patients survive to develop the complication[33]. The interrelationship of the severity of malabsorption, liver involvement and abnormalities of bile acids is not entirely clear.

Gallbladder problems, including non-visualized and micro-gallbladder and cholelithiasis, were reported in 40% of patients in a multicentre study and both diet and pancreatic supplementation may be relevant in their pathogenesis[34].

A further anatomical problem relevant to the malabsorption occurs in those patients who have had part of the intestinal tract resected in the neonatal period, at the time of their initial presentation with meconium ileus.

Functional consequences of the anatomical changes

The intestinal malabsorption which occurs in untreated cystic fibrosis is severe[5] and greater than occurs in coeliac disease[35].

Many CF patients receiving treatment with pancreatic extracts who are considered to have satisfactory control of their gastrointestinal symptoms and signs continue to have significant intestinal malabsorption when dietary assessments and faecal fat studies are performed[36,37]. Steatorrhoea occurs when more than 90% of pancreatic function is lost[38]. Although 10-15% of CF patients are usually described as having minimal or no clinical evidence of pancreatic insufficiency[39], in the majority there is severe reduction in the pancreatic secretion of water, bicarbonate, electrolytes and enzymes. Stimulated pancreatic function tests, using intravenous pancreozymin and secretin, constantly show abnormalities of function even if only of bicarbonate secretion[40,41].

Deficiency of lipase, colipase, bicarbonate and bile salts possibly all contribute to the severe fat malabsorption. Fat absorption bears a linear relationship to fat intake and it is of practical importance to know that dietary fat restriction does not improve fat absorption[42,43].

Lipase activity is low in the duodenal fluid in CF, the pH is abnormally low[44] and much of the pancreatic extract taken by mouth is destroyed in the stomach[45]. Although raising the pH by administration of bicarbonate[5] or H_2 antagonists, e.g. cimetidine and ranitidine[10,46,47], will improve fat absorption by reducing the destruction of lipase by acid conditions, the effect is only limited due to the limiting effect of the lipase deficiency[5].

The administration of pancreatic extracts improves fat absorption[48] but by no means returns the situation to normal. Whilst the role of pancreatic colipase is of importance, the improved availability of lipase in the small bowel by the use of acid-resistant microsphere preparations has resulted in impressive improvement in fat absorption[10,11].

The role of bile acids has received considerable attention as a contributory factor in the fat malabsorption and excessive faecal bile acid losses have been well documented[49]. The faecal bile acid loss correlates with the severity of the malabsorption and does not occur in those who are pancreatic-sufficient[50,51]. The losses are reduced when pancreatic extracts are used and when an increased proportion of the ingested fat is in the form of medium-chain triglycerides[52]. Wide-spectrum antibiotic therapy has been demonstrated to reduce the faecal bile acid loss, possibly by influencing the faecal flora and reducing the anerobes[53].

Most workers consider the faecal bile acid losses and the reduced bile acid pool to be a significant contributory factor in the fat malabsorption. Taurine supplements to provide substrate for taurine containing bile acids have been shown to reduce the severity of malabsorption[54]. A primary mucosal bile acid transport defect has been postulated[55].

Protein absorption, although markedly impaired in the untreated CF individual, is more commonly corrected by pancreatic supplements[5]. A number of studies have demonstrated that the increased faecal

nitrogen excretion is reduced more effectively than fat losses by pancreatic extracts[11,35,47,48].

In patients treated with modern pancreatic extracts, there is little clinical or biochemical evidence of protein deficiency[37]. Our recent experience confirms this. Pancreatic extracts normalize absorption of protein, as evidenced by the subsequent plasma alpha-amino nitrogen levels[56] and normal faecal nitrogen excretion[11].

Carbohydrates appear to be well absorbed despite the deficiency of pancreatic amylase. As already noted, both glucose and xylose are absorbed normally, or even better than normal[31], and disaccharidase activities of small intestinal mucosa are normal[30].

Thus, available evidence suggests that there are multiple reasons for the severe intestinal malabsorption which affects the majority of CF individuals. While the pathogenesis is complex, severe pancreatic insufficiency is central to the problem, with perhaps secondary bile acid and mechanical problems. The absorption of fat seems to be particularly affected, with less problems from protein absorption and relatively few problems with carbohydrate absorption.

Although absorption of carbohydrate from the gut is not a major problem, carbohydrate metabolism may be relevant in the context of nutritional status, particularly as dietary energy supplements used are commonly high in carbohydrate. The progressive pancreatic damage eventually impairs the function of the islets of Langerhans in many patients; eventually 10%-20% of older CF patients develop clinical diabetes[24]. The significance of this gradual reduction of glucose tolerance, particularly during the months and years preceding the onset of clinical diabetes, in the context of optimal utilization of ingested energy, is unknown. We have found that fasting blood glucose and glycosylated haemoglobin levels are not infrequently above normal, even in young patients. It is therefore important that all patients be monitored for the onset of diabetes mellitus by routine urine tests at every clinic attendance, and also have their fasting glucose and glycosylated haemoglobin checked at their annual assessment.

Various other hormonal and endocrine abnormalities have been described, including elevated neurotensin levels[57] and enhanced motilin response in adults but not in children[58]. These findings are unlikely to have immediate relevance to the present dietary recommendations.

Although isolated deficiencies of minerals and trace elements have been described, in most patients the levels are within the normal range[59,60]. Iron deficiency is relatively common in CF patients referred to our unit for assessment[61]. However, the theoretical disadvantages of iron supplementation in the presence of infection[62] and the variation in growth characteristics of Pseudomonas depending on the availability of iron[63], make the wisdom of routine iron supplementation doubtful.

Vitamin B_{12} and folate levels are almost invariably normal, although occasional vitamin B_{12} levels are high[36,37]. As fat absorption is rarely completely corrected, plasma fat-soluble vitamin levels are commonly subnormal, even when usually recommended doses of conventional vitamin supplements are given. Water-soluble vitamin levels are usually normal[36]. Vitamin E deficiency is particularly common and, in the absence of adequate supplements, can reach very low levels - particularly in adolescents and adults in whom clinical vitamin E deficiency may occur[64]. Vitamin A levels are commonly low despite routine supplementation of 4000 units daily. The levels usually improve with twice the daily recommended dose, that is 8000 units per day[36]. Although CF patients do not appear to develop rickets, osteoporosis and low plasma vitamin D levels are well documented[65]. Vitamin K deficiency is an unusual problem but can occur in young infants and those with liver disease: routine supplementation is usually unncessary[66].

The essential fatty acid (EFA) status of CF patients has received considerable attention and abnormalities are well documented[67]. It appears probable that such abnormalities are more likely to be a result of the fat malabsorption rather than a basic abnormality of CF. In fact, CF patients who are 'pancreatic-sufficient' have normal essential fatty levels[68]. The role of EFAs in the production of prostaglandin, whilst well established, appears to have little relevance to practical management. Oral supplements of EFAs will correct deficiencies[69-71], but the initial claims of clinical improvement and even reduction of the elevated sweat electrolyte levels[72] have not been substantiated by controlled studies[73,74].

Poor energy intake

Despite the widespread belief that CF individuals have voracious appetites, their actual energy intakes are commonly subnormal when detailed dietary analysis is performed[75-78]. Chase reported 10 children who took only 82-89% of the recommended daily energy allowance (RDA) for their age. In other CF clinics where detailed assessments have been made, energy intakes of 80-90% of the RDA have been reported[77,79].

In our CF unit, patients who receive their routine care at a variety of hospitals attend for detailed assessment of their condition[37]. As part of their assessment a seven-day dietary assessment of the nutritional intake is carried out by the dietitian (AM). Of the 90 CF patients assessed during the past year, the mean energy intake was 108% of the RDA for age[9]. Thirty-nine (43%) had previously had no regular contact with a dietitian; their mean energy intake was only 97% of the RDA for age. However, 39 (43%) who had seen a dietitian at least twice in the year preceding assessment had a mean energy intake of 119% of RDA for age. Twelve further patients (13%) who had had previous assessments, including dietary advice, had a mean energy intake of 117% of RDA for age despite lack of dietetic advice at their local hospital since their last assessment at the CF unit.

There are many reasons for the poor energy intake, including anorexia, dietary dislikes and emotional problems, but most would now agree that an obligatory reduction in energy intake is almost inevitably associated with advice to follow the traditional low-fat diet. Of the 39 patients (43%) who had had no dietetic contact, no less than 25 were still restricting their fat intake; in 18 this was because fat restriction was considered to be beneficial in CF and in 7 a low-fat intake was regarded as part of a healthy diet. The general belief that a low-fat intake leads to better health has compromised the energy intake of some of these patients.

It is difficult to achieve a daily energy intake of more than 120% of RDA if the dietary fat intake is restricted. In fact, it has been suggested that as much

as 40% of the daily energy must be provided from fat if total energy intakes of more than 125% of RDA are to be achieved[78].

Our data clearly demonstrate the need for regular advice by an experienced dietitian for *all* patients: a single consultation at the time of diagnosis is quite inadequate.

Increased energy requirements

In addition to the problems of low energy intake and excessive energy losses from intestinal malabsorption, CF individuals have other causes for an increased energy requirement[80]. Infections are well known to increase energy intake over and above the associated anorexia. There is a well described catabolic state which is corrected with the control of the infection[81]. Fever has been estimated to increase energy intake by 13% for each degree centrigrade of fever[82].

A number of studies have documented the increased energy utilisation by CF patients. Adeniye-Jones and colleagues found CF patients had 30% higher energy expenditure than controls[83]. Pencharz *et al.*[84], in a detailed study of 6 undernourished CF adolescents and young adults during nutritional rehabilitation, demonstrated overall energy needs of 25-80% higher than in healthy controls. The patients were assumed to be in a stable state with regard to the activity of the chest infection, although few details were given other than 'postural drainage and antibiotic therapy were continued following standard routines for the particular subject throughout their stay'. This is mentioned in view of the major influence the chest infection has on the nutritional state and the commonly observed impressive weight gain which occurs during a course of treatment with an appropriate antibiotic. Furthermore, the effect of antibiotic therapy on bowel flora and faecal bile acids may have considerable relevance[53].

In Pencharz's study, as less than 3% of the energy administered as Vivonex is lost, the increased energy requirement demonstrated can be taken as that over and above the unavoidable faecal loss present in many CF patients. The lean body mass, as judged by total body potassium and nitrogen, was relatively well preserved and the patients were in a positive nitrogen balance before the nutritional rehabilitation. However, there was significant wasting of adipose tissue which improved significantly during the enteral Vivonex feeding[84].

Buchdahl[80] studied 23 CF children, who were all in a stable state, by indirect calorimetry measuring oxygen consumption and carbon dioxide production, and demonstrated an increased resting energy expenditure in the CF children of some 10% more than in healthy controls. Higher energy expenditure was associated with poorer pulmonary function.

The survival at CF centres where treatment and dietary advice has resulted in better growth and physical state is impressive and there are many theoretical reasons why a better nutritional state should lead to an improved prognosis. Thus, it is logical to strive for normal nutritional state and growth for our CF patients.

Strategies for improving energy intake

Due to the increased nutritional requirements, a diet containing 120-150% of the RDA for age[9] is recommended, although this depends on the individual. It is our present practice to recommend that of the increased energy needs, 35% of the calories are derived from fat, 15% from protein and 50% from carbohydrate. The exact food to be taken depends upon the patients' preferences, family eating habits and even religious customs. The dietitian should see every patient regularly, ensure that adequate energy is taken and decide the need for additional energy supplements. The exact type of fat taken is probably of less importance now that more efficient pancreatic extracts are available, and there now seems to be little place for the use of medium-chain triglycerides in either cooking or in dietary supplements.

Patients and families who are familiar with the NACNE recommendations to reduce dietary fat and sugar and increase dietary fibre as a move towards a healthier lifestyle may be confused[85]. These families should be assured that fat malabsorption is rarely completely corrected in CF individuals and the chances of absorbing excessive amounts of fat are unlikely. The dangers of suboptimal energy intake far outweigh any theoretical advantage of a low-fat, supposedly 'healthy diet'.

These dietary recommendations are not new[5] and were put into effect in our own and other clinics before the microsphere pancreatic preparations were available. However, the present diets have been made much more feasible with the use of large doses of the new microsphere pancreatic supplements.

Dietary supplements

The use of additional dietary supplements to increase energy intake varies in different clinics. If there are problems achieving an energy intake adequate to sustain normal nutrition and growth in the long term or during acute illness, it is our policy to use a variety of commercially available energy and protein supplements. Although there are many such supplements available, we prefer glucose polymers (Maxijul - Scientific Hospital Supplies; Polycal - Cow & Gate), concentrated glucose drinks (Hycal - Beechams) and the complete supplemented milk-based feeds (Build Up - Carnation; Complan - Farleys) and the new prescribable milkshake Fresubin (Fresenius - Dylade). The recognition of suboptimal energy intake and thus the need for dietary supplements increases when there is regular contact with a dietitian.

It is preferable to advise a specific amount of the supplement, divided into 2 or 3 doses per day given after meals so that appetite is not impaired. The quantity recommended is age-dependent and although often individualized, a general guide would be that children between 3 and 8 years are given a daily supplement containing 400-500 calories; older children would receive 400-1000 calories depending on their tolerance of the supplementary feed.

Further practical suggestions for improving energy intake embodying the present dietary recommendations have been detailed elsewhere[86].

Oral elemental diets

Prior to the availability of the new microsphere pancreatic preparations, attempts were made to improve absorption and nutrition by providing part of the total nutritional intake using constituents considered to be more easily assimilated and less dependent on pancreatic function, i.e. presenting the nutrients in a predigested form. Feeds of casein hydrolyte and glucose had been shown to reduce nitrogen losses[56,87]; also faecal fat losses could be

reduced by the use of medium-chain triglycerides (MCT)[88]; however, improved growth with such treatment could not be confirmed by others[89].

Much interest and publicity followed the use of elemental diets, particularly the Allan diet, as the sole source of energy. Initial studies using beef hydrolysate, MCT and a glucose polymer demonstrated impressive weight gains in a proportion of patients. Although the study was uncontrolled, there was dramatic improvement in the growth of selected patients[90]. Subsequent studies of this type have all demonstrated improvements, mostly in weight, but compliance has been a major problem. The nutritional gains were frequently not sustained on return to conventional diet and in consequence elemental diets were not advised or widely used[91-93].

Enteral feeding

In view of the difficulties with acceptance of and compliance with the supplementary feeding regimens, nasogastric feeding techniques have become more popular[94-97]. Although the composition of the feed and methods of administration have varied, the principles are the same. Popular regimens employ a fine nasogastric tube which the patient is taught to pass and the administration of the feed over 8-10 hours using an infusion pump. The night may be used as a convenient time to infuse the extra nutrition. Most studies have demonstrated improved nutrition and growth in the short term, over and above that achieved by modification of the diet and pancreatic supplements. The patients have often been less than 90% of ideal weight for height[84,95-98]. Others have reported use of gastrostomy[99] or jejunostomy[98,100,101].

The feeds used for enteral feeding have either provided the total energy intake or, more commonly, a proportion of the RDA, e.g. 30% from 1000 calories over 8 hours. Patients seem to tolerate smaller volumes of more concentrated feeds rather than larger volumes of more dilute feeds. The type of feeds used have either been elemental (e.g. Vivonex - Norwich Eaton) or whole protein fat containing feeds (e.g. Ensure plus - Abbott). There is evidence that partial enzyme hydrolysates of whole protein contribute the most suitable nitrogen source[102,103]. High molecular weight glucose polymers are also well absorbed even though luminal amylase activity is low[104]. If MCT is added to the elemental feeds, pancreatic enzyme supplements are required[105]. These may be given intermittently during the administration of the feeds, ideally every two hours but at greater intervals if more convenient, e.g. three times during the night. It is our practice to use feeds containing whole protein and fat (e.g. Ensure or Ensure plus) as it is easier to obtain the high energy intakes using these preparations.

Other strategies have included intravenous nutrition. Shepherd and colleagues[106] gave 130% of RDA for three weeks and demonstrated improved nutrition and respiratory function maintained at six months, although admittedly the numbers were small and the study uncontrolled.

All feeding regimens where major dietary modifications are made should be carefully supervised to ensure that iatrogenic deficiency problems are not created.

Control of intestinal malabsorption

Pancreatic supplements

The availability of significantly more effective pancreatic preparations - the acid-resistant microspheres, Pancrease and Creon - has improved the efficiency of pancreatic enzyme replacement therapy. However, the details of administration are of importance and often receive scant attention. Pancreatic enzyme supplements are indicated for patients who have clinical or chemical malabsorption. The absence of symptoms and signs is not a contraindication for treatment, for the difficulties of achieving an energy intake of more than 120% of the RDA are such that losses of fat and other nutrients in the stools, even though not causing major symptoms, should be minimized.

The object of treatment should be to control symptoms, to improve chemical steatorrhoea to reasonable levels (absorption of >85% of ingested fat), and to achieve this objective using a regimen which is socially acceptable, causing the patient the least disturbance and embarrassment. The ultimate aim is, of course, to achieve normal nutrition (weight for height), growth (height for age) and development.

The choice of preparations has become less of a problem, and we would start all patients on one of the acid-resistant microspheres, either Pancrease or Creon. Infants not taking solids would be started on Cotazym or a similar powdered preparation. We have less success than others in persuading small infants to take microspheres, but change from Cotazym powder to microspheres during the first year as soon as significant quantities of weaning foods are taken.

The method of administration is important. Cotazym may be taken in or out of the capsule. For infants, the powder is usually mixed in a little milk and taken at the beginning of the feed; it should not be added to the bottle. It should be washed down at once by the rest of the feed, for the powder is damaging to skin and should not be allowed to remain in contact with the skin or mouth. Soreness of the mother's nipples may occur when CF infants are breastfed. We suspect that dissolved powdered preparations may exacerbate oesophagitis, and microspheres should be considered in such circumstances. The effect of powdered pancreatic extracts in reducing the fibronectin content of the buccal epithelial cells has been suggested as predisposing to bacterial colonization of the pharynx with gram-negative organisms[107].

The microspheres may be taken in or out of the capsule but should not be chewed. They may be mixed with food and will remain intact for 20 minutes even if the pH is above 5.0-5.5 at which they release their enzymes. Thus, although they can be mixed with food, this is best avoided as a significant proportion are likely to be crushed, permitting acid destruction in the stomach.

The timing of administration should be clearly specified. One young lady took the whole days' supply before breakfast to avoid forgetting later doses! Most would agree that the enzyme should be taken throughout the meal - in practice half at the start and half in the middle. It is particularly important that the standard powders are not taken long before food as even more of their enzyme activity will be destroyed by the stomach acid, unbuffered by food. With meals is as satisfactory as hourly administration[45] and therefore the enzymes should be taken with meals.

Dosage is usually underestimated for a number of reasons, including the manufacturers' too-modest recommendations, the acceptance of gastrointestinal symptoms by patients, their relatives and their doctors, and a failure to detect the inadequacy of

control of the steatorrhoea by failure to estimate faecal fat excretion. We would usually start with between 1 and 3 capsules of a microsphere preparation per meal and perhaps one with snacks depending on the food. The dosage would be gradually increased every day or two by one capsule per meal until complete control of symptoms and signs was achieved whilst taking a full diet as described. Commonly about 6 capsules per meal are required, but in exceptional patients 10 or even 15 per meal are needed to obtain maximum control of symptoms - pain, flatulence, bloating, abdominal distension, abnormal frequent stools - and a reasonable faecal fat absorption of more than 85%. Patients will eventually know the dose required for certain meals, increasing the dose for particularly fatty food. Many of the practical aspects of pancreatic enzyme administration have been covered in a useful recent review[108].

We have encountered few problems from overdosage. An occasional patient transferred from an older preparation to microspheres will become constipated, and hence these preparations should be started cautiously with a lower dose than the conventional preparations.

The potential renal problems from uric acid have not been encountered with either Cotazym or the microsphere preparations[109,110]. We have not observed raised serum uric acid levels on routine assessments of patients on a wide variety of doses of pancreatic supplements[37].

There are a few patients who, despite large doses of new pancreatic preparations, will continue to be intolerant of particularly fatty foods or have continuing abdominal symptoms and poorly controlled steatorrhoea. These patients require thorough gastroenterological investigation, particularly to exclude anatomical abnormalities and other causes of malabsorption. In such patients gastric acid may be effectively reduced and pancreatic extract preserved by the administration of sodium bicarbonate[111] or more effectively reduced by administration of an H_2 blocker, cimetidine or ranitidine[112]. These preparations, by preserving enzyme activity in the non-acid-resistant preparations, result in reduction in symptoms and steatorrhoea[47,113] and improved intraduodenal conditions[114]. In practice these preparations are only required in a minority of patients and should not be used until large doses of one of the microsphere preparations have been tried.

If the above strategies are followed, the distal ileal obstruction syndrome or meconium ileus equivalent, reviewed recently by Weller and Williams[115], should be a rare occurrence.

Nutrition in infancy

Breastfeeding has been widely advocated for the CF infant[116,117]. It is thought to be ideal because not only does it provide protective factors, it also contains lipase. Undoubtedly, adequate weight gain can be achieved by breastfeeding, but it is not without problems. It has been associated with the development of hypoproteinaemia, oedema and anaemia in untreated CF infants[118]. In addition, an increased incidence of electrolyte depletion has been recognized in CF babies being fed on breast milk[119]. Pancreatic enzyme preparations still need to be given with each feed and their administration and determination of exact dose are difficult. Furthermore, the anxiety created by the diagnosis of CF in the baby may result in reduced production of breast milk. Although it is our practice to encourage breastfeeding, it is on the understanding that adequate weight gain is maintained. We have found the supplementation of breast feeds to be unhelpful.

Table 2. Recipe and analysis for cystic milk

Recipe (use SMA Gold Cap scoop)
2 level scoops SMA Gold Cap (Wyeth)
2 level scoops Marvel (Cadburys)
2 level scoops Maxijul (SHS) or Polycal (Cow & Gate)
4 oz (114 ml) boiled water
Analysis per 100 ml
75 kcal
2.4 g protein
2.0 g fat
12.3 g carbohydrate
1.4 mmol sodium

A useful high-protein formula milk we have successfully used on more than 20 infants is a feed based on a normal infant milk, skimmed milk powder and a glucose polymer[117]. The recipe and analysis of this is summarized in Table 2. This milk is not only higher in energy, it contains more protein and sodium than standard modified formula milks; it appears to meet the CF infant's increased nutritional needs and most thrive well on it.

In contrast, infants who require surgery following meconium ileus may develop a temporary disaccharide intolerance. Alternative lactose-free and even sucrose-free milks such as Pregestimil (Mead Johnson) or even comminuted chicken (Cow & Gate) with an additional fat, disaccharide-free carbohydrate, vitamin and mineral source, may be necessary. Pancreatic extracts are still needed with these milks.

CF infants usually require 200 ml of the feed per kg daily. Essentially, weaning is the same as for any other baby but is encouraged early, usually from 3 months, and if required solids are given four times daily.

Vitamin supplements

These are described elsewhere[59]. Present recommendations are daily supplements for all patients of vitamin A 8000 units, vitamin D 800 units and vitamin E 100 to 200 mg.

Reduction in energy requirements

The extent and activity of the respiratory infection is closely related to the increased energy requirement, and this is reflected in the short term by significant weight change during antibiotic therapy. Any approach to prevent or reverse nutritional problems must include an aggressive approach to even a low-grade respiratory infection. Even slight fall off in weight gain is commonly an early sign of increased activity of the chest infection and one of the most valuable signs recorded in the clinic.

Conclusions

Modern dietary recommendations will result in correction of the poor energy intake by introducing a high-energy, high-protein diet without any fat restriction, improvement in the often incompletely controlled intestinal malabsorption by adequate doses of a modern microsphere pancreatic supplement, and reduction in the excessive energy expenditure by aggressive antibiotic treatment of the chest infection.

Regular detailed monitoring of nutrition and growth, dietary intake and intestinal losses should be performed to determine the continuing adequacy of all aspects of treatment, which should be further evaluated at an annual comprehensive assessment[37]. Application of these recommendations to a large population of CF patients attending the Leeds Regional Cystic Fibrosis Unit has resulted in significant improvement in nutrition and vitamin status observed at subsequent annual assessments[120].

Finally, it is cause for concern that many CF children and adults in this country have, as yet, failed to benefit from these simple rational changes in dietary advice and from the quite impressive advantages of the new microsphere pancreatic preparations. Introduction of these recommendations will permit most CF patients to achieve normal or near normal nutrition and growth, which should be the aim of all those members of the CF team who undertake the responsibility for advising on management.

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