

Nutrition and survival in cystic fibrosis

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The principal clinical manifestations of cystic fibrosis are bronchiectasis with chronic pulmonary infection and pancreatic malabsorption due to destruction of the exocrine pancreas.¹ The interactions between the lung disease and nutrition are important because nutritional state usually parallels declining lung function and is a predictor of survival.² A better understanding of how these two factors relate to each other and influence survival may lead to further gains in outcome for patients.

A number of factors work together to cause most older patients with cystic fibrosis to be underweight.³ Malabsorption of fat is the major primary abnormality with nutritional consequences. This often presents in infancy with failure to thrive and steatorrhoea and is the clinical presentation resulting in a diagnosis of cystic fibrosis in 50% of patients in the absence of neonatal screening.³ Although malabsorption can be clinically corrected by pancreatic enzyme replacement, many patients with cystic fibrosis continue to have evidence of maldigestion and consequent malabsorption. Despite apparently adequate enzyme replacement which controls bowel movements, patients with cystic fibrosis lose about 15% of energy taken orally.⁴

Most adults with cystic fibrosis have a resting energy expenditure (REE) which is on average 20% higher than healthy age and sex matched volunteers.⁵⁻⁷ There have been suggestions that, at the cellular level, the consequences of abnormal function of the cystic fibrosis transmembrane conductance regulator (CFTR) gene are energy requiring. Epithelial cells from cystic fibrosis cell lines have increased oxygen consumption and this may be a consequence of abnormal function of the energy requiring CFTR protein which has a large number of ATP binding sites on the nucleotide binding folds of the CFTR molecule.^{8,9} This, however, is not likely to be clinically important as infants with cystic fibrosis have similar resting energy expenditure to healthy controls,¹⁰ and in older patients with cystic fibrosis the main determinant of energy expenditure is abnormal lung function.^{5,6}

As pulmonary disease progresses during the second and third decades, energy demands increase due to the effects of airflow obstruction on lung mechanics. Overinflation of the lungs increases the oxygen cost of ventilation, which may account for up to 10% of REE.⁵ In patients with chronic obstructive pulmonary disease the increase of oxygen cost of breathing accounted for all of the increase in REE,¹¹ while in patients with cystic fibrosis increased oxygen cost of ventilation only accounted for about 50% of the elevation in REE.⁶ An explanation for this is that chronic infection and inflammation may have energy requiring consequences, probably mediated by the effects of cytokines such as tumour necrosis factor alpha, interleukin 1, and interleukin 6 which have been noted to be raised in patients with cystic fibrosis.^{7,12} Increased sympathetic nervous system activity has also been described and may further increase energy requirements.⁷

During exacerbations of pulmonary disease, patients with cystic fibrosis have a further increase in REE with an associated increase in systemic inflammatory activity and a fall in spirometric measures of lung function.^{5,13-15} These changes may be reversed by antibiotic treatment which is

associated with a weight gain of about 1 kg.¹⁵ The changes in energy expenditure are associated with a reduction in acute phase reactants such as C-reactive protein and changes in lipid metabolism towards normal. This suggests that, in addition to the relentless progression of lung disease, acute exacerbations of chronic infection adversely affect the nutritional state in these patients. During the terminal phase of their life many patients with cystic fibrosis enter into a vicious cycle of repeated respiratory exacerbations with evidence of pulmonary and systemic inflammation, little change in lung function measurements, and declining body weight.¹⁶ This evidence strongly suggests that the systemic consequences of infection and inflammation are in part responsible for weight loss in patients with cystic fibrosis.

Some of the inflammatory and metabolic abnormalities seen in patients with cystic fibrosis are similar to those seen in patients with chronic infections secondary to AIDS, and in both diseases reduced body weight is a predictor of poor survival.¹⁷ Chronic infection may also cause anorexia due to physical factors such as increased mucus production and the anorectic effects of cytokines. Thus, in patients with cystic fibrosis there may be reduced energy intake, reduced nutrient absorption due to maldigestion, and an increase in energy expenditure resulting from abnormal pulmonary function and chronic sepsis. These factors promote weight loss and many studies have confirmed that older patients with cystic fibrosis are significantly underweight.¹⁸

It is also possible that poor nutritional state predisposes to a decline in lung function. In a study of predictors of survival from the Toronto Group, lung function measured as forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC), and body weight expressed as a percentage of weight for height predicted, were good indicators of medium term survival.² Body mass index, a good measure of nutritional state, is directly related to lung function and suggests that both poor nutritional state and abnormal pulmonary function have a combined detrimental impact on prognosis.

In a retrospective comparison between the cystic fibrosis units in Boston and Toronto a divergence in survival emerged with a median survival of 21 years in the Boston clinic and 30 years in the Toronto clinic.¹⁹ Demographic, anthropometric, and clinical parameters in the two populations were similar and management of patients in both units was comparable, except for nutritional advice provided to patients. The traditional approach of a low fat, high calorie diet was advocated in the Boston clinic whereas, from the early 1970s, high fat, high energy intakes with additional enzyme supplementation to counter steatorrhoea were encouraged in the Toronto clinic. The female patients in Boston were shorter than in Toronto yet, when weight was related to height (weight for height percentiles), this was greater in patients in Boston than in Toronto despite lower survival rates. In males, while height was greater in Toronto, the weight corrected for height was similar and the influence of height on survival persisted. This suggests that reduced height (stunting) is a more important determinant of survival than reduced body mass for height (wasting). The effect of stunting on survival may

be influenced by growth failure early in life during the important period of lung development and growth.

The data in the paper by Nir *et al* in this issue of *Thorax* provide some further interesting information regarding nutritional status in patients with cystic fibrosis.²⁰ The explanation for the slightly higher body weights in children during the first five years of life is not clear, but may be due to the enthusiastic response of parents to dietary advice to provide a higher energy diet. The study indicates clearly that nutritional problems become a major issue in the second and third decades of life. However, patients with cystic fibrosis achieve near normal height, albeit about two years later than healthy controls, which is reassuring in light of the Boston/Toronto data. Their weight starts to decline during late teenage years and this persists into adulthood. This might be explained by progression of lung disease but issues surrounding adolescence such as adherence to diet, pancreatic enzymes, and other treatments may have a significant influence on nutritional status.

This study does not directly link survival with measures of body composition but highlights the importance of assessing nutritional state and taking appropriate interventions to maintain body weight as close to normal as possible in patients with cystic fibrosis. It is reasonably clear that declining pulmonary function has an effect on nutrition but it is not clear whether a poor nutritional state accelerates declining lung function. Further work is needed to help understand in more detail the interaction between declining lung function and nutrition, and to establish whether interventions designed to improve nutrition retard declining lung function and improve prognosis.

Improving nutrition in patients with cystic fibrosis requires dedicated intervention by nutritionists and physicians to optimise pancreatic enzyme replacement, vitamin supplements, and supplemental energy as oral feeds and, in some patients, by enteral feeding. This form of intervention has been shown to improve body weight by about 5 kg over a period of 12–24 months and there have been suggestions that it may also improve or help to maintain lung function.^{20–23} One study showed an improvement in FEV₁ and FVC after 18 months of enteral feeding²² and two studies have suggested a reduction in the rate of decline in lung function.^{21,22} The number of patients in these studies was small, and there is a need for longer multicentre studies to assess whether aggressive nutritional intervention can reduce the progression of pulmonary disease and improve survival. In addition to optimising energy intake and pancreatic enzyme replacements, it is important to supplement fat soluble vitamins and, in some patients, trace elements. Clinical deficiencies of vitamins A, E, and K have been described and, as vitamin A and E are antioxidants, they may be important in attenuating the effects of proinflammatory oxygen derived free radicals.²⁴

Survival into adulthood is now the norm for patients with cystic fibrosis.²⁵ The paper by Nir *et al* highlights

these improvements in median survival and emphasises the importance of accurately assessing nutritional state. They suggest that particular vigilance is needed for adolescents and adults with cystic fibrosis to help to maintain body weight.

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