Nutrition in Cystic Fibrosis

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ABSTRACT

Cystic fibrosis (CF) is mostly recognized for its pulmonary morbidity, but the earliest manifestations of the disease are related to its gastrointestinal and nutritional derangements. Destruction of acinar pancreatic tissue, pancreatic ductular obstruction, and lack of enzymatic activity lead to malabsorption (particularly of fats), diarrhea, and failure to thrive. A minority of CF patients carrying milder CF transmembrane conductance regulator (CFTR) mutations have preserved pancreatic secretory activity and are free from significant malabsorption early in life. However, these patients are at risk for losing pancreatic function over time.

Nutritional status plays an important role in the progression of the pulmonary disease in CF. Further, CF patients with better nutritional status have a survival advantage. Several factors contribute to impaired nutritional status in CF (e.g., pancreatic insufficiency, chronic malabsorption, recurrent sinopulmonary infections, chronic inflammation, increased energy expenditure, suboptimal intake). Progressive lung disease further increases calorie requirements by increasing the work of breathing. Treatment programs that place an emphasis on higher caloric intake and more aggressive nutritional management in CF patients report better outcomes. Basic tenets of nutritional repletion in CF include the use of pancreatic enzyme replacement therapy and following a high calorie, high protein, unrestricted diet. At the Stanford Cystic Fibrosis Center, nutritional status is assessed on an ongoing basis through anthropometric parameters and annual assessment of body composition, bone density, glucose tolerance, and various biochemical and micronutrient levels. Based on the anthropometric data obtained on routine clinical encounters, patients are categorized as to their nutritional risk. This proactive approach for the early identification of nutritional risk has become a major theme within the network of US CF centers. Aggressive nutritional support with adequate pancreatic replacement management should lead to both normal growth and lung function preservation. In addition, nutritional status has to be monitored closely during routine encounters to allow for early intervention once derangements are noted. This will include increasing calories in the early stages of lung disease and being vigilant of gastrointestinal symptomatology and complications.

KEYWORDS: Cystic fibrosis, pancreatic insufficiency, malabsorption, gastrointestinal, nutrition, CFTR

Although cystic fibrosis (CF) is mostly recognized for the pulmonary morbidity associated with it, the earliest and most notable manifestations of the disease are related to its gastrointestinal and nutritional derangements.[1,2] The absence of normal CF transmembrane conductance regulator (CFTR) function leads to

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abnormalities in endocrine glands that are most notorious in the gastrointestinal tract by the destruction of the acinar pancreatic tissue due to ductular obstruction.[3] As a result there is a loss of the ability to secrete pancreatic enzymes and bicarbonate into the duodenum from pancreatic insufficiency (PI). A direct consequence is the absence of enzymatic breakdown of nutrients in the upper bowel lumen as well as a decrement in the ability to buffer gastric contents as they empty into the duodenum.[4] An additional detrimental effect is the precipitation of bile salts due to the low duodenal pH.[5] The combination of the lack of enzymatic activity and normal bile salts leads to malabsorption of ingested nutrients, and particularly fats, which is manifested by diarrhea and failure to thrive. Only a minority of CF patients carrying milder CFTR mutations have preservation of their pancreatic secretory activity and are free from significant malabsorption early in life. However, this subgroup of patients are still at risk for losing their pancreatic function over time.[6]

NUTRITION AND LUNG DISEASE PROGRESSION IN CF

While it is clearly recognized that in CF patients pulmonary function is the primary predictor of death and that the yearly rate of decline of forced expiratory volume in 1 second (FEV_1) is the most important variable predicting mortality,[7,8] the factors responsible for the long-term preservation of lung function in the oldest survivors have not been completely identified. Multiple previous studies suggest that nutritional status plays an important role in the progression of the pulmonary disease.[9,10] Longitudinal cohort studies point to a survival advantage among patients with the best nutritional status.[11,12] Pulmonary function per se does not have as strong an effect, and thus survival seems more strongly associated with growth, and particularly with height.[13] A second important finding of previous studies is that treatment programs that place an emphasis on higher caloric intake and more aggressive nutritional management report better outcomes.[11,14]

PI with chronic malabsorption, recurrent sinopulmonary infections, chronic inflammation, and increased energy expenditure coupled with suboptimal intake are major determinants of malnutrition in patients with CF. In addition, progressive pulmonary function deterioration contributes to malnutrition because it will influence both energy expenditure and activity. More importantly, the pulmonary disease even in its subclinical stages is an early contributor to the nutritional status seen in patients.[15] It is well recognized that obstructive lung disease increases energy expenditure from the high demands of the work of breathing,[16] and this is prominent in older CF patients with severe lung compromise,[17–20] but the actual temporality of the causal relationship between malnutrition and pulmonary dysfunction in CF is not completely clear. Clinical studies in infants diagnosed by newborn screening[21–23] have pointed to the presence of an active inflammatory process in the airways even before lung dysfunction becomes clinically apparent.

Energy Expenditure in CF

The majority of people with CF have a higher energy need, estimated to be between 120 and 150% of normal requirements. This is thought to be partly due to an increased resting energy expenditure (REE).[24–26] Children with CF have consistently been found to have higher REE compared with control children, and both in children in preclinical stages[26,27] and in children with different degrees of disease severity.[28] This information has been taken as evidence for a phenotypic primary defect in the metabolism of these children, leading to an increase in energy requirements. At the basic level, there is some supporting evidence from studies showing evidence for a disruption in the intracellular energy use associated with the presence of a defective CFTR and this leading to increases in energy expenditure.[29,30] However, investigations in infants diagnosed by newborn screening with the use of appropriate methodological adjustments have shown that their REE is within the values seen in normal controls.[31,32] This evidence clearly establishes that REE in infants with CF is comparable to the REE of controls and that the growth deficits noted were explained by their PI and malabsorption. There is also evidence for the REE to increase over predicted values only once significant lung dysfunction is present.[33] This argues against a genetically determined alteration in energy metabolism. What is clear is that progressive obstructive lung disease further increases calorie requirements as it increases the work of breathing.[34]

Body Mass in CF

Irrespective of a genetically determined increase in energy expenditure, the more clinically relevant issue of the influence of nutrition on lung disease remains incompletely understood. It is intuitive to assume that during the early stages of the child's growth and development, any impairments may affect the rate at which the lungs grow, and this in turn will become a strong determinant for the development of lung disease.[35] There is some support for this possibility in the observation that CF patients who are not pancreatic insufficient not only have better nutritional parameters but also a lower rate of pulmonary deterioration.[36] In addition, studies conducted in infants diagnosed through newborn screening indicate that growth failure still occurs in this patient population despite the early diagnosis,[23,37] and this

Table 1 Factors that Contribute to Malabsorption in Cystic Fibrosis

Pancreatic insufficiency
Duodenal luminal acidity
Bile salts abnormalities
Upper bowel bacterial overgrowth
Delayed gastric emptying
Bowel motility abnormalities
Intestinal mucosal abnormalities

The presence of these gastrointestinal abnormalities should be investigated in patients who do not respond to adequate pancreatic enzyme replacement therapy.

seems to precede the decline in pulmonary function.[37] Thomson et al in a prospective evaluation of their CF patient population were able to identify important relationships between changes in growth and pulmonary function.[38] In their study, an accretion of total body potassium within the expected range was associated with a decline in FEV_1 at a rate of less than half that observed in children who were not able to accrue at an acceptable rate. These findings suggest that in the early stages of the lung disease certain components of the body mass may play a stronger role in determining the preservation of the lung function.

The body mass can be seen as mainly consisting of two compartments: fat mass and fat-free mass, with the fat mass reflecting the energy stores and the fat-free mass representing mainly muscle and protein stores. Then the body weight by itself is an indirect marker of protein mass and energy stores, and changes in body weight measured serially over long periods in patients without fluid problems reflect changes in the protein mass and/or energy content. The main components of the fat-free mass are the skeletal muscle, water, and bone mass, with muscle constituting the largest. All of these components of the body mass can be estimated from calculations based on anthropometric measurements, or more directly from isotope studies or by dual-energy x-ray absorptiometry (DXA), among other methods.[39] Studies that have specifically looked at the different components of the body mass in children with CF have been inconsistent in their findings when compared with control groups, with some studies finding important differences,[40,41] whereas others have found only small, nonsignificant differences.[42,43] The only long-term longitudinal study reported to date that has looked at body composition changes in children with CF[44,45] has reported significant relationships between the fat-free mass and REE and also a divergence over time in the accrual of fat-free mass between children with CF and controls.

These findings have important implications for the possible role of nutrition in the development of CF lung disease. Although weight gain per se is important, maintenance of normal muscle mass may be intimately connected with both normal growth and good pulmonary function in CF children. There are several reports of increased protein catabolism in poorly growing children with CF.[46–49] The presence of a delay in the accrual of an adequate fat-free mass will imply lower development of the skeletal muscle, including the respiratory muscles. Previous studies using measures such as the maximum inspiratory and expiratory pressures (P_{Imax} and P_{Emax}) and the maximum voluntary ventilation (MVV) have shown abnormalities in the performance of the respiratory pump in CF patients with different degrees of

Table 2 The Stanford Cystic Fibrosis Center Nutrition Screening Protocol

Patient Assessment Worksheet
Children and Adolescents (Ages 2–20 years)
Weight velocity
Current wt (kg):_____ wt %ile:_____ Date: _____
Wt (kg) last clinic visit: _____ Date: _____
Net change in weight: _____ Number of days between weights: _____
Daily wt gain (gm/day) _____ **Points:** _____
Height velocity
Current ht (cm):_____ ht %ile:_____ Date: _____
Ht (cm) prior to current visit:_____ Date: _____ (***use 3 to 12 months interval***)
Net change in ht:_____ Annualized height velocity (cm/year)_____ **Points:** _____
BMI: _____ BMI Percentile: _____ **Points:** _____
Adults (Ages >20 years)
Height (cm): _____ Current Weight (kg): _____ Date: _____
BMI: _____ **Points** _____
IBW (kg): _____ Current % IBW: _____ **Points** _____
Wt (kg) last clinic visit: _____ % weight change: _____ **Points** _____
Current FEV_1: _____%-pred. **Points** _____
Total Points: _____ **Risk Level**_____

The information entered is used to assign a risk category to the patient.

Table 3A Pediatric Categorization of Nutrition Risk—the Stanford Cystic Fibrosis Center Nutrition Screening Protocol

	0 Risk Points	1 Risk Point	2 Risk Points
Weight/stature	BMI ≥50%ile for age	BMI 10–50%ile	BMI <10%ile
Weight velocity*	If BMI ≥50%ile, actual wt gain ≥10%ile for expected	If BMI ≥50%ile, actual wt gain ≤10%ile for expected weight gain ≥3 months	Wt loss or no gain >6 months
	If BMI <50%ile, actual wt gain >50%ile for expected	Or, if BMI <50%ile, actual wt gain <50%ile for expected wt gain ≥3 months	
Height velocity**	Actual ht gain ≥10%ile expected velocity	Actual ht gain ≤10%ile expected velocity	Female (up to 14 years): no ht gain >6 months Male (up to 15 years): no ht gain >6 months

*Expected weight and height velocities are taken from the Fels longitudinal study data: Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. Am J Clin Nutr 1986;43:711–722.
**Height velocity categorization is adjusted to take into account pubertal stage and midparental height predicted ht percentile. 1 point is substracted if pubertal stage is below that expected for current age and/or if within the ht%ile expected based on midparental height estimation. Pubertal stage is assessed based on the tables by Tanner,[67] and midparental height estimation according to the formulas by Luo et al.[68]

Table 3B Adult Categorization of Nutrition Risk—the Stanford Cystic Fibrosis Center Nutrition Screening Protocol

	0 Risk Points	1 Risk Points	2 Risk Points
BMI	Men >23 Women >22	Men ≥20–22 Women >20–22	Men or Women ≤19
% IBW*	≥90%	85–89%	≤84%
Weight change	Stable weight or weight gain	≤5% weight loss in 3 months	>5% weight loss in 3 months
$FEV_{1\%}$ pred.	>75% pred.	40–75% pred.	<40% pred.

*Percent ideal body weight (%IBW) is calculated by dividing the actual weight by the IBW and multiplying by 100. The IBW can be estimated using the formulas proposed by Budd and colleagues,[69] which apply across the age span:
Females: $IBW\ (kg) = e^{(-0.3198 \times Ln(Ht\^4) + 7.5767 \times Ln(Ht\^3) - 63.306 \times Ln(Ht\^2) + 222.74 \times Ln(Ht) - 299.6)}$,
Males: $IBW\ (kg) = e^{(-1.0504 \times Ln(Ht\^4) + 20.689 \times Ln(Ht\^3) - 151.4 \times Ln(Ht\^2) + 490.3 \times Ln(Ht) - 592:49)}$,
where Ht is height in centimeters and Ln is the natural logarithm.

Table 3C Nutrition Risk Levels (Any Age Group)—the Stanford Cystic Fibrosis Center Nutrition Screening Protocol

Low Risk	Moderate Risk	High Risk
0–1 points	2–3 points	≥4 points

Assessment and categorization is performed at every clinic visit and based primarily on the anthropometric data obtained.

pulmonary dysfunction, and particularly with respect to their respiratory muscle strength.[50–52] However, respiratory muscle weakness was not found in children with CF with normal pulmonary function when compared with controls; implying that the loss of muscle mass or strength precedes the development of lung disease.[53] More recent studies provide evidence for a defect in the muscle mass that is not specific to CF and probably related to the chronic infectious and inflammatory process because non-CF disease controls demonstrate similar deficits in oxygen extraction.[54] In addition, studies on the effect of nutritional intervention for malnourished CF patients have shown that, although gains in pulmonary function may not be consistently achieved, positive changes in the respiratory muscle function can be achieved.[55] Of interest, one study showed that the improvement in FEV_1 seen with nocturnal gastrostomy tube supplementation was correlated to change in lean body mass (LBM), rather than to change in body fat.[56] In addition, reversal of protein catabolism stabilizes pulmonary function and decreases the number of hospitalizations for acute pulmonary exacerbation.[48] Further, the reported experience with the use of growth hormone in CF patients points to improvements in both respiratory status and LBM.[57,58] In these small controlled trials, prolonged therapy led to improvements in pulmonary function parameters, measures of respiratory muscle strength, hospitalization rates, and gains in exercise capacity in the patients randomized to active treatment. It is possible then that the effect of nutrition on CF lung disease from early on in life is borne out of inadequate growth of the lung as well as a deficit of the respiratory pump to meet efficiently the requirements imposed by the airway disease.

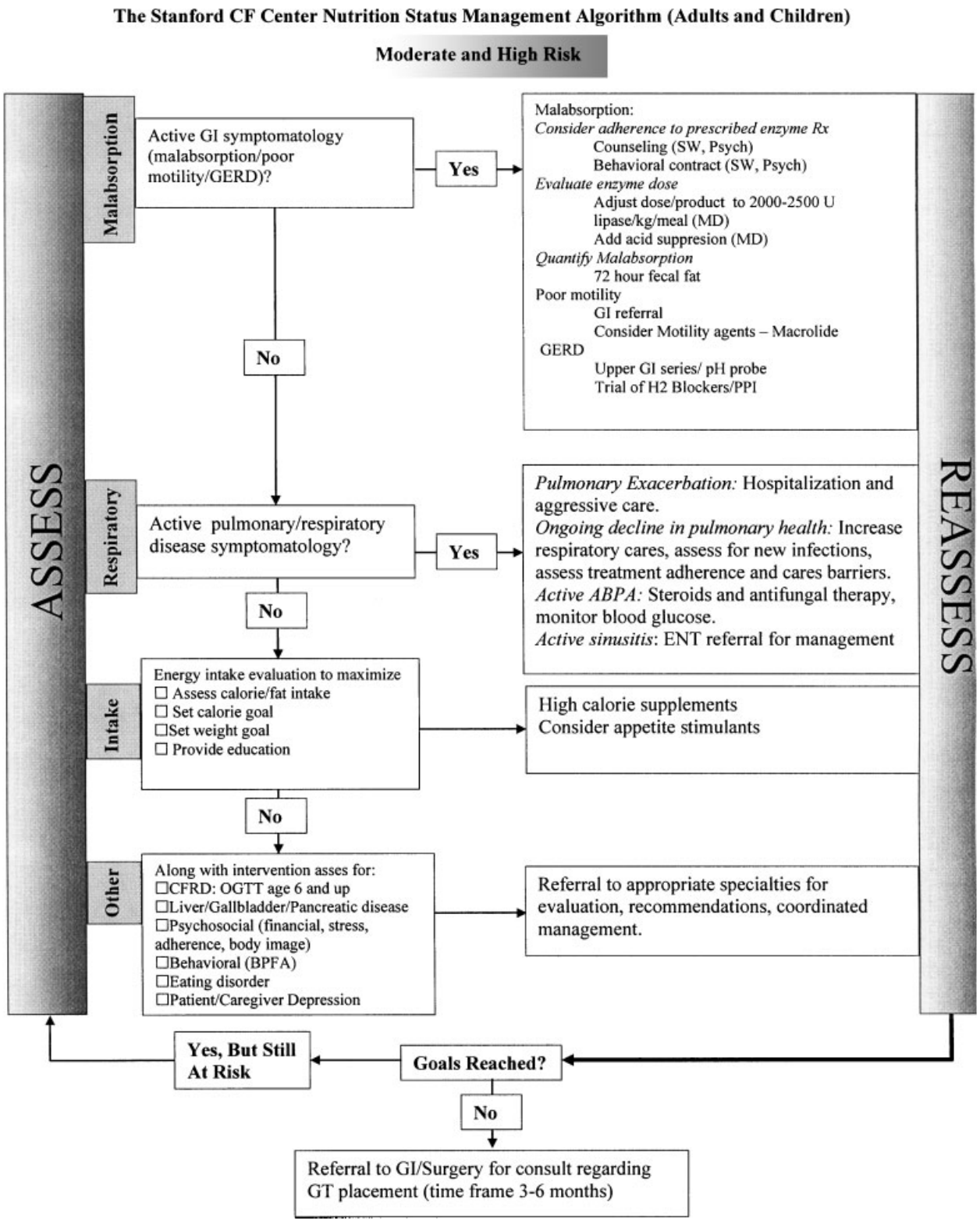

Figure 1 Nutritional management algorithm followed at the Stanford cystic fibrosis center for patients identified with a moderate or high nutritional risk. A plan of care is formulated with clear goals identified and presented to the patient and family.

NUTRITIONAL INTERVENTION AND MANAGEMENT

The basic tenets of the nutritional management of CF patients with PI includes the use of pancreatic enzyme replacement therapy (PERT) and following a high calorie high protein unrestricted diet.[59] Guidelines are available for the management of PERT with the main goal of achieving adequate levels of absorption of nutrients while maintaining doses within recognized safe ranges.[60,61] For the most part dosing guidelines are based on consensus and the limited evidence available from small studies. It should be noted that recent evidence from a study on infants with CF points to significant levels of malabsorption when infants are maintained on doses that may be taken as within an adequate range.[62] What is important is to be aware that several factors beyond PI are involved in the malabsorptive process in CF patients, and these are likely to change over time and depending on changes in health (Table 1). Thus just maximizing the dose of pancreatic enzymes may not necessarily lead to better absorption.[4]

Nutritional intervention with high calorie supplements in CF patients is predicated on the assumption that improved nutritional status will improve pulmonary function. However, as noted on a Cochrane review,[63] there is a lack of firm evidence from controlled trials to support this recommendation and much less data to guide what types of interventions might be most effective. The review identified the need for multicenter randomized trials to assess the efficacy and possible adverse effects of supplemental enteral tube feeding compared with normal oral feeding and oral supplement feeding in CF. The evidence available from small uncontrolled studies suggests that patients do benefit from enteral supplements. Still, which interventions will be of most value (e.g., energy supplementation vs protein supplementation vs additional exercise as a component) depend to some extent on which components of the body mass are most important in maintaining pulmonary function, and this is not completely clear from the data available. From a clinical perspective, what is apparent in many patients is that oral calorie intake is frequently affected by the inappetence associated with respiratory infection, and the abdominal discomfort from malabsorption and side effects of medications. It also needs to be taken into account that even with adequate control of fat malabsorption using PERT, patients with CF may still be unable to meet their increased energy requirements.[64,65]

At the Stanford Cystic Fibrosis Center, an important component of the nutritional management of CF patients is the assessment of their nutritional status on an ongoing basis through anthropometric parameters. In addition, at least on a yearly basis patients undergo more comprehensive assessment with body composition and bone density analysis by DEXA, screening for cystic fibrosis related diabetes by oral glucose tolerance testing (OGTT), as well as biochemical and micronutrient levels assessment. Based on the anthropometric data obtained on routine clinical encounters (Table 2), patients are categorized as to their nutritional risk (Tables 3A, B, and C). The main goal of this categorization is to identify patients early and intervene appropriately, hopefully at a time when they will be more amenable to respond to intervention. In addition, this ensures that a uniform protocol is followed for all patients so as to decrease variability in care practices. Patients considered to be at medium or high nutritional risk are evaluated following the algorithm presented in Fig. 1. This proactive approach for the early identification of nutritional risk has become a major theme within the network of US CF centers. Multiple examples of successful quality improvement initiatives centered on nutritional outcomes have accumulated over the last decade[66] and been driven by an initiative sponsored by the US CF Foundation.

CONCLUSION

In conclusion, the findings of multiple longitudinal and interventional studies consistently point to a strong influence of growth and nutrition in CF lung disease. Because early in life the nutritional deficiency is primarily related to PI and malabsorption, it can be assumed that aggressive nutritional support with adequate pancreatic replacement management should lead to both normal growth and lung function preservation. In addition, nutritional status has to be monitored closely during routine encounters to allow for early intervention once derangements are noted. This will include increasing calories in the early stages of lung disease and being vigilant of gastrointestinal symptomatology and complications. Given the progressive deterioration of the lungs that CF patients experience, there is an ongoing need to identify more effective nutritional interventions through long-term controlled studies, and particularly in the early stages of the disease before significant malnutrition has occurred.

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