Nutrition and Lung Disease in Cystic Fibrosis

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It is well recognized that among patients who have cystic fibrosis (CF), lung disease is a significant reason for morbidity and pulmonary function is the primary predictor of death [1]. Consequently, the rate at which pulmonary function is lost is the most important variable predicting mortality [2]. To this day, despite the importance given to pulmonary cares and the multiple advances in this aspect of the disease, the long-term preservation of lung function remains difficult to accomplish. Long-term preservation of lung function is likely a multifactorial process whereby the factors with the strongest influence remain unclear or difficult to control.

Nutritional status is clearly recognized as a factor that is tightly intertwined in this process, and the temporality of this association has long been debated. Still, from the time when the first effective therapeutic strategies for the management of CF were described [3,4], aggressive nutritional support has been a fundamental component of the recommended treatment regimens.

Magnitude of the problem

The most recent consensus statements on nutritional management for patients who have CF [5,6] introduced important changes in the assessment parameters and categorization schemes recommended for the classification of nutritional status (Table 1) [7,8]. With the availability of the Centers for Disease Control and Prevention body mass index (BMI) percentiles and the increased familiarity of adult care providers with this parameter, BMI is now favored over percentage ideal body weight (%IBW) as the preferred assessment parameter for children and adults. Added to the fact that the calculation of %IBW remains cumbersome, comparative studies have demonstrated a better discriminatory ability of BMI percentile over %IBW for the detection of underweight malnutrition [9,10]. Further, recent reviews of the US Cystic Fibrosis Foundation Patient Registry (CFFPR) have revealed that BMI percentile in children and BMI values in adults are directly and strongly correlated with pulmonary function parameters such as forced expiratory volume in 1 second (FEV₁) (Fig. 1). In view of this finding, the current recommendation is to aim for a BMI at the 50th percentile for children and a BMI of 22 kg/m² for adult women or 23 kg/m² for adult men [11]. In addition, added emphasis is given to the assessment of linear growth in children not only in terms of height-for-age percentile but also by interpreting this percentile in relation to the child’s growth potential as determined by the target adult height percentile.

Epidemiologic studies

Given that many early studies showed good correlation between the degree of malnutrition and the severity of pulmonary disease, this finding has been taken as indirect evidence for the influence that nutrition has on the course of the lung disease and subsequent mortality [12]. Despite these observations, malnutrition continues to be one of the main clinical manifestations of CF across the age span, regardless of the time from diagnosis. The most recent estimates in the United States continue to indicate that inadequate weight gain and linear growth retardation are highly prevalent among children who have CF. Data reported by the CFFPR show that 22% of children who have CF...
Fall below the 10th percentile for weight and that 14% fall below the fifth percentile for height [11]. In addition, and not surprising given its high prevalence in childhood, as age increases, so does the prevalence of malnutrition among adult patients. According to the most recent estimates available, on average, 60.8% of adults who have CF have a BMI below the recommended levels [11], and the rate of nutritional failure (BMI < 19 kg/m²) is estimated to be 38.5% [13].

In contrast, over 2 decades ago, the Toronto Cystic Fibrosis Center reported that their patient population had growth parameters that did not differ from the available normative data [14]. Their data showed, on average, fairly normal height percentiles in male and female patients. In addition, although weight percentiles were lower in female patients, underweight rates were lower than those reported from other centers. This report was followed by the classic Boston–Toronto comparison study. The study demonstrated clear-cut differences in the median survival of the two cohorts of patients: 21 years in Boston versus 30 years in Toronto. There was also a sharp contrast in the average growth parameters observed at each clinic, with the children in Toronto being ahead in their percentiles, particularly for height. Most interesting was the fact that pulmonary function parameters were comparable between the two groups. Given the differences noted in growth parameters, the survival advantage of the Toronto cohort was ascribed to their better nutritional status [15].

A second important finding of this study was that the main difference between the treatment programs was the approach to dietary intervention, with the Toronto site being unrestricted in terms of fat intake [16]. A second look 10 years later at the United States and Canadian data revealed that although there were still differences in the nutritional parameters, the gap noted on the previous study had already narrowed [17], probably as a reflection of the adoption of the Canadian nutritional support approach by United States centers [18].

Multiple previous longitudinal and cross-sectional studies that have looked at the relationship between morbidity and nutritional status concur that in CF patients, growth abnormalities and development of lung disease are linked [19–21]. Further, there is also evidence that interventions to establish weight gain are associated with improvements in pulmonary function [22–24].
addition, in agreement with the findings of the Toronto group, a review of the CFFPR data revealed that children who had a height percentile below the fifth percentile at age 5 or 7 years had a higher risk of death from the disease, with the risk estimates ranging from 3 to 6 times higher and without significant differences between boys and girls [25]. These results are in concordance with the assertion that growth, particularly linear growth, is intimately connected to the evolution of lung health in children who have CF.

From a clinical perspective, regardless of disease entity, the link between malnutrition and lung dysfunction is well established. The lung disease seen in patients who have CF primarily involves the airways and produces obstructive changes. Severe obstructive lung disease increases energy expenditure from the high demands of the work of breathing [26], and this is prominent in CF patients who have more advanced stages of lung disease [27–31]. The causal relationship between malnutrition and pulmonary dysfunction, however, particularly in terms of its temporality, remains unclear in CF. In the early, presymptomatic stages of lung disease during infancy and childhood, it is intuitive to assume that because this stage is crucial for lung growth and development, any nutritional derangements may affect the rate at which the lungs grow. This decreased growth, in turn, becomes a strong determinant for the development of lung disease [32,33]. There is some support for this possibility in the observation that CF patients who do not suffer from pancreatic insufficiency not only have better nutritional parameters but also a lower rate of pulmonary deterioration [34,35].

Perhaps the interrelations between nutrition and lung disease could become clearer if studied in infants, because 85% have digestive manifestations even in the newborn period, and lung disease is not apparent in many young infants. Clarifying these interrelations, however, might not be so simple because studies on infants diagnosed by newborn screening [36,37] and studies with CF fetal airways [38] have demonstrated that there is an active inflammatory process present in the airways even before chronic infection and a symptomatic stage are reached.

Several longitudinal and prospective observational studies have provided mounting evidence for the temporal and potential causal relationship between malnutrition and pulmonary dysfunction in CF. Thomson and colleagues [33], in a prospective evaluation of their CF patient population, were able to identify important relationships between changes in growth and pulmonary function. In this study of CF patients who had pancreatic insufficiency, growth was assessed by conventional anthropometric parameters and accretion of body cell mass was assessed by total body potassium. Potassium is the main intracellular cation, and the change in its total content in the body is an accurate surrogate for the change in the cell mass [39]. Children who kept their cell mass accrual within the expected range experienced a decline in FEV₁ at a rate of less than half of that observed in children who were not able to accrue at an acceptable rate. Thus, this finding suggests that the
lack of adequate growth also affected the growth and preservation of the lung tissue mass.

At a larger population level, information from longitudinal studies has also suggested that the presence of malnutrition precedes the development of lung dysfunction. In a report from the German CF Quality Assurance database, malnourished patients had significantly lower pulmonary function parameters, independent of the presence of infection with *Pseudomonas aeruginosa* [40]. More important, during childhood, patients who had good nutrition kept stable levels of FEV₁. In addition, a negative trend in weight-for-height over a 3-year period was associated with a decline in FEV₁, suggesting that maintaining weight was an important determinant of stability in lung function.

The author and colleagues [41] further investigated the effect of changes in growth parameters at a younger age on pulmonary function. A retrospective analysis of the Minnesota Cystic Fibrosis Database, a large repository of prospectively collected clinical data, revealed important associations between the rate of weight gain and changes in FEV₁. Children who maintained an adequate rate of weight gain between ages 6 and 8 years experienced significantly higher gains in FEV₁ during the same period. By repeated-measures regression analysis, sex and age at diagnosis did not play a role in the longitudinal trends in pulmonary function. Weight at first observation, however, had a strong effect, with a 55-mL difference in FEV₁ for every kilogram of difference in the initial weight ($P < .0001$). More important, weight gain during the 2-year follow-up was also strongly associated with change in FEV₁. An increase in weight of 1 kg was associated with a 32-mL increase in FEV₁ ($P < .0001$). Height and change in height from first observation were not significantly associated with FEV₁ values ($P = .08$ and $P = .20$, respectively). These results could be interpreted as reflecting better lung growth among children who experienced adequate rates of body mass accrual.

A larger study of the data prospectively collected in the Epidemiologic Study of Cystic Fibrosis on children who had their clinical information collected at ages 3 and 6 years demonstrated important effects of growth parameters on pulmonary function [42]. Significant differences were noted in the pulmonary function measurements at age 6 years according to the percentiles recorded at age 3 years. These differences were more pronounced for the relationship between weight-for-age and FEV₁, in which there was a difference of 15 points between children in the highest and lowest percentile categories. In addition, changes in weight-for-age between ages 3 and 6 years were directly associated with changes in FEV₁.

**Insights into mechanisms**

From a developmental and mechanistic perspective, multiple animal and human studies have provided mounting evidence for a causal association between malnutrition and pulmonary abnormalities. Studies conducted in populations in which nutritional deprivation in early childhood is highly prevalent have shown important deficits in lung function. A study with Indian children showed significant associations between low BMI and differences in FEV₁, in addition to relationships between head circumference and lung function [43]. The differences noted increased with age, suggesting that as the child grows older, the differences in lung capacities become more profound, possibly because of differential rates of lung growth. Further, peak expiratory flow rate corrected for height was affected to a much lesser degree, suggesting that a reduction in airway caliber was unlikely to be responsible for the differences in pulmonary function. This finding was taken to be consistent with a reduction in lung volumes from impaired lung alveolar growth during postnatal life. A second study with children in Africa confirmed important pulmonary function deficits in a group of stunted and underweight children [44]. In addition to confirming the findings of previous, similar studies, this study found a direct relationship between fat-free mass (FFM) and lung function. Although forced vital capacity and FEV₁ were lower in the malnourished group compared with control subjects, the spirometric pattern that was noted was of an obstructive process. This finding was not further investigated to see whether it represented airway disease, but the enrolled children were free from respiratory disease and had a negative respiratory history. These findings were interpreted as indicative of the limited energy expenditure associated with malnutrition hampering lung development and function.

The potential mechanisms behind these associations can be drawn out from animal studies. Animal models of caloric deprivation have shown significant changes in the terminal airspaces, with consequent changes in the lung mechanical
properties [45]. Investigations that have focused on the effects of nutritional deprivation in the early stages of postnatal lung development have demonstrated immediate and long-term alterations in the lung structure. In rats, intermittent food deprivation in the first week of life leads to the development of enlarged alveoli from defective septation, with thicker walls and decreased deposition of elastin [46]. In addition, early nutritional deprivation induces disruption of epithelial differentiation in bronchioles; this effect seems permanent because it persists after re-establishing adequate food intake [47]. At later stages in life, malnutrition also has important effects on lung structure and function. Increases in surface forces with a decrease in tissue elasticity are noted in excised lungs, perhaps reflecting changes in surfactant properties and remodeling of the connective tissue support. Of interest, with refeeding, surface forces return to normal, but the elastic forces only partially recover [45]. Evidence for alveolar remodeling with expansion of the terminal airspaces has been demonstrated in multiple animal studies [48–50], which concurs with the lung findings in anorectic humans [51,52]. Of interest, air trapping is a common finding in CF patients, being noted in young asymptomatic infants [53–55] and correlating with the degree of malnutrition [56]. Further, Massaro and colleagues [57] identified an up-regulation in caspasases and granzymes in association with the development of emphysematous changes in the lungs of starved mice, suggesting activation of cytotoxic T lymphocytes and natural killer cells. As a corollary to this finding, it could be proposed that on the background of the heightened inflammatory response typical of CF, malnutrition could provide an additional mechanism for immune activation. In addition, vitamins and other nutrients seem to have a strong influence on respiratory health [58]; their deficiencies are known to have deleterious effects on lung defense mechanisms such as ciliary activity, antioxidant balance, and innate immunity [59].

Together, these different deleterious effects have important implications for CF. As summarized in Fig. 2, these effects are likely to compound the airway surface defects that are known in the pathophysiology of CF lung disease. More important, these effects likely play a role during crucial periods of lung development early in life and may condition the rate at which the lung disease progresses.

Pancreatic insufficiency and the resultant chronic malabsorption is a major determinant of malnutrition in patients who have CF. This state is compounded by the added effects of chronic infection and inflammation with poor appetite and the development of comorbidities like CF-related diabetes mellitus (CFRD) and other gastrointestinal pathology. Given that these factors affect the intake and retention of nutrients, the nutritional problems in CF patients can be best understood if seen as the end result of an unfavorable energy balance as proposed by Pencharz and Durie [60]. Thus, to maintain growth rates and a nutritional status comparable to healthy controls, it has

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**Fig. 2.** Interactions in the lung (beyond abnormal mucus clearance) between the presence of CF (italic letters) and the effects of malnutrition (bold letters); effects likely to be conditioned by both are underlined. CTL, cytotoxic T lymphocytes; NK, natural killer; PMN, polymorphonuclear leukocyte; ROS, reactive oxygen species.
long been recommended that children who have CF should reach 120% to 150% of the typical recommended daily caloric intake [5,61]. Studies have shown, however, that the actual dietary intake of CF patients frequently falls short of these recommendations [62]. This deficit in energy balance will certainly be aggravated as the lung disease reaches a symptomatic stage and the repeated episodes of infection further promote a catabolic process. Many patients then fall into a vicious spiral that over time contributes to lung disease progression and overall health decline, as summarized in Fig. 3.

Data on resting energy expenditure (REE) in children who have CF consistently show increases compared with control children, children in preclinical stages [63,64], and children who have different degrees of disease severity [65]. 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, some studies show supporting evidence for a disruption in the intracellular energy use associated with the presence of a defective cystic fibrosis transmembrane conductance regulator, leading to increases in energy expenditure [66,67]. Bronstein and colleagues [68], however, reported a normal REE in a group of CF infants who did not have clinical signs or symptoms of the disease. This finding was confirmed by Bines and colleagues [69], establishing that REE in CF infants is comparable to that in healthy controls. Further, the growth deficits noted can be explained solely on the basis of pancreatic insufficiency and malabsorption, thereby arguing against a genetically determined alteration in energy metabolism. What is important is that the presence of even mild lung disease is associated with elevations in REE, suggesting that REE could be a sensitive marker of clinical status before lung disease becomes clinically apparent [70], although there seems to be a differential response between boys and girls [71]. Certainly, the development and progression of the lung disease determines increases in REE, which in turn adds to the energy imbalance [72], and the presence of chronic infection with Pseudomonas, with its consequent exuberant inflammatory state, magnifies this effect [73].

The nutritional status of a CF patient can be seen as the result of a very dynamic process influenced by energy intake and the presence of all of the factors known to influence the energy balance against the metabolic demands imposed by the lung disease. The body weight at any point in time reflects the status of this balance. Weight by itself can be interpreted as an indirect marker of protein mass and energy stores, and changes in body weight measured serially in patients who do not have fluid problems reflect changes in the protein mass, energy content, or both [74]. Body weight can be seen as reflecting the amounts of two basic components: fat mass and FFM. The main components of the FFM are skeletal muscle,
water, and bone mass, with muscle constituting
the largest component. These components of
body mass can be estimated from calculations
based on anthropometric measurements or more
directly from isotope studies or by dual-energy
x-ray absorptiometry, among other methods [74].

Studies that have specifically looked at the
different components of body mass in patients
who have CF compared with control subjects
have been inconsistent in their findings, with some
studies finding important differences [75,76] and
others finding small, nonsignificant differences
[77,78]. The only long-term longitudinal study re-
ported to date that has looked at body composi-
tion changes in children who have CF [70,79]
reported significant relationships between FFM
and REE and a divergence over time in the ac-
crual of FFM between children who have CF
and control subjects. In adults who have CF, im-
portant associations between FFM and circulating
inflammatory mediators have been noted
[28]. In addition, patients who have an already
compromised FFM had higher markers of catab-
olism and inflammation during pulmonary exacer-
bations and showed a lower response in these
markers after therapy for the exacerbation [80].

These findings could have important implica-
tions for the possible role of FFM in the pro-
gression of CF lung disease. Although weight gain
per se is important, maintenance of normal muscle
mass may be intimately connected with normal
growth and with good pulmonary function in
patients who have CF. There are several reports of
increased protein catabolism in poorly growing
children who have CF [81–84]. The presence of a
delay in the accrual of an adequate FFM implies
lower development of the skeletal muscle, includ-
ing the respiratory muscles. Previous studies using
measures such as the maximum inspiratory and
expiratory pressures and the maximum voluntary
ventilation have shown abnormalities in the
performance of the respiratory pump in CF pa-
tients who have different degrees of pulmonary
dysfunction, particularly with respect to their
respiratory muscle strength [85–87]. Respiratory
muscle weakness, however, was not found in chil-
dren who have CF and normal pulmonary func-
tion compared with control subjects, implying
that the loss of muscle mass or strength precedes
the development of lung disease [88]. 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 [89].
Also of interest, one study showed that the
improvement in FEV1 seen with nocturnal gastro-
stomy tube supplementation was correlated to
change in lean body mass rather than to change
in body fat [90]. In addition, reversal of protein
catabolism stabilizes pulmonary function and
decreases the number of hospitalizations for acute
pulmonary exacerbation [83].

**Nutritional intervention in cystic fibrosis**

With the clear recognition of the important
role that nutrition plays in the clinical course of
CF, current guidelines recommend considering
aggressive intervention in the presence of malnu-
trition despite an appropriate nutritional regimen
[5,91]. This intervention usually entails the institu-
tion of enteral supplementation through the use of
tube feedings. Several interventional studies have
been conducted to look at the benefits of aggres-
sive nutritional support [22,83,90,92]. A meta-
analysis of the interventions available classified
them into behavioral, oral supplements, enteral
supplements, and parenteral nutrition [93]. All of
the reported interventions, regardless of class,
were found to be effective at inducing weight
gain and to comparable degrees. Although most
studies were small and of relatively short dura-
tion, of interest is that less aggressive interven-
tions like behavioral modification were as
efficacious as more aggressive interventions, par-
ticularly when applied early.

Most studies, however, have looked only at the
effects of regimens aimed at the nutritional rescue
of the most severely affected patients. A recent
Cochrane review of enteral feedings in CF con-
cluded that despite the wide acceptance of this
treatment modality, its efficacy has not been fully
evaluated and the available data are limited [94].
The studies found in the literature have reported
on interventions in the clinical setting using differ-
ent strategies for enteral supplementation, which
makes interpretation and generalization of results
difficult. Most of these studies have shown modest
but significant gains in weight and other nutri-
tional markers. At the same time, positive gains
in pulmonary function were not consistently
achieved, and mortality did not seem to be influ-
enced by the intervention [95–97]. These results
should be interpreted with caution because most
studies were small and did not include an appro-
perate control group to be able to draw more
firm conclusions. It is likely, however, that in
a severely compromised patient population, a control group with no intervention may experience worst outcomes and may be ethically unfeasible. It must also be taken into account that these interventions are not free from complications. Problems such as gastroesophageal reflux and formula intolerance [97], hyperglycemia [98], stoma infections, and equipment malfunction can frequently be encountered. There is also a potential trade-off between the gains to be obtained from the intervention and the deleterious effects that could be induced. Certainly, in the sickest patients, it is likely that this risk–benefit balance needs careful consideration and close monitoring for complications is required. This risk of failure also implies that after the patient has reached a stage where there is severe lung damage already present, the potential gains may not have an effect strong enough to offset the disease progression. In a report on the long-term outcomes of a group of patients who had severely compromised lung function, Milla and Warwick [2] noted that nutritional status did not seem to influence the risk of mortality. It is therefore intuitive to assume that it is the earlier stages of the disease in which interventions are more likely to have a stronger positive influence.

Controlled trials on other interventions to improve nutrition have included the use of appetite stimulants and growth hormone. Small randomized controlled trials of megestrol acetate as an appetite stimulant have noted significant gains in weight and pulmonary function during treatment [99,100]. In one of the studies, however, only half of the subjects completed the trial and some lost the gains during the washout phase [100]. By body composition analysis, the main component of the weight gain was in fat mass. The caveat to this intervention is that such gains seem to be short-lived given that most of the weight gained represents water and fat, and there is the risk of important side effects such as glucose intolerance and adrenal suppression [100,101]. A small trial with cyproheptadine as an appetite stimulant has shown a better safety profile and more sustained weight gains [102]. Two small controlled trials with growth hormone given for 1 year have shown improvements in respiratory status in association with significant gains in lean body mass [103,104]. The study by Hardin and colleagues [103] demonstrated a significant improvement in forced vital capacity and improvements in measures of respiratory muscle strength and hospitalization rates in the treated group. Schibler and colleagues [104] did not find any improvements in pulmonary function but found important gains in exercise capacity in the group randomized to active treatment.

Given the high prevalence of glucose metabolism abnormalities in CF [105] and the impact that the development of CFRD has in disease progression [106,107], early identification of CFRD though screening and aggressive management of this complication have been clearly recognized as important components of the management of CF patients [108]. Because insulin deficiency is one of the key pathophysiologic features of CFRD, insulin is the currently recommended standard treatment. Although there is a lack of randomized trials supporting this recommendation, previous small observational studies suggest that aggressive insulin therapy for CFRD might have a beneficial effect on CF pulmonary disease [109]. A large long-term multicenter study is currently underway in the United States and Canada to more formally evaluate the benefits of chronic insulin therapy in the management of CFRD [110]. The management of patients who only have glucose intolerance remains controversial. Case series reports point toward a benefit of starting early insulin therapy with small doses [111,112]. In some of these patients, however, the diabetic condition might be temporary and often related to their overall health status, with great fluctuations over time. A recommendation for long-term insulin therapy is therefore difficult to justify, and more studies are needed in this area given the potential implications for maintaining an adequate nutritional status and long-term preservation of pulmonary health.

Summary

A large body of data provides significant evidence for a link between nutritional status and lung health in CF. In addition, adequate growth plays a role in the development of lung function in children who have CF. More important, these studies suggest that the development of lung function abnormalities can be influenced by changes in nutritional status. Based on this information, it could be argued that aggressive nutritional support needs to start before significant nutritional derangements are noted. Not only is it likely that such an early intervention should have better chances of success but it also has the potential to decelerate or even prevent lung function deterioration and to positively affect survival. Because the
nutritional deficiency frequently seen early in life is primarily related to pancreatic insufficiency and malabsorption [69], aggressive nutritional support and adequate pancreatic replacement management should lead to normal growth and to lung function preservation. Further, the relationship between protein and energy metabolism that is present in patients who have CF may have important prognostic and therapeutic implications; however, the relative importance of these factors in determining pulmonary function deterioration remains unknown. It is also not clear whether this relationship is due to inadequate growth of the lung or from an inability of the respiratory pump to efficiently meet the requirements imposed by the airway disease.

Nutritional intervention for CF patients is predicated on the hypothesis that improved nutritional status improves pulmonary function, which in some small studies seems to be the case. Which interventions will be of most value and have sustained gains is not completely clear from the available data. It is possible that the most effective interventions will have to include multiple components and go beyond the simple addition of caloric supplementation. Taking into account that several factors condition the deficits that lead to malnutrition in CF, multidisciplinary interventions are likely to give the best results. A comprehensive individualized management program should involve optimizing pancreatic enzyme use, addressing gastrointestinal comorbidities, identifying CFRD, maximizing caloric intake, addressing behavioral maladaptive responses, and controlling lung disease. More research is certainly needed not only to better dissect the nutritional factors involved in the lung disease but also (and perhaps more important) to identify effective and safe interventions through systematic controlled trials.

References


