BMI as a Predictor of Health Outcomes in Cystic Fibrosis: 
A Case for Advancements in Practice

by

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Introduction

Cystic Fibrosis (CF) is a life-shortening, complex disease that plays a deleterious role in multiple organ systems of the human body, notably the lungs, pancreas, gastrointestinal tract (GI), and liver. Discovered in 1989, it is defined as a mutation in both copies of the cystic fibrosis transmembrane conductance regulator (CFTR) gene ("About Cystic Fibrosis", n.d.). In the United States today, 1 in every 3,400 births receives a CF diagnosis, and between 900 and 1,000 new cases are diagnosed each year ("About Cystic Fibrosis", n.d.). 1 in every 29 Caucasians is an unaffected carrier of the CFTR mutation. The data reflects this demographic-specific, increased risk: 93.8% of the CF population is white, 4.6% is African American, and 3.3% is another race (2015 Patient Registry, 2016).

Over 1,800 known CFTR mutations exist, all of which alter the production of the CFTR protein responsible for regulating epithelial transport of chlorine and sodium ions (Bunting, Mills, Ramsey, Rich, & Trout, 2013). As a result, dehydration leads to thick viscous secretions that manifest in the lungs, causing decreased ciliary function and creating an environment hospitable for bacteria responsible for respiratory infections. Over time, decreased lung function can progress to chronic lung damage, and in some cases, warrant transplantation. Lung disease is the chief mortality predictor. This is measured by the annual rate of decline in the percentage of the predicted forced expiratory volume in one second (FEV1%) (Megias, Vasco, Albarran, Ferreiro, & Carro, 2015). In sweat glands, the dysfunction causes elevated sweat chloride levels. In the liver, CFTR is expressed in biliary epithelium, allowing for thick secretions that decrease bile flow. Over time, progressive damage may induce inflammation, fibrosis, and cirrhosis and can also warrant transplantation. Pancreatic insufficiency ensues from damage (by the thick secretions) to the acinar cells and from the obstruction of ducts. Consequently, this manifests as protein and fat malabsorption, the hallmark of the disease. An objective measure of pancreatic function is assessed using a fecal elastase test, which measures the concentration of fecal elastase (CELA3B) to accurately reflect the amount secreted from the pancreas (Pancreatic Elastase, 2014).

Prior to supplemental digestive enzymes, practitioners remedied intolerance of dietary fat secondary to CF with a low-fat diet. However, malnutrition resulted as a downstream effect of decreased energy intake and fecal nutrient loss (Steinkamp & Wiedemann, 2002). The intolerance of dietary fat and its subsequent effect was revolutionized when acid resistant pancreatic enzymes hit the market in the mid 1980s. Since then, the longstanding association between CF, nutritional failure and growth retardation has weakened (Steinkamp & Wiedemann, 2002). Still, malnutrition
remains one of the most crucial physiological endpoints to monitor, since it can lead to a host of disease-progressing comorbidities such as Cystic Fibrosis related Diabetes (CFRD), Asthma, Cystic Fibrosis related Lung Disease (CFLD), Gastroesophageal Reflux Disease (GERD), Sinus Disease, and osteopenia. Despite the linear association between malnutrition and poor health status, median predicted survival age has improved – from about 29 years during 1986 to 1990, to 41.1 years during 2011 to 2015 – as a product of increased research, including advancements in nutritional management (2015 Patient Registry, 2016).

While CF is an incurable chronic disease, symptoms can be managed to improve one's quality and length of life. The CF pediatric population commonly experiences failure to thrive (FTT) in infancy, followed by malabsorption, pulmonary distress, hyperglycemia, low bone density, and mental health issues throughout childhood and onward. Therefore, an interdisciplinary team – involving a pulmonologist, respiratory therapist, endocrinologist, nurse, social worker, psychiatrist, and dietitian – is considered by many to be the gold standard of treatment and follow-up care. Specifically, the dietitian plays a fundamental role in nutritional management and is responsible for monitoring physiological endpoints. These include body mass index (BMI), nutrient absorption from pancreatic enzyme replacement therapy (PERT), bone density, fat-soluble vitamin labs and blood glucose levels. In addition to using experienced clinical judgment when prescribing medical nutritional therapy, dietitians supplement their treatment plan with evidence-based practice recommendations. The Cystic Fibrosis Foundation (CFF) provides these and they are developed from systematically reviewed evidence in literature, as well as data from the annual CFF Patient Registry.

To achieve and maintain appropriate growth, patients with CF require aggressive nutrition support. They have increased needs (metabolism and infections), increased losses (malabsorption from pancreatic, liver, and GI disease; CFRD), and/or poor nutrient intake (anorexia, gastroesophageal reflux disease (GERD), abdominal pain, constipation, periods of illness, and medications) (Corkins et al., 2010; Stallings, Stark, Robinson, Feranchak, & Quinton, 2008). Thus, current guidelines for estimated needs are 110% to 200% of standard energy needs compared to a healthy population, and 150% to 200% of standard protein needs compared to a healthy population or higher, not to exceed 4 grams per kilogram per day except for cases of severe malabsorption (Bunting et al., 2013). And while it is virtually obsolete in practice today, percent ideal body weight (%IBW) was once the anthropometric measure used to assess growth and health
status. However, current guidelines parallel research published in 2004 by Zhang & Lai, which found BMI% to be more strongly associated with, and sensitive to, changes in percent predicted FEV1 (Zhang & Lai, 2004). Using the 2005 Patient Registry data set, the CFF found that better FEV1 status (around 80% or above predicted) was associated with a BMI at the 50th percentile and higher; therefore, they advise that children ages 2 to 20 maintain a BMI at or above the 50th percentile to achieve optimal lung function (Stallings et al., 2008). Furthermore, the CFF website counsels children and caregivers to meet their energy needs with PERT in conjunction with eating three meals a day and “easy access snacks”, such as bagels, muffins, yogurt drinks, cheese, deli meat, dried fruit, pudding snacks, etc. In other words, calorie dense, high-carbohydrate and/or high-fat foods to easily gain weight, which is also the strategy seen in practice. When patients are unable to meet age-dependent anthropometrics despite appropriate evaluation and intervention by the interdisciplinary team, the CFF recommends enteral nutrition in order to meet estimated energy and protein intake (Schwarzenberg et al., 2016).

While in recent decades researchers achieved vast strides in CF research, nutrition management guidelines remain malleable so as long as researchers continue to uncover the disease’s complexities. Study designs are challenged with confounders and unknowns when attempting to unveil a black and white association between risk factors and symptoms. For example, lung function declines at different rates and from different baselines for each person with CF. Additionally, the decline in lung function with age, which is universal in CF, affects the data in comparative studies. Regression models or age matching are typically able to incorporate this effect. However, age matching is less useful since the variability in function at all ages is pronounced (Corey, Edwards, Levison, & Knowles, 1997). Furthermore, it is difficult to make general conclusions about nutrition status and lung function because the manifestation of CF depends on a variety of factors. These include which of the 1800 mutations the individual has, the number of mutations (one or two), and the class (I-V) that they fall under. In other words, it is difficult to untangle the fact that specific mutations predispose subjects to specific health outcomes (obesity, respiratory distress, CFRD, cirrhosis, etc.) more severely than other mutations (2015 Patient Registry, 2016).

When looking at the evidence for the general, healthy population, discrepancies still exist in using BMI as the diagnostic measure for defining obesity both in practice and in epidemiological studies. While it is useful as a surrogate marker to indicate body fat, it is less direct in measuring
excess fat versus excess weight. And though it is fair to argue that BMI measurement is simple, inexpensive, non-invasive and correlates with health risks, literature also agrees that it is best suited as a screening tool for obesity (Body Mass Index, n.d.). Limitations include: the influence by age, sex, level of sexual maturation, and/or ethnicity; distinguishing bone mass; and distinguishing distribution of the adipose tissue (i.e., carrying excess adipose around the waist, known as “apple shape”, versus a “pear shape” figure which carries a lower morbidity risk). Most importantly, it fails to distinguish muscle mass, or fat free mass (FFM), from fat mass (Body Mass Index, n.d.).

After considering the plethora of research variables and the limitations of BMI, it is worth considering if BMI is the best indicator of nutritional status as it pertains to lung function (FEV1). Research is also starting to question if lung function is higher in leaner patients of the same BMI. If so, should we consider the ratio of fat mass to FFM as a nutritional indicator instead of BMI in this critical patient population? Lastly, the blooming prevalence of obesity in the adult and pediatric CF population, as well as the rapid increase of patients diagnosed with CFRD is concerning (Kelly & Moran, 2013). Accordingly, what is the relationship between excess body fat and CFRD? Furthermore, what evidence is available to say that the current medical nutritional therapy used in practice is contributory to the increased rate in excess body fat and/or CFRD? The remainder of this review shines light on these questions by analyzing the current research and a relevant case study to reveal implications in practice. I then offer suggestions for guidelines and future research.

**Literature Review**

**Obesity Prevalence and Lung Function: CF versus the General, Healthy Population**

The CDC defines obesity in ages 2 to 19 as a BMI greater than or equal to the 95th percentile, and overweight status as the 85th percentile up to the 95th percentile. Obesity prevalence in the overall pediatric population has remained stable at about 17% over the past decade. Nonetheless, it has tripled since 1980, and according to 2011-2014 NHANES data, rates of extreme obesity are on the incline. Furthermore, the rates for obesity starting at an early age (ages 2 to 5) have significantly increased (“Obesity Rates”, n.d.).

Historically, obesity in the CF population was unheard of and if anything, a rarity. In 2012, the University of Pittsburgh CF center reported that of their 233 children (ages 2-18), 13% were overweight and 7% were obese (Hannah & Weiner, 2014). However, in 2015 Hannah et al. published the first pediatric specific (ages 2-18) study describing the prevalence of overweight and
obesity in CF patients using a cross-sectional study design. They queried the CFF Patient Registry for all of the patients seen at the Children's Hospital of Pittsburgh of UPMC between June 2011 and June 2012. Data was abstracted from 226 patients who were then divided into five weight status groups according to the CFF guidelines. Results revealed that 7% were in nutritional failure, 12% were at risk for nutritional failure, 57% were of healthy weight, 15% were overweight, and 8% were obese. Surprisingly, there were 1% more obese children than there were children in nutritional failure, which highlighted a distribution new to this population.

It can be argued that obesity status is preferred over nutritional failure in children with CF; however, because increased obesity in CF is a novel arrival, further evidence of the effects of excess body fat on pulmonary function are needed. In the general, healthy population the deleterious health outcomes of obesity, such as type II diabetes and hypertension, are widely discussed in the literature. In the adult literature, there is direct evidence to show that overweight and obesity (as defined by BMI) have a mechanical influence on lung function via reduction in functional residual capacity (FRC) (Robinson, 2014). FRC represents the resting volume of gas left in the lungs after a tidal expiration. The elastic recoil force of the lungs opposes that of the chest wall, and at FRC, this closed system is at equilibrium. A lowered FRC means that the lungs are less compliant and it often indicates respiratory distress or disease (Duncan & Aurora, 2014). In the instance of obesity-related mechanical stress forces on both the thorax and upper abdomen, induced by adipose tissue accumulation around the rib cage, abdomen, and within the visceral cavity, one's FRC can lower as a result of stiffening of the lungs and diaphragmatic movements that make it difficult to breathe (Robinson, 2014); explicitly, the decreased expiratory reserve volume pushes tidal breathing more towards smaller, high resistance airways, limiting expiration (Kongkiattikul, Sritippayawan, Chomtho, Deerojanawong, & Prapphal, 2015). Furthermore, FRC is required to calculate the lung clearance index (LCI), which is a sensitive measure of ventilation inhomogeneity measured by multiple breath washouts, not spirometry as in FEV1. Gas mixing becomes inhomogeneous increased LCI and decreased FRC – in diseased airways from inflammation, mucous plugging and damage to the airway wall. While FEV1 in early disease predominantly reveals the health of the proximal airways, LCI is considered to suggest smaller airway abnormalities (Davies, Cunningham, Alton, & Innes, 2008).

Yet, in the general pediatric literature, direct evidence for the detrimental effect of obesity on lung function, or asthma, is of smaller magnitude than that of the general adult literature. The correlation is less researched and the available evidence shows a disparity in outcomes and/or outcome measures, such as FEV1 versus FRC versus LCI. For example, in a study of school-age
children with CF, as well another study of children with CF evaluated over an age range of 6-20, LCI was shown to be more sensitive than spirometry (FEV1) in detecting abnormal pulmonary function (Duncan & Aurora, 2014). Therefore, although FEV1 correlates with LCI in terms of disease progression, there is concern that conventional measures are insufficiently sensitive in detecting abnormalities at the mild and moderate stages of disease that occur at younger ages (Davies et al., 2008).

Aside from outcome measures, it is likely that the mechanism by which obesity, and duration of obesity, affects the respiratory tract in both CF and non-CF children is less understood because childhood is a period of rapid development and age 6-14 implies peak period of lung growth (Brashier & Salvi, 2013). For example, in a non-CF pediatric study by Gold et al., results of lung function and BMI demonstrated that there was an increased risk of asthma in the boys and girls with the largest annual increase in BMI during follow-up. Additionally, a higher BMI at the entry of the study increased the risk of asthma for girls, but this was not seen for boys (Gold, Damokosh, Dockery, & Berkey, 2003). In another non-CF pediatric study by van de Griekdt El et al., statistically significant improvements in lung function were seen with weight loss (mean of 13.85 kg) after 6 months in children ages 8.5 to 18.9 years. Specifically, the expiratory reserve volume (ERV), a summand of FRC, drastically increased by 14.8%. Changes in ERV were also statistically significantly correlated with delta BMI standard deviation and delta waist circumference. While FEV1 improved by 2.91% after weight loss, the change in BMI Z score (+3.38 to +2.91) and change in mean waist circumference (122.2 cm to 110.9) were not significantly correlated with changes in FEV1, which may or may not be a result of spirometry sensitivity as described previously (Griekdt et al., 2012). Interestingly, a similar study (of non-CF children ages 7-18) by Li et al. based the assessment of obesity on both dual-energy x-ray absorptiometry (DEXA) and BMI measures. A significant negative correlation between lung function (FRC) and degree of obesity was described when obesity was based on DEXA, but interestingly, this relationship was not seen when BMI was used as a marker of obesity (Robinson, 2014). This ambiguity in results highlights the fact that using a screening tool (BMI), versus the gold-standard tool (DEXA) for measuring excess fat is also potentially to blame for the discrepancy of lung function outcome measurements in the pediatric literature. This distinction, of an increased BMI from muscle versus an increased BMI from fat, is especially relevant to lung function results for boys since they have more muscle mass relative to girls. Lastly, it suggests that the effects of obesity during this sensitive period of peak lung growth might further enhance the risk of pulmonary distress in both CF and non-CF populations (Brashier & Salvi, 2013).
BMI Guidelines in the CF Population

In addition to the prevalence of obesity among the CF pediatric population, another parameter measured in the aforementioned study by Hannah et al. was FEV1%. As hypothesized, FEV1% was lowest in the nutritional failure group among the five weight groups (nutritional failure, at risk, healthy, overweight, and obese) of children with CF. However, no statistically significant decrease in FEV1% between the other four groups was found (Hannah & Weiner, 2014). The results from a longitudinal study by Stephenson et al. support this finding as well. The objective of the study was to describe longitudinal trends in nutritional status and to evaluate the relation between nutritional status and lung function by following a cohort of 909 adults. The evidence revealed that the benefit of nutrition, or BMI, on lung function was blunted at a BMI above 25 (Stephenson et al., 2013). The authors attribute the relationship to the widely accepted mechanism of obesity and overweight on lung function decline in the general population, as described previously. Importantly, both of the study results juxtapose the current CF guidelines that are based off of data from the 2011 Patient Registry Annual Data Report. The report reads that the direct relationship between BMI percentile and improved pulmonary function continues to increase without plateauing (Hannah & Weiner, 2014). While both studies call the guidelines into question, it is worth accounting for study design. The cross-sectional design, used in Hannah et al. as well as the evidence substantiating the guidelines, is limiting because it explores data from a point in time rather than looking at growth more realistically via trends in BMI.

Steinkamp et al. looked at BMI from a longitudinal perspective in their study of the relationship between nutrition status and lung function in patients with CF. Patients were defined as malnourished if data indicated wasting and/or stunting – that is, if (1) weight was below 90% of the predicted normal value for sex and height in children, if BMI was <19 kg/m2 in adults or if (2) weight was <80% of the median normal value for sex and age, or if (3) height was <90% of the median normal value for sex and age. It was found that in a cohort of 536 children ages 6 to 11.9 observed over one year, if weight for height (BMI) decreased by 5% or more in normally nourished children with CF, there was a simultaneous mean value decline in FEV1 of 12.8%. In malnourished children with CF, the results were similar but less severe. Their mean value decline in FEV1 was 7.5%, which is almost half the magnitude of the normally nourished decline (Steinkamp & Wiedemann, 2002). While this evidence supports the philosophy behind the CFF guidelines, i.e. that BMI and lung function are co-dependent variables in CF, the longitudinal nature adds layer of complexity unidentified by cross-sectional studies: even when BMI decreases but stays within
normal range, lung function is still deteriorating at a fast rate. More noteworthy is the fact that the rate of deterioration in nourished children was almost double than that of the malnourished patients. Overall, Steinkamp et al. was successful in underlining the importance of longitudinal monitoring: trends in weight fluctuations are more significant than an absolute value of BMI at any given time, even if the BMI is still considered “normal” after decline.

Similarly, Megias et al. looked at the relative change in weight and BMI and their association with lung function in both teenagers and adults with CF. Overall, a positive relative change in weight greater than or equal to 6% was associated with a 9.31% increase in FEV1%, as compared to those with a weight loss of at least 2%, who had a 12.09% fall in FEV1. When analyzing BMI, a positive, relative increase in BMI was borderline significant for improvements in FEV1%; yet, when classifying BMI by Z score, comparisons between the groups did not reach statistical significance (Megias et al., 2015). Limitations of the study include the fact that, unlike Steinkamp et al., the study population was heterogeneous (adults and children older than 14 years) and the sample size was small (64 patients). Nonetheless, the study supports the need for longitudinal versus cross-section research on BMI, and at the same time, delineates the inconsistency of using BMI as an endpoint.

**Alternative Outcome Measures to BMI**

To explain the aforementioned results, which challenge the idea that weight for height is directly correlated to lung function, recent studies have dissected further and looked at the association of body composition and lung function. Their evidence suggests that BMI can mask the ratio of fat-free mass (FFM) to fat-mass (measured in kilograms) and that singling out FFM allows for a more precise, measurable endpoint of health status. For example, Engelen et al. randomly selected 77 children with CF (ages 14.9 ± 2.9) to determine if FFM was a better indicator of nutritional failure than BMI. They defined nutritional failure as a BMI less than the 10th percentile and/or a FFM index less than the 5th percentile. FFM, fat mass, bone mineral content and density were measured using DEXA. Authors found that 14% of the children showed a depletion of FFM and this depletion was associated with an adequate BMI (25th – 50th percentile) in up to 50% of them. Only 52% of the patients with FFM (muscle) depletion were detected when using the criteria BMI less than 10th percentile. Patients with FFM depletion had reduced values for FEV1, independent of BMI, and lower values for whole body, spine and hip bone mineral density. In terms of BMI percentile, a BMI less than or equal to the 20th percentile was associated with a large drop in FFM, reduced FEV1, and bone mineral loss (Engelen, Schroder, Hoorn, Deutz, & Com, 2012). Thus, a
sizable proportion of patients with nutritional failure or compromised nutritional status were left undiagnosed when BMI was used as the only nutritional endpoint.

In a similar cross-sectional study of 52 subjects, Alvarez et al. looked at adiposity in adult subjects with CF, and paralleled them to a reference group of non-CF adults to analyze the association of body composition and lung function. Body fat percent, fat mass, and FFM measurements were obtained using air displacement plethysmography (BOD POD), and then associations with lung function were compared between the following three groups of subjects: normal weight (lean), normal weight obesity (NWO, i.e. a high body fat percentage with normal BMI), and overweight/obese (O/O). Obesity, independent of weight, was defined as having a body fat percentage greater than 30 in women and greater than 23 in men. Despite lower height and BMI, there were no significant differences in fat mass, fat mass index, or percent body fat between subjects with CF and the control group. Authors found that lean subjects had statistically similar FEV values and FFM values as the other two groups (NWO and O/O). Importantly, the lean group had BMIs equivalent to the NWO group and lower BMI than O/O, but lean subjects had less body fat percentage and less fat mass than both of the groups (Figure 1) (Alvarez, Ziegler, Millson, & Stecenko, 2015). Therefore, the data suggests that FFM is the driver for increased lung function, even when BMI is the same or lower.

**Figure 1**
Body composition category differences in adults with cystic fibrosis. One-way analysis of variance indicated statistically significant group differences in percent body fat (top left), fat mass index (bottom left), fat-free mass index (top right), and FEV1% predicted (bottom right). ($P < 0.01$ for all). Groups not connected by the same letter are significantly different (determined by Tukey's post-hoc comparisons). FEV1%, percentage of predicted forced expiratory volume in 1 s; NWO, normal weight obesity.
When comparing the NWO with the O/O group, body fat percentage was not statistically different, even though O/O had a statistically higher BMI attributed to their statistically higher FFM. Therefore, this data also supports the notion that it is not BMI or amount of fat that improves lung function, but instead, it is the amount of FFM (or lean tissue mass) that improves pulmonary function and health status. The authors propose that, despite the absence of statistical power in the study given the small sample sizes, the evidence supports the need for additional prospective studies. Furthermore, as the pediatric CF population ages into an obesogenic environment, nutritional monitoring and interventions may necessitate a re-evaluation of the current guidelines in order to advance appropriately (Alvarez et al., 2015).

**Association of Body Composition CFRD, and the Contribution of MNT**

As previously discussed, obesity and CFRD rates in the CF population are climbing, and recent literature has given attention to their etiology and aftermath. Since the 1980s, the CF population has acknowledged CFRD as the foreshadowing of decreased survival, as it has been associated with a nearly 6-fold greater mortality rate (Kelly & Moran, 2013); despite early identification advancements and insulin therapy, mortality currently remains over three times higher in individuals with CFRD (Kelly & Sheikh, 2015). Interestingly, recent work has attempted to identify the mechanism by which CFRD is associated with worse survival in males than females, particularly when females have a higher prevalence of CFRD at every age. The study looked at body composition and pulmonary function and deduced that the greater FFM (or lean body mass) deficit in males versus females might rationalize one avenue by which CFRD differentially affects CF outcomes (Sheikh, Zemel, Stallings, Rubenstein, & Kelly, 2014; Kelly & Sheikh, 2015).

The principal defect in CFRD is insulin deficiency via CF's collateral damage; specifically, the viscous secretions instigate fibrosis, fatty infiltration, and the destruction islet cell makeup. In adult studies, insulin deficiency is shown to subsequently lead to protein catabolism and clinical deterioration, and as a result, worse pulmonary function regardless of age (Kelly & Moran, 2013). Similar to T2DM, it is proposed that hyperglycemia and inflammation, likely through oxidative stress, also directly contribute to this physiological decline. This evidence explains why a decreased BMI is observed in the years preceding CFRD diagnosis, and why unlike T2DM, CFRD is not necessarily associated with obesity (Kelly & Moran, 2013).

Aside from insulin deficiency, data also suggests that modest insulin resistance presents in the setting of CFRD. The magnitude of impairment may be furthered with acute pulmonary distress,
chronic severe lung disease, and glucocorticoid therapy (Kelly & Moran, 2013). Additional mechanisms at play for blunted insulin secretion and insulin resistance may include: pancreatic insufficiency status, incretin hormone status, dietary constituents, reduction of the transcription factor FOXO1, obesity, altered gene expression and impaired autophagy, to name a few (Kelly & Sheikh, 2015). It remains unknown whether or not fat mass, specifically visceral fat mass, contributes the same cytokine inflammation and insulin resistance evident in T2DM. The same unknown holds true for increased FFM (or muscle mass) via glycogen storage in muscle tissue (Sheikh et al., 2014). The current literature on the subject of obesity in CFRD is still inconclusive and contributed by the incongruence in obesity assessment – BMI versus body composition - between studies. Therefore, all things considered, one can appreciate the difficultly in exploring the sequestered effect of diet on CFRD. Yet, some authors consider the CFF nutrition guidelines to be single-minded, as they fall short of parameters for the management of childhood obesity and overweight status (Hannah & Weiner, 2014).

The CFF nutritional guidelines for the CF population recommend a high calorie, high protein diet with no restriction on fat so fat can meet around 35% to 40% of total calories. Specifically for CFRD, carbohydrate recommendations are as follows: individualized; monitored to achieve glycemic control; artificial sweeteners should be used sparingly due to lower calorie content (Moran et al., 2010). Of note, it is commonly believed that hypertriglyceridemia in the CF population, unlike the general, healthy population, is not of concern; also, concentrations of cholesterol are typically low in patients with CF (Figueroa, Milla, Parks, Schwarzenberg, & Moran, 2002). Therefore, the literature implies that lipid profiles should not be a marker of obesity status in patients with CF, as hypertriglyceridemia was also unrelated to common correlations such as: glucose tolerance status, OGTT glucose excursion or insulin secretion, age, sex, weight, BMI, or blood pressure. Instead, the authors suggest that the isolated hypertriglyceridemia may be related to dietary macronutrient absorption (Figueroa et al., 2002). They propose actual dietary fat intake in CF patients is more than what is actually absorbed, and that even with enzyme supplementation, 5% to 20% remains unabsorbed. The ratios of macronutrient absorption may be further compounded by the fact that enhanced absorption of glucose and other sugars via the jejunum has been shown, and in the presence of excess carbohydrates, the liver shunts glucose toward metabolic pathways for triacylglycerol formation. Together, these abnormalities in fat and carbohydrate absorption may lead to a postprandial metabolic climate similar to that found in healthy individuals consuming a low fat, high carbohydrate diet, especially when carbohydrates are monosaccharides (Figueroa et al., 2002).
Moreover, in reference to the pro-inflammatory effects of hyperglycemia on clinical outcomes, the aforementioned study by Megias et al. also suggested that the control of carbohydrate metabolism could contribute to slowing down the decline in lung function (Megias et al., 2015). While the only recommended treatment for insulin insufficiency in patients with CFRD is insulin therapy, those who achieve glycemic control exhibit improvements in weight, protein anabolism, pulmonary function, and survival (Moran et al., 2010). It has also been shown that patients start insulin therapy later if they are in stable condition with compliance to a diet of low-glycemic index foods (Plechowiak, Trippenbach-Dulska, & Walicka-Serzysko, 2015). Lastly, for patients with diabetes who are not being treated with insulin and do not wish to reduce total calories, the University of Minnesota uses the strategy of minimizing carbohydrate loads and distributing carbohydrates evenly throughout the day (Brunzell & Schwarzenberg, 2002).

A Case Study

The case study of Monte¹, a 14 year old male with CF, is unique in that it reveals the complexity of managing CF related comorbidities amidst obesity, a (once) rarity in children with CF. Secondly, lessons learned from the case serve as an educational tool for developing future plans of care, while also supporting current interventions in the management of CF. Finally, the evidence brings current guidelines into question and shines light on unmet research.

Monte presented to the emergency room at 3 months of age for huge hepatomegaly, fever and emesis. He was referred from the Gastrointestinal (GI) clinic for FTT, malabsorption and dermatitis. Patient history showed that he was not premature (born at 41 weeks gestation), and had no family history of CF. His maternal aunt had T2DM, and both maternal aunts had hypertension. His maternal grandfather was diagnosed with Hepatitis B and his maternal grandmother was jaundiced at death, but the reason for death was unknown. At 6 months of age he was diagnosed with CF, and no further medical history was available on his record until he was 3 years old. Between the ages of 3 and 4 he was noted to be positive for Pseudomonas aeruginosa, a bacterial infection that compromises lung function. At 4 years of age he had a BMI of 93.27%, had caught up with developmental milestones, and his liver and lung status had stabilized. At 8 years of age he was reported to have good weight gain with some malabsorption. He was drinking Pediasure and had a BMI of 93.86%; despite his promising nutritional status, he grew Methicillin-resistant Staphylococcus aureus (MRSA) and Stenotrophomonas. Social history included that he now only

¹ The patient’s name was changed for privacy purposes.
lives with his mom, he prefers video games to sports and physical activity, his mom is on child support and finances are a struggle. At 9 years of age, Monte returned to the CF clinic with his mother, who required a Spanish interpreter at each visit. At this point, his weight was at the 94.35 percentile, his height was at the 44.19 percentile, and his BMI was at the 97.04 percentile using CDC growth curves. Since last visit, he fell from weight and BMI curves secondary to intentional weight loss of 0.5 grams per day. Mom was happy about this, as she reduced his portion sizes. Monte was on PERT, a proton pump inhibitor (PPI), vitamin D supplementation, and Vitamax, a CF-specific supplement that included all fat-soluble vitamins. Per his mom’s report, Monte’s stools were greasy but formed and occurred three times per day. The RD estimated his energy needs at 1.1 to 1.3 times the recommended daily allowance (RDA) and his protein needs at 2 times the RDA for age. The RD made two diagnosis at this visit: food and nutrition related knowledge deficit related to lack of prior exposure to nutrition-related information as evidenced by questions related to increasing daily exercise; impaired nutrient utilization related to compromise of organs related to digestion of fat and protein as evidenced by possible signs of malabsorption. The intervention was as follows: continue current diet plan of high calorie, high protein; continue to exercise but increase to a daily basis; continue current enzyme dose; mom to monitor stools over the next few days and call RD with update; reduce fat soluble vitamin supplementation to 1000 IU of vitamin D3 daily to maintain normal levels during the winter. Finally, Monte would be evaluated at next visit for: weight trends, growth velocity, signs and symptoms of malabsorption, compliance with nutritional recommendations, and fat-soluble vitamin labs.

Over the next four months, there was no change in his energy needs, his physical activity increased to 1 to 2 hours per day, and Monte began Miralax for constipation. Six months later signs of non-compliance were evident, as his mom reported that he was sneaking snacks and skipping his enzymes. His height and weight increased from the previous visit and he was now at a BMI of 94.94%. Physical activity was minimal, and his MRSA returned. Importantly, his 2-hour oral glucose tolerance test (OGTT) was elevated at 211 mg/dL and his glucose level was 274 mg/dL, and he was referred to endocrinology. Over the next 4 months he was reported to have a history of no-shows, limited physical activity, and weight gain of 22.5 grams per day with a BMI peaking at 96.43%. This was followed by an unintentional weight loss over the next month of 1.3 kilograms; he was admitted to the in-patient unit for CFRD with several malodorous bowel movements. Monte was discharged on an insulin regimen, a restriction to limit carbohydrates to less than 15 grams at snacks, and to increase carbohydrates with physical activity.
Over the next seven months, his glucose was poorly controlled secondary to his mom’s confusion with insulin regimen and poor compliance to carbohydrate counting. His BMI increased from 96.43% to 97% and he was now 11 years old. His insulin regimen was increased and his comparative standards for energy were reduced to 1 to 1.1 times the RDA, though the RD still encouraged him to exercise, continue a high calorie, high protein diet and to mix juice with water. Seven months later, it was reported that Monte had intentional weight loss and his BMI dropped to 95% from 97%, and the RD encouraged him to not let his BMI drop below the 50th percentile.

Seven months later he was 12 years old, positive for liver cirrhosis, on an increased insulin dose, and at a BMI of 91% from 95%. The RD documented his average weight loss - of 19.1 grams per day over seven months - as acceptable because it was intentional. Monte attributed his weight loss to the replacement of carbohydrates with protein at breakfast and to increased exercise. A little over six months later, his pulmonary function was noted to be stable but down from the previous visit. Monte had lost an average of 15.5 grams per day, but he and his mom were happy with the weight loss. His BMI was down to 83% and so the RD encouraged him to not let it drop below the 50th percentile. His blood glucose levels were still uncontrolled and his insulin regimen was switched to ICR (insulin to carb ratio).

Seven months later Monte’s history of recorded blood sugars was reported to be consistently high. For the first time, his appearance was noted as, “thin extremities, round belly” and his BMI was down to the 72nd percentile with an average weight loss of 4.4 grams per day. Six months later, in the last note documented on file, the following was reported in his medical note: non-compliance with Miralax, diarrhea, lack of understanding in calculating the carbohydrate content in food, positive for Pseudomonas aeruginosa, splenomegaly, progression of liver disease to gradual Thrombocytopenia, drop in FEV1% from the 90th percentile range to the 70th percentile, glucose consistently ranging from 200 to 300 mg/dL, and precarious nutritional status (Figure 2). Monte’s weight was in the 39th percentile, his height was in the 26th percentile, and over one year his BMI dropped from 83% to 51% (Figure 3). No values of FFM were documented. His primary care doctor recommended increasing his enzyme dose, increasing his insulin dose, and prescribed Boost Kids Essentials 1.5 at a minimum of two times per day.
Figure 2
Trends in glucose, BMI, and lung function of the case study patient

Avg. BG (mg/dL), average blood glucose measured in milligrams per deciliter; BMI%, percentile of body mass index; FEV1%, percentage of predicted forced expiratory volume in 1 s.

Figure 3
Growth chart of the BMI percentile of the case study patient

BMI (kg/m²), body mass index measured in kilograms of mass per meters of squared height. Values are plotted as the corresponding BMI-for-age percentile on a CDC BMI-for-age growth chart.

Discussion

Monte’s unique case is a single, unique example of an issue in the field of CF that the treatment guidelines failed to capture. While interpretation of his case does not warrant application or extrapolation to other cases, it offers points to consider in future research of health status. Health is multidimensional and captures how people feel and function outside of their medical care. Consequently, a number of factors created the perfect storm for Monte’s nutritional decline. The following influences were documented about Monte in various medical notes written by members
of the interdisciplinary team: bullied at school, negative body image, language barrier, cognitive delay, low socioeconomic status, lives in unsafe neighborhood, and non-compliance. The field of dietetics cannot intervene on all of these barriers. However, it is important to consider them when analyzing the literature, creating interventions, and modifying guidelines, as they are sources of bias that others may advance on.

Monte's case supports the literature's philosophy that BMI is a flawed indicator of health status in CF. His BMI measurements at each visit illustrate the limitation of cross-sectional studies. In other words, the severity of nutrition status, according to the guidelines, goes under-diagnosed when a single measurement attempts to understand health status. Throughout the entire twelve years that Monte was plotted on the growth chart, he remained above the 50th percentile and maintained normal nutrition status per the CF guidelines. When comparing his pulmonary function to his BMI, the positions of Hannah et al. and Stephenson et al. are underscored: as Monte fluctuated between the 90th and 97th percentiles, his lung function did not necessarily continue to increase indefinitely as his BMI increased.

Additionally, his lung function status likely reflects the evidence seen in Steinkamp et al., which argues that lung function in 6 to 11.9 year olds declines with weight loss at a faster rate in normal weight children than in children with malnutrition. Apart from the fact that Monte's lung function significantly deteriorated after this age bracket (12 to 14 years) it was still within the peak period of lung growth (6 to 14 years) previously mentioned. Considering Monte's substantial depreciation in pulmonary status, despite the fact that his BMI remained above the 50th percentile, Steinkamp et al.'s theory may hold true. Therefore, in the case of obesity, we should emphasize the importance of the rate of weight loss instead of BMI to better indicate nutritional status as it pertains to lung function.

Thirdly, while we did not have evidence of his FFM, it is fair to reason that his increased BMI was secondary to increased adiposity for any of the following reasons: his physical activity was inconsistent and he preferred sedentary activities such as reading and video games; he was described as being thin with a large belly, which likely indicates central adiposity, a measure of increased fat mass in the general population; and poor carbohydrate control that likely caused muscle catabolism. Finally, since low income was a recurring barrier, it is possible that the foods highest in protein were not consumed in adequate amounts because of the increased price point. If increased adiposity were in fact true, Monte's health outcomes would also validate the results from the studies by Engelen et al. and Alvarez et al. These suggest that FFM is the driver for lung function and a more accurate endpoint of health status than BMI in this patient population. It is worth noting
that the reason BMI tends to be a more accurate and accepted measuring tool in the general, healthy population is because increases in BMI at lower BMI largely reflect increases in lean body mass. Inflammation from chronic disease and infection result in a catabolic state and, in addition to malabsorption, lends to protein and muscle loss in CF (Sheikh et al., 2014). This therefore may disturb the expected positive relationship between FFM and BMI seen in healthy individuals. Research also shows that subjects with CF have lower FFM Z scores compared to controls with similar BMI scores (Sheikh et al., 2014), in addition to lower BMIs as a result of stunted height (Alvarez et al., 2015).

Lastly, while a direct link is less clear, it is possible that Monte’s diet, aside from poor insulin control, contributed to his worsening glucose levels. Consequently, the ratio of fat mass to FFM increased. The CF guidelines advise against the restriction of calories or any macronutrients, except in the case of CFRD, where carbohydrate ranges are based individually (Moran et al., 2010). Additionally, the guidelines do not specify limiting or increasing specific types of fat or carbohydrates. Even though a few of the nutritional interventions from Monte’s dietitian encouraged the consumption of healthy fats and foods with increased fiber, these were rarely reported on Monte’s dietary recalls. One can assume that fiber rich carbohydrates were not a staple of his daily consumption for any of the following reasons: he ate the school subsidized lunch, which likely lacked appealing whole grains; healthier foods, such as fruit, fresh vegetables and whole grains are more expensive than refined; it took mom awhile to agree to stop serving juice; and both Monte and his mother had a history of non-compliance to nutritional recommendations as a result of the number of other therapies they were asked to perform. If this assumption were in fact true, Monte’s poor glycemic control likely contributed to his decline in weight, protein catabolism, and consequently, worsening pulmonary function as suggested by the literature.

While Monte’s case does not represent the average CF patient, it allows practitioners to retrospectively look at his plan of care and identify the treatment modalities in need of improvement. The literature presented in this review offers evidence for possible advancements of the interventions recommended in two critical time periods of Monte’s case. For example, when he was obese prior to age 12 and following along a growth curve, preventative measures should have been taken. First, his weight loss should not have been praised, as this might have led to feelings of self-satisfaction that are often welcomed at this difficult stage of life. Though the evidence remains inconclusive on the detrimental effects of obesity in the CF pediatric population, a general consensus exists that increased muscle mass likely improves lung function. Specifically, lower lean
Body mass may result in muscle impairments of the diaphragm or accessory respiratory muscles, which leads to subordinate lung function (Sheikh et al., 2014). In this example, using DEXA to identify FFM and adiposity would have been optimal for assessing the source of weight loss. Even if DEXA did not exist, other measurements of actual body adiposity are available, including the following: waist/hip ratio (WHR), which reflects central adiposity; subscapular skin-fold thickness, which reflects thoracic adiposity; and skin-fold thickness, which reflects general obesity (Brashier & Salvi, 2013). Furthermore, body site-specific measurements are more telling than changes in overall body fat. Evidence argues that fatty tissue deposits in abdominal and thoracic regions interdependently impart mechanical restriction to the diaphragm and lungs. However, deposits on other areas such as the thighs and hips do not have an effect on pulmonary movements. In other words, weight loss from abdominal obesity is less concerning, as this may improve FEV1 and FVC (Brashier & Salvi, 2013). Another area of improvement in the early stages of intervention is a greater emphasis on physical activity. Only two of the medical notes from the dietitian mentioned increasing physical activity. During the sessions it was discussed, the dietitian gave Monte a handout of suggested activities such as jumping rope, jumping jacks, dancing, hiking, and push-ups. Apart from the fact that 46% of adults with CF use exercise as a primary or secondary airway clearance technique, exercise also improves muscle mass, insulin sensitivity, and bone health (2014 Patient Registry, 2016). Likewise, considering both the unsafe neighborhood that Monte lived in and the fact that aerobic exercises—such as dancing and jumping jacks—increase muscle mass to a lesser extent than weight bearing exercise, he likely would have benefitted to a greater extent from strength training movements at home or when feeling too tired to engage in cardio movements. Ideally, a physical therapist should visit patients during annual follow-ups to propose ideas for strength training exercise to learn proper form and so the patient finds one they enjoy. Lastly, while he was far from risk for malnutrition during these earlier years, the CF Foundation recommends that patient and family education about nutritional care, including the role of enteral tube feeding, continue throughout the lifetime of every individual with CF (Schwarzenberg et al., 2016). Though some might argue that starting the conversation increases stress and may not be appropriate for caregivers with a history of resistance, introducing the awareness early on will likely decrease the burden if supplemental feeding becomes necessary in the future. Furthermore, it allows for sufficient time to research the intervention, address questions and discuss the treatment with other parents who agreed to the decision. If nothing else, it delineates how important nutritional status is to survival in CF.
During the ages of 12 to 14, Monte lost a significant amount of weight, and it was not until he dropped to from the 95th to the 51st percentile that the physician encouraged nutritional supplements (Boost Kids Essentials 1.5). Of note, prior to this recommendation, the dietitian did not see a purpose for adding another means of therapy to Monte’s life, principally because he never reported a modest appetite. Despite these reasons, he likely did not qualify for subsidized oral supplements since he was never medically diagnosed as “at risk” per CF guidelines. However, supplements should have been proposed when Monte went below the 85th percentile, which described his ideal centile according to the team. Oral supplements would have expectedly boosted his protein and nutrient intake. Moreover, they would have improved his blood glucose levels after his snack had they replaced the snack he was choosing to eat at home or school, since the corresponding insulin administration was based on a pre-determined carbohydrate count at each snack. Despite the given instructions, Monte and his mother never fully comprehended nor performed carbohydrate counting at each snack. Consequently, the prescribed bolus of insulin rarely covered the amount of carbohydrates consumed with snacks, reflected in the elevated glucose levels. Replacing one or two snacks with supplements likely would have improved protein intake and postprandial blood sugar, which minimize catabolism. Furthermore, since supplements contain a concentrated volume of carbohydrates, the variety of supplement is meaningful, as previously described evidence showed monosaccharide loads to be detrimental to blood glucose levels (Figueroa et al., 2002). A supplement catered to the CF population does not currently exist, but if it did, it should be modeled specifically for patients with CFRD and high in calories, fat, and protein, while mindful of carbohydrates and sugar. Until such a formula is created, Optisource appears to be the most comparable option. Per 100 mL it contains: 5.1 g of carbohydrates, 2.5 g of fat, and 10.2 g of protein, and each bottle is 250 mL (Bunting et al., 2013).

Conclusion

Patients with Cystic Fibrosis (CF) typically present with a number of comorbidities, including malnutrition, CF related diabetes (CFRD), CF related liver cirrhosis, and chronic respiratory infections. For the majority of non-CF adolescents, common comorbidities include obesity and diabetes. Research has recognized successful solutions and guidelines for optimizing this population’s health at a young age. However, gaps still remain in the literature, and therefore the guidelines, pertaining to management of obesity in the CF patient population.
The case of Monte identifies these gaps by presenting an issue that the CF population is now familiarizing itself with at the same time the obesity epidemic in the general pediatric population continues to expand. Using the available evidence going forward, it is fair to conclude that guidelines should address assessing body composition in children using DEXA. Unlike the BOD POD, DEXA measures bone mineral density, a measurement critical to this population. Additionally, it is preferable due to its widespread availability, its accuracy in measurements, its non-invasive nature, and the fact that the Cystic Fibrosis Consensus recommends screening for decreased bone mineral density on select patients using DEXA. Furthermore, guidelines need to validate other methods besides BMI for assessing body composition as a measure of nutritional status in the CF population when DEXA is not available, such as WHR, subscapular skin-fold thickness, and skin-fold thickness. Alternatively, guidelines should classify the crossing of centiles as a risk factor for malnutrition even when BMI is above the 50th percentile. From a nutritional standpoint, more attention needs to be given to the sources of calories instead of taking the easy way out – i.e., eating junk foods in abundance – to increase weight gain. This is particularly important while the obesity epidemic expands, as more research becomes available for obesity as a comorbidity of CF, and as the effect of macronutrients on CFRD is better understood.

Lastly, the evidence presented signals a call to action for increased longitudinal research in the field of CF. Specifically, studies with large sample sizes and obese patients are needed in order to take factors such as age, gender, body composition alterations during puberty, mutation type, blood glucose and CFRD, rate of weight loss, exercise, body composition methodologies, and the like into consideration. When reviewing evidence and attempting to make substantiated conclusions, the most important factor to consider is the way in which we define obesity. Thus far, the majority of studies lack the distinction in body composition behind a patient’s “obese” or “normal” BMI. If studies fail to streamline the method for which obesity is defined and diagnosed, outcomes will continue to explain inconsistent correlations of nutritional status and pulmonary function. The literature and case study prove why the tendency to take a read-and-memorize approach to the guidelines will continue to fail in practice. Until enough credible evidence is available to catch the CF guidelines up to speed, no real progress can be made.
References


Steinkamp, G., & Wiedemann, B. (2002, January 24). Relationship between nutritional status and lung function in cystic fibrosis: Cross sectional and longitudinal analyses from the German CF quality assurance (CFQA) project. *Thorax, 57*(7), 596-601. doi:10.1136/thorax.57.7.596


Figures

Figure 1
Body composition category differences in adults with cystic fibrosis. One-way analysis of variance indicated statistically significant group differences in percent body fat (top left), fat mass index (bottom left), fat-free mass index (top right), and FEV1% predicted (bottom right). (P < 0.01 for all). Groups not connected by the same letter are significantly different (determined by Tukey’s post-hoc comparisons). FEV1%, percentage of predicted forced expiratory volume in 1 s; NWO, normal weight obesity.

Figure 2
Trends in glucose, BMI, and lung function of the case study patient

Avg. BG (mg/dL), average blood glucose measured in milligrams per deciliter; BMI%, percentile of body mass index; FEV1%, percentage of predicted forced expiratory volume in 1 s.
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Growth chart of the BMI percentile of the case study patient

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