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Abstract

Malnutrition is one of the main burdens of disease in cystic fibrosis (CF) along with lung disease. Data from the most recent Cystic Fibrosis Foundation registry report show the prevalence of malnutrition is decreasing in the CF population primarily from interventions focusing on preventing malnutrition. Despite success of interventions and decreased prevalence of malnutrition in this population, prevention of malnutrition in CF patients remains a dilemma that must be managed throughout the life cycle. The pathogenesis of malnutrition in CF can be further categorized into 3 main areas: increased energy losses, increased energy needs, and inadequate calorie intake. The purpose of this review is to further explore the causes of malnutrition and explain current research to prevent malnutrition in the CF population. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

cystic fibrosis; pancreas; pancreatic diseases; nutritional status; lung diseases; liver diseases

Cystic fibrosis (CF) is a genetic, autosomal recessive disorder. Malnutrition and lung disease are 2 of the main burdens of CF. Approximately 1 in every 3500 babies born in the United States has CF. While it is most common in Caucasians, CF can affect all racial and ethnic groups. The most recent CF Foundation Registry report published in 2011 revealed that the median age of survival is 36.8 years. There are over 1800 identified mutations since the gene, cystic fibrosis transmembrane conductance regulator (CFTR), was initially discovered in 1989.[1,2] The role of nutrition in CF care changed dramatically after the 1988 article comparing CF patients in Boston and Toronto.[3] It was discovered that the Boston group was recommending low fat diets to curb the effects of malabsorption with a lower pancreatic enzyme supplementation while the Toronto was recommending a high-calorie, high-fat diet with ample pancreatic supplementation. The findings showed that the Toronto group had markedly better survival rate with a median age of survival of 30 years old vs the Boston group, which had a median survival of 21 years old. The role of nutrition in CF was forever changed due to this hallmark study indicating that nutrition has an impact on survival.[3]

In 2008, the CF Foundation released the most recent evidence-based recommendations for the nutrition management of children and adults with CF. The recommendations were made after an analysis of the CF Patient Registry data found an association between weight-for-stature and lung function measured as percentage predicted forced expiratory volume in 1 second (FEV1). Due to a comparison showing body mass index (BMI) percentile being more sensitive to changes in lung function than percentage ideal body weight, the CF Foundation recommended discontinuing the use of percentage ideal body weight as an assessment tool. Instead, it is recommended that children and adolescents maintain a BMI at or above the 50th percentile while adults should maintain a BMI at or above 22 kg/m^2 for females and 23 kg/m^2 for males.[4] The new guidelines, however, do not provide recommendations on how to otherwise classify or assess the nutrition status of patients with CF.

Prior to the 2008 Guidelines, a Consensus Report for U.S. Pediatric Patients with CF was released in 2002. An acceptable nutrition status was defined with a percentage ideal body weight ≥ 90%, and a weight-for-length > 25th percentile or a BMI > 25th percentile. A patient considered to be at nutrition risk was defined as a percentage ideal body weight ≥ 90% with weight loss or weight plateau, and a weight-for-length or BMI between 10th to 25th percentile. Nutrition failure was defined as having a percentage ideal body weight < 90%, and/or a weight-for-length or BMI < 10th percentile.[5]

In pediatrics, acute malnutrition can be assessed using Waterlow criteria measuring the degree of wasting, calculated as percentage ideal body weight, with 80%-89% indicating mild wasting, 70%-79% indicating moderate wasting and < 70% indicating severe wasting . Chronic malnutrition can also be assessed using Waterlow criteria measuring the degree of

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stunting (height/age % standard) with 90%-95% mild, 85%-89% moderate and < 85% severe. The World Health Organization defines malnutrition as moderate or severe using weight-for-length and length-for-age standard deviation scores with or without edema. A weight-for-length or a height-for-age *z* score of –2 to –3 without edema is classified as moderate malnutrition. A weight-for-length or a height-for-age *z* score < –3 with edema is classified as severe malnutrition. A BMI < 10th percentile for age can be used to identify patients 2-20 years old that are underweight or at risk for being underweight.[2]

The definition of malnutrition in adults can also be assessed by 2 different methods. Mild malnutrition is defined as 80%-90% of ideal body weight; moderate malnutrition is defined as 70%-79% of ideal body weight and severe malnutrition if percentage ideal body weight is < 70%. Protein-energy malnutrition can be classified by BMI utilizing the following ranges: BMI 17-18.4 kg/m^2 is grade I, BMI 16-16.9 kg/m^2 is grade II, and a BMI < 16 kg/m^2 is grade III.[6]

According to the CF Foundation Registry report, collected in 2011 revealed that the median BMI for ages 2-19 is 51.3 percentile. For adults aged 20-40 the median BMI is 22.1 kg/m^2.[1]

There are several suggested mechanisms leading to the cause of malnutrition in CF. They can be grouped in to 3 main groups, including energy losses due to the disease, inadequate caloric intake, and increased energy metabolism.

Energy Losses

Malnutrition seen in this patient population is a result of the energy losses and nutrition deficits caused by malabsorption, CF-related liver disease (CFLD), CF-related diabetes (CFRD), and various psychosocial issues, including stress and noncompliance.

Exocrine pancreatic insufficiency (PI) is the most common gastrointestinal complication associated with CF and is seen in 85%-90% of the population.[7] This is due to a mutation of the CFTR protein, which results in abnormal sodium and chloride transport. This causes the pancreas to have abnormally viscous secretions as well as an acidic lumen. The accumulation of mucous leads to ductal obstruction which causes tissue degradation, fibrosis, fatty replacement and ultimately, pancreatic insufficiency.[8] The exocrine function of the pancreas is disrupted and the pancreas is unable to release the necessary enzymes critical to the digestion and absorption of fat, protein and fat-soluble vitamins. Pancreatic enzyme replacement therapy (PERT) is currently used to manage PI and associated malabsorption. Current preparations of PERT consist of enteric coated microspheres that are designed to decrease enzyme deterioration by stomach acid and improve the efficacy of enzyme release in the duodenum, when pH exceeds 5.[8] Despite optimizing PERT, CF patients continue to experience fat malabsorption, displaying 85%-90% of intestinal fat absorption as opposed to the >95% fat absorption of non CF individuals.[9] Due to a combination of an insufficient secretion of pancreatic bicarbonate and an influx of gastric acid entering the duodenum, duodenal pH is on average 1-2 units lower than normal in CF patients.[10] A normal pH is essential for adequate digestion and absorption of fat, and thus CF patients, in spite of PERT, experience energy losses. It has become routine to provide CF patients with bicarbonate supplementation or acid suppression to improve the efficacy of PERT. One study, which focused on the addition of bicarbonate to enteric coated pancreatic enzymes to adult CF patients, found that average fat absorption increased from 75% to 82% of the ingested amount of dietary fat.[11] A similar study, conducted on pediatric patients, found the average fat absorption did not increase but half of the patients showed >5% improvement in fat absorption after bicarbonate supplementation.[12] A separate review of several studies evaluated the effect of acid suppressants on fat absorption and if they improved nutrition status. The review found mixed results with some studies displaying improved fat absorption after acid suppressive therapy and other studies reporting no improvements. While some patients experienced improved fat absorption, nutrition status was not enhanced.[13] Enzyme dose should be adjusted when there is a poor response to therapy. This can be defined as abdominal pain/bloating, increased number of stools, loose stools, steatorrhea, and/or poor growth. Enzyme dose can be increased until the maximum recommended dose has been reached. If the patient does not respond to treatment other factors should be addressed such as adherence, abnormal intestinal pH or other non-CF-related gastrointestinal problems.[14] Maximum dosing cutoffs for enzymes have been established at 10,000 units lipase per kilogram body weight maximum per day or 4000 units lipase per gram dietary fat consumed per day.[4] Excessive dosing in upward of 20,000-50,000 units lipase per kilogram body weight per day has resulted in fibrosing colonopathy.[15] This is a severe condition, which is categorized by submucosal fibrosis in the proximal colon and strictures. Typical presentation includes abdominal pain, distention, vomiting and diarrhea. These symptoms are similar to distal intestinal obstructive syndrome (DIOS), but will not resolve with the usual management of DIOS. Often surgery is required to correct the strictures.[16] Overall, the outcomes show that using acid suppressive therapy for CF patients with PI does not necessarily provide significant benefits as it relates to fat absorption and improved nutrition status but it may provide some benefit in individual cases.

As discussed, patients experiencing malabsorption also are at risk for fat-soluble vitamin deficiencies. Fat-soluble vitamins are required for immune function and bone health, and their deficiencies can lead to prolonged recovery from CF exacerbations. Fat-soluble vitamin supplementation is provided through CF-specific formulated preparations and dose is dependent on age. In regard to micronutrient deficiencies CF patient have been indentified to be at risk for the following deficiencies: calcium, sodium, iron, and zinc. Fat-soluble vitamin replacements contain additional zinc and patients are counseled to add additional sodium to foods. Calcium supplements are recommended when patients are not consuming

Table 1. Comorbidites of Cystic Fibrosis.

Comorbidity	Cause	Nutrition Consequences
Cystic-fibrosis-related diabetes	• Obstructive damage to the exocrine pancreas • Progressive fibrosis and fatty infiltration destroys islet and insulin producing cells • Insulin resistance	• In hyperglycemic state, the body burns fat and muscle to generate energy • Energy losses secondary to ketones and glucose in the urine
Cystic-fibrosis-related liver disease	• Dehydration in biliary ductules • Increase bile salt concentration • Decrease in bile flow • Ductular obstruction • Cholestasis	• Disrupts the body's ability to absorb fats and fat-soluble vitamins • Further complicates malabsorption

recommended amounts for their age group as defined by the U.S. recommended dietary allowances (RDA). Iron status should be monitored yearly and supplemented based on hemoglobin and hematocrit.[5]

A secondary gastrointestinal manifestation and nutrition complication of CF is CFLD, particularly biliary cirrhosis and portal hypertension. Between 2% and 15% of patients with CF develop cirrhosis and roughly 5%-7% of patient with CF develop significant portal hypertension, with the median age of diagnosis being 9-10 years.[17,18] The absence of functional CFTR in biliary ductules causes dehydration which leads to an increased concentration of bile salts in hepatobiliary secretions and a decrease in bile flow, which ultimately leads to ductular obstruction and cholestasis. A lack of bile and decreased bile flow affects the body's ability to absorb fats and fat-soluble vitamins, further complicating the issue of malabsorption in CF.[19] Corbett et al demonstrated in a case-controlled study that CF patients with advanced liver disease were shorter, lighter and had diminished fat free mass likely due to a combination of an increase in REE, abnormalities in intake secondary to anorexia, and energy losses secondary to malabsorption.[20] While current data do not indicate a causal relationship between poor nutrition status and the development of CFLD, they do suggest that patients with CFLD are at greater risk for decline in nutrition status than CF patients without liver disease.[17]

Further complicating the already present nutrition issues of CF, is CFRD, which has been associated with a nearly 6-fold greater mortality rate and is a distinct form of diabetes mellitus, separate from type 1 and type 2 diabetes. The defective chloride channel that is present in CF results in viscous secretions that lead to obstructive damage to the exocrine pancreas. This causes the progressive fibrosis and fatty infiltration that destroys islets and the insulin producing cells.[21] Insulin deficiency is the primary cause of CFRD but insulin resistance is also seen in patients with CFRD, likely due to decreased uptake of glucose by the muscle and impaired suppression of hepatic glucose production.[22,23] Insulin resistance has also been shown to worsen with acute pulmonary exacerbation, glucocorticoid therapy and chronic severe lung disease.[24] Nutrition issues arise with hyperglycemia (be it from glucocorticoids, insulin deficiency or insulin resistance) as the body burns fat and muscle, as opposed to glucose, to generate energy, furthering energy losses that CF patients already experience secondary to malabsorption. Energy is also lost when ketones and glucose are released in the urine. Studies have shown that slight glucose abnormalities are relevant in CF, specifically as it relates to nutrition issues. One study found that having a serum glucose >140 mg/dL for ≥4.5% of the time during continuous glucose monitoring predicted greater declines in weight and FEV1% over the previous 12 months verses a percentage time <4.5% in adolescents that had normal glucose tolerance or impaired glucose tolerance.[25] Further highlighting the role of insulin and nutrition status with CF is a study that showed improved BMI in adults with CF without fasting hyperglycemia that were treated with subcutaneous insulin for a year.[26] Smaller studies in pediatric patients have shown similar improvements in weight when the patients were provided insulin, even prior to the development of CFRD.[27-29] A link has been established between CFRD and worsening pulmonary function as declines in clinical status can occur in the years prior to diagnosis. The rate of pulmonary deterioration over a 4 year period has been correlated with the degree of insulin deficiency at baseline, highlighting the relationship between the loss of the anabolic effects of insulin, the ensuing protein catabolism and clinical deterioration.[21] As the CF population continues to age, the incidence of CFRD increases. The annual incidence of CFRD is reported to increase with age at 5.0% per year in patients 10 years and greater and 9.3% per year in patients >20 years pointing to a greater need for a better understanding of CFRD and its nutrition outcomes.[22] See Table 1.

CF is not only plagued by organic issues that lead to energy losses but also psychosocial issues related to the family environment and to individual behaviors. Adherence to treatment, including taking pancreatic enzymes and providing adequate calories to meet increased energy needs, which often takes place in the home, varies for the CF population. One study that examined adult's compliance with CF treatments found 76% took prescribed drugs 90% of the time while compliance with

physiotherapy was reported to be 54%.[30] Another study explored adherence amongst 40 hospitalized adolescents with CF and found females were more likely to be nonadherent than males, with older adolescents being the most nonadherent.[31] When compliance becomes an issue with PERT, energy losses ensue secondary to steatorrhea and protein and fat malabsorption. Patients with CF also lose energy by not taking advantage of meal and snack times. Some studies imply the constant focus on caloric intake make meal and snack times stressful, which actually results in decreased intake.[32] It has been observed that parents of children with CF describe meal times as a battleground and diet has been cited as one of the least adhered to pieces of CF treatment, particularly for young children.[33,34] Parental reports and direct observation of parents of children with CF have shown that parents are using ineffective strategies to increase compliance and caloric intake, including commanding the child to eat, coaxing, using physical prompts, making additional meals and feeding the child. Similar reports have demonstrated that children with CF use mechanisms to delay eating, refuse food, spit out food, and leave the table more frequently than their counterparts without CF.[35] One study examined the effects of a behavioral component of a combined behavioral and nutrition education intervention for children with CF by comparing it solely to the education component of the intervention. The authors anticipated the behavioral intervention would produce increased caloric intake and weight gain. The study found that the children in the behavioral intervention group increased their caloric intake by 1035 calories per day while their counterparts in the education group increased their caloric intake by 407 calories per day, demonstrating the importance of teaching parents behavior management tactics to make meals less stressful while still promoting increased caloric intake. The study also found that children in the behavioral intervention group had more weight gain than the education group (1.42 kg vs 0.78 kg) and 2 of the 3 children in the behavior group improved their weight-for-age percentiles while only 1 child in the education group achieved similar gains. The weight results show the increase in caloric intake was not just reported but indeed achieved. Finally, the study measured interactions between the parent and child with the goal of providing strategies to improve behaviors, attitudes, and interactions during meals. While it did not find significant changes in parent–child interventions, it did find that mothers in both groups reported improved moods during meals and well as decreases in the frequency and difficulty of challenging situations related to meals and weight.[33] While it is seen that educating CF patients on the importance of compliance with the nutrition related components of the disease (PERT and increased calorie intake) is key to reducing energy losses, it is necessary to provide behavioral intervention tools, such as problem solving, reinforcement, and self-reward, to ensure that nutrition components are achieved.

Inadequate Calorie Intake

There are many factors that contribute to inadequate calorie intake and weight loss in patients with CF. Calorie losses can be experienced from malabsorption and increased energy expenditure from lung infections.[36] The connection between good nutrition status and better lung function has been established in the CF population.

The goals of nutrition intervention are to promote optimal growth and development, enhance quality of life and improve survival.[37] To reach these goals patients with CF need to follow an unrestricted diet that is high in calories (30%-40% of the calories from fat), have optimal PERT and use supplemental nutrition (orally or enterally) when appropriate.[37]

As previously discussed pancreatic insufficiency, requiring the use of pancreatic enzymes is found in 85%-90% of the CF population.[38,39] Pancreatic insufficiency is confirmed by a random fecal elastase level that can be measure before or during enzyme therapy.[38] PERT are porcine-based, enterically coated microspheres that resist activation by gastric acid.[37,38] PERT dosing is based on kilogram body weight of an individual (500-2500 units of lipase/kg) or grams of fat per meal (<4000 units of lipase/gram of fat).[4,36] Malabsorption of fat will occur (10%-20%) even when PERT is used in the most optimal way.[37] There are many factors that affect an individual's response to PERT including duodenal pH, storage conditions of the enzymes, and adherence.[37,38] According to the PERT storage conditions, enzymes should be stored at room temperature and be protected from moisture. O'Brien et al conducted an online survey on the CF nutrition list serve and found there are a variety of times practitioners are having patients take PERT in relation to meals, but the majority dosed them at the start of meals.[39] A study on PERT administration in relation to meals found that digestion was better when PERT were taken during or after meals.[38]

The first step in reaching nutrition goals is determining calorie needs. Calculations used by nutrition professionals are just estimates and need to be adjusted according to actual intake and growth. It has been stated in multiple resources that the calorie needs of patients with CF are 110-200% higher than the healthy population.[4,40-42] The 1992 nutrition assessment and management in CF: a consensus report provided recommendations on using a formula that took into account physical activity, pulmonary function and degree of malabsorption.[41]A study of 53 subjects (6-8 years old, with mild to moderate lung disease) evaluated 6 proposed formulas and compared them to the energy requirements for children with CF.[43] The formula found to be the most accurate was estimated energy requirement (EER) for age and gender at the active level. See Table 2.

It is hypothesized that patients that snack on food all day may not have a strong hunger and satiety pattern, so they may eat less and have a difficult time with enzyme administration.[36]

Table 2. Energy Requirements for Children Who Are Physically Active.

Gender and Age	Energy Expenditure Equation
EER for males 3-8 years old	EER = 88.5 – (61.9 × age (y)) + 1.26 (active PA*) × (26.7 × wt (kg)) + 903 × ht (m) + 20
EER for females 3-8 years old	EER = 135.3 – (30.8 × age (y)) + 1.31 (active PA*) × (10 × wt (kg)) + 934 × ht (m) + 20

EER, estimated energy requirement; PA = physical activity coefficient, age in years, weight in kilograms, and height in meters. Source: Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC. National Academies Press; 2005.

There are multiple issues that can contribute to poor appetite or lack of hunger including acute illness, pulmonary exacerbation, and gastrointestinal symptoms (independent of PERT administration). Gastrointestinal symptoms include gastroesophageal reflux disease (GERD), poor gastric emptying, small intestinal bacterial overgrowth (SIBO), constipation, and DIOS. GERD has been reported in 30% of adult patients with CF; symptoms include heartburn and dysphasia.[44] The cause of GERD is transient lower esophageal sphincter relaxation (TLSR), so that contents of the stomach backflow into the esophagus.[37] According to CF registry data 60% of CF patients are taking acid blocking medicines.[44] It is also common practice for patients to be prescribed acid blocking medications to help with the efficacy of enzymes.[37,38,45] The studies on gastric emptying have been inconsistent and shown rapid to delayed gastric emptying.[45] SIBO occurs when bacteria from the terminal colon end up in the small intestines. The intestinal environment of most CF patients make them predisposed to SIBO, including the use of gastric acid suppression medications, slowed intestinal transit and poor hydration in the intestinal tract.[44-46] Patients with SIBO may experience diarrhea and weight loss.[45] DIOS is defined as complete or incomplete fecal obstruction in the ileo-cecum, while constipation is impaction in the colon.[47] Patients at increased risk for DIOS include those with pancreatic insufficiency and a history of meconium ileus. Episodes of constipation and DIOS are typically related to decreased water secretion associated with the CFTR gene defect.[44] These episodes can cause a decrease in appetite related to abdominal pain, gas, and bloating. Other gastrointestinal diagnoses documented in the CF population includes celiac disease and eosinophilic esophagitis.[43,48]

Medications used in CF patients can decrease appetite or cause taste changes and abdominal pain. It is common for CF patients to have nasal polyps or sinusitis which can cause poor taste and smell, pain with chewing, and difficulty breathing while eating. The emotional and physical burden of doing all therapies including eating 3 meals and 1-3 snacks per day can cause depression, anxiety and stress. Lack of knowledge and understanding can cause food avoidance. Patients may avoid foods high in carbohydrates for fear that it will increase the risk of getting CFRD. Food avoidance could be from the idea that a high-fat food will cause abdominal pain, gas, and bloating; or that milk and milk products increase mucus production.[49]

Missed opportunities can also lead to inadequate energy intake. The individualized nutrition assessment of children's eating habits found that out of 100 meals or snacks children omitted an average of 10 ± 11 feedings. Children missed the opportunity to have a meal or snack approximately 10% of the time; they missed the opportunity to take enzymes 15% of the time. Half of all foods consumed were low fat; therefore, only 10% of the children consumed 120% of the RDA for energy. In addition, children only used high-fat additives and spreadables on 16% of the foods eaten.[50]

If all other nutrition related symptoms have been ruled out or treated and a patient is unable to meet nutrition needs, the third step is usually nutrition support. Nutrition support can be provided as oral supplementation (seen in >37% of the CF population) or tube feeding (seen in >13% of the CF population) as described in the update on enteral nutrition (EN) support for CF.[40] At this time there are no published guidelines on when it is appropriate to initiate gastrostomy tube (GT) placement and start tube feedings; however the 1992 CF nutrition consensus report recommended starting tube feeding if a patient was below 85% of their ideal body weight and failed other nutrition intervention.[40]

CF patients with a GT for supplemental nutrition therapy typically get night time tube feeding providing about 50%-75% of estimated energy needs.[37,42] GT feedings are well tolerated and helpful in improving nutrition status, but there are risks involved (decreased lung function, and poor pulmonary status) that will prevent weight gain even with EN supplementation.[40] Bradley et al conducted a retrospective study that found at 6 months post GT placement patients were 10 times more likely to reach a BMI at or above the 50th percentile. However by 1-year follow-up the mean BMI was lower.[42] Results from a small retrospective study demonstrated that GT feedings do not significantly improve lung function or decrease the number of pulmonary exacerbations.[37] Patients with advanced lung disease can have poor clinical outcomes following GT placement related to poor growth and little improvement of lung function; patients with less severe lung disease will receive a greater benefit from GT placement.[37,40] Young children with poor growth will benefit from early intervention with GT before malnutrition becomes an issue.[40]

Survey results on the CF nutrition list serve indicate there are common practices regarding the nutrition care of patients; however the evidence is lacking to provide specific recommendations.[39]

Increased Energy Requirements

A heavily studied area within CF has been examining resting energy expenditure (REE). REE was measured using indirect calorimetry in all studies. A large proportion of the studies

examined the differences in REE between healthy subjects and patients with CF who were well nourished. These studied showed that at rest REE was greater than similar healthy non-CF patients.[51-56] An additional study also showed REE was also greater than predicted REE compared to the Schofield H-W equation.[57] Studies also demonstrated that there is a strong correlation between pancreatic sufficiency status and REE. Those patients who were diagnosed as being pancreatic sufficient exhibited normal REE compared to healthy subjects.[57] A longitudinal study in well children in Australia concluded that males typically have a lower REE than females. In addition, liver disease did not play a significant role increasing REE.[56] Other studies also confirmed a difference between REE in males vs females, however it is still controversial if this increase is due to the effect of the menstrual cycles as different studies have had opposite results.[58]

Other studies looked at the role of increased energy expenditure being related to completing activities of daily life, which was proven invalid.[59] One study sought to examine if genetic differences within CF could account for differences in REE within comparable groups of CF patients. Fourteen patients with homozygous deltaf508 compared to 9 patients with different genotypes were studied, but still pancreatic insufficient showed no difference in REE or lung function.[52]

Studies looking at newborns diagnosed with CF have shown that their REE is equivalent to their non-CF counterparts, leading researchers to believe that there are other unknown factors contributing to the increased REE.[53]

A study conducted by Barry and Gallagher revealed a cause-effect relationship between increased steroid doses and decreased muscle mass. Corticosteroids are commonly used to treat pulmonary exacerbations in CF.[60] Further gene research is looking into the presence of the defective CFTR gene alone leading to increased energy expenditure.[61] Specifically, in mice with CF researchers Divangahi and colleagues have established that the lack of CFTR activity in skeletal muscle predisposes these mice to have muscle wasting.[62]

There is a known correlation between increased lung function and increased BMI. The CF Foundation examined the 2005 Patient Registry data set and found that FEV1 status of 80% or higher was correlated with BMI at 50 percentile or higher. This led the CF Foundation to change its guidelines to recommend that children with CF achieve a minimum of a BMI at the 50th percentile for age to promote lung health.[4] A recent longitudinal study conducted by Stephenson et al looked at individuals over time and further confirmed that patients who had a higher BMI typically had higher lung function or FEV1.[63]

Pulmonary exacerbations resulting from infections and inflammation are a possible cause for increased REE in CF, however 2 different studies showed different results regarding REE and exacerbations. One study showed no change in REE during hospital admissions for exacerbations, while another study showed an increase in REE during acute illness.[64,65] Another study looking at nutrition status during pulmonary exacerbations showed that oral intake was decreased during this time period. This doesn't support the hypothesis that REE is increased during exacerbations; however it can contribute to weight loss in CF patients and eventually lead to patients becoming malnourished.[66]

Challenges/Limitations

When classifying malnutrition in CF patients and determining a plan of action several limitations and challenges exist. In regard to the CF Foundation guidelines that patients should be at a BMI or weight/length > 50th percentile, these guidelines were developed using the entire CF patient population, but did provide separate guidelines based on genotype-specifically whether patients were pancreatic sufficient or pancreatic insufficient. Research shows that patients whose genotypes are classified as pancreatic sufficient tend to have better outcomes and a near normal REE.[57] This raises a question whether different nutrition recommendations should be made for these patients. Another limitation with the CF Foundation guidelines is that there is no guidance for classifying patients below the goal of the 50th percentile for BMI. In the 2002 guidelines there were recommendations for categorizing these patients as "at risk" or in nutrition "failure." Risk classifications assist in determining nutrition algorithms for treatment.[5] Algorithms may be utilized and developed at a care center for standardization of patient care.

Future Research

The Baby Observational and Nutritional Study (BONUS) is a multicenter study designed to understand the nutrition factors that contribute to an infant's nutrition status and how that may affect nutrition outcomes. The study focuses on growth patterns of infants with CF during their first year of life and how nutrition, inflammatory, and respiratory factors influence incremental weight gain and linear growth. The study is currently in progress and no results are available at the time of printing of this article.[67]

The diet for CF is high-calorie, high-protein with a focus on calorically dense fat as a good source of energy in the traditional CF diet. As patients with CF are living longer, it is important to identify any long-term negative effects from this type of diet, such as dyslipidemia, in adults with CF. There is some research to suggest that people with CF that are pancreatic sufficient are more likely to develop dyslipidemia than those that are pancreatic insufficient.[68] This may suggest a change in dietary recommendations for people that are pancreatic sufficient to maintain a desirable BMI while preventing dyslipidemia.

A new drug, Ivacaftor, was recently approved by the FDA for use in CF patients with the specific mutation G551D. This drug helps restore CFTR function and patients taking this drug

experience near normal sweat chloride levels. During clinical trials it was reported that patients taking the drug had 2.8 kg weight gain compared to patients receiving a placebo over the 48 week study period.[69,70] Currently only 4% of people with CF living in the United States have this mutation. Further research is exploring additional drugs which may help people with other mutations.[71]

Conclusion

Overall the outlook for patients with CF has dramatically improved over the past several years.[1] This involves respiratory treatments evolving to help treat and prevent respiratory infections and an increased emphasis on helping patients achieve nutrition success. While malnutrition is still a pressing issue for patients with CF, one that most battle with every day, overall its prevalence within the CF population has declined. In 2005 the median BMI for females was 21 kg/m^2 and for males was 22 kg/m^2 and the all center median BMI was at the 44th percentile.[4] Currently, the national median BMI is 21.5 kg/m^2 for adults and 51.3 percentile for children aged 2-19 years old.[1] As the median survival age of people with CF continues to increase, nutrition care guidelines should evolve accordingly as other health issues arise.[1]

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