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Protein is an important but undervalued macronutrient in the nutritional care of patients with Cystic Fibrosis

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Abstract

Purpose of review—Achieving an optimal nutritional status in patients with Cystic Fibrosis (CF) is important to maintain better pulmonary function, physical performance and to prolong survival. So far nutrition care in CF has mainly focused on fat intake and achieving energy balance but there is increasing information on the clinical importance of muscle maintenance and protein intake in CF.

Recent findings—Low muscle mass is consistently associated with pulmonary decline, bone mineral loss and poor survival in CF. High energy and fat intake contributes to an increased prevalence of overweight and obesity in CF. Obesity per se is not related to better lung function in CF, and has negative metabolic and clinical consequences particularly when muscle wasting is present. Protein digestion capacity is severely impaired in CF but high protein intake is needed and essential amino acid mixtures appear highly anabolic even in those with severe muscle loss.

Summary—Body composition assessment and achieving protein balance in the routine care in CF is important to prevent muscle loss and further improve clinical and overall outcome of these patients. New approaches are needed to optimize the interaction between high essential amino acid rich protein intake and pancreatic enzyme regimen in CF. The optimal level of protein intake needs to be assessed in clinically stable CF patients as well as those recovering from an acute exacerbation.

Keywords

Cystic fibrosis; malnutrition; dietary protein; essential amino acids; protein balance; muscle mass; clinical outcome

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Conflicts of interest

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INTRODUCTION

Cystic fibrosis (CF) is the most common life threatening autosomal recessive disease affecting about 1 in 32,000 live births in Caucasians in the United States. Over the past 20 years, the average life expectancy for patients with CF has increased to a median survival of over 40 years (1). The better clinical status and improved survival of patients with CF is the result of treatments that target respiratory infections, inflammation, mucociliary clearance and nutritional status (2).

The association between nutritional status, lung function, growth, clinical outcome and survival in CF has been consistently demonstrated in the past and confirmed more recently in early childhood (3). CF adolescents with worse nutritional status are at risk for substantial decline in lung function in early adulthood (4). Furthermore, acceleration of body mass index (BMI) decline around the age of 18y predicts a substantial drop in lung function (4). These findings suggest that more intense monitoring of nutritional status and nutritional intervention during adolescence is required to reduce lung function decline. Thirty percent of children with CF have low values for fat-free mass (FFM), mainly consisting of muscle mass, and these patients are characterized by reduced lung function, bone mineral loss, muscle function, and high frequency of exacerbations and hospitalizations (5–7). Furthermore stunting, which is related to FFM depletion, is an independent predictor of mortality in CF (8). A low BMI and FFMI is more prevalent in CF patients who die before or after lung transplantation, indicating that a worse nutritional status also negatively affects survival in lung transplantation candidates with CF (9).

Mechanisms leading to malnutrition in CF

Malnutrition is very common in CF and relates to many factors including reduced nutrient intake, macronutrient malabsorption, enhanced inflammatory response, and increased need for certain nutrients (1, 10). Reduced nutrient intake is due to a variety of issues like nausea and gastrointestinal tract abnormalities, gastroesophageal reflux, decreased appetite, esophagitis, psychosocial aspects, and CF-related diabetes. Also, CF patients have increased systemic inflammation (increased plasma CRP, IL6, IL8, soluble TNF receptors, immunoglobulin (Ig)G) that is correlated with the severity of lung disease, nutritional depletion (FFM loss), reduced exercise capacity, and early re-exacerbation (11–13). In addition, physical inactivity, corticosteroid therapy, reduced IGF level, insulin resistance and defective insulin secretion is often present in CF, and the majority of CF patients have increased energy needs due to increased work of breathing (1, 10, 14). All these factors contribute to malnutrition and most important may induce muscle loss in CF. Malnutrition is a key issue in CF but not always characterized by a low body weight or BMI only.

Obesity and (hidden) FFM depletion in CF—Increased fat mass leading to overweight and obesity is becoming a concern also in CF. In a longitudinal cohort study including 909 CF subjects, the proportion of underweight individuals with CF decreased from 20.6% before 1990 to 11.1% in the most recent decade, whereas the overweight and obese subjects increased from 7.0% to 18.4% (15). Obese CF patients are older, have better lung function and milder genotypes, and are more often male and pancreatic sufficient (15, 16). In a recent

study in CF aged 2–18 years, 15% were overweight and 8% were obese (17). A significant number of these patients were pancreatic insufficient, had glucose intolerance, CF related diabetes and/or hypertension. Moreover, overweight and obesity was not associated with further improvement of lung function in CF.

Interestingly, low values for FFM have been found in 25–38% of CF adults and 14–20% of CF children with normal or elevated BMI (5, 18). Low FFM was undetectable by BMI in 58% of the CF adults (18) and children (5). Low FFM was related to lung function impairment in CF adults (18) and associated with impaired lung function and bone mineral loss independent of loss of fat mass in CF children (5). Although the presence of obesity appears to be a paradoxical protective factor for survival in other chronic wasting diseases, data show consistently that obese patients with a relatively low muscle mass (sarcopenic obesity) often have the poorest prognosis (19–21). Furthermore, there is a potential multiplicative effect of too much fat mass and depleted muscle mass on clinical outcome (e.g. insulin resistance, metabolic syndrome, and cardiovascular disease (CVD) risk factors) (22, 23). Moreover, sarcopenic obesity is associated with abnormal basal protein turnover and anabolic resistance to resistance exercise (24). These studies indicate that body composition needs to be assessed in all overweight and obese patients with CF to identify those with FFM wasting. Although BMI has improved the past decades, the prevalence of FFM loss is still high in CF. Nutritional care in CF should therefore aim at improving muscle mass instead of focusing only on increasing body weight or BMI.

Current nutritional guidelines and evaluation of nutritional intervention studies in CF

European and American consensus guidelines recommend that CF children receive over 120% of energy requirements for age, with 35–40% from fat (1, 10). The United States Cystic Fibrosis Foundation (CFF) published a systematic review with clinical care guidelines to encourage evidenced-based practice (25). The CFF recommends an energy intake 110–200% of standards for healthy population in children and adults to support proper weight gain in children and weight maintenance in adults. Furthermore to support better lung function, BMI 50th percentile was recommended for children, and BMI 22 kg/m² (females) and 23 kg/m² (males) for adults with CF (25). Although several epidemiologic studies showed that CF patients who maintain BMI 50th percentile have improved lung function, survival and body composition, BMI still needs to be carefully interpreted because of the large variability in the levels of fat mass and FFM in both adults and children with CF (5, 18).

Even to date, high calorie high fat diet diets and pancreatic enzyme replacement therapy is considered the standard of care in CF (1). However in line with the increasing prevalence of overweight and obesity in CF, there are serious concerns about the long term health effects of the recommended high calorie, high fat diet in CF (26). After the age of eight years, there is a consistent imbalance of fat-sources with over-dependence on saturated fats in CF (27) which may increase the risk of cardiovascular disease (28). The elevated saturated fat intake in CF patients contributes more to development of obesity than other forms of fat and exacerbates inflammation. Moreover, the high fat intake does not increase muscle mass or reduce the severity of CF (1). For individuals with growth and/or weight deficit, the CFF

recommends nutritional supplements (oral/enteral) in addition to usual dietary intake (25). Early and aggressive nutritional support with adequate pancreatic replacement management has been recommended as it leads to both normal growth and better lung function (2).

Several studies have been conducted in the past in CF examining the effects of adding high energy supplements to usual dietary intake. A Cochrane review of three randomized clinical trials in a total of 131 (mostly pediatric) patients concluded a lack of evidence of the efficacy of these products in promoting weight gain in moderately malnourished children with CF (29). A more recent review of 4 trials describing the effectiveness of nutritional interventions, indicated that oral supplements were successful in improving weight in 2 trials, increasing caloric intake in 3 trials but without improving pulmonary function (30). Although enteral tube feeding appears to be effective in improving nutritional status and slowing decline of lung function, this is unclear for oral supplements. However, criticisms of the trials were the very small group of adults studied, the overestimated intake estimation, the fact that < 50% of the children did not return their food diary, the heterogeneity of the intervention groups, and the duration of the studies. Furthermore, no attention was paid to the level of regular food intake and the actual protein intake from the nutritional supplements. A recent study in CF candidates for lung transplantation examining the effects of high caloric intake with oral nutritional supplements, tube feeding or both, showed that these dietetic interventions hardly improved BMI or FFMI of these patients before lung transplantation (9).

Although it is recommended that 20% of the calories should come from protein (10), the optimal protein needs of CF patients are likely to be much higher as indicated in other chronic inflammatory disease states (31). So far, there are no evidence based recommendations available for optimal daily protein intake in CF (25). Insight in the optimal protein intake of CF patients is crucial to prevent muscle loss in CF. The optimal protein intake of CF patients depends on several factors including the extent to which protein digestibility is impaired, the efficacy of the pancreatic enzymes to increase digestion of dietary protein, as well as the anticipated higher protein requirements in CF because of the increased work of breathing, the chronic inflammatory state, and the presence of acute exacerbations.

Role of impaired protein digestion on protein anabolism

Exocrine pancreatic insufficiency occurs in 85–90% of CF patients and results in deficiencies of essential nutrients. Malabsorption is a term often used in CF as a combined process of impaired digestion and absorption of nutrients due to exocrine pancreatic insufficiency. Presence of impaired fat digestibility is generally accepted but until recently it remained unclear to what extent protein digestion capacity is impaired due to lack of accurate methodology to measure it. Impaired protein digestion capacity reduces the anabolic potential of a meal, and leads to high loads of undigested proteins in the colon and production of harmful toxins by gut bacteria and diarrhea (e.g. sulfur, amines). Recently a new method to quantify protein digestibility was published using combined oral intake of ¹⁵N-labeled spirulina protein and ²H₅-labeled phenylalanine (32). This study revealed that protein digestibility is severely reduced (47% of healthy subjects, see figure) in both children and adults with CF (32). Protein digestibility normalized after intake of pancreatic

enzymes, albeit with a severe delay (of 100 min). Changing the source of proteins into more slowly digested proteins, hydrolyzed proteins or free dietary amino acids is a way to get around the impaired protein digestibility in CF while still on pancreatic enzyme replacement therapy. More research is needed if changing the exact timing of pancreatic enzyme intake in relation to meal intake, and modifying the dose and/or composition of the pancreatic enzyme capsules might improve protein digestion capacity in CF as well.

Protein metabolism and the response to a (protein) meal

As mentioned above, there are many disease-related factors contributing to the loss of skeletal muscle in CF by altering the balance between whole body protein breakdown (PB) and protein synthesis (PS). There are several older studies reporting increased protein catabolism in stunted CF children, and recently elevated values were found for both whole body PB and PS in stable CF children (6). Net protein balance however was comparable to that of healthy controls (6). Only a few older studies are available with less optimal methodology showing conflicting data on PB and PS during an acute exacerbation of CF. More research is therefore needed on the exact alterations in protein metabolism during and following a CF exacerbation as local and systemic inflammation is increased and therefore the need for amino acids for building muscle and other proteins (ie acute phase proteins) is elevated. The association between FFM depletion and the number of exacerbations in the preceding year in CF children (6) suggest that with the present nutritional approaches FFM maintenance or gain in pediatric patients and probably also adults are hard to achieve. Studies examining the anabolic effects of feeding in CF remain scarce. Some older studies point toward a defective anabolic capacity of meals as reflected by a limited capacity of CF patients to reduce protein breakdown. However, more recent data show that protein and amino acid supplements are able to induce protein anabolism in CF (33, 34). A dose-response effect on protein synthesis was observed in stunted children with stable CF when protein is provided at 1.5, 3 and 5 g protein kg/d for 4 days (33). PS was 30% higher in the high compared to the low-protein group which resulted in more protein anabolism, and a trend towards higher plasma insulin concentrations were observed with increasing protein intake. This indicates that large amounts of protein are required to increase protein anabolism in patients with CF. However to prevent the colonic load of undigested, not absorbed proteins, intake of highly easily digestible proteins or meals containing free amino acids is recommended in CF if pancreatic enzymes are not able to fully restore protein digestibility (34).

Elemental and free amino acid diets—Diets that compose of free amino acids, simple carbohydrates and fats have been used for many years in CF. Earlier studies have shown that digestion of fats and protein is comparable in a semi-elemental diet that contains peptides, medium-chain triglycerides and carbohydrates when compared to a regular, complex nutritional formula with added pancreatic enzymes, and that overnight feeding with an elemental diet is able to increase body weight and lung function during hospital stay in CF. This indicates that free amino acids in elementary diets have the potential to stimulate anabolism in CF as they are taken up by the gut without the need for pancreatic enzymes.

In the past years, a strong theoretical rationale has been demonstrated for the use of amino acid mixtures in populations suffering from muscle wasting (35). Amino acids are the main nutrients responsible for acute stimulation of muscle protein synthesis, and essential amino acids (EAA) are solely responsible for the amino acid induced stimulation of muscle protein anabolism in healthy individuals and insulin-resistant states (36). Although dairy proteins have high levels of EAA, free EAA mixtures are more anabolic on weight basis and therefore preferred in CF and particularly in those patients with a reduced appetite. In clinically stable CF children, intake of 6.7g EAA resulted in more protein anabolism than the same dose of a balanced mixture of EAA and non-EAA as present in whey protein (34). In line with previously observed in other chronic diseases (37), a linear relationship was found between the amount of EAA intake via a meal (expressed per kg of FFM) and net PS in CF patients with and without nutritional failure. The linear relationship observed between amino acid availability and net protein gain remained at high protein or amino acid intakes (37), suggesting continued protein accretion at intakes greater than the requirement level. Whether chronic EAA intervention prevents or ameliorates muscle loss in CF and benefits quality of life and outcome is still unclear. Twelve weeks of EAA supplementation was able to improve muscle mass and function in healthy young (38) and older adults (39), and in glucose-intolerant subjects (36). Patients with severe COPD were able to improve the daily-life performance, quality of life, nutritional and cognitive status, and muscle strength after chronic EAA intervention (40), and rehabilitation patients with brain injury reduced the occurrence of nosocomial infections (41). Although dietary EAA are very effective in inducing protein anabolism in CF, incorporation of free EAA mixtures in long term nutritional care in CF is challenging due to the bad taste of free amino acids. Dairy protein hydrolysates have better digestion characteristics, but it remains unclear whether the anabolic efficiency is comparable to that of free EAA mixtures in CF.

SUMMARY/CONCLUSION

Current guidelines and clinical practice forces CF patients to consume high fat and caloric nutrients. This causes anxiety and daily struggle in the family as it is difficult to achieve in CF particularly in those patients with reduced appetite, abdominal pain, and/or gastro-oesophageal reflux. Furthermore, it has a potential to increase central fat accumulation, negatively influencing their clinical outcome. Current evidence indicates a stronger focus on high quality protein intake and assessment of body composition instead of BMI in the routine care of CF patients to induce FFM gain while preventing central obesity. The clinical phenotype varies in siblings with CF with the same CFTR mutation (42) indicating that individualized nutritional care may be needed especially for individuals with increased CF related morbidities and for those who need enteral supplements to obtain a good nutritional status. A further fine tuning of nutrition is required in CF patients with an enhanced inflammatory response and reduced appetite. This might involve compounding nutritional formulations containing high EAA levels and knowledge of the severity of the protein digestibility impairment in order to induce a protein anabolic response. Future research should therefore focus on compounding palatable high dose mixtures of free EAA, creating EAA rich easily digestible proteins, and optimizing pancreatic enzyme replacement therapy by optimizing the dose and regimen, and by making pancreatic enzyme capsules with the

highest enzyme activity for proteins. Although it is clear that the protein needs of CF patients are elevated, insight in the exact protein requirements is required to further improve nutritional care in CF, and to establish guidelines with recommendations for optimal protein intake for these patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, are highlighted as:

*of special interest

**of outstanding interest

1. Gaskin K. Nutritional care in children with cystic fibrosis: are our patients becoming better? *European journal of clinical nutrition*. 2013; 67(5):558–64. [PubMed: 23462946]
2. Cohen-Cymberknob M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. *Am J Respir Crit Care Med*. 2011; 183(11):1463–71. [PubMed: 21330455]
3. Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *The Journal of pediatrics*. 2013; 162(3):530–5. e1. [PubMed: 23062247]
4. VandenBranden SL, McMullen A, Schechter MS, Pasta DJ, Michaelis RL, Konstan MW, et al. Lung function decline from adolescence to young adulthood in cystic fibrosis. *Pediatric pulmonology*. 2012; 47(2):135–43. [PubMed: 22241571]
- *5. Engelen MP, Schroder R, Van der Hoorn K, Deutz NE, Com G. Use of body mass index percentile to identify fat-free mass depletion in children with cystic fibrosis. *Clinical nutrition (Edinburgh, Scotland)*. 2012; 31(6):927–33. Cross-sectional study in 77 pediatric patients with CF showing that (hidden) fat-free mass depletion occurs in a substantial group of these patients and is undetected in many of them when only Body Mass Index is used as screening method.
6. Engelen MP, Com G, Luiking YC, Deutz NE. Stimulated nitric oxide production and arginine deficiency in children with cystic fibrosis with nutritional failure. *The Journal of pediatrics*. 2013; 163(2):369–75. [PubMed: 23419590]
7. Amin R, Ratjen F. Cystic fibrosis: a review of pulmonary and nutritional therapies. *Advances in pediatrics*. 2008; 55(1):99–121. [PubMed: 19048729]
8. Vieni G, Faraci S, Collura M, Lombardo M, Traverso G, Cristadoro S, et al. Stunting is an independent predictor of mortality in patients with cystic fibrosis. *Clinical Nutrition*. 2013; 32(3):382–5. [PubMed: 22974535]
9. Hollander F, van Pierre D, de Roos N, van de Graaf E, Iestra J. Effects of nutritional status and dietetic interventions on survival in Cystic Fibrosis patients before and after lung transplantation. *Journal of Cystic Fibrosis*. 2013
10. Matel JL. Nutritional management of cystic fibrosis. *Journal of Parenteral and Enteral Nutrition*. 2012; 36(1 suppl):60S–7S. [PubMed: 22237878]
11. Van De Weert-Van Leeuwen P, Slieker M, Hulzebos H, Kruitwagen C, Van der Ent C, Arets H. Chronic infection and inflammation affect exercise capacity in cystic fibrosis. *European Respiratory Journal*. 2012; 39(4):893–8. [PubMed: 21885387]
12. Wojewodka G, De Sanctis JB, Bernier J, Bérubé J, Ahlgren HG, Gruber J, et al. Candidate Markers Associated with the Probability of Future Pulmonary Exacerbations in Cystic Fibrosis Patients. *PLoS one*. 2014; 9(2):e88567. [PubMed: 24533110]
13. King SJ, Nyulasi IB, Bailey M, Kotsimbos T, Wilson JW. Loss of fat-free mass over four years in adult cystic fibrosis is associated with high serum interleukin-6 levels but not tumour necrosis factor-alpha. *Clinical Nutrition*. 2014; 33(1):150–5. [PubMed: 23664115]
14. Milla CE. Nutrition and lung disease in cystic fibrosis. *Clinics in chest medicine*. 2007; 28(2):319–30. [PubMed: 17467551]

- **15. Stephenson AL, Mannik LA, Walsh S, Brotherwood M, Robert R, Darling PB, et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. *The American journal of clinical nutrition*. 2013; 97(4): 872–7. Longitudinal cohort study in 909 individuals with CF showing increased prevalence of overweight and obesity in CF, and that the small lung function benefit needs to be balanced against health risks of obesity. [PubMed: 23388659]
16. Panagopoulou P, Maria F, Nikolaou A, Nousia-Arvanitakis S. Prevalence of Malnutrition and Obesity Among Cystic Fibrosis Patients. *Pediatrics International*. 2013
17. Hanna RM, Weiner DJ. Overweight and obesity in patients with cystic fibrosis: A center-based analysis. *Pediatric pulmonology*. 2014
18. King SJ, Nyulasi IB, Strauss BJ, Kotsimbos T, Bailey M, Wilson JW. Fat-free mass depletion in cystic fibrosis: associated with lung disease severity but poorly detected by body mass index. *Nutrition*. 2010; 26(7–8):753–9. [PubMed: 19931415]
19. Amundson DE, Djurkovic S, Matwyoff GN. The obesity paradox. *Critical care clinics*. 2010; 26(4):583–96. [PubMed: 20970043]
20. Lainscak M, von Haehling S, Doehner W, Anker SD. The obesity paradox in chronic disease: facts and numbers. *Journal of cachexia, sarcopenia and muscle*. 2012; 3(1):1–4.
21. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. *The American journal of clinical nutrition*. 2014; 99(5):999–1005. [PubMed: 24572565]
22. Prado C, Wells J, Smith S, Stephan B, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. *Clinical Nutrition*. 2012; 31(5):583–601. [PubMed: 22809635]
23. Chung J-Y, Kang H-T, Lee D-C, Lee H-R, Lee Y-J. Body composition and its association with cardiometabolic risk factors in the elderly: a focus on sarcopenic obesity. *Archives of gerontology and geriatrics*. 2013; 56(1):270–8. [PubMed: 23079031]
24. Nilsson MI, Dobson JP, Greene NP, Wiggs MP, Shimkus KL, Wudeck EV, et al. Abnormal protein turnover and anabolic resistance to exercise in sarcopenic obesity. *The FASEB Journal*. 2013; 27(10):3905–16. [PubMed: 23804240]
25. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, et al. Clinical Practice Guidelines on G. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. 2008; 108(5):832–9. [PubMed: 18442507]
26. Lake, E. Food for thought: patients' and carers' views on dietetic care in cystic fibrosis. Cystic Fibrosis Trust; London: 2010.
27. Woestenenk JW, Castelijns SJ, van der Ent CK, Houwen RH. Dietary intake in children and adolescents with cystic fibrosis. *Clinical nutrition (Edinburgh, Scotland)*. 2014; 33(3):528–32.
28. Smith C, Winn A, Seddon P, Ranganathan S. A fat lot of good: balance and trends in fat intake in children with cystic fibrosis. *Journal of Cystic Fibrosis*. 2012; 11(2):154–7. [PubMed: 22119390]
29. Smyth RL, Walters S. Oral calorie supplements for cystic fibrosis. *The Cochrane database of systematic reviews*. 2012; 10(1):CD000406. [PubMed: 23076887]
- *30. Woestenenk J, Castelijns S, van der Ent C, Houwen R. Nutritional intervention in patients with Cystic Fibrosis: A systematic review. *Journal of Cystic Fibrosis*. 2013; 12(2):102–15. Systematic review describing the effectiveness of behavioral, oral supplementation and enteral tube feeding intervention studies. [PubMed: 23232324]
31. Deutz NEP, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. *Clinical Nutrition*. 2014; (0)
- **32. Engelen MPKJ, Com G, Anderson PJ, Deutz NEP. New stable isotope method to measure protein digestibility and response to pancreatic enzyme intake in cystic fibrosis. *Clinical Nutrition*. 2014; (0) A clinical study presenting a new and easy to use stable isotope method to quantify protein digestion capacity. This study shows that protein digestion capacity in CF is 40% of normal during sip feeding and that normalization is severely delayed after intake of pancreatic enzymes. The response to a bolus feed requires further study.

33. Geukers VG, Oudshoorn JH, Taminiau JA, van der Ent CK, Schilte P, Ruiter AF, et al. Short-term protein intake and stimulation of protein synthesis in stunted children with cystic fibrosis. *Am J Clin Nutr.* 2005; 81(3):605–10. [PubMed: 15755829]
- **34. Engelen MP, Com G, Wolfe RR, Deutz NE. Dietary essential amino acids are highly anabolic in pediatric patients with cystic fibrosis. *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society.* 2013; 12(5):445–53. A randomized double-blind crossover study comparing the metabolic response, using stable isotope methodology, after intake of two free amino acid compositions showing that even pediatric CF patients with nutritional failure respond highly anabolic to a dietary essential amino acid mixture. [PubMed: 23357545]
35. Jonker R, Engelen MP, Deutz NE. Role of specific dietary amino acids in clinical conditions. *The British journal of nutrition.* 2012; 108(Suppl 2):S139–48. [PubMed: 23107525]
36. Borsheim E, Bui QU, Tissier S, Kobayashi H, Ferrando AA, Wolfe RR. Effect of amino acid supplementation on muscle mass, strength and physical function in elderly. *Clinical nutrition (Edinburgh, Scotland).* 2008; 27(2):189–95.
- *37. Deutz NE, Wolfe RR. Is there a maximal anabolic response to protein intake with a meal? *Clinical Nutrition.* 2013; 32(2):309–13. Opinion paper indicating that there is no practical upper limit to the anabolic response to protein and amino acid intake with the meal. The linear relationship between amino acid availability and net Protein Synthesis observed in healthy and several chronic diseases was also found in Ref 71 in CF. [PubMed: 23260197]
38. Vieillevoys S, Poortmans J, Duchateau J, Carpentier A. Effects of a combined essential amino acids/carbohydrate supplementation on muscle mass, architecture and maximal strength following heavy-load training. *European Journal of Applied Physiology.* 2010; 110(3):479–88. [PubMed: 20521064]
39. Dillon EL, Sheffield-Moore M, Paddon-Jones D, Gilkison C, Sanford AP, Casperson SL, et al. Amino acid supplementation increases lean body mass, basal muscle protein synthesis, and insulin-like growth factor-I expression in older women. *The Journal of clinical endocrinology and metabolism.* 2009; 94(5):1630–7. [PubMed: 19208731]
40. Dal Negro RW, Testa A, Aquilani R, Tognella S, Pasini E, Barbieri A, et al. Essential amino acid supplementation in patients with severe COPD: a step towards home rehabilitation. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace/Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo.* 2012; 77(2):67–75.
41. Boselli M, Aquilani R, Baiardi P, Dioguardi FS, Guarnaschelli C, Achilli MP, et al. Supplementation of essential amino acids may reduce the occurrence of infections in rehabilitation patients with brain injury. *Nutrition in Clinical Practice.* 2012; 27(1):99–113. [PubMed: 22307494]
42. Bradley GM, Blackman SM, Watson CP, Doshi VK, Cutting GR. Genetic modifiers of nutritional status in cystic fibrosis. *The American journal of clinical nutrition.* 2012; 96(6):1299–308. [PubMed: 23134884]

Key points

- Stronger focus is needed on the assessment of body composition in the routine care of CF patients to detect (hidden) muscle loss and (central) fat accumulation
- Optimal protein intake is critical in the nutritional care of patients with CF
- Free amino acid mixtures (and most likely easily digestible proteins) with high essential amino acid levels are effective in inducing protein anabolism in CF
- Adjustments in the pancreatic enzyme regimen are necessary to account for the severely reduced protein digestion capacity in CF
- Optimal protein intake need to be established in CF to provide guidelines for optimal daily protein intake

Figure 1. Protein digestion in children and adults with cystic fibrosis, relative to the protein digestion in healthy young adults (adapted from (32)).