The optimal approach to nutrition and cystic fibrosis: latest evidence and recommendations

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Purpose of review
Cystic fibrosis (CF) is a progressive genetic disease that affects multiple organ systems. Therapy is directed to maintain and optimize nutritional status and pulmonary function, as these are key factors in survival. In this review, the most recent findings regarding nutritional management associated with pulmonary function and outcome will be explored.

Recent findings
Evidence-based and expert-based guidelines emphasize the need for adequate nutritional intake to improve nutritional status. For infants and young children, the aim is to achieve the 50th percentile of weight and length for a healthy same-age population up to age 2 years. For older children and adolescents 2–18 years, the target is a BMI of at or above the 50th percentile for healthy children. For CF adults of at least 18 years, the target is a BMI of at or above 22 kg/m^2 for women and at or above 23 kg/m^2 for men. Recently, new drugs are developed with the aim to treat the malfunction of the cystic fibrosis transmembrane conductance regulator gene. This potentiator/corrector therapy improves lung function and nutritional status and decreases the number of infective exacerbations. As survival is improving and the CF population is aging, it is important to focus on micronutrient and macronutrient intake of CF patients in different age and disease stages.

Summary
Recent evidence-based nutritional guidelines and improved medical treatment support the nutritional monitoring and interventions in CF patients. Nutritional care should be personalized and provided by a specialized CF dietitian because patients' care needs may change dramatically during their disease progress.

Keywords
cystic fibrosis, cystic fibrosis transmembrane conductance regulator, evidence-based guidelines, nutrition, pulmonary function

INTRODUCTION

Recent decades have shown a great improvement in survival of individuals with cystic fibrosis (CF) [1]. Registries in Europe, the USA and Canada now demonstrate that median survival for CF is around 40–50 years (UK 45.1, USA 41.1 and Canada 49.7 years). The median age at death worldwide is around 30 years [1,2] because of health inequalities with the dramatic variation in the survival of CF individuals across Europe [1]. The increased survival can be explained by implementation of centralized care, newborn screening (NBS) programmes and evidence-based guidelines including better nutritional care and the introduction of drugs aimed at the modulation of cystic fibrosis transmembrane conductance regulator (CFTR) protein.

NBS programmes for CF have been widely adopted in several European countries, Australia, New Zealand and the majority of states in North America. Major improvements in both nutritional status and lung function in young children, adolescents and adults as a result of NBS have been reported. Early diagnosis of CF by NBS and early intervention, including nutritional supplementation to prevent

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KEY POINTS

- Recent evidence-based and expert-based nutritional guidelines provide important guidance for the optimal treatment of each individual with CF in different age and disease stages.
- More experiences of CFTR modulation and its effects on nutritional status and lung function will offer challenges to adapt dietary interventions in CF care in the near future.
- Future research needs to focus on perfecting bedside monitoring of body composition and energy – and protein requirement in CF to improve nutritional status.
- Nutritional care is an important part of personalized medicine provided by a specialist CF dietitian.
- Nutritional management of CF is a continuously evolving field and warrants rigourous nutritional scientific research.

malnutrition, mucolytic therapy and aggressive treatment of infection with *Pseudomonas aeruginosa,* may have contributed to these improvements [3,4].

Moreover, nutritional status is positively associated with pulmonary function and survival in patients with CF. This strongly supports the nutritional strategies and the efforts to obtain normal growth in CF children, and the importance to maintain adequate nutritional status in adults with CF. Careful nutritional monitoring as recommended in European Society of Parenteral and Enteral Nutrition (ESPEN)-ESPHAN-European Cystic Fibrosis Society (ECFS) guidelines [5▪▪] should continue to apply current early growth recommendation, with goal weight-for-length (WFL) at or above the 50th percentile on growth charts before age 2 [6▪▪,7]. Timely and focused interventions to improve nutritional status are of great importance to improve prognosis and survival in CF.

The standard nutritional care for CF has been a high caloric diet with pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamin supplementation to achieve an adequate nutritional status [5▪▪]. The nutritional status can also be improved by using CFTR modulators, including correctors and potentiators. The effect of CFTR potentiation on clinical outcome and subsequently improved nutritional status is well described by Borowitz *et al.* [8▪▪] (Table 1). A CFTR potentiator,

Table 1. Potential mechanisms through which Ivacaftor might contribute to improved nutritional status

Effect of CFTR potentiation	Associated clinical outcome that could lead to improved nutritional status
In the sinuses and lower respiratory tract	
↑ Fluidity of respiratory tract mucus	
↓ Sinus mucus	↑ Sense of smell → improved appetite
↓ Airway mucus →	↓ Work of breathing →↓ energy expenditure and improved appetite
↓ Airway obstruction → fewer pulmonary exacerbations	
In the gastrointestinal (GI) tract	
↑ Bicarbonate and fluid flow through pancreatic duct, Brunner's glands, and biliary tract	
. . .Leads to improved fat/nutrient absorption	Lipolytic: improved pH optimum for pancreatic enzymes, possible unplugging of pancreatic ductules and 'rescue' of acinar function
	Postlypolytic: improved micelle formation
	↓ Thickness of gut mucus layer
	↓ Inflammation → improved enterocyte absorption
. . .and increase fluid in GI tract	
↓ Obstipation	↑ Appetite
↓ Small intestinal bacterial overgrowth	↓ Competition for intestinal nutrients
	Less inflammation → appetite
. . .and better action of defensins	Change in fecal microbiome
	Less inflammation →improved appetite, ↓energy expenditure
Systemic	
Improved insulin secretion	↓ Loss of calories through glycosuria
	↑ Protein anabolism
	Less inflammation → improved appetite, ↓energy expenditure

Reproduced from [8▪▪].

known as Ivacaftor and commercially available as Kalydeco, has produced results as respiratory function gain, and pulmonary exacerbation reductions, and several other achievements, such as better control of diabetes, improvement of pancreatic function, increase of body weight, improvement of BMI and BMI *z* scores and quality of life [9–12,13▪,14]. Other studies show an improvement in lung function [12], a slower rate of lung function decline [10] or no significant changes [11]. With more knowledge about genetic modifiers of the disease, the individual prognosis can be better defined and individualized therapy can be optimized.

As survival has increased, the number of adults with CF is expanding, as the majority of children with CF now live into adulthood. Evidence-based nutritional guidelines for CF have been developed recently with more attention to adequate treatment of nutritional-related complications in CF such as CF-related diabetes (CFRD) and malnutrition [15,16].

NUTRITIONAL MANAGEMENT OF CYSTIC FIBROSIS; AN UPDATE FOR ADEQUATE TREATMENT ACROSS THE LIFESPAN

Recently, excellent evidence-informed and practice-based guidelines on nutrition care of infants, children and adults with CF have been developed by the ESPEN-European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)-ECFS [5▪▪], and also the Cystic Fibrosis Foundation (CFF) evidence-informed guidelines on enteral tube feeding (ETF) [17]. In addition, the Australian evidence-based guidelines are expected for October 2017 [18▪▪].

Also (systematic) reviews on oral calorie supplements for CF, vitamin D, vitamin E, omega-3 poly unsaturated acids, probiotics, insulin and oral agents for managing CFRD endorse the importance of adequate nutritional treatment at different age and disease stages in CF [19–24,25▪▪,26–28].

IMPORTANCE OF ADEQUATE GROWTH AND NUTRITIONAL ASSESSMENT

BMI and BMI percentile for age are important measures of nutritional status in both adults and children with CF. The goal is a WFL of at or above the 50th percentile in children less than 2 years of age and a BMI of at or above the 50th percentile for children older than 2 years, meaning that nutritional status is comparable with that of well-nourished healthy children [5▪▪,6▪▪,7]. The rationale for this goal is that a positive association exists between pulmonary function, generally measured by forced expiratory volume in 1 s (FEV1) percentage predicted and nutritional status [6▪▪,29]. Children with CF who achieve higher WFL at age 2 years have improved pulmonary and survival outcomes into adulthood. CF care providers should be using growth charts appropriate to the nationality and ethnicity of the patients. If these are not available, the WHO growth charts should be used www.who.int/childgrowht/standards/en/ [5▪▪]. Growth and nutritional status should be monitored as part of routine CF care, including pubertal status [6▪▪]. For CF adults over the age of 18 years, the target is a BMI of at or above 22 kg/m^2 for women and 23 kg/m^2 for men [5▪▪,30▪]. Methods and timing of assessment and monitoring of nutritional status in age-related CF people are well described in the ESPEN-ESPGHAN-ECFS guidelines [5▪▪]. In adults, assessment of body composition is becoming clinically important as depleted or low fat free mass (FFM) is associated with significant lung disease and impaired pulmonary function [15] and independent of BMI level [30▪]. In children, bone mineral content (BMC) is a more sensitive indicator of nutritional deficit than low BMI; low values of BMC are correlated with impaired pulmonary function in children with CF [5▪▪]. Furthermore, total body potassium counting is a body composition assessment method that measures the body cell mass (BCM). The BCM is the metabolically active component of the FFM and reflects the functional cellular components of the body involved in biochemical processes and energy metabolism. BCM is not influenced by hydration. In contrast to the interpretation of total FFM, which can be affected by hydration changes with growth and disease [31]. Therefore, BCM measurements are an important reflection of nutritional status in growing children and those with clinical conditions. However, this method may not be widely available and other methods such as bioelectrical impedance analysis and dual energy X-ray absorptiometry can provide information on fat mass and FFM and should be used where possible. Future research needs to focus on perfecting bedside techniques to assess body composition, which will assist in improving nutrition-related outcome measures [31].

ENERGY BALANCE IN CYSTIC FIBROSIS

Optimal energy intake is critical to the overall health of people with CF. Insufficient nutritional intake is common in the CF population and is caused by poor appetite, malabsorption and disturbed body image. This, in combination with increased caloric expenditure, makes it often difficult to attain an appropriate nutritional status [6▪▪].

The energy balance is not only determined by energy intake (food), energy expenditure (activity,

maintenance and increased demands with inflammation) and losses (diarrhea and vomiting). In CF, a variety of factors contribute to individual energy needs, including nutrient maldigestion and/or malabsorption, presence of pulmonary exacerbation, pulmonary function, FFM, sex, pubertal status, CFTR mutation, age and other medical complications, such as liver disease and CFRD [6▪▪].

Loss of energy due to malabsorption is a problem in CF patients with exocrine pancreatic insufficiency. PERT is essential to improve fat malabsorption in pancreatic insufficient patients [32▪]. Eighty-five percent to 90% of people with CF have pancreatic insufficiency, leading to malabsorption of nutrients, especially fat and fat-soluble vitamins [6▪▪,32▪]. Addition of proton pump inhibitors may improve the effectiveness of PERT [32▪]. Current guidelines recommend lipase intake by age of the patient, by body weight and by grams of fat ingested per day [5▪▪], but a large variability and inconsistency with new guidelines on nutrition and PERT-use was found in six European pediatric CF centers [33]. The MyCyFAPP Project has been started to develop educational and self-management tools for patients' better adherence to therapies [33].

Increased caloric expenditure is mainly caused by increased work of breathing due to chronic lung infection and loss of pulmonary function. In addition, chronic pulmonary infection and inflammation lead to cytokine-induced catabolism [6▪▪]. In patients with end-stage CF, predication equations for energy needs underestimate resting energy expenditure (REE) [34].

There is a wide variation in the energy requirements of people with CF. To achieve a normal growth and nutritional status, energy intake targets for age may need to be increased in children with CF, although obesity should be avoided [5▪▪]. For this reason, recommendations for energy needs are 110–200% of those required by the healthy population of the same sex and age [5▪▪,15]. Improvement in weight gain can be achieved using energy dense diets, and additional oral nutritional supplements (ONS), behavioral interventions, ETF or parenteral nutrition [5▪▪,15].

A recent systematic review of ONS in three randomized clinical trials (total of 131 patients) found that ONS did not promote additional weight gain in moderately malnourished children with CF over and above the use of dietary advice and monitoring alone [19]. In contrast with children, the use of ONS in adults with CF has not been adequately studied [5▪▪]. Although the Cochrane review concluded that there is not enough evidence to support the use of ONS, practice-based evidence has shown that in clinical practice, individually prescribed supplements have increased energy intake and weight in undernourished patients [5▪▪], but further research should investigate the long-term effect of supplement use.

The CFF recommends the use of ETF in people with CF who are unable to attain caloric requirements to meet growth/weight maintenance goals despite evaluation by a multidisciplinary team [17]. Using this intervention, it is important to monitor for complications such as glucose intolerance and glucosuria. Gastrostomy tubes are commonly used in patients using ETF, and jejunostomy tubes are placed in patients with gastro paresis [30▪].

Although CF is commonly associated with malnutrition, the proportion of overweight and obese individuals is increasing. In one US pediatric CF center, 23% of patients with CF aged 2–18 years were found to have an average BMI percentile greater than 90. Surprisingly, 88% of the overweight patients and 69% of the obese patients had CFTR mutations associated with pancreatic insufficiency. In a longitudinal cohort study that spanned from 1985 to 2011, the proportion of overweight or obese adults in a Canadian CF center increased from 7 to 18%. The benefit of increasing BMI greater than 25 in adults seems to be small as improvement in pulmonary function seems to be blunted [30▪]. Moreover, recent studies show a higher proportion of obese individuals with CF having elevated serum triglycerides and total cholesterol [30▪]. Furthermore, a cross-sectional study in 32 adults with CF and a reference group of 20 adults without CF showed that a normal-weight BMI with elevated percentage body fat is associated with reduced lung function [35▪]. Dietary recommendations should therefore focus on a balanced diet and a healthy lifestyle with good exercise habits to achieve an adequate body composition with normal fat and FFM percentages.

SPECIALIZED NUTRITION-RELATED TREATMENTS IN CYSTIC FIBROSIS

For CF patients with pancreatic insufficiency, recent guidelines recommend the evaluation of plasma levels of fat-soluble vitamins after the start of enzyme and vitamin supplementation 3–6 months after initiation or change in vitamin therapy; and annually thereafter [5▪▪]. A review of Li *et al.* [36] compared recent reports of actual dietary intake and nutritional status of micronutrients such as minerals, trace elements and vitamins with relevant dietary recommendations for CF. They conclude that although dietary intake and nutritional status in CF have improved significantly in recent decades, micronutrient status seems to have diverged.

Recommendations for different age groups differ between countries [36]. The optimal dosages of long-term micronutrient supplementation require further investigation, so that safety and effect on reducing lung disease severity and CF-related complications are balanced [20,36]. Vitamin D is under investigation for its potential role in gut microbiota modification [37], intestinal calcium absorption and bone health [5▪▪,22], recovery from pulmonary exacerbations [22] and improvement of lung function [23]. The positive results observed in CF and non-CF trials of vitamin D supplementation provide a strong rationale for larger, randomized control trials of long-term, high-dose vitamin D3 supplementation in CF patients [23].

CF patients usually have abnormal intestinal microbiota because of exposure to antibiotics. Probiotics could modify the gut microbiota. Several reviews examined the use of probiotics in the treatment of CF pulmonary exacerbation and intestinal inflammation [25▪▪,26,28,38]. Unfortunately, they lack the scientific quality that is needed for a recommendation. Until there is more robust evidence supporting the safety of probiotics in clinical care, they should be used with caution with high-risk patients such as those with acute exacerbations or those with severe respiratory function [25▪▪].

Also the evidence for dietary supplementation of fatty acids to improve lung function or anti-inflammatory effects [39] in children or adults with CF is too limited for recommendations in daily practice [5▪▪,21].

Treatment of CFRD includes education on diabetes self-management, insulin therapy and aerobic exercise. Although some CF centers use oral medications to help control diabetes, the CFF clinical practice guidelines support the use of insulin therapy and this remains the most widely used treatment method [24]. The achievement of adequate blood glucose levels would be best to prevent decline in pulmonary function [27]. Patients need to learn to adjust their insulin dose to the carbohydrate content of the meal, sip feeds or ETF. CFRD patients can benefit from being seen periodically by a specialized team with expertise in both diabetes and CF [5▪▪].

For CF women planning to become pregnant, a daily supplement of 400 μg of folic acid in the preconception period and throughout the first trimester to prevent neural tube defects is recommended [5▪▪], similar to non-CF women. A variety of complications may occur in pregnant CF women, including impaired airway clearance, chronic respiratory tract infections, diabetes mellitus, pancreatic insufficiency and nutritional deficiencies. Pregnancy is advised against if the FEV1 is less than 30% predicted or if pulmonary hypertension is present [40]. Pregnant women with moderate pulmonary function increase the probability of an optimal outcome [41]. Management includes adequate nutrition with PERT and fat-soluble vitamins, management of the chest infections with antibiotics and monitoring of maternal diabetes [40]. The third trimester may be associated with increasing dyspnea that may necessitate bed rest with supplemental oxygen and nutritional supplements [41].

Lung transplantation (LTx) is a well-established treatment option for CF patients with end-stage lung disease. Ongoing weight loss despite aggressive nutritional supplementation is one of the criteria for listing for LTx [42]. It is a challenge for dietitians to optimize energy requirements for improving the nutritional status in pre-LTx patients with CF. Measurement of REE can be a helpful tool to optimize nutritional intervention as prediction equations seem to underestimate REE in end-stage CF patients [34]. After LTx, patients with CF are at risk of developing diabetes, and both tacrolimus and systemic steroids are known to increase the risk of diabetes posttransplant [43].

CONCLUSION

Nutritional care should be closely adapted to the various stages and complications of CF across the lifespan to extend survival and to improve quality of life. Moreover, new therapies, such as CFTR modulators and transplantation techniques, change the needs for nutritional intervention. Recent evidence-based and expert-based guidelines provide up-to-date information for optimal nutritional care of the general patient, but for treatment of individual CF patients personalized treatment by a specialized CF dietitian is recommended.

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