Clinical Nutrition 43 (2024) 413–445

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN-ESPGHAN-ECFS guideline on nutrition care for cystic fibrosis

Michael Wilschanski [a, *], Anne Munck [b], Estefania Carrion [c], Marco Cipolli [d], Sarah Collins [e], Carla Colombo [f], Dimitri Declercq [g], Elpis Hatziagorou [h], Jessie Hulst [c, i], Daina Kalnins [j], Christina N. Katsagoni [k, l], Jochen G. Mainz [m], Carmen Ribes-Koninckx [n], Chris Smith [o], Thomas Smith [p], Stephanie Van Biervliet [q], Michael Chourdakis [r]

[a] Pediatric Gastroenterology, Hadassah Hebrew University Medical Center, Jerusalem, Israel
[b] Cystic Fibrosis Centre, Hopital Necker-Enfants Malades, AP-HP, Paris, France
[c] Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Canada
[d] Cystic Fibrosis Center, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[e] CF Therapies Team, Royal Brompton & Harefield Hospital, London, UK
[f] University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
[g] Cystic Fibrosis Reference Centre, Ghent University Hospital and Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium
[h] Cystic Fibrosis Unit, 3rd Pediatric Dept, Hippokration Hospital, Aristotle University of Thessaloniki, Greece
[i] Department of Pediatrics and Department of Nutritional Sciences, The University of Toronto, Toronto, Canada
[j] Department of Clinical Dietetics, The Hospital for Sick Children, Toronto, Canada
[k] Department of Clinical Nutrition, Agia Sofia Children's Hospital, Athens, Greece
[l] EFAD, European Specialist Dietetic Networks (ESDN) for Gastroenterology, Denmark
[m] Brandenburg Medical School, University Hospital. Klinikum Westbrandenburg, Brandenburg an der Havel, Germany
[n] Pediatric Gastroenterology and Paediatric Cystic Fibrosis Unit. La Fe Hospital & La Fe Research Institute, Valencia, Spain
[o] Department of Dietetics, Royal Alexandra Children's Hospital, Brighton, UK
[p] Independent Patient Consultant Working at Above-disease Level, UK
[q] Paediatric Gastroenterology, Hepatology and Nutrition, Ghent University Hospital, Belgium
[r] School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece

ARTICLE INFO

Article history:
Received 17 November 2023
Accepted 18 December 2023

Keywords:
Cystic fibrosis
Nutrition
Guideline update

SUMMARY

Background: Nutritional status is paramount in Cystic Fibrosis (CF) and is directly correlated with morbidity and mortality. The first ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with CF were published in 2016. An update to these guidelines is presented.
Methods: The study was developed by an international multidisciplinary working group in accordance with officially accepted standards. Literature since 2016 was reviewed, PICO questions were discussed and the GRADE system was utilized. Statements were discussed and submitted for on-line voting by the Working Group and by all ESPEN members.
Results: The Working Group updated the nutritional guidelines including assessment and management at all ages. Supplementation of vitamins and pancreatic enzymes remains largely the same. There are expanded chapters on pregnancy, CF-related liver disease, and CF-related diabetes, bone disease, nutritional and mineral supplements, and probiotics. There are new chapters on nutrition with highly effective modulator therapies and nutrition after organ transplantation.

1. Introduction

Cystic fibrosis (CF) is a life-threatening genetic disorder that occurs in all ethnic groups [1,2]. The incidence of CF is about one in 3,500 white births in Europe [3]. The mean prevalence in the United States (US) and the European Union (EU) is similar, 0.74 and 0.80 in 10,000 persons, respectively [4].

The CF phenotype results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which results in CFTR deficiency or dysfunction, changes that disable the transport of sodium and chloride ions across epithelial and other cell membranes [5,6]. As a result, fluid transport is abnormal, and mucous secretions become thickened, ultimately impairing function of organs such as the lungs and pancreas,

* Corresponding author.
E-mail address: michaelwil@hadassah.org.il (M. Wilschanski).

https://doi.org/10.1016/j.clnu.2023.12.017
0261-5614/

Abbreviations

BIA	bioelectrical impedance analysis
BMD	bone mineral density
CF	cystic fibrosis
CFA	coefficient of fat absorption
CFLD	Cystic fibrosis associated liver disease
CFRD	cystic fibrosis related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CFTRm	cystic fibrosis transmembrane conductance regulator modulator
DXA	dual-energy X-ray absorptiometry
EFA	essential fatty acid(s)
EN	enteral nutrition
ETI	elexacaftor-tezacaftor-ivacaftor
FENa	fractional excretion of sodium
FEV1	forced expiratory volume in 1s
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
FVC	forced vital capacity
HFA	height-for-age
LCT	long-chain triglycerides
MCT	medium-chain triglycerides
MI	meconium ileus
NWO	normal weight obesity
OGTT	oral glucose tolerance test
ONS	oral nutritional supplements
PEG	percutaneous endoscopic gastrostomy
PERT	pancreatic enzyme replacement therapy
PI	pancreatic insufficiency, pancreatic insufficient
PN	parenteral nutrition
PPI	proton pump inhibitors
PS	pancreatic sufficiency, pancreatic sufficient
RCT	randomized controlled trial(s)
TH	target height
WFL	weight-for-length

Societies/institutions mentioned in the guideline

CDC	Center for Disease Control and Prevention
CFF	Cystic Fibrosis Foundation
ECFS	European Cystic Fibrosis Society
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
IOTF	International Obesity Task Force
LT	lung transplantation
SIGN	Scottish Intercollegiate Guidelines Network
WHO	World Health Organization

as well as the liver, gallbladder and intestines [1,6]. In the lungs, thickened mucus adheres to airway surfaces, which leads to decreased mucociliary clearance, and increased risk for inflammation and infection. In the pancreas, thickened secretions obstruct intra-pancreatic ducts, reducing delivery of digestive enzymes into the duodenum and impairing absorption of key nutrients [6].

The ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with Cystic Fibrosis was published in 2016. ESPEN with the agreement of ESPGHAN and ECFS launched an update of these guidelines in 2021 The group included physicians, dieticians and patient representatives as well as the update guidelines coordinator (MC). All are authors of this guideline.

There is a lack of randomized controlled trials (RCT) in the field of nutrition in CF. Many of our recommendations and statements are based on consensus expert opinion.

There have been significant changes in the nutrition fields since 2016 which are reflected in this update. The paper is divided into 16 subsections of CF nutrition with expanded updates on malnutrition including underweight and obesity, adulthood, bone disease, CF related diabetes, CF related liver disease and probiotics. There are new sections including one following the introduction of highly effective CFTR modulators. This has resulted in a paradigm shift towards treating the basic defect rather than the complications of the underlying disease with exciting consequences in nutrition. Indeed, these drugs have proved to be so effective that the classical high fat diet in CF has changed to healthy eating There are further new sections on transplantation and pancreatic sufficiency.

Several zoom meetings were held with one Face to face meeting in Rotterdam in 2022 at the ECFS annual meeting. The update was based on the GRADE method with literatures search conducted from 2014 to 2022.

A list of all statements and recommendations was sent to all ESPEN members with an option to provide justification if not approved. The initiative followed the rules for ESPEN guidelines, while for ESPGHAN and ECFS it qualifies as a position paper. The ESPGHAN Council and ECFS Board have approved the final version.

2. Methods

The present guideline was developed according to the standard operating procedure for ESPEN guidelines [7]. The guideline is an updated version of the “ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis” that was developed in 2016 by Turck et al. [8]. The guideline was developed by an expert group including physicians, dieticians and patient representatives.

Following the standard operating procedures for ESPEN guidelines and consensus papers, the first development step of this guideline was to check the 2016 PICO questions check for further applicability and extension. PICO questions are designed to address specific **p**atient groups (or **p**roblems), **i**nterventions, **c**ompare different therapies, and be **o**utcome-related [7]. The 2023 guideline update is divided into 16 main chapters entitled “nutritional assessment and monitoring”, “malnutrition: undernutrition and overweight”, “pancreas enzyme replacement therapy”, “fat-soluble vitamins”, “pancreatic sufficiency” “nutrition and pulmonary function”, “feeding infants, toddlers, and children”, “nutrition in adults”, “cystic fibrosis nutritional supplements”, “supplementation of trace elements”, “bone disease”, “cystic fibrosis related diabetes”, “cystic fibrosis associated liver disease”, “probiotics”, “nutrition and cystic fibrosis transmembrane conductance regulator modulator therapy”, and “transplantation”. To answer the PICO questions, a literature search that covered the period since the last guideline was performed to identify suitable meta-analyses, systematic reviews, and primary studies (for details see below, “search strategy”). Each PICO question was allocated to subgroups/experts for the different topics and, initially, 86 recommendations and eleven statements answering the PICO questions were formulated. The grading system of the Scottish Intercollegiate Guidelines Network (SIGN) [9] was used to grade the literature. The allocation of studies to the different levels of evidence is shown in Table 1. Supporting the recommendations, the working group added commentaries to explain their basis.

Table 1
Definition of levels of evidence.

1++	High-quality meta-analyses, systematic reviews of RCT, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system [9]. RCT, randomized controlled trial.

Table 2
Definition of grades of recommendation [7].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

The grades of recommendation were decided according to the levels of evidence assigned (Table 2). In some cases, a downgrading from the generated grades of recommendation was necessary based on the levels of evidence according to Tables 1 and 2, e. g. due to a lack of quality of primary studies included in a meta-analysis. Such cases are described in the commentaries accompanying the respective recommendations. The wording of the recommendations reflects the grades of recommendations since level A is indicated by the use of the word “shall”, level B by the word “should” and level 0 by the word “can” or “may”. The good practice points (GPP) are based on experts’ opinions due to the lack of studies, for which the choice of wording was not restricted.

Between 19th June and 18th July 2023, an online voting (Delphi round) on the recommendations was performed using the guideline-services.com platform. All ESPEN members were invited to agree or disagree with the recommendations and to provide comments. A first draft of the guideline was also made available to the participants on that occasion. All 86 recommendations and eleven statements reached an agreement >90 % (indicating a strong consensus, see Table 3), making a subsequent Consensus Conference unnecessary. To support the recommendations and the assigned grades of recommendation, the ESPEN guideline office created evidence tables of relevant meta-analyses, systematic reviews, (randomized) controlled trials, and cohort studies. These evidence tables are available online as supplemental material to this guideline.

2.1. Search strategy

The literature search was conducted by the working group members between October and December 2021. Literature search was conducted using the following terms: cystic fibrosis AND (nutrition* OR diet* OR nourishment OR nutrient OR nutriment OR malnutrition OR malnourishment OR undernourishment OR calorie* OR lipid* OR trace OR vitamin* OR protein* OR taurine OR pancreatic enzyme replacement therapy OR PERT OR fatty OR micronutrient* OR antioxidant* OR probiotic* OR supplement* OR insulin OR enteral OR parenteral OR EN OR TPN OR PN). The search period began with the end of the search for the previous guideline, in 2014. After the end of the literature search, relevant papers published in the meantime were added in an expert-driven manner.

Table 3
Classification of the strength of consensus.

Strong consensus	Agreement of >90 % of the participants
Consensus	Agreement of >75–90 % of the participants
Majority agreement	Agreement of >50–75 % of the participants
No consensus	Agreement of <50 % of the participants

According to the AWMF methodology [10].

3. Nutritional assessment and monitoring

3.1. General

Recommendation 1

Standard assessment and monitoring of nutritional status in people with CF (pwCF) should be accurately performed regularly and should include as minimum the following parameters which need to be interpreted together and longitudinally:

- **Infants: z-scores for weight-for-age, length-for-age and weight-for-length (WFL) as well as head circumference-for-age every one to two weeks until evidence of adequate nutrition and ideal nutritional status is established, then monthly through the first year of life.**
- **Children >1 and ≤ 2 years: z-scores for weight-for-age, length-for-age and WFL as well as head circumference for age every two to three months.**
- **Children >2 years: z-scores for weight-for-age, height -for-age and BMI-for-age at least every three months.**
- **Adults: BMI at least once every three to six months.**

Patients with poor nutritional status and/or growth should have more frequent monitoring than patients with adequate nutritional status.

Grade of recommendation GPP – Strong consensus 100 % agreement

Recommendation 2

Incorporation of a correction for target height (TH) based on parental heights, can be considered when assessing height-for-age (HFA) z-scores in children with CF.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 3

When assessing growth and nutritional status in children with CF or comparing between centers or countries, careful interpretation should be considered when using different references (e.g., country specific charts, WHO, and CDC).

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 4

Longitudinal assessment of body composition to obtain estimates of fat mass (FM) and fat-free mass (FFM), rather than sole reliance on BMI, should be performed in pwCF because their association with (respiratory) outcomes is stronger than for BMI alone and because a low or normal BMI can mask high FM or low FFM. The choice in body composition method should be guided based on availability, resources, technical factors and clinical factors such as age and hydration status.

Grade of recommendation B - Strong consensus 92 % agreement

Commentary

The accurate assessment and regular monitoring of growth and nutritional status is a cornerstone of the management of pwCF to improve outcomes. In infants and children, assessment of nutritional status must be comprehensive, using multiple data points over time and preferably multiple different parameters. For infants who are diagnosed by newborn screening, attention to nutrition is key to maintain normal growth—even before signs of the CF phenotype become evident [8]. Monitoring of growth should be more frequent at a younger age or if the patient has a poor nutritional status at any age [8].

Adequate nutrition in infants and children with CF is considered when growth is similar to that of an age-matched healthy population with an additional focus on body composition. The goal of WFL >50th percentile in children <2 years and BMI ≥50th percentile in those over two to 18 years old should continue to be used [11]. For CF adults over 18 years of age, the target is a BMI at or above 22 kg/m^2 for females and 23 kg/m^2 for males [8]. It should be noted that WFL or BMI might be falsely normal or high in stunted patients [12].

TH can be included to evaluate if a child is growing within genetic potential [13,14]. Height evaluation based on HFA alone may result in underestimation or overestimation of growth, which may induce inappropriate nutrition interventions. Using HFA adjusted for TH (HFA/TH) which means HFA-z-score minus TH for age z-score, can indicate how the current HFA z-score relates to the TH z-score. Generally, a difference of more than ±2 SD z-score is considered abnormal and indicates growth outside the genetic potential which could be related to nutritional deficits.

Pediatric growth charts should be chosen according to the regular practice in the country or center [11,15–17]. CDC, WHO, and IOTF charts provide comparable associations between BMI z-scores and pulmonary function [18]. Despite this, some studies have emphasized that there are differences that should be noted when interpreting the growth charts [11,15–17]. CDC and WHO charts show some discrepancies when determining underweight in infants, toddlers, and school-aged children [18–20]. CDC charts more frequently classify children aged zero to two years and those at school age as underweight while WHO charts would not, while adolescents show comparable estimations of thinness between the CDC and WHO charts [19,20]. This indicates that WHO charts are adequate to diagnose both under and overnutrition [21] but may provide a “false sense of security” when applied for CF, especially in younger children [22]. Additionally, children who reached the 50th percentile WFL at two years of age by both WHO and CDC charts had better clinical outcomes [11,15]. IOTF has been widely employed in epidemiology but may not be appropriate in the clinical setting [23,24].

Since the development of the previous guideline, there is growing evidence that body composition is a fundamental component of a comprehensive nutritional status assessment in pwCF and a target of care as BMI does not represent body composition and can mask a low FFM and/or high FM [23,25–36]. There is a stronger association between various outcome parameters (such as lung function) to FFM than BMI, and a low FFM is associated with decreased inspiratory muscle strength [22,23,25–37].

Additionally, adults with CF that have normal weight obesity (NWO, normal BMI <25 kg/m^2, body fat percentage >30 % in women and 23 % in men) had even lower fat-free mass index (FFMI) and forced expiratory volume in 1s (FEV1) in percent when compared to overweight and obese pwCF. This indicates that increased adiposity along with low FFM may be even more detrimental to pulmonary function in pwCF and that using a BMI >0 SD as the goal to maximize overall health status including lung function can actually mask low FFM [12].

PwCF have less FFM, and bone mineral density (BMD) when compared with controls [37]. This translates into a higher risk of sarcopenia and osteopenia. Therefore, the assessment of body composition may allow timely interventions to increase FFM such as exercise and/or anabolic therapies (i.e., growth hormone after endocrinology assessment), to reduce the risk of metabolic and respiratory complications [27,37].

3.2. Methods of body composition assessment

Recommendation 5

Readily available body composition data (FFM, FM and body fat distribution) obtained through routine dual-energy X-ray absorptiometry (DXA) scan for assessment of bone health can be used for monitoring of nutritional status of pwCF.

Grade of recommendation 0 - Strong consensus 92 % agreement

Recommendation 6

Bio-electrical impedance (BIA), which is a non-invasive, bedside and simple technique, can be considered to assess body composition in pwCF; the use of specific prediction equations or use of raw values for resistance and reactance are preferred.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 7

Serial hand grip strength measurements may be considered in adults and children ≥ 6 years with CF as it may help detect early changes in muscle function and therefore can function as an indicator of nutritional status.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 8

Arm anthropometry including mid-upper arm circumference and skinfold measurements may be considered as method of body composition assessment, especially in case DXA or BIA are not available.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

There are several methods to assess body composition which have been studied in pwCF. These include arm anthropometry (mid-upper arm circumference, triceps skinfold thickness, arm muscle area), DXA, BIA, air displacement plethysmography, double-labelled water measurement, hand grip strength, and ultrasound technology [8,22]. There is an ongoing debate on which method is the best for this assessment, and factors such as availability in the clinical setting, and costs should be considered when selecting the method. The most frequently used methods to assess body composition in pwCF were DXA followed by BIA. Nevertheless, there is large variability in the methods to determine body composition in CF and comparison between methods is challenging [36]. Moreover, studies on changes in body composition over time and the ability of the various methods to detect changes are lacking.

DXA has been the most used method of body composition assessment because of its high accuracy, and the detailed information it provides on total and segmental FFM and FM, as well as being commonly used for research [36]. The nomenclature for body composition assessment varies depending on the method used and distinguishes between the two-compartment model, which categorizes body composition using techniques such as BIA, arm Anthropometry, and air displacement plethysmography, which categorizes body composition into FM and FFM, and the three-compartment model, which further subdivides body composition into fat mass FM, bone mass, and lean body mass using DXA. Throughout this document, we use the term fat-free mass (FFM) when referring to non-fat mass components. In CF care, DXA has been used routinely for assessment of BMD in children aged > 8–10 years; since DXA also provides information on body composition, additional tests to monitor body composition may not be needed in this age group. However, DXA can be expensive and is not readily available in all clinical settings [22,35]. Studies using DXA for body composition determination in CF have shown that FEV1 has a positive association with FFM and a negative association with FM for various age groups. Furthermore, BMI had a significant but weaker correlation to pulmonary function than FFM [26,31,34].

BIA calculates the parameters related to body composition with prediction equations using direct measurements of the impedance of the human body [36]. BIA is an adequate method to determine body composition in CF. Also, decreased FFM determined by BIA correlates to lower pulmonary function [23,27,28]. Since the publication of the last guideline a CF-specific equation has been validated for children, adolescents, and young adults [27]. Although BIA is more widely available than other methods, its main limitations in CF are the potential electrolyte imbalances and lack of a CF-specific equation for the adult population. To address these concerns some authors have used raw data or the vectors of resistance and reactance rather than the equations [22,25,27,28].

Air displacement plethysmography is another adequate method to assess body composition in CF, but mainly available in research settings [22]. Using this method to assess body composition in CF a positive correlation has been found between FEV1% and FFM, FFMI.

An additional method to assess body composition is arm anthropometry, which can be easily performed in the clinical setting, but there is conflicting evidence on the accuracy of arm anthropometry in assessing body composition in CF [25,33]. Mid-upper arm circumference is relevant to determine malnutrition, but it may not correlate to pulmonary function as well as other body composition methods [17,38].

Ultrasound can be used to evaluate muscle thickness and subcutaneous fat. Although not extensively studied in CF there are some promising results showing that a reduction in subcutaneous fat content and quadriceps muscle thickness correlated with the forced vital capacity (FVC) and nutritional parameters [15,22,24,25].

Hand grip strength assessment is an adequate method to detect changes in muscle function and muscle loss for pwCF older than six years of age [18–22]. PwCF tend to be weaker than age and gender-matched peers [20]. Hand grip strength may be particularly helpful to monitor body composition in youth with a BMI <50th percentile because lower hand grip strength regardless of BMI may indicate less FFM which negatively impacts their pulmonary function shown by more exacerbations, lower FEV1% and FVC% [20,21].

3.3. Other tools

Recommendation 9

The use of CF-specific nutrition screening tools, may be used as an initial step next to anthropometric assessment to early identify children with CF at risk for undernutrition and in need for further assessment and management by a dietitian, especially in case of limited availability or resources.

Grade of recommendation GPP - Strong consensus 92 % agreement

Recommendation 10

Regular dietary review including assessment of adherence to dietary advice may be performed every three to six months in children with CF and every six to twelve months in adults with CF.

Grade of recommendation 0 - Strong consensus 100 % agreement

Commentary

In general, nutritional screening tools can be helpful for identifying children at nutritional risk, even those with normal anthropometric parameters, who need further assessment and management by a dietitian [35]. The use of a screening tool can be especially helpful in case of limited availability of dietitians or limited resources, as it can help in directing the highest risk patients to be evaluated by a dietitian.

Studies using CF-specific nutritional screening tools are limited, but two instruments [39,40] have been described. McDonald [39] developed the first tool in 2008 incorporating BMI and longitudinal data of weight gain and growth to stratify patients 2–20 years as low, moderate or high nutritional risk. This tool has been validated for pwCF in small studies [22,28,41,42] and should be a supplement to traditional nutritional assessment with anthropometry. The second tool developed for use in pwCF aged 6–18 years by Souza dos Santos Simon et al. [40] incorporates ten clinical parameters believed to be risk factors of malnutrition in CF including BMI, weight gain and height gain but also the presence of PI, suboptimal dietary intake and cystic fibrosis related diabetes (CFRD) among others. In adults with CF, the nutritional risk screening instrument 2002 (NRS 2002) [43] has been used [18]. This validated screening

tool gives scores of different levels of nutritional status to patients, based on weight loss, BMI in combination with general condition, disease severity, age and food intake.

A relevant practice in the nutritional assessment of pwCF is regular dietary assessment, including the assessment of adherence to dietary advice. CF. A 24-h diet recall is helpful, but a longer 3-5-day diet record is frequently necessary for a quantitative evaluation of energy, macro- and micronutrient intake to fully assess patients at nutritional risk, or in children when not meeting recommended weight gain [8]. However, it should be stressed that increasing caloric and fat intake might not target potential micronutrient deficiencies and may also lead to unhealthy eating habits i.e., a lower Healthy Eating Index-2015 (HEI-2015) [31] which has been associated with higher visceral adipose tissue. This highlights the importance of not only focusing on quantity but also diet quality and supplementations could be provided timely [44–48].

Biochemical markers of nutrition status in pwCF may include blood count, serum albumin, iron status, plasma fat-soluble vitamin levels, and electrolyte measurements. However, there is not a single marker to accurately estimate nutritional status. The assessment of nutritional status should be based on a combination of clinical, anthropometric, body composition and biochemical parameters.

4. Malnutrition: undernutrition and overweight

4.1. Statement of the problem: cystic fibrosis and malnutrition

Since the publication of the previous guidelines, the nutritional landscape of pwCF has dramatically changed. Especially in the developed countries, the number of undernourished patients has decreased over time [49–51] whereas simultaneously an observed increase in overweight and obesity was observed over the past two decades with a varying reported frequency of 6–33 % [12,50–59]. An important discrepancy became apparent between developed countries reporting a malnutrition rate of 4–19 % of children and adults with CF and the developing countries struggling with malnutrition in 25–50 % of their patients [18,53–57,59–66].

There is a classical mismatch between energy needs and actual food intake. Although avoiding undernutrition using high-calorie, high-fat diet with pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamin supplementation was the standard of nutritional care for CF for decades [67], a healthier diet is becoming standard practice to avoid obesity.

4.1.1. Description of nutritional status in studies

Recommendation 11

Future studies describing underweight should use standard cut-offs to increase comparability between studies:

- **for adults BMI <18.5 kg/m^2**
- **for children**
  - **Underweight: weight for age < -2 SD or BMI <5th percentile, <-2 SD (= 2nd percentile) of the median reference value for age and sex.**
  - **Stunting: height for age < -2 SD of the mean reference value for age and sex.**

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 12

Future studies describing overweight and obesity in pwCF should use standard cut-offs to increase comparability between studies.

- **for adults**
  - **BMI 25–29.9 kg/m^2 for overweight**
  - **BMI ≥30 kg/m^2 for obesity**
- **for children two years and older**
  - **BMI between 85th-94.9th percentile OR BMI >1 SD (~84th percentile) above the WHO Growth reference median for sex and age) for overweight**
  - **BMI ≥95th percentile obesity OR BMI z-score >2 SD (~98th percentile) above the WHO Growth Reference median for sex and age for obesity**

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Due to the large variety of definitions and cut-off criteria used in studies to describe undernutrition, overweight and obesity it is difficult to obtain a clear view on actual prevalence rates and to compare these between centers and countries. It is important to realize the difference between the definition of nutritional states in health [68] and the nutritional targets in pwCF. When describing a population, standard definitions should be used to improve comparability between studies [62].

4.1.2. Nutritional targets for pwCF

Recommendation 13

Targets for optimal nutritional status in pwCF remain higher than in the general population e.g., according to the CDC/WHO definition. PwCF with stagnant weight or growth expressed as a downward trend in percentiles or z-scores, should undergo further nutritional assessment.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

As there remains an association between undernutrition and clinical outcomes such as pulmonary function, quality of life, and mortality risk the target BMI in CF is higher than just avoiding malnutrition [53–55,59,63,64,69–75]. In the Cystic Fibrosis foundation report of 2021, there is an optimal plateau in FEV1% if the BMI percentile is around P50 in children and around BMI 22 kg/m^2 for female and 23 for male adults. Ashkenazi et al. describe an increased transplantation risk if the BMI is below −0.75 SD [69]. In the study of Bodnar et al., a BMI < P25 was associated with a significantly lower FEV1 [62].

For infants with CF, nutrition is considered adequate if they achieve normal weight and height percentiles similar to the non-CF population by two years of age. In children with CF, nutrition is considered adequate when growth is similar to that of an age-matched non-CF population aiming at a BMI around the P50 [47]. Current registry reports still identify a height deficit in children with CF despite the improved weight and BMI percentiles (CFF registry report 2021). As final height is an independent predictor of longevity; it deserves to be studied more intensively [76,77].

For CF adults, the threshold is a specific BMI goal for women and men [47].

BMI as sole indicator of nutritional status is not very sensitive, as NWO has been described in up to 30 % of pwCF [12]. NWO indicates a normal BMI with low FFM. The strong association between pulmonary function and lean BMI (stronger than between pulmonary function and BMI), FFM and FFMI indicates that patients might need an additional evaluation of their body composition and adapted strategies have to be studied to avoid normal weight obesity [12,73].

4.2. Undernutrition

Statement 1

Undernutrition in CF remains associated with poorer pulmonary outcome, increased *Pseudomonas aeroginosa* colonization, decreased quality of life, and risk of death.

Strong consensus 100 % agreement

Statement 2

Frequency of undernutrition in CF might be negatively influenced by absence of neonatal screening, unavailability of certain treatments (DNase treatment, pancreatic enzymes), exocrine pancreatic insufficiency (PI), food insecurity, *Pseudomonas aeruginosa* colonization and age at diagnosis.

Strong consensus 100 % agreement

Statement 3

Early growth recovery in CF is critical, as undernutrition during infancy tends to persist and catch-up growth after age two years is difficult. The longer adequate growth is maintained after early growth recovery, the better the pulmonary outcomes at age six to seven years and twelve years.

Strong consensus 100 % agreement

Commentary

The most recent European Cystic Fibrosis patient registry reports a median BMI of 21.9 kg/m^2 for adults and a median BMI z-score of −0.2 in children. Meanwhile there still exist important differences in the percentage of undernourished pwCF between countries [66]. The frequency of undernutrition might be negatively influenced by PI, absence of neonatal screening, unavailability of certain treatments (DNase treatment, pancreatic enzymes), food insecurity, *P. aeruginosa* colonization and age at diagnosis [60,63,64,78]. Undernutrition remains associated with poorer pulmonary outcome, decreased quality of life, increased risk for transplantation and increased risk of death [53–55,59,63,64,69–75].

4.3. Overweight and obesity

Statement 4

Patient specific factors currently associated with overweight or obesity in CF are later age at diagnosis, older age, pancreatic sufficiency (PS), lung function, at least one allele with class IV or V, prescribed ivacaftor, low social economic status, and male sex.

Strong consensus 100 % agreement

Statement 5

Studies reporting on pulmonary function (FEV1) and association with being overweight are contradictory in pwCF with some studies describing an association of improved FEV1 while others not observing an additional FEV1 advantage. Being obese is associated with higher frequency of hypertension, hypercholesterolemia, and liver steatosis.

Strong consensus 100 % agreement

Recommendation 14

Obesity should be avoided as associated problems such as hypertension, hypercholesterolemia and diabetes do occur in pwCF and obesity.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Several studies report an increased frequency of obesity in pwCF with varying frequency from 6 to 33 %. The prevalence seems to increase steadily over the past two decades in the developed countries [12,50,52–59,66]. Overweight and obesity in pwCF are associated with PS, older age at diagnosis, age above 46 years, lower income area and male gender [54,57,58,79]. Conflicting results are reported concerning the association between FEV1 and overweight/obesity in CF. Some studies describe an improved FEV1 while others do not observe any additional FEV1 advantage. Interpretation of the analyses is difficult as limited data exist that assess the role of overweight/obesity in FEV1. Being overweight or obese is however, associated with higher frequency of hypertension, hypercholesterolemia and liver steatosis [12,50,52,54,55,57,58,70,80,81]. Despite the absence of long-term data on the impact of overweight and obesity in pwCF, in analogy to the general population, it seems good clinical practice trying to avoid it.

5. Pancreatic enzyme replacement therapy

Recommendation 15

Pancreatic enzymes shall be started in all patients who have evidence of exocrine PI. The intake of pancreatic enzymes results in improved anthropometric outcomes and maldigestion related gastro-intestinal complications.

Grade of recommendation A - Strong consensus 100 % agreement

Recommendation 16

The pH in the small intestine determines the release of pancreatic enzymes from the enteric coated beads. Evidence is lacking around routine use of proton pump inhibitors (PPI) to improve enzyme efficacy.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 17

Evaluation of pancreatic enzyme dose may be done on an individual basis and using the most appropriate denominator to prescribe pancreatic enzymes.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 18

Pancreatic enzymes can be administered orally at the start of enteral nutrition (EN) and during the night if the patient is awake. Enzymes in non-enteric or powder form can be mixed in with the feed if oral intake of enzymes is not possible.

Grade of recommendation GPP - Strong consensus 91 % agreement

Commentary

PI occurs in more than 85 % of the CF population. Exocrine pancreatic disease begins in utero. PI results in the inability to deliver pancreatic enzymes to the duodenum. An impaired pancreatic bicarbonate secretion (HCO_{3-}) results in a prolonged acidic environment in the proximal duodenum after gastric emptying. PI is diagnosed by low levels of measured fecal elastase −1 (≤100 μg/g stool −borderline100-200 μg/g) [6,8,82,83]. PERT is a required therapy to correct nutrient maldigestion and malabsorption. PERT contains lipase, protease and amylase. Pancreatic enzymes should be taken with every meal containing fats, proteins and complex carbohydrates. A variety of pancreatic enzymes is on the market characterized by variations of strength, content and forms (enteric coated spheres (varying size) or tablets or non-enteric coated tablets or powder). All PERT are porcine based. Non-porcine enzymes have been developed and documented in clinical trials but at present there is no effective alternative available [84]. The enteric-coated capsules release enzymes at an effective rate when pH in the duodenum reaches a level of approximately 6.0 [6,82,85–92]. Since 2009, the FDA approved PERT formulations (based on specifically designed studies) proving the efficacy of the PERT formulation compared to placebo in pwCF and PI.

Studying the efficacy of PERT is challenged by factors related to type of food [92–94], gastro-intestinal transit, inter- and intra-individual variation in enzyme requirements and level of acidity in the proximal duodenum [6,82,89,92,95].

As there are limited trials and lack of evidence, agents that reduce gastric acidity should not be used empirically to improve fat absorption and reduce gastro-intestinal symptoms [96,97]. If prescribed, the clinical outcomes of patients treated with such medications should be monitored closely. These agents should be discontinued unless ongoing monitoring suggests continued improvement in documented symptoms. Long-term use of PPI in children should be balanced against potential side effects [98]. A recent study in adults with CF found that prolonged use of PPI may increase risk of pulmonary infection, while offering no improvement in nutritional status [99].

Despite the observed improvement in nutritional status, growth parameters and gastrointestinal symptoms after starting PERT [85,86,89,90,100,101], no recommendations on optimal dosing can be made [90,95,101–104]. In addition, in infants with CF, increased enzyme dose was not associated with improved clinical outcomes compared to doses at lower recommended range [105]. An overview of the current recommendations on PERT is given in Table 4 [8]. PERT recommendations are expressed as lipase units (LU)/gram dietary fat, LU/kg body weight and per kg body weight per meal. The variation in denominator results in a variable intake of pancreatic enzymes per meal.

The MyCyFAPP Project was initiated within the European Union's Research and Innovation Programme, Horizon 2020 to develop an innovative method to optimize intake of pancreatic enzymes and support self-management in pwCF by means of a mobile application but it is currently unavailable [94,102].

Studying an optimal dosage of pancreatic enzymes in pwCF would be easier if patient- and staff-friendly methods would be available. PERT efficacy studies use evolution of anthropometric parameters and coefficient of fat absorption (CFA) as outcome parameters [82,85,89,100,106,107]. The calculation of CFA is recognized as the reference standard for dietary fat absorption [106]. This method is cumbersome for patients and staff. Retrospective analysis of CFA and dietary dairies showed a variability of CFA in response to PERT [88,108]. Alternatives, such as the use of nutritional biomarkers or malabsorption blood test, are suggested to evaluate PERT [109–111]. However, more research in this field is required.

The role of PERT in CF complications has been studied [112,113]. In an observational study no difference in pancreatic enzyme dose was observed in the prevalence of distal intestinal obstruction syndrome [112]. Based on the results of a small RCT, the intake of pancreatic enzymes might reduce post prandial hyperglycemia by normalizing incretin secretion and reducing gastric emptying [113]. Independently of dosage, PERT compliance is a challenging issue for healthcare providers, families and pwCF. Compliance likely becomes more challenging in older children due to a combination of increased independence and reduced parental reliance. In the presence of parents who report high rates of depressive symptoms, adherence to PERT was also at a lower rate. Adherence was significantly associated with weight gain. Over a 3-month period average weight gain was 0.5 (0.2) z-scores in children that reported a >50 % adherence compared to −0.1 (6.1) in those who reported <33 % adherence [114]. Limited evidence found an association between self-reported adherence to PERT and number of annual admissions to the hospital [240]. The cohort with the highest adherence also reported the highest BMI [8,115]. In a recent adult study, lower adherence to PERT for snacks revealed patients to have an increased frequency of diarrhea. This supports the evidence of improved gastrointestinal symptoms with adherence to PERT [116].

Practical recommendations on PERT are conflicting due to the small body of literature [82,91,95,117,118]. The effective timing of enzyme-intake can vary between individuals. More research in this field is warranted [91,95,117,118].

Patients receiving overnight tube feeding may face additional challenges with respect to timing of enzyme dosing. Standard recommendations are to advise oral intake of pancreatic enzymes, adjusted for fat intake, at the start of tube feeding and during the night if the patient is awake. There is some limited evidence that the use of a new, inline cartridge (available in the US) improves nutrient (lipid) absorption [119,120]. This cartridge contains lipase. If used, protease and amylase should be supplemented via PERT to digest protein and carbohydrates. This in-line cartridge can be supportive in some pwCF [119]. However, for most pwCF on tube feeding, PERT alone supports good outcomes. At this time, consideration of use of the in-line cartridge must be made on an individual basis, e.g., when patients are not responding to treatment with usual enzyme therapy dosing (at appropriate U lipase per gram fat dose of enteral formula), and where patients continue to have gastrointestinal issues interfering with delivery of supportive enteral feeds. However, these supportive enteral feeds are not available in Europe. Cost of the treatment must also be taken

Table 4
Pancreatic enzyme lipase replacement therapy: consensus guideline.

Age	Suggested supplementation
Infants (up to 12 months)	2000–4000 U lipase/120 mL formula or estimated breast milk intake and approximately 2000 U lipase/gram dietary fat in food
Children 1–4 years	2000–4000 U lipase/gram dietary fat, increasing dose upward as needed (maximum dose 10,000 U lipase/kg/d)
Children >4 years and adults	Consider starting at 500 U lipase/kg/meal, titrating upward to a maximal dose of: - 1000–2500 U lipase/kg per meal, or - 10,000 U lipase/kg/d, or - 2000–4000 U lipase/gram dietary fat taken with all fat-containing meals, snacks and drinks.

into account before considering a change in clinical practice, without supportive evidence. The use of the in-line cartridge compared to routine enzyme therapy is costlier [119,121,122].

In clinical practice, administration of enzyme microspheres to infants can be challenging. Enzymes may be offered mixed with different vehicles for delivery. Enzyme microspheres can be mixed with a small volume of expressed breast milk or formula, or with an acidic puree e.g., applesauce and be delivered by spoon. If the infant still refuses the microspheres the use of non-enteric coated or unprotected powder enzymes can be considered. Pancreatic enzymes should never be added to the infants' oral feed. Regardless of the form of enzyme used, care should be taken to rinse out the infant's mouth after enzyme delivery to clear gums of residual enzymes and prevent irritation. Protecting the buttocks is also recommended in the first few months of life as enzyme therapy begins. Covering the buttocks skin with a zinc based cream and frequent diaper changes can help to prevent skin excoriation.

For those being treated with PERT, we recommend monitoring at regular intervals to determine the adequacy of treatment. This includes observation of acute symptoms such as abdominal distension and steatorrhea and chronic symptoms in the form of growth and nutritional status. It is recommended to obtain height and weight measures monthly or more frequently for infants at the start of enzyme therapy (considering infant's weight, age, response to treatment-see section on infants, assessment) and every three months for older children and adolescents, and every six months for adults.

6. Fat-soluble vitamins

Recommendation 19

Biochemical assessment of vitamins and trace elements should be interpreted with caution during CF exacerbation.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 20

For pwCF and exocrine PI, plasma levels of fat-soluble vitamins may be evaluated after initiation of enzyme and vitamin supplementation; three to six months after initiation or change in vitamin therapy; and annually thereafter.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 21

For pwCF and exocrine PS, fat-soluble vitamins may be assessed annually using plasma levels.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 22

25(OH)D should be measured annually. Individuals with levels of 25(OH)D <20 ng/mL (<50 nmol/L) should be considered deficient, and levels >30 ng/mL (>75 nmol/L) should be sufficient. The goal 25 (OH) levels should be 30–50 ng/mL (75–125 nmol/L) and levels should not exceed 100 mg/mL (250 nmol/L).

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 23

Vitamin supplements in pwCF with exocrine PI should be taken together with high fat food and pancreatic enzyme supplements to improve absorption. This does not apply if the formulation is water soluble

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 24

When biochemical deficiency is detected despite adequate vitamin supplementation, poor adherence or poor absorption of supplements should be ruled out before adjusting the dosage.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 25

Patients should take Vitamin D as Cholecalciferol (D3).

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 26

The type of vehicle used to administer vitamin D can contribute to insufficient levels. If unable to achieve sufficient status with an oil-based vehicle, a water or powder-based vehicle may be used.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 27

If levels are insufficient or deficient, the clinician should rule out poor adherence to the prescribed regimen as the etiology of the deficiency. We should consult the endocrinology service if there is continued difficulty with maintaining levels of vitamin D above 30 ng/mL (≥75 nmol/L) and there is confirmed adherence to the prescribed regimen.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

The disturbed mechanism of fat absorption resulting from exocrine PI can cause pwCF to become deficient in fat-soluble vitamins, particularly vitamins A, E, D and K [123,124].

Micronutrient deficiencies caused by exocrine PI due to impaired absorption of lipid soluble vitamins can lead to ecchymoses due to clotting (vitamin K deficiency), ataxia and peripheral neuropathy (vitamin E deficiency), impaired night vision and xerophthalmia (vitamin A deficiency), contraction or muscle spasms, osteomalacia and osteoporosis (vitamin D deficiency). Even pwCF who are PS have been shown to be at risk for deficiencies of fat-soluble vitamins [125].

Fat-soluble vitamin deficiency is common, occurring in 10–35 % of children with PI despite supplementation. It is unusual, however, for pwCF to show clinical signs of overt deficiency [126]. Instead, the goal of evaluation and treatment is to correct suboptimal levels and achieve optimal biochemical values of these vitamins [127]. Plasma levels of fat-soluble vitamins should be measured at least annually in all pwCF.

We recommend evaluating plasma levels of fat-soluble vitamins in PI patients after initiation of enzyme and vitamin supplementation; three to six months after initiation or change in vitamin therapy; and annually thereafter.

Supplementation of fat-soluble vitamins should be taken together with high-fat food and pancreatic enzyme supplements to improve absorption. When available, we recommend multivitamin liquid formulation or pills which will aid in compliance. When biochemical deficiency is detected, poor adherence or poor absorption of supplements must be ruled out before adjusting the dosage. For PS patients, we recommend assessing vitamin sufficiency annually using plasma levels.

PwCF on modulator treatment need to have levels checked three months after initiation of therapy especially in young children and adolescents who may require a reduction in dosage.

6.1. Vitamin D

Vitamin D insufficiency is still a problem in pwCF, even in those receiving supplementations. Hypovitaminosis D is often the result of fat malabsorption, but other contributors include increased latitude, poor nutritional intake, decreased sun exposure, impaired hydroxylation of vitamin D, and non-adherence to the prescribed vitamin D regimen. Vitamin D is critical for calcium homeostasis and optimal skeletal health, and vitamin D deficiency in CF can lead to skeletal complications of osteopenia and osteoporosis. Over time, there are recommendations for higher doses of vitamin D to achieve target levels of circulating 25 hydroxyvitamin D [128]. Insufficiency is common among young children with CF. Vitamin D insufficiency is prevalent even in children who are PS [129].

Adults with CF and vitamin D deficiency are at a higher risk of developing CFRD and are at risk for earlier CFRD onset. The maintenance of a serum 25(OH)D concentration above 20 ng/mL may decrease the risk of progression to CFRD [130].

Without adequate sun exposure, these individuals can also become vitamin D deficient. Even pwCF who are PS have been shown to be at risk for deficiencies of fat-soluble vitamins. Fat-soluble vitamins deficiency is common occurring in 10–35 % of children with exocrine PI. Plasma levels of fat-soluble vitamins should be measured at least annually in pwCF. Seasonal differences with the different hours of sunlight should be taken into account.

Vitamin D is vital for bone health. Supplementation should reach the optimum serum concentration (Table 5). Pregnant women must take additional supplementation of 600 IU (15 μg) per day.

6.2. Vitamin A

Low vitamin A levels are associated with worse lung function and increased pulmonary exacerbations. Vitamin A supplementation should lead to normalization of the level. High retinol serum concentration should be avoided and must be ruled out post-transplant or while on modulator therapy [126,127].

6.3. Vitamin E

Vitamin E deficiency has severe clinical consequences including hemolytic anemia, neuromuscular, retinal and cognitive disorders. Adequate dosing is vital for lung health and antioxidant status [126,127].

6.4. Vitamin K

Vitamin K deficiency has effects on clotting and bone health. There are no clinical biochemical indicators of vitamin K status. Special attention should be given to neonates and pwCF with cystic fibrosis associated liver disease (CFLD) [126,127].

7. Pancreatic sufficiency

Recommendation 28

In PS patients, fat-soluble vitamins should be supplemented as per PI recommendations with individualisation as indicated.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 29

In PS patients, pancreatic function should be ideally assessed annually by fecal pancreatic elastase-1 determination, with the test repeated when inadequate growth and/or nutritional status occur(s).

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 30

Additional care of weight tracking in PS patients for increasing BMI over the target should be undertaken due to the association of PS to risk of over nutrition.

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 31

As patients with PS compared to patients with PI may experience similar health consequences and obesity-related diseases as those observed in the general population,

Table 5
Fat-soluble vitamin guidelines for pancreatic insufficient people with cystic fibrosis.

Vitamin	Supplementation	Serum reference values and monitoring frequency
Fat-soluble vitamins		
Vitamin A	Amounts dependent on serum values, and supplement form:	Normal reference range provided by the laboratory processing the sample
	Retinol (preformed):	
	- Start low	Monitor annually and 3–6 months after a dosage change.
	- Adapt rapidly to target normal serum reference range	Also test when pregnancy is considered.
	Beta carotene (provitamin A):	
	- Prescribe 1 mg/kg/d (maximum 50 mg/d) for 12 weeks	
	- Follow with maintenance dose (maximum 10 mg/d)	
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure:	Serum-25 (OH) D minimum 20 ng/mL (50 nmol/L)
	- Starting dose of D3 (cholecalciferol)	Monitor annually, and check 3–6 months after a dosage change
	◦ Infants 400 IU/d (advance to upper limit of 1000 IU/d)	
	◦ All others 800 IU/d (advance to upper limit of 2000 for children 1–10 years, and 4000 IU/d for older)	
	- Maintenance dose: adapt to annual serum values, preferably measured at the end of dark months	
Vitamin E (tocopherols)	α-tocopherol dosing:	Plasma α-tocopherol:cholesterol ratio >5.4 mg/g
	100–400 IU/d	Monitor annually, and check 3–6 months after a dosage change
	50 IU/d for infants <12 months (1 mg = 1.49 IU)	
Vitamin K	Vitamin K_1	
	- Infants: 0.3–1.0 mg/d	Routine biochemical measurement not widely available
	- Older children and adults: 1–10 mg/d	

Abbreviation: 25(OH)D = 25-hydroxyvitamin D.

screening for standard cardiovascular risk factors (e.g. dyslipidaemia) should be performed.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

PS occurs in approximately 15 % of pwCF. Some who are initially PS at birth may later become PI due to the progressive nature of the condition, associations with class I-III mutations and also through an association with recurrent episodes of pancreatitis [131].

In the new era of CFTR-modulators (CFTRm) the opposite is now also a possibility with historically PI pediatric patients having reports of improvement or even full recovery of pancreatic function [132–135]. As the possible flow of pancreatic status is now multidirectional, assessment and monitoring of pancreatic status is increasingly important. Fecal pancreatic elastase-1 remains the standard and should be repeated annually in PS patients or if concerns arise relating to growth, nutritional status or symptoms [8,136,137].

Evidence supporting routine supplementation for fat-soluble vitamins in PS patients remains very limited. Previous guidelines have supported the notion that PS patients remain at risk for fat-soluble vitamin deficiencies [8]. As such, fat-soluble vitamin status assessed with a multimodal approach including dietary intake and plasma levels may occur annually as it would with PI patients [8,126,138,139]. Deficiency and risk of deficiency of vitamin D is reported to be similar in both PI and PS groups [136,140]. A study in pediatrics however suggests lower rates of fat-soluble vitamin deficiency in PS children compared to PI [126]. Data in patients with PS is still emerging and it is too early to draw conclusions.

Emerging and novel data suggest the relationship between nutritional status and lung function in CF differs significantly by pancreatic status [141]. Data suggest patients with PS may have higher FEV1% [79], are less likely to experience severe lung disease [142] and have a slower rate of FEV1 decline [141,143] which does not appear to differ by BMI [141] compared to PI patients.

Furthermore, there may be a smaller positive effect of BMI on FEV1 among PS and the negative impact of this on FEV1 may be more pronounced than PI [141]. Registry data suggest an alarming rise in overweight and obese pwCF [50] and PS patients may have a lower prevalence of underweight status [141] and higher prevalence/incidence of overweight status [50,55,57,79]. Therefore, additional care of weight tracking in PS patients for increasing BMI over the target should be undertaken.

There are few studies related to the impact of overweight and obesity on clinical outcomes in pwCF suggesting similar health consequences and obesity-related diseases as those observed in the general population [144]. However, limited data exist in terms of the role of pancreatic status. A study assessing the association of pre-diabetic and pancreatic status on pulmonary and nutritional status in adults with CF, concluded that normoglycemic PS pwCF had significant higher levels of BMI compared to PI patients who maintained normoglycemia or had diabetes [145].

While PI is more strongly associated with inflammation, PS might promote a proatherogenic lipid profile. A cross-sectional study assessing the metabolic profile of children with CF based on their pancreatic status concluded that children with PS had worse lipid profile (i.e., higher levels of total cholesterol, low-density, and high-density lipoprotein cholesterol) and higher percentages of abnormal lipids compared with patients with PI [79]. Researchers showed that the intake of saturated fatty acids was above the recommended level for the general population (15.8 %, >10 %) and that could contribute to the development of cardiovascular disease later in life in pwCF. In another cross-sectional study [146] that obtained an extended set of clinical and atherosclerosis-related laboratory parameters in pwCF, PS patients were found to have increased intima–media complex thickness compared to PI which underscored the need of reassessment of dietary guidance in PS CF [146].

8. Nutrition and pulmonary function

Recommendation 32

In pwCF, a normal BMI and normal body composition (i. e. fat mass and fat-free mass within normal range for age and sex) should be achieved and maintained, in order to improve lung function and longer survival.

Grade of recommendation B - Strong consensus 92 % agreement

Commentary

In children with CF, regaining birth weight z-score by age two years and maintaining BMI and height z-score throughout childhood was associated with the highest FEV1% predicted (pred.) later in life compared to those who did not in studies referencing CDC growth charts. Children who maintained a weight, length, WFL, and BMI >50th percentile from infancy and early childhood had better FEV1% pred. values, although there was no added improvement for those who maintained growth parameters >85th percentile compared with >50th percentile. Normal growth parameters during childhood were associated with increased FEV1% pred. in long-term follow-up studies (4–16 years) [139].

In adults with CF, data were mixed, but one large retrospective cohort study suggested that BMI $\geq$25 kg/m^2 is associated with decreased decline in FEV1% pred. and BMI <18.5 kg/m^2 is associated with increased decline in FEV1% pred. after a follow-up of up to 13 years. Baseline FEV1% pred. was also associated with change in BMI over time [49]. It is likely that the relationship between weight parameters and lung function is bidirectional [139].

BMI has a significant and clinically relevant effect on FEV1% pred. after adjusting for age. Patients with a lower BMI experience a six-fold increased odds ratio (95 % CI 5.0–7.3) of having severe lung disease (FEV1 <40 % pred.) compared to patients with normal BMI [142].

Weight percentile below 10 % during the first two years of life is a significant risk factor for lower FEV1 at age six to seven years. Interventions that improve nutrition in early life may lead to improvements in later lung function [74,147].

Measures to improve nutrient intake (diet high in energy and fat) and digestion (PERT) are essential for patient care and have contributed to observed increases in pulmonary function and lifespan.

The appropriate nutritional intervention to pediatric pwCF with malnutrition decreases the frequency of lung infections, and improves respiratory function [72].

PwCF who are overweight/obese or experience significant weight gain over time, have better pulmonary function, but also present adverse cardiometabolic risk factors [54]. Pancreatic status also seems to play a role in pulmonary function, as presence of PS in pwCF compared to PI is associated with higher FEV1 levels, better pulmonary function [79], less severe lung disease [142] and slower rate of FEV1 decline [141,143] which does not appear to differ by BMI [141].

Early weight-for-age, specifically at one year of age, and weight-for-age trajectories across early childhood are associated with the later course of lung function [148].

Recommendation 33

Pulmonary function may be performed at least every three months and is assessed as FEV1 in % predicted; normal ranges of weight-for-age/length-for age in children below the age of two years or optimal BMI in older children and adults correlate with better FEV1.

Grade of recommendation 0 - Strong consensus 100 % agreement

Commentary

For children and adults with nutritional deficits, the CF Foundation has insufficient evidence to make a recommendation about the relationship between improved rate of weight gain following nutritional interventions and improved FEV1 [149].

Undernutrition is associated with lower pulmonary function and increased early mortality. There is a clear association between higher BMI and better pulmonary function as assessed by FEV1 [150].

Nutritional intervention for weight gain and growth improvement is expected to improve FEV1 in individuals who are underweight or small-for age [151,152].

9. Feeding infants, toddlers, and children

9.1. Feeding infants

Recommendation 34

Regardless of pancreatic status, infants with CF should be exclusively breast fed until the appropriate introduction of complementary foods and then alongside complimentary foods up to two years.

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 35

Promotion of breastfeeding may include lactation support **as soon as possible in hospital or community settings.**

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 36

In infants diagnosed with CF, we recommend providing breast milk fortification or appropriate formula supplementation as necessary for the first year of life with the aim to regain birth weight z-score and achieve normal growth for age.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 37

Complementary foods should be introduced at the same age as recommended for the general population.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 38

Good eating behaviors, positive food relationships and nutritional counselling for families should be part of a multidisciplinary team care.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Newborn screening for CF is now widely implemented in Europe and worldwide to facilitate early diagnosis of infants with CF who are for the majority asymptomatic [153,154]. Newborn screening has been consistently associated with improvement in nutritional status [71,78,155,156]. Monitoring at specialized centers according to the Standards of Care [47] with preventative nutritional approach and appropriate timely intervention strongly reduces the risk of malnutrition [8].

Dietitians specializing in CF care are invaluable resources supporting infant care and feeding in the first few months of life [157]. Growth measured and assessed by a dietitian will help to identify any feeding challenges early on and provide nutritional guidance (exclusive breast feeding or formula fortification) as needed.

Currently, there is still a lack of high-quality evidence (i.e., RCT) to support recommendations for infants newly diagnosed with CF. Two prospective observational studies failed to find an association between modalities of feeding (breastmilk, formula feeding or combined) and anthropometric outcomes at one year [155] and two years of age [71]. Even if breast feeding was associated with more constipation in infancy [158], the authors continue to advocate for breast milk in all infants with CF.

Modalities of feeding were not associated with an increased risk of gastrointestinal [159] or respiratory related hospitalization in the first three years of life [160].

A small study suggests that any breast milk exposure compared to exclusively formula feeding increased microbiome diversity in the gut and the respiratory tract and delay the time to first pulmonary exacerbation [161]. Breast milk may provide some protection against *P. aeruginosa* with a trend toward delayed time to first *P. aeruginosa* acquisition in two studies [71,161].

In a review on breast feeding in infants with CF [162], of nine controlled studies which were mainly retrospective, the data was controversial, but the author's conclusion was that breast feeding can be considered as standard for infants with CF.

Nutritional guidelines across Europe [8], the US [139] and Australia and New Zealand [136] recommend providing breast milk for as long as possible.

Promotion of breastfeeding should include lactation support as soon as possible in hospital or community settings [139] as it improves the duration of breast feeding [163].

An increasing number of studies performed in the general population reported many health benefits of breast milk on immunity, neurocognitive development and long-term protection against chronic diseases that may also be beneficial in the pwCF [164] whose survival has improved significantly [165]. When breast feeding is not possible, a standard infant formula is recommended [8,136]. Evidence-based recommendations remain limited on the assessment, monitoring and supplementation of sodium; however, the period of infancy is recognized to be of particular importance [166]. Additional care should be taken with those who are breast fed, have ostomies or have acute vomiting or diarrhea [136,166].

Energy intake should be increased only as necessary for the first year of life by providing breast milk fortification or formula supplementation with the aim to regain birth weight z-score and achieve normal growth for age [8,71,75,139,155]. The critical importance of achieving optimal nutritional status in infancy due to its likely influence on later CF health continues to be re enforced [148].

Complementary foods, defined as solids and liquids other than breast milk of infant formula [167] should be introduced at the

same age as recommended for the general population. Specifically, they should not be introduced before four months but should not be delayed beyond six months with advancement of textures by nine months. Methods of weaning [168–170] and their impact on outcomes (i.e. food preferences, growth) have not been studied in children with CF.

Good eating behaviors, positive food relationship and nutritional counselling for families should be part of multidisciplinary education and care [8].

9.2. Feeding infants with meconium ileus (MI)

Recommendation 39

Patients who present with MI should be considered at high nutritional risk in respect to short and long-term outcomes. They should be supported **by a wider CF multidisciplinary team including specialists in pediatric surgery, neonatology, gastroenterology and dietetics.**

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 40

Infants with MI requiring surgical intervention (approx. 70 %) should initially be supported **by parenteral nutrition (PN) to** support **their growth (GPP). Formulation choice of total PN may favor a lipid anti-inflammatory profile including medium-chain triglycerides (MCT) and fish oil to minimize the risk of cholestasis (0).**

Grade of recommendation GPP/0 - Strong consensus 100 % agreement

Recommendation 41

As soon as deemed appropriate following resolution of occlusion of MI, EN should be started and advanced readily as tolerated. The choice of feeding for MI may be diverse (including breast milk, standard formula or specialized formula (e.g. amino acid, protein hydrolysate and MCT)) according to clinical practice. Regardless of feed choice and even in presence of enterostomies an appropriate pancreatic enzyme dose should be provided.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Infants with CF presenting with MI should be considered at higher nutritional risk for short and long-term outcomes compared to non-MI cases with CF [16,75,155,171]. It has been shown that early growth recovery and longer adequate growth are critical for pulmonary outcomes later in life [75,171].

Increased awareness and vigilance of CF health care providers should be supported by the multidisciplinary team in charge of CF and specialists in pediatric surgery, neonatology, gastroenterology and diet [171,172].

Infants with MI requiring surgical intervention (approximately 70 %) should initially be supported by total PN [172,173]. Formulating the choice of total PN should favor a lipid anti-inflammatory profile including MCT and fish oil to minimize the risk of cholestasis [172,174]. As soon as possible after resolution of occlusion the gastrointestinal tract should be used for EN and advanced readily as tolerated [172]. The choice of EN can be diverse including breast milk, specialized formula (i.e., amino acids, protein hydrolysate and MCT) [172] according to clinical practice. As the infant continues to recover and gastrointestinal tolerance improves, breast milk or standard formula can be introduced. Breast milk may be protective on both infant growth and *P. aeruginosa* (PA) colonization in one retrospective study [173].

Long et al. [175] showed that time to full EN is shorter in cases with successful non-operative management compared to those who required surgery. Of note, regardless of feed choice and even in presence of enterostomies, an appropriate pancreatic enzyme dose should be provided, as well as sodium and volume supplementation which should be adapted to the daily ileostomy output.

9.3. Feeding toddlers

As toddlers are introduced to table foods, it is important that the diet must be balanced. and diverse, with moderately increased fat and protein content. Parents need to be in control and the child should limit “grazing”. Mealtime should not turn into a battleground and the CF dietician and the psychologist should help promote positive interactions and behaviors around meals. This is important to build the foundations to lifelong positive attitudes to foods [176].

9.4. Feeding children

School age is the stage at which the child should be encouraged to obtain a basic knowledge of the physiological processes, leading to taking increasing responsibility for nutritional and pancreatic enzyme management [177].

10. Nutrition in adults

Recommendation 42

In women with CF who plan to get pregnant and during pregnancy, a nutritional assessment and an individual approach to achieve an acceptable BMI and appropriate weight gain, as well as supplements with adequate amounts of vitamins and micronutrients should be performed. Nutritional assessment should be performed more frequently in pregnancy.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 43

In the aging CF population, an appropriate nutritional intervention, adequate hydration and physical activity should be advised to improve FFM or prevent its loss.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

With the evolution of the disease and the increase in life expectancy in the CF population an increasing rate of complications has been observed. With introduction of highly potent CFTR-modulators an increase in overweight or obesity, including enhanced cardiometabolic risk factors are reported. Furthermore, CFRD, osteopenia and osteoporosis, malignancies, as well as kidney disease, are frequent in adult pwCF [8,31,54,153,178–180].

We recommend to make a distinction between pwCF who are PI and PS with regard to nutritional therapy. Adults with PI and impaired pulmonary function are at increased risk for undernutrition. PS adults with milder pulmonary symptoms are at risk for over nutrition [54,180]. However, overweight and obese CF adults with PI are also reported [54,181]. The differences in nutritional status require an individualized nutritional therapy. Some individuals prefer to be overweight as they associate losing weight

with a worsening clinical status [181]. If adults are diagnosed with co-morbidities, we recommend to refer them for a complete nutritional assessment and to adjust nutritional therapy to improve the nutritional status. In overweight pwCF, an improvement in weight can be associated with an improvement in pulmonary function but also with an increase in insulin resistance and elevated triglycerides [31,54]. Due to the evolution of the disease, pulmonary function in adults with CF can worsen, which is associated with a further deteriorating nutritional status [178,182]. Adults can also be referred for transplantation (see chapter 18). This argues for more intensive follow-up and measurement of body composition.

Adults with CF can have higher caloric needs compared to healthy controls and the level of increased nutrient intake is related to the clinical status [8,18,31,54,179]. Increase in body weight is suggested to be related to an improvement in body composition. However, adults with CF with a high FM and low FFM appear to have a worse pulmonary function compared to those with a better FFM. This imbalance in body composition can also increase metabolic complications [8,18,31]. Presently, we cannot give evidence-based recommendations for daily macronutrient intake and the balance between fats, carbohydrates and proteins. Therefore, we recommend to use the national recommendation concerning balance for macronutrient intake, to adjust the macronutrients according to the requirements of the individual and to assure adequate intake of pancreatic enzymes. In patients with good absorption, it is fair to limit intake of saturated fatty acids and trans-fatty acids [8,183,184]. Further studies are required.

10.1. Pregnancy

As a consequence of improvements in therapy and care, life expectancy increases and adult women with CF can make the choice to have families. Pregnancy and breast feeding increase nutritional demands for the mother. Accordingly, a thorough pre-conceptional nutritional assessment is warranted, as far as possible. We recommend increasing the frequency of monitoring in patients planning a pregnancy and in pregnant pwCF [8,185,186]. A low pre-pregnancy BMI is associated with a lower birth weight [187]. It is recommended to have a BMI of $\geq$22 kg/m^2 before the pregnancy. If this is not achieved, guidelines on the rate of weight gain during pregnancy have been published [185]. For instance, women with a pre-pregnancy BMI <18.5 kg/m^2 a weight gain during pregnancy of 12.5–18.0 kg is recommended. To reach this goal nutritional interventions can be intensified starting from dietary modification to adding oral nutrition supplements to initiate tube feeding or considering PN [8,185]. When starting tube feeding an increased risk for gastroesophageal reflux should be considered [186]. Digestion should be optimized as much as possible by adapting pancreatic enzyme intake according to nutrient intake. Dosing of vitamin A $\geq$ 10000 IU/d is not recommended due to the association with increased risk for miscarriage and congenital birth defects, and vitamin levels in serum should be controlled, accordingly. A review of food intake is warranted so that foods with a high content of retinol can be identified [8,185,186]. As in the non-CF population supplementation of other vitamins and minerals should be considered if there is a possibility for deficiency or in the prevention of fetal complications. It is recommended to start prenatal folic acid at a dosage of 400 μg [8]. As in the non-CF population pregnant women with CF should be screened for gestational diabetes. During pregnancy and breast feeding it is important to have a sufficient fluid-intake. The thirst-drive can be disturbed in pwCF [166]. Lactating mothers in general require a mean supplement of 500 kcal/d [8,185]. When not achieving the nutritional requirements a rapid decline in body weight can occur [185].

10.2. Aging

In the non-CF population aging is associated with alterations in body composition [188]. This might also be expected in the CF population. This transition can be accelerated or more pronounced due to the course of the disease [31,54,178]. We encourage to perform a thorough nutritional assessment before the nutritional status deteriorates. In the absence of specific evidence on nutritional therapy in elderly with CF, nutritional interventions in this cohort should be based on guidelines specific for this age-group. Interventions can be adapted according to specific CF related nutritional needs.

11. Cystic fibrosis nutritional supplements

Recommendation 44

Clinicians may consider the use of oral nutritional supplements (ONS) for children and adults who fail to achieve optimal growth rates and nutritional status with oral dietary intake and PERT alone.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 45

Clinicians should regularly review and re-evaluate patients who are taking ONS to determine the impact and consideration of continued use.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 46

If optimization of oral feeding fails to maintain nutritional status, EN can be considered to increase nutrient intake in pwCF.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 47

The initiation of EN should be considered before periods of accelerated growth.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 48

We recommend clinicians should discuss use of EN in a timely manner with the patient and family when patients do not grow according to their genetic potential.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 49

The use of PN may be reserved for exceptional cases when EN is not possible or failed.

Grade of evidence 0 - Strong consensus 100 % agreement

Commentary

Requirements for energy and nutrients are not constant across the life span of pwCF. During periods of rapid growth and development, nutritional requirements increase. As a consequence, several nutritional interventions can be used in CF to improve growth and to achieve the desired BMI [8,189–191].

11.1. Oral nutritional supplements

ONS may be beneficial for patients whose nutritional status remains poor despite dietary modifications, optimizing PERT and

the absence of health-related factors or behavioral concerns that could contribute to undernutrition [8].

A review of three randomized clinical trials (total of 131 patients) found ONS do not promote additional weight gain in moderately malnourished children with CF compared to dietary advice and monitoring alone. The use of ONS in adults with CF has not been adequately studied [192]. One small cross-sectional study reported despite a higher caloric intake compared to CF adults not using ONS a worse pulmonary function and lower BMI [193].

Given the limited evidence, results of the Cochrane review should be interpreted with caution and do not mean that these supplements are not beneficial to all patients. In clinical practice, short term use of individually prescribed supplements has been shown to increase energy intake and weight in undernourished patients [8].

Furthermore, supplements may also be used to improve the status of specific nutrients such as EFA, minerals and vitamins [193].

To ensure ONS provide additional nutrition and does not replace meals, attention to quantity and timing of supplement intake is important. The wide variety of forms and flavors now available improves the likelihood of finding a product that appeals to personal preferences and minimizes taste fatigue often reported with long-term supplement use [8].

11.2. Enteral nutrition

When a fortified diet and ONS fail to achieve adequate nutritional status, EN is used in several CF centers. The number of patients on EN varies widely between centers, as well as the prescribed formula [194–196]. Despite the widespread use of tube feeding for pwCF, the efficacy of this feeding method on clinical outcomes has not been assessed by randomized control trials [8]. Most evidence is derived from observational studies [194–198]. Despite a deteriorating nutritional status and pulmonary function, the start of EN varies [196,199]. A registry study found that up to six years before the start of EN, patients had already a worse BMI and FEV1 compared to controls. BMI and FEV1 further declined towards the starting point of EN [196]. Another small case–control study found a negative association between the age of starting EN and growth velocity [197]. A decrease in further rapid decline or preservation of pulmonary function is observed after starting EN [196–198,200].

The route, formula, and timing for EN are determined by the patient's preference and clinical status. Enteral formula can vary from polymeric, to elemental or hydrolyzed feeds [8,195,196]. EN is started with the intention to improve nutritional status, however, often results in preventing further decline [195,196,198]. There is insufficient evidence to make a statement on the effect of tube feeding on pulmonary function. We recommend to screen for abnormalities in the glucose metabolism when EN is started [196].

Gastrostomy feeding is usually preferred to nasogastric tubes for long-term nutritional support. It is vital to thoroughly explain feeding needs and choices to the patient in order to increase the likelihood of success. Feeds are usually introduced gradually as tolerated and administered as continuous infusions overnight, bolus feeds (gravity or pump assisted) during the day, or a combination of both [201].

With nocturnal feeds, it is possible to encourage patients to eat a high-energy diet during the day. Most patients tolerate a high energy polymeric feed (1.5–2 kcal/mL). If this is not well tolerated, an elemental or semi-elemental feed may be beneficial [8,194,201].

EN requires pancreatic enzyme therapy; dose, strength and route of administration varies [194]. Dose and strength of PERT should be individualized based on symptoms of maldigestion [8,201].

11.3. Parenteral nutrition

PN is not routinely recommended as a method of nutritional support for pwCF due to the benefits of EN, risk of complications, difficulty of administration and high cost.

PN may be essential as short-term nutritional support following intestinal resection in infants presenting with MI and children and adults following major gastrointestinal surgery where EN is not possible [202].

It may also be beneficial for severely compromised patients awaiting transplantation [203].

12. Supplementation of trace elements

12.1. Calcium

Recommendation 50

Daily calcium intakes should achieve the recommendations by the European Food Safety Authority for same age healthy children and adults.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 51

Calcium intake should be assessed at least annually.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 52

Individuals with suboptimal calcium intakes should increase dietary intake of calcium-rich foods and should be advised to take calcium supplements if dietary intake remains low.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Calcium plays several key roles in bodily functions. The predominant attention of its role is its involvement in bone health as it is well established that pwCF have a high prevalence of low bone mineralization. Several factors influence calcium status and absorption including dietary intake, PERT usage, and vitamin D status. With no simple biochemical indicator of calcium status, clinical practice assessment will be dependent on a multimodal dietary assessment.

Historical data suggested that pwCF are at increased risk of negative calcium balance that may adversely affect bone health [204]. This is despite evidence that dietary intake was generally sufficient [205,206]. Since 2014 several pediatric publications have reported dietary intakes compared to recommendations for healthy populations. Reports have ranged from 78 % of children achieving calcium requirements or exceeding [207] to 78 % who had a low calcium intake [30,208]. In an Australian study 9.8 % of children were not meeting calcium requirements [44]. Furthermore, this study stratified by age and calcium intake was seen to significantly reduce with increasing age groups. Importantly, 29.2 % of high school CF children were shown not to meet their RDIs and given that most bone mass is developed during adolescence this is a key finding for clinical practice.

There is no new evidence of a specific additional requirement for pwCF or that supplementation above the RDI confers any additional benefit [136,209,210]. However, identification and addressing suboptimal intake should be a priority. Calcium intake should be assessed at least annually by a dietitian to ensure maximize skeletal accretion and optimize bone health in CF.

Current data supports the target of national or international age-appropriate guidelines [136] and daily calcium intakes should at least achieve the recommendations by the European Food Safety Authority for same age healthy children and adults.

0–6 months: 200 mg; 7–11 months: 280 mg; 1–3 years: 450 mg; 4–10 years: 800 mg; 11–17 years: 1150 mg; 18–25 years – 1000 mg; >25 years 950 mg

Individuals with suboptimal calcium intakes should increase dietary intake of calcium-rich foods and should be advised to take calcium supplements if dietary intake remains low. There is insufficient data to conclude that routine supplementation with calcium has any additional benefits on bone health.

12.2. Zinc

Recommendation 53

Zinc supplementation for pwCF who have proven zinc deficiency or who are at risk of concerns of zinc insufficiency (e.g. sub optimal growth, assessed low dietary intake, increased susceptibility to infections, delayed sexual maturation, and acrodermatitis) may be considered. Routine additional zinc supplementation for pwCF may not confer any clinical benefit.

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 54

Assessment of zinc status should include biochemical markers (interpreted with caution) in combination with clinical examination and assessment of dietary intake

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Assessment of zinc status should be performed with caution. The level of evidence to guide assessment of zinc status in pwCF in clinical practice is insufficient [136] Plasma zinc levels may not be reliable and may not reflect deficiency [138,211]. This biochemical marker is recognized to be fragile and susceptible to a wide range of situations such as inflammation which may influence the result [138]. In the absence of reliable markers and specific clinical symptoms, marginal zinc deficiency can be implied with a positive response in growth with zinc supplementation [136]. A study in infants identified 32 % who had biochemical intermittent zinc insufficiency [212], a study of both pediatric and adults patients showed 41 % of cases were considered to be at elevated risk of zinc deficiency [211] and an adult study showed 22 % found to have low plasma zinc [213].

Characteristics that may increase risk of zinc deficiency include vegetarians/vegan diets, high intake of phytates and fiber, lactation and pregnancy, breast fed infants beyond six months and those with ileostomies [136,214].

Dietary intake of zinc is important and increased focus is reflected in recent literature. A study from Australia [44] identified 2.4 % of pediatric pwCF not meeting the RDI although this was lower than the control group (6.1 %). A European study from Greece however reported dietary zinc intake was not met in 31 % boys and 20.5 % of girls [207].

An adult study reports lower lung function and an increased prevalence of bone disease and impaired glycemic status in pwCF who have sub-optimal zinc levels [213]. A systematic review highlighted a single zinc supplementation study in pediatrics that was associated with less exacerbations [215]. In a recent Cochrane review, zinc supplementation in children probably made no difference to the number of pulmonary exacerbations [216]. Zinc supplementation probably does not improve FEV1 [216]. The relationship of zinc to growth also remains inconclusive [212,217].

The considerations of empiric supplementation in the presence of normal biochemical markers have been proposed in certain circumstances. These include persistent sub optimal growth, assessed low dietary intake, increased susceptibility to infections, delayed sexual maturation, eye problems, and poor appetite. There is insufficient evidence to support the routine supplementation of zinc with regards both nutritional and respiratory outcomes [136,217,218].

In clinical practice the treatment of proven or suspected zinc deficiency supplementation can be considered as follows: Infants 1 mg/kg/d (max 15 mg/d) or children 15 mg/d and adults 25 mg/d for a period of six months [136].

12.3. Selenium

Statement 6

There is insufficient data/evidence to conclude any benefit of additional selenium on nutritional or respiratory outcomes.

Grade of recommendation 0

Commentary

Selenium is an essential micronutrient with a proposed role in stimulating antioxidant action [219]. The most efficient way to obtain it systemically is through a well-balanced diet [220]. Data on the selenium content in diet and status in pwCF is very limited. Studies and reports of dietary intake of micronutrients have increased in recent years, however, these have not specifically reported selenium.

Selenium was included in both an updated CF specific Cochrane review [219] and CF specific systematic review [215] to assess impact on clinical outcomes. Studies included however, were limited to oral antioxidant combinations which included selenium but not in isolation [221,222]. Evidence ranged from very low to moderate quality and the Cochrane review concluded selenium does not seem to improve clinical outcomes [219].

If required, treatment is generally effective and can be given either orally (including dietary manipulation) or parenterally [220]. The benefit of antioxidants like selenium in pwCF who receive CFTR modulators therapies may need attention in the future.

12.4. Iron

Recommendation 55

Supplementation:

In cases of iron deficiency, underlying inflammation should be resolved and supplementation with iron should only occur if deficiency persists.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 56

In children, adolescent and adult patients, serum iron should be monitored annually, differentiating between iron deficiency anaemia and anaemia of chronic inflammation; if iron deficiency is suspected the frequency of monitoring should be increased.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Iron deficiency is common in pwCF, with wide prevalence rates reported across different age ranges and disease severities. In children with CF, iron deficiency and iron deficiency anemia has been shown to be present in 17 % and 11 %, respectively [223]. In an adult CF population, the prevalence of iron deficiency was 41.8 % and iron deficiency anemia 33.3 % with iron deficiency rising to 58 % in those with severe lung disease [224].

Many factors can contribute to iron deficiency including chronic infection and inflammation, insufficient dietary iron intake and chronic blood loss [224–226]. Malabsorption may play a role in iron metabolism although some studies have demonstrated no significant relationship between PI and iron deficiency [223,224,227]. It is suggested that the risk of anemia is associated with markers of severe CF disease including low BMI, diabetes, bone disease and vitamin A deficiency [224]. However, iron deficiency anemia also occurs in healthy children and adults with CF [223,224].

Monitoring iron level in pwCF, can be challenging due to the effects of inflammation. Therefore, where possible, aim to assess iron status when patients are clinically stable [136]. Serum ferritin is increased and transferrin saturation is often decreased by inflammation, this can lead to an under or over-estimation of total body iron store [224,228]. Serum soluble transferrin receptor is not affected by acute phase response of pulmonary exacerbations in CF [229] but it is not widely available [230]. In cases of iron deficiency, underlying inflammation should be resolved and supplementation with iron should only occur if deficiency persists.

In pwCF, serum iron should be monitored annually, if low further measures will be required to differentiating between iron deficiency anemia and anemia of chronic inflammation. Serum ferritin, total iron binding capacity, or transferrin saturation can facilitate differentiation between anemia due to iron deficiency versus anemia resulting from chronic inflammation Table 6 [225,231]. When iron deficiency anemia and anemia of chronic disease are both present, serum ferritin and total iron binding capacity may be increased, decreased, or within the normal range, due to offsetting influences of the two conditions.

12.5. Sodium

Recommendation 57

In infants, children and adults with CF, specific levels of salt supplementation may be required depending on age and clinical condition, physical activity and climate situation (see Table 7).

Grade of recommendation GPP - Strong consensus 100 % agreement

Approximately ¼ teaspoon salt contains about 25 mmol or 575 mg of sodium.

Recommendation 58

The need for salt/sodium supplementation can be assessed by measuring fractional excretion of sodium (FENa) and maintaining a FENa level between 0.5 % and 1.5 %. For routine practice, a urinary sodium:creatinine ratio is easier to measure and correlates with FENa.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

As a result of CFTR dysfunction, pwCF have two to four times higher concentrations of sodium and chloride in their sweat compared to healthy controls [232]. PwCF are therefore at increased risk of electrolyte disturbances. The risks for sodium loss is greater in hot environments, during respiratory infections and where there are increased losses due to vomiting, diarrhea or raised body temperatures [233]. The clinical consequence of sodium deficiency includes faltering growth, which is particularly a problem in infants [233–235]. In infants and young children sodium status is further influenced by increased required associated with rapid growth and by the relatively low sodium content in breast milk, infant formula and many initial weaning foods [8].

12.5.1. Monitoring

For all pwCF, sodium status needs to be monitored and replacement varied according to individual needs. We suggest the need for sodium supplementation can be assessed by measuring FENa; maintaining a FENa level between 0.5 % and 1.5 %, however in routine clinical practice it can be more difficult to do as it requires

Table 6
Use an additional measure of iron deficiency to differentiate between forms of anemia.

Use normal reference range[b] for	Iron deficiency anemia	Anemia of chronic inflammation	Both forms of anemia
Serum iron	Below normal	Below normal	Below normal
Serum ferritin	Below normal	Above normal	Varies
Total iron binding capacity	Above normal	Below or normal[a,b]	Varies
Transferrin saturation, percent	Below normal	Below normal	Below normal

[a] Use normal reference range provided by the Laboratory processing the sample.
[b] Ether below the normal reference range or within the normal reference range.

Table 7
Sodium supplementation.

Age	Sodium supplementation[a]	Detail
Breastfed infants 0–6 months	1–2 mmol per kg/d	For infants at risk of sodium deficiency give salt in small portions throughout the day, diluted in water or fruit juice
For infants with special considerations (see detail, right	Up to 4 mmol per kg/d	Increase intake for infants living in hot ambient temperatures; or for those with increased fluid loss due to vomiting, fever, diarrhea, or tachypnea; or infants with ostomies.
Older children until adulthood	Salty foods, sodium chloride capsules/vials	Supplement in stress situations when excessive sweating is expected (i.e., fever, exercise/sports, hot weather).

[a] To convert mol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35, or 58 (the molecular weights of sodium, chloride, and sodium chloride), respectively.

paired blood and urine samples. For routine practice, a urinary sodium: creatinine ratio is easier to measure and correlates with FENa (corresponding range 17–52 mmol/L) [234], however as muscle mass increases with age specific cut-offs for older patients are required [236].

12.5.2. Infants

Guidelines for the management of infants with CF recommend routine sodium supplementation for all infants with CF, to a maximum of 4 mmol/kg body weight/d [237,238]. Sodium supplementation should be assessed on an individual basis taking into account sodium losses and climate [237,239]. For the majority of infants, supplementation with 1–2 mmol/kg should correct deficiency [237,239] although more may be needed [166]. For infants, sodium supplements can be given as sodium chloride solution and it can be added to infant formula, expressed breast milk or infant juices and taken in small quantities throughout the day [239].

12.5.3. Older children and adults

CF children, of all ages, have been shown to consume significantly more sodium than controls [44]. There is very limited data concerning dietary sodium intakes in adults with CF, with current dietary practices seeming to provide adequate sodium for most older children and adults. However, sodium requirements need to be assessed on an individual basis taking into account dietary intake, climate, clinical status, exercise and bodily losses. The need for sodium supplementation can be assessed by measuring fractional excretion. If supplementation is necessary, sodium chloride capsules (or sodium chloride doses distributed in vials) can be administered several times a day.

12.6. Glutathione

Statement 7

There are no data supporting the use of glutathione therapy in pwCF.

Strong consensus 100 % agreement

Commentary

Oral glutathione supplementation did not impact growth or change serum or fecal inflammatory markers in PI children with CF when compared with placebo.

12.7. Essential fatty acids

Statement 8

Further studies are required before EFAcan be recommended.

Strong consensus 91 % agreement

Commentary

Two fatty acids are known to be essential for humans: alpha linolenic acid (an omega-3 fatty acid) and linoleic acid (an omega-6 fatty acid). Some other fatty acids are classified as conditionally essential, meaning that they become essential under some developmental or disease conditions, i.e. docosahexaenoic acid (an omega-3 fatty acid) and arachidonic acid (an omega-6 fatty acid).

Altered fatty acid profiles have been reported in infants and children with CF [240]. The mechanisms underlying these abnormal fatty acid profiles remain incompletely understood. A connecting link between abnormal fatty acid levels and CFTR membrane protein deficiency is not known [241]. In infants and children with CF, low EFA levels are not necessarily accompanied by usual clinical signs, e.g., dermatitis and learning disabilities. However, low linoleic acid was reported to correlate with poor pulmonary status and impaired growth in infants and children, while low docosahexaenoic acid with high arachidonic acid (i.e., high arachidonic acid to docosahexaenoic acid ratio) was associated with impaired BMD in both children and young adults with CF. Researchers have advocated omega-3 fatty acids as part of the routine treatment for CF [242].

However, because evidence is still not sufficient, we are not able to make specific practice recommendations regarding dietary supplementation of fatty acids for improved lung function or anti-inflammatory effects in children or adults with CF. Well-designed prospective studies are necessary to confirm and extend these preliminary findings [240].

12.8. Appetite stimulants

Statement 9

We are not able to offer an evidence-based guideline on use of appetite stimulants for pwCF.

Strong consensus 100 % agreement

Commentary

PwCF and their families are concerned about poor appetite. Appetite stimulants have been used to help pwCF increase the amounts they eat so they gain weight and improve overall health. While appetite stimulants offer potential benefits, there are concerns that they may have side effects [243,244].

The Cochrane review included four trials (70 participants) comparing appetite stimulants (cyproheptadine hydrochloride and megestrol acetate) to placebo [245]. At six months in adults and children, appetite stimulants improved only two of the outcomes of this review: weight (or weight z-score) and subjectively reported appetite. Insufficient reporting of side effects prevented a full determination of their impact. Whilst the data may suggest the potential use of appetite stimulants in treating anorexia in adults and children with CF, this is based upon low-certainty evidence from a small number of trials, therefore firm conclusions cannot be drawn. Clinicians need to be aware of the potential adverse effects of appetite stimulants and actively monitor any individuals prescribed these medications accordingly. Research is required to determine meaningful surrogate measures for appetite and to define what constitutes quality weight gain. As a result, we are not able to offer an evidence-based guideline on use of appetite stimulants for pwCF.

13. Bone disease

Osteopenia and osteoporosis are common among adolescents and adults with CF [246,247], though one study suggests that rates appear to be declining over ten years (2000–2012) [248]. In fact, one study using a new technique evaluating bone infrastructure suggested that CF children and teenagers (in good nutritional status) when compared to controls had only mildly lower bone infrastructure [249]. Though declining rates of low BMD have been reported in adults with CF [250], reduced BMD with increased fracture risk remains of concern in this population [47,251–254]. Low BMD can also occur in children [255,256].

13.1. Prevention

Recommendation 59

PwCF may routinely engage in weight-bearing exercise (see Table 8).

Grade of recommendation 0 - Strong consensus 100 % agreement

Commentary

We suggest pwCF to routinely engage in weight-bearing exercise [257], as physical activity is strongly correlated with increased BMD [257,258] (see Table 8). Children and adolescents should be encouraged to exercise (high impact weight bearing physical activities) for 20 to 30 min three times a week in addition to their usual activities. In one study, exercise supported overall well-being, and improvement in physical health, though no positive association in BMD was observed in this study in children [259]. Adults should be encouraged to perform regular weight bearing and resistance activities.

13.2. Assessment

Recommendation 60

An annual assessment of risk factors (see Table 9) should be completed as well as obtaining fracture history in all pwCF.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 61

An assessment of bone health can be completed by measuring BMD with DXA for all pwCF ≥ 8 years old and express BMD as z-scores (using height adjusted Z-scores in children).

Grade of recommendation 0 - Strong consensus 100 % agreement

Recommendation 62

A BMD assessment (using height adjusted z-scores in children) should be done every one to five years, depending on the age of the pwCF, the presence of risk factors and the value of the previous scan:

- **Annually if BMD was severely reduced: BMD z-score < -2 in children, t-score < -2.5 in adults**
- **Every two years if BMD was moderately reduced: BMD z-score between -1 and -2 in children, t-score between -1 and -2.5 in adults**
- **Every five years if BMD was normal: BMD z-score > -1 SD in children, t-score > -1 in adults**

Grade of recommendation GPP - Strong consensus 100 % agreement

Table 9
Risk factors for poor bone health.

General	Adults
Poor nutritional status (BMI z-score < -2)	Smoking
Low pulmonary function (FEV1 z-score < -2)	Alcohol
Frequent hospitalization	Caffeine intake
Decreased muscle mass	
Delayed puberty	
Lack of weight-bearing exercise	
Glucocorticoid treatment	
Hypogonadism	
Vitamin D deficiency	
Low calcium intake	
Vitamin K deficiency	
Celiac disease	
Liver Disease	

Recommendation 63

PwCF with diagnosed osteopenia or osteoporosis should be screened for other underlying conditions that may be detrimental to bone health such as: celiac disease, primary and secondary hyperparathyroidism, and endocrinopathies such as delayed puberty, hypogonadism, and growth hormone deficiency/resistance; other risk factors may be considered as reported outside of CF and include organ transplantation, major depression, frequent use of PPI, and chronic liver disease.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Multiple risk factors have been associated with poor bone health in pwCF, both children and adults (see Table 9) [246,248,258,260–264]. Low BMD has been associated with low FFM in children and adults [26,30,251,265–267]. Glucocorticoid treatment is a risk factor for decreased bone mass [251,268]. Past history of MI is also a risk factor for low BMD [265]. The main indicators of nutritional risk are poor nutritional status; delayed puberty; and deficiencies of vitamin D, calcium and vitamin K [208,256,261,269].

We emphasize routine monitoring of bone health using DXA for all pwCF ≥8 years, with a frequency depending on results and clinical status (see Fig. 1) [251,256,260,265,270–273]. For patients younger than 20 years of age whose height is more than one standard deviation below age- and sex-matched healthy controls, BMD z-score should be adjusted for height or statural age to avoid over estimating deficits in BMD in people with short stature [274,275]. If available, we recommend the use of high-resolution peripheral quantitative computed tomography (HR-pQCT) for assessment of bone quality and microarchitecture associated with fracture risk [249,250,252,253,276–278].

Table 8
Exercise recommendations for people with CF for preserving bone health (adapted from Swisher [257]).

For young child/children/adolescent: at least 60 min of moderate-to-vigorous physical activity daily.
For adults: resistance training
- Frequency: 2–3 times per week
- Intensity: at least 70 % of 1-repetition maximum
- Volume: 1–3 sets of 8–15 repetitions
- Type: a program that includes upper body, lower body, and trunk muscles is recommended. Multi-joint motions using large muscle groups should be performed before small or single-joint motions. Resistance can include body weight, resistance bands, or weight equipment.

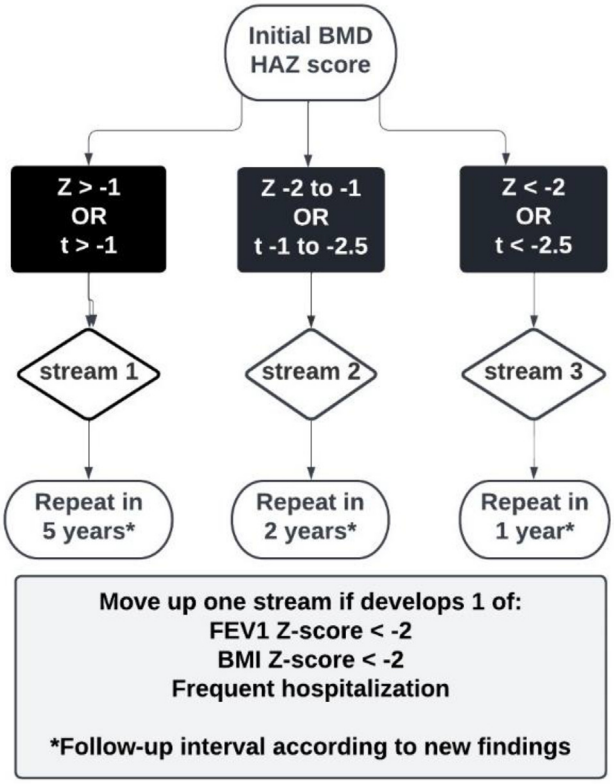

Fig. 1. Frequency of BMD assessment (Adapted from Atlas [260]).

13.3. Treatment

Recommendation 64

PwCF with osteopenia or osteoporosis should have nutritional intervention to achieve normal weight gain and growth in children and an optimal body weight in adults, including adequate intake of calcium-rich foods and a balanced fatty acid diet. Provision of supplemental calcium, vitamin D, and vitamin K may be necessary.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

We recommend treatment by provision of adequate calcium, vitamin D, and vitamin K [269,273,279]. Interestingly, emerging studies in the non-CF population suggest a window of improved benefit of calcium supplementation. In a systemic review and meta-analysis by Liu et al., 2022 evidence suggests that supplemental calcium can support bone health, in those <35 years, and specifically in ages 20–35 and 'that the improvement of bone at femoral neck was more pronounced in the peri peak bone mass population (20–35 years) than the pre peak bone mass population (<20 years) [280]. Supplemental treatments for calcium and vitamins D and K have been discussed previously in the individual sections.

13.4. Anti-osteoporotic agents

Recommendation 65

Clinicians should carefully weigh benefits (improved BMD) versus risks (bone pain, associated malaise) when making decisions about use of bisphosphonates in pwCF for prevention or treatment of low bone mineral density. In children with low BMD, bisphosphonates can support improvement in BMD z-scores and may be a consideration to support BMD health in later years.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

While we do not make absolute recommendations of bisphosphonate treatment for pwCF with or at risk of low BMD, we recognize that some patients will benefit. An endocrinology consultation could be useful in the decision making. In children, oral bisphosphonates did not confirm a benefit for fracture risk, but did improve lumbar spine BMD, with no adverse events related to muscle pain or gastrointestinal symptoms in a 12-month study [281]. Longer term studies in children are required (considering preventative possibility) to assess outcome measures on bone health later in life, when lower BMD may be more prevalent. In adults, several intervention studies with both IV and oral bisphosphonates supported improved BMD with some studies also reported some and others no change in fracture risk, after 12–24 months of treatment. In lung transplant patients, bisphosphonates have been shown to improve BMD after 12–24 months of treatment, with one study showing some improvement while another no change in fracture risk [281,282]. Assessment of bone health before and after transplant would be suggested in this more vulnerable population, given the potential impact on bone health by required medications post-transplant. Bone pain has been reported with use of IV bisphosphonates, and less often with oral bisphosphonates, and may affect tolerance of treatment and quality of life [281,283]. Newer therapies to support bone health (monoclonal antibodies, anabolic one therapies) require further investigation before they can be recommended [279].

Finally, low-dose estrogen supplementation in premenopausal women with CF was associated with lower BMD although a causative effect of the intake of contraceptive pills cannot be ascertained. One recent study did report an improvement in BMD in adult women with CF < 21 years who were on low-dose estrogen therapy, but no benefit after this age was found [284]. Future studies are required on the benefit (if any) of low-dose estrogen supplementation in CF, including the optimal formulation, route of administration, timing and dose to accrue and preserve bone mass in premenopausal women with CF [285].

14. Cystic fibrosis related diabetes

Recommendation 66

All pwCF should have annual screening for CFRD from the age of ten years.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 67

In case of unexplained clinical decline or development of liver disease before the age of 10, screening for abnormal glucose tolerance should be performed.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 68

Patients with CFRD or abnormal glucose tolerance should be assessed on an individual basis and given appropriate dietary advice, education and medical treatment based upon clinical and nutritional status.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 69

Patients should be educated about the relationship between carbohydrates and insulin. Information about the use of carbohydrate counting, glycemic index and glycemic load of meals should be individualized.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 70

Patients with CFRD should regularly be seen by a specialized team with expertise in diabetes and CF. Healthcare professionals should support patients with CFRD or abnormal glucose tolerance to meet their nutritional requirements and optimise their glycaemic control.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 71

PwCF with impaired glucose tolerance or CFRD should have an annual diabetes review to screen for diabetes related complications.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

CFRD is an established complication in CF in parallel with the increasing life expectancy [286–289]. CFRD is linked to an increased morbidity and mortality [287,290]. Research has shown associations between CFRD or abnormalities in glucose metabolism and a worse pulmonary function and nutritional status [287,291–294]. Higher blood glucose levels promote bacterial colonization in the lungs [295]. However, this negative association is not always confirmed by other studies [145,296–298].

The pathogenesis of CFRD is complex and eventually the end stage of progressive damage of the β-cells [299]. Other factors such as insulin resistance, genetic propensity for diabetes type 2, PI and CFTR-defect play a role in the pathogenesis [290,299–301]. Some suggest also glucose abnormalities in PS patients [302]. Before the diagnosis of diabetes several stages of abnormal glucose tolerance are present [303]. A few studies have already shown a worsening of the clinical status before the actual diagnosis of diabetes [287,304]. This resulted in recommending screening for glucose abnormalities in CF by the use of an oral glucose tolerance test (OGTT). Other methods, such as HbA1c and continuous glucose monitoring, have been studied as an alternative for an OGTT [305–311]. Patients report abnormal continuous glucose monitoring profiles despite a normal OGTT on 2-h. Therefore, it is suggested to measure glucose peak at 1 h during an OGTT. Indeterminate glycemia is associated to a worse pulmonary function and nutritional status [291,292,294,312]. An OGTT is often reported as cumbersome for patient and staff [313]. However, screening for glucose abnormalities is of relevance for patients' outcome [314]. Therefore, we can suggest that different screening methods can be used in parallel. For instance, after an OGTT a continuous glucose monitoring can be used to screen for glucose abnormalities in real life.

Several possible risk factors are discussed in the literature [286,290,293,297,303,312,315–317]. It is suggested that height is a more sensitive nutritional parameter than the use of BMI in predicting the presence of abnormal glucose tolerance [297]. Measuring body composition can also be more sensitive compared to BMI as there is a link between insulin secretion and FFM [318]. Nutritional status between five to ten years can be predictive for CFRD in adolescence [293].

Due to the different stages of abnormal glucose tolerance several therapies are suggested [319–323]. Based on the current evidence, insulin may not always be the preferred therapy [322] to manage the different stages of glucose abnormalities seen in pwCF and consideration should be given to dietary modification and other available anti-diabetic agents. However, in the presence of clearly insufficient insulin secretion, insulin is the recommended therapy.

Medical nutrition therapy is one of the corner stones in the management of diabetes. To reduce postprandial glucose excursion and glucose exposure, counting carbohydrates is advised. In CF, the methodology of fixed insulin doses versus flexible insulin doses is inconclusive. The awareness of carbohydrates in the food, is of importance. The used method can differ from center to center [324,325]. There is no evidence concerning the balance between different macronutrients [326]. We suggest to advise a well-balanced diet according to the nutritional needs of the patient with a low glycemic load and glycemic index meals to reduce glucose fluctuations [327].

As part of the nutritional management therapy, we suggest that attention is paid to the intake of pancreatic enzymes replacement therapy. An optimal digestion of macronutrients can play a role in the incretin hormone response and thus postprandial glycemia [113]. Insulin therapy and nutritional therapy differs between CFRD and diabetes type 1. Patients with CFRD have a higher carbohydrate intake and lower insulin need compared to patients with diabetes type 1. Both groups are more aware of carbohydrates in foods and can show avoiding behavior [328].

Physical activity is the second corner-stone of the diabetes management. We suggest to increase physical activity to improve insulin sensitivity. This can improve glycemic control and reduce the amount of required insulin [329]. PwCF with an abnormal glucose tolerance have an increased risk for hypoglycemia. This risk is not only increased when on insulin therapy. A reactive hypoglycemia is also reported after OGTT and can occur on specific moments. We suggest to discuss strategies to prevent or manage hypoglycemia [330].

15. CF-associated liver disease

Recommendation 72

PwCF with cirrhosis and/or portal hypertension are at risk of malnutrition and should receive a thorough nutritional assessment every six months by a dietician experienced in CF in order to identify and/or prevent specific nutritional deficiencies and plan appropriate personalized interventions.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 73

Enteral nasogastric feeding should be considered in pwCF with established malnutrition and in those with anorexia to ensure adequate caloric intake when awaiting a liver transplant. MCT supplementation may result in better intestinal absorption.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 74

Percutaneous endoscopic gastrostomy insertion should be avoided in patients with oesophageal varices and/or portal gastropathy for the risk of gastric hemorrhage.

Grade of recommendation GPP - Strong consensus 100 % agreement

Recommendation 75

The use of potentially hepatotoxic drugs should be avoided/limited in pwCF with advanced liver disease, including CFTR modulators. In addition, all pwCF should be screened for alcohol use (followed by educational intervention), and referred for treatment in cases of excessive use particularly for those with liver dysfunction of any severity.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

Optimal nutrition is crucial for pwCF with cirrhosis and/or portal hypertension, which should be considered highly catabolic conditions. The pathogenesis of malnutrition is multifactorial in these patients with potential of multiple nutritional deficiencies. Fat malabsorption in cirrhotic patients may be aggravated by cholestasis, in addition to underlying PI that should be corrected by adequate doses of pancreatic enzymes to allow optimal absorption of long-chain fatty acids and EFA. Regardless of the presence of cholestasis, fat-soluble vitamins need to be monitored, replaced, and supplemented at large doses as needed [331].

Accordingly, pwCF and advanced liver disease should receive a comprehensive nutritional assessment every six months by a dietician experienced in CF in order to identify and/or prevent specific nutritional deficiencies and plan appropriate personalized interventions.

Increasing energy intake may be required (up to 150 % estimated average requirement), by increasing the proportion of fat (40–50 % of the energy intake), with special attention to PUFA and supplementation with MCT. The optimal proportion of total lipids as MCTs for nutritional management is estimated between 30 and 50 %. Much higher MCT content in the diet (i.e. >80 %) without adequate supplementation of PUFA should be avoided, since this may lead to a deficiency in EFA. Although MCT (C-8 to C-12 fatty acids) have a lower energy content (about 16 % lower than long-chain triglycerides (LCT)), they are used as a lipid supplement (MCT-enriched formula) as their shorter chains allow their passive spreading through the gastrointestinal tract bound to albumin and their direct absorption into the portal circulation. In fact, unlike LCTs, MCTs do not require micellar solubilization and re-esterification, because they completely bypass the lymphatic system, with approximately 95 % bioavailability, even in cases with severe cholestasis. Unless the levels of MCT exceed the metabolic capacity of the liver, they undergo liver metabolism, with energy release. However, MCTs may reduce appetite, probably due to interaction with the peptides YY and cholecystokinin, with possible interference with the metabolism of adipose tissue [332].

Protein intake should be adequate in relation to age and limited only in cases of liver failure to avoid encephalopathy. In case of severe liver disease, limitation of salt supplementation is also recommended to reduce its possible effects on ascites.

Enteral nasogastric feeding should be considered in pwCF with established malnutrition and in those with anorexia to ensure adequate caloric intake when awaiting a liver transplant. MCT supplementation may result in better intestinal absorption.

Rarely, PN may be necessary in cases of severe malnutrition, oral aversion, or anorexia secondary to organomegaly.

As insulin deficiency and diabetes is common in pwCF, supplemental EN via nasogastric or gastrostomy tube feeding may favor the uptake of calories from fat rather than from carbohydrates.

The decision to use gastrostomy or nasogastric feeds, usually given overnight, should not be delayed once it is seriously proposed, because clinical experience has indicated that patients who benefit most are those whose nutritional deficits are relatively mild, while the results are usually disappointing when wasting is advanced. The technique of choice is percutaneous endoscopic gastrostomy (PEG), and overnight feeding up to a maximum volume of 1000 mL in adults is generally well tolerated. The aim is to provide about 50 % of the daily calorie requirements [123].

However, PEG insertion is rarely performed in patients with esophageal varices and/or portal gastropathy for the risk of gastric hemorrhage. PEG constitutes a de novo portosystemic shunt and severe peristomal varices can develop. In addition to the potential of causing severe and intractable bleeding, these could become a major obstacle for future liver transplantation (LvT) [333]. Although reports on this issue in current literature are scarce, the use of abdominal ultrasound has been suggested to provide an adjuvant tool for percutaneous endoscopic gastrostomy insertion [334].

Finally, the issue of avoiding or at least limiting the use of potentially hepatotoxic drugs or substances in pwCF with advanced liver disease (including CFTR modulators) should include also screening for alcohol use in all pwCF.

Although the specific risks related to alcohol consumption on the liver of pwCF are poorly defined, a recent survey on alcohol consumption patterns in 952 pwCF in the US gave alarming results [335]. Of the respondents, 77 % (n = 729) of included pwCF currently consumed alcohol, and excessive alcohol use occurred at a much higher proportion of 54 % (n = 391), compared to 31 % in the general population. Of the pwCF excessively consuming alcohol 30 % reported to have experienced symptoms of harmful alcohol use. Remarkably, a substantial percentage of pwCF who met the criteria for excessive alcohol use also had medical co-morbidities, including diabetes (32 %) and CFLD (10 %) despite the well-known alcohol hepatotoxicity.

Consequently, screening for alcohol use and for its excessive use is recommended in the whole CF population. In addition, there is an essential need for educational interventions, and referral for treatment in cases of excessive use, particularly for those pwCF with liver dysfunction of any severity.

16. Probiotics

Statement 10

There is no evidence to support the long-term use (i.e., four to six months) of probiotics to improve FEV1% or anthropometrics in pwCF

Strong consensus 100 % agreement

Statement 11

There is no evidence to support the chronic use of synbiotics to improve QoL, FEV1% and anthropometrics in pwCF.

Strong consensus 100 % agreement

Recommendation 76

Probiotics may not be used to improve FEV1 or nutritional status.

Grade of recommendation 0 - Strong consensus 100 % agreement

Commentary

CF is associated with an early state of chronic dysbiosis which might accentuate gastrointestinal problems observed in pwCF [336,337]. Many treatments such as recurrent or chronic antibiotics use and the high-fat high-energy poor-quality diet further accentuate the dysbiosis [338]. Patients often take probiotics/synbiotics on their own account [339,340] without a medical advice.

Since the previous published guidelines [8], the seven studies [341–347] looking at clinical improvements from the use of

probiotics or symbiotic on respiratory or nutritional outcomes in pwCF were not able to confirm previously reported trends. No effects of probiotics/synbiotics were observed on nutritional status [342–344,347] and pulmonary function [341,342,344,347] as well as on quality of life [346]. The results on gastrointestinal complaints/health were conflicting but none of the studies [342,347] used the recently developed CFAbd-score to capture more specifically the gastrointestinal problems encountered in CF [348]. There was no impact on days of antibiotic treatment or hospitalizations from the use of probiotics [341,347] as well as in pulmonary exacerbations. Although the Di Nardo study [341] showed an improvement in pulmonary exacerbations between the intervention and the placebo group, the two groups did not differ statistically in the mean number and duration of hospitalizations per pulmonary exacerbation at the end of the study. Two studies [341,347] did not demonstrate a significant change in fecal calprotectin levels after the use of probiotics compared to the placebo groups in two studies, in contrast of the studies of Bruzzeze et al. and Del Campo et al. [342,345]. The study of Bruzzeze et al. [345] demonstrated a significant decrease in calprotectin levels in the probiotic group whereas the placebo group had a non-significant decrease. In the Delcampo et al. study [342] also a significant reduction in calprotectin levels was shown in patients using probiotics, however the median calprotectin was normal in both groups and no patient had a calprotectin above 100 μg/g.

In conclusion, the quality of the evidence remains low. It is currently not possible to advise probiotic or symbiotic use with the purpose of improving clinical CF outcomes despite the fact that many pwCF take them without a medical advice. Furthermore, caution must be taken to avoid problems with adherence when increasing therapy burden with treatments that didn't prove a beneficial effect [349].

17. Nutrition and CFTR modulator therapy

Recommendation 77

Appropriate dietary counselling should be provided for pwCF starting on CFTR modulator therapy, this should include advice about limiting and managing weight gain

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 78

The nutritional status and dietary intake of pwCF on CFTR modulator therapy including salt intake and fat-soluble vitamin status should continue to be regularly reviewed and modifications recommended according to changes observed

Grade of recommendation B - Strong consensus 100 % agreement

Commentary

CFTR modulator therapy has caused a paradigm shift in CF. Treatment is now directed to the basic defect of CF and there has been a major improvement in the nutritional status of pwCF. Improved pulmonary function, demonstrated by increase in the percentage predicted FEV1 has been observed in pwCF taking Ivacaftor [350], lumacaftor-ivacaftor [351] tezacaftor-ivacaftor [351] and elexacaftor-tezacaftor-ivacaftor (ETI) [352–356].

The effect of CFTR modulators upon body weight and BMI varies according to the genetic mutation of the pwCF and the type of CFTR modulator [357]. Improved weight gain and BMI has been observed in pwCF treated with Ivacaftor [350,358–360], lumacaftor-ivacaftor [351], tezacaftor-ivacaftor [351] and ETI [352–354]. The most significant increases in body weight and BMI have been observed in individuals on ETI compared to those receiving a dual combination therapy or placebo [352,354]. Appropriate dietary counselling should be provided prior to starting CFTR modulators, this should include discussions about possible weight gain and exploration of any potential concerns regarding body image. Healthcare professional need to be aware of patient's own perception of their weight and interventions should focus on improving health and lifestyle rather than just weight. Individualized advice should be provided and regular nutritional reviews should continue as part of standard CF care.

Significant increases in the prevalence of overweight and obesity have recently been observed in patients on ETI, changes from baseline to follow-up showed increase in overweight from 19.4 % to 31.3 % and obesity from 7.5 % to 9.7 % [361].

The mechanisms for changes in body weight on CFTR modulator treatment has not been fully established. A reduction in resting energy expenditure has been reported in patients on Ivacaftor [362]. Improvements in pulmonary function and fewer pulmonary exacerbations may reduce catabolic impact which in turn could reduce energy requirements [360]. In addition, CFTR modulation has been shown to improve the proximal small intestinal pH profile in patients with the G551D CFTR mutation and this improvement was associated with a clinically relevant, contemporaneous weight gain [363]. Further research within this area is required to help inform nutritional management decisions.

CFTR modulator therapy has been shown to alter plasma fat-soluble vitamin levels, therefore routine monitoring of fat-soluble vitamin following the introduction of CFTR modulator therapy is required [364,365]. CFTRm have been suggested to lower the risk of fat-soluble vitamin deficiency in pwCF and reports have emerged of hypervitaminosis [364,366,367]. Of particular concern is the case report of hypervitaminosis A with fulminant secondary intracranial hypertension following Elexacaftor/Tezacaftor/Ivacaftor initiation in a preadolescent with cystic fibrosis [366].

There is limited data with regard to the effects of CFTR modulators upon body composition. Stallings et al., 2018 demonstrated increases in FM and FFM after three months of Ivacaftor treatment. King et al. (2020) showed small increases in weight and FFM in the first month of ivacaftor treatment, however by six months the weight gain observed was mainly associated with increases in FM and these changes were then found to plateau by 2.5 years [360]. The effects of ETI upon body composition are yet to be determined. Further studies are therefore required to establish the effects of the different CFTR modulators upon body composition and the significance of this in the long-term.

Recommendation 79

Gastrointestinal symptoms should be closely monitored following the initiation of CFTR modulator therapy and this should continue as part of routine CF care

Grade of recommendation B - Strong consensus 100 % agreement

Commentary

Improvements in gastrointestinal symptoms have been shown after commencing ETI [368]. Intestinal inflammation may be reduced by the effects of CFTR modulator therapy upon the abnormal pathophysiology and microbiota in the CF gastrointestinal tract [369]. Changes in intestinal inflammation have been observed after commencing Lumacaftor-ivacaftor, this may evolve independently of respiratory function [370]. Consideration should be given to the use of fecal calprotectin levels in evaluating the effects of CFTR modulator therapy [370].

In young children with CF, aged 12–24 months, a mean absolute change in fecal elastase of +164 μg/g was observed after 24 weeks of ivacaftor therapy, with six of the nine subjects who had a low FE at baseline (<50 μg/g) showing improvements to >200 μg/g at week 24 [133]. No change in FE was observed in pwCF, aged from 5 to 61year, between baseline and three months of ivacaftor treatment [362]. However, the study did demonstrate a significant change in the co-efficient of fat absorption which positively correlated with change in FEV1 in PI patients [362]. The impact of CFTR modulator therapy on pancreatic function is likely to be influenced by the age they are started.

Recommendation 80

In view of the fact that CFTR modulators may improve beta cell function and insulin secretion, blood glucose levels should be monitored regularly to avoid hypoglycemia when assuming the same insulin dose prescribed before starting modulators.

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 81

PwCF on CFTR modulator therapy should have their blood pressure routinely monitored three months after commencing therapy and at least annually and appropriate medical management started if clinically indicated.

Grade of recommendation B - Strong consensus 92 % agreement

Recommendation 82

PwCF on CFTR modulator therapy may have their lipid profiles checked annually and appropriate dietary advice and medical management should be given if required.

Grade of recommendation GPP - Strong consensus 92 % agreement

Commentary

Variable effects of CFTR modulators on cardiometabolic parameters, including changes in blood pressure and in glycemic and plasma lipid profiles, have been reported and deserve consideration.

The effects on blood pressure were consistently observed and ranged from mild elevation to clinically significant hypertensive emergency described almost exclusively for lumacaftor-ivacaftor [371].

Information on the cardiometabolic effects of ETI were recently explored in a single-center, observational, retrospective analysis of 134 adults with CF after one year of treatment [361]. A few of these changes were conventionally considered favorable to cardiometabolic health, such as the decrease in random blood glucose and hemoglobin A1c (in patients without CFRD) and the increase in HDL-cholesterol (in patients with CFRD). However, unfavorable effects were also documented including modest increase in systolic and diastolic blood pressure (in the full cohort), and an increase in total cholesterol and LDL-cholesterol (in patients with CFRD). Although the increases in blood pressure may be partially related to increases in body weight (which was consistently observed even in this real-world setting), it is also possible that reduced salt losses in the setting of CFTR modulator therapy contribute to the modest increase in blood pressure observed. The legacy CF diet encourages salt, closer attention to sodium intakes may therefore be warranted in the context of emerging hypertension. These data indicate that pwCF on ETI may be at risk of developing hyperlipidemia and hypertension and should be appropriately monitored.

There is preliminary evidence that highly efficacy CFTR modulators may have not only direct benefits on pulmonary function and nutritional status, but also indirect benefits by improving glycemia [372] and by reducing diabetes-related complications and morbidity with time. Although the consistency and the pathophysiological mechanism of this improvement require further investigation, these findings support the hypothesis that CFTR may have a direct role in β-cell function. It is also possible that the observed effects may relate to reduced systemic inflammation induced by ETI.

In addition, data from CF Registries suggest favorable trends in the prevalence of CFRD in pwCF on Ivacaftor monotherapy for over 5 years as compared to an untreated comparator cohort [373]. Further studies are needed to investigate the mechanism and the long-term impact of ETI on dysglycemia and progression to CFRD.

18. Transplantation

18.1. Lung transplantation

Recommendation 83

Prior to lung transplantation (LT) nutritional status should be optimized for all patients with particular care for severely malnourished patients.

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 84

Prior to lung transplantation special attention should be given to optimize bone health using available treatments on a case-by-case evaluation.

Grade of recommendation B - Strong consensus 100 % agreement

Recommendation 85

Post transplant, nutritional support should aim at early BMI recovery (i.e., BMI to ≥18.5 kg/m^2).

Grade of recommendation B - Strong consensus 100 % agreement

Commentary

Despite improved treatments and survival in CF, LT remains the cornerstone therapy for patients with end-stage lung disease. The lung allocation score (LAS) has been used to prioritize access to transplantation in pwCF [374]. Although several updates to LAS system have been made [375], specific patients' characteristics such as underweight or severe malnutrition have been considered as relative contraindications for LT. Indeed, listing for LT seems to be less likely for severe malnourished patients (BMI ≤17 kg/m^2) leading to a higher death risk without listing [376]. It is therefore important to improve their nutritional status with all means available to assure their listing.

Poor final height has been associated with higher mortality risk in transplant candidates waiting for LT ([377]. This stresses further the importance of height assessment and interventions aiming at an improved growth during childhood. Moreover, in the Swiss LT centers (validation cohort 2008–2017) for CF adults listed for LT, deterioration on the waiting list was associated with the frailty index, which included BMI as one of the 66 extra-pulmonary-age-associated deficits for increasing adverse event vulnerability [378].

Seeking or maintaining an adequate nutritional status before transplantation is considered good clinical practice. Of note, a pre-transplant BMI below 18.5 kg/m^2 was more prevalent in patients who died on the waiting list [195], while their risk of dying within

90 days post-transplant was increased [379]. In addition, in adults with CF listed for LT in the Toronto LT Program (development cohort 2005–2015), frailty index was positively associated with post-transplant mortality [378]. However, several studies have failed to reveal a significant negative effect of underweight (i.e., BMI<18.5 kg/m^2) in patients' post LT survival [380–383]. As a low BMI is associated with increased mortality risk [384], current LT guidelines include a low BMI (<18 kg/m^2 in adults and <5th percentile in children) as additional factor for referral to a transplant center [385].

During the last decade, the prevalence of overweight and obesity in pwCF is increasing as a result of the adherence to the high-fat diet, reduced exercise tolerance, therapeutic advances, and general population trend [386]. Although an increased BMI may be favorable in pwCF in terms of better pulmonary function and survival, pre-transplant overweight (i.e., BMI >25 kg/m^2) has been associated with a lower survival post-LT [380]. This observation is not completely confirmed, as registry CF data in pediatrics do not support a significant negative effect of overweight on survival in CF children after LT [382].

LT has a positive impact on the BMI and FFMI [195,387–389], probably as a result of decreased resting energy expenditure [388–390]. Furthermore, BMI recovery (i.e., BMI to $\geq$ 18.5 kg/m^2) or BMI increase (i.e., +1.9 kg/m^2) 1-year post-LT might be associated with better survival, especially in severely malnourished patients [380,383]. Nutritional support should therefore aim at maximal BMI recovery post LT.

Special attention should be given to bone health in LT recipients. The majority of patients have reduced bone mineral density and suboptimal vitamin K and calcium levels status pre and post-transplantation [269]. Moreover, rates of vitamin D deficiency reach 33 % and 71 % using cut-off values for serum 25-OH-Vitamin D of <50 nmol/L and <75 nmol/L, respectively [391]. 30 % have already osteopenia and hypovitaminosis D [269,391,392]. Available treatments (adequate nutrition, weight-bearing exercise, supplementation of calcium, vitamin D, vitamin K, bisphosphonates) should be offered on a case-by-case evaluation. However, no improvement in bone health is expected after transplantation with a risk of further deterioration [391,392].

18.2. Liver-transplantation

Recommendation 86

Prior to LvT nutritional status should be optimized for all patients with particular care for severely malnourished patients.

Grade of recommendation GPP - Strong consensus 100 % agreement

Commentary

CFLD is considered as the third largest cause of mortality in pwCF [393]. LvT can be a life-saving procedure for patients with CFLD especially to those with complications such as portal hypertension or cirrhosis [394].

Nutritional status has an impact in patients waiting for LvT. Indeed, growth failure has been linked with higher mortality risk on the LvT waiting list [395], while it could also have a negative effect on post-LvT survival [395]. This highlights the fundamental role of nutritional support in children and adults with CFLD, waiting for or undergoing LvT.

LvT does probably not improve the nutritional status in pwCF [394,396,397]. In adults the BMI was preserved at one and five years post LvT, [396]. Whereas in children, case series described conflicting results [394,396,397].

CF-related low BMD has been well-documented in both adults and children with CF [398]. The etiology is multifactorial but primarily it is related to imbalanced bone deposition and resorption. LvT might have a positive impact on BMD after LvT compared to non-transplanted patients [394], as a result of restoration of bile flow allowing better absorption of nutrients, improvement of protein anabolism, and increase in physical activity because of better quality of life [246,247].

18.3. Multiple organ transplant

Since literature of combined organ transplants (liver-pancreas, liver-lung) is limited to case reports or small case series, it is impossible to make evidence-based recommendations.

19. Conclusion

Nutrition remains a vital part of the lives of pwCF. Good nutritional management of pwCF has been one of the major causes of the increased survival. Nutritional advances in CF care including the effects of modulator therapies on nutrition are outlined in this updated guideline.

Funding statement

This guideline was solely financed by ESPEN, the European Society for Clinical Nutrition and Metabolism.

Disclaimer

This guideline has been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using this guideline shall do so only after consultation with a health professional and shall not mistake this guideline as professional medical advice. This guideline must not substitute seeking professional medical and health advice from a health professional.

This guideline may not apply to all situations and should be interpreted in the light of specific clinical situations and resource availability. It is up to every clinician to adapt this guideline to local regulations and to each patient's individual circumstances and needs. The information in this guideline shall not be relied upon as being complete, current or accurate, nor shall it be considered as inclusive of all proper treatments or methods of care or as a legal standard of care.

ESPEN makes no warranty, express or implied, in respect of this guideline and cannot be held liable for any damages resulting from the application of this guideline, in particular for any loss or damage (whether direct or indirect) resulting from a treatment based on the guidance given herein.

ESPEN shall not be held liable to the utmost extent permissible according to the applicable laws for any content available on such external websites, which can be accessed by using the links included herein.

Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors

(ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict of interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.12.017.

References

[1] Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis. Nutr Clin Pract 2013;28:676–83.
[2] FitzSimmons SC. The changing epidemiology of cystic fibrosis. J Pediatr 1993;122:1–9.
[3] Southern KW, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros 2007;6:57–65.
[4] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008;7:450–3.
[5] Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis. Am J Respir Crit Care Med 2011;183:1463–71.
[6] Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis 2014;46:865–74.
[7] Bischoff SC, Singer P, Koller M, Barazzoni R, Cederholm T, van Gossum A. Standard operating procedures for ESPEN guidelines and consensus papers. Clin Nutr 2015;34:1043–51.
[8] Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr 2016;35:557–77.
[9] Scottish Intercollegiate Guidelines Network (SIGN). Revised version. In: Sign 50: a guideline developer's handbook. Edinburgh: SIGN; 2014.
[10] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Ständige Kommission Leitlinien. AWMF-regelwerk. 2012. https://www.awmf.org/fileadmin/user_upload/Leitlinien/AWMF-Regelwerk/AWMF-Regelwerk.pdf.
[11] Usatin D, Yen EH, McDonald C, Asfour F, Pohl J, Robson J. Differences between WHO AND CDC early growth measurements in the assessment of Cystic Fibrosis clinical outcomes. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16:503–9.
[12] Alvarez JA, Ziegler TR, Millson EC, Stecenko AA. Body composition and lung function in cystic fibrosis and their association with adiposity and normal-weight obesity. Nutrition 2016;32:447–52.
[13] Hak SF, Arets HGM, van der Ent CK, van der Kamp HJ. Rapid early increase in BMI is associated with impaired longitudinal growth in children with cystic fibrosis. Pediatr Pulmonol 2019;54:1209–15.
[14] Woestenenk JW, Gulmans VA, van der Ent CK, Houwen RH. Height assessment in the Dutch-origin pediatric cystic fibrosis population. Nutr Clin Pract 2017;32:130–2.
[15] Machogu E, Cao Y, Miller T, Simpson P, Levy H, Quintero D, et al. Comparison of WHO and CDC growth charts in predicting pulmonary outcomes in cystic fibrosis. J Pediatr Gastroenterol Nutr 2015;60:378–83.
[16] Zhang Z, Shoff SM, Lai HJ. Comparing the use of centers for disease control and prevention and world health organization growth charts in children with cystic fibrosis through 2 Years of age. J Pediatr 2015;167:1089–95.
[17] Poulimeneas D, Grammatikopoulou MG, Petrocheilou A, Kaditis AG, Troupi E, Doudounakis SE, et al. Comparison of international growth standards for assessing nutritional status in cystic fibrosis: the GreeCF study. J Pediatr Gastroenterol Nutr 2020;71:e35–9.
[18] Schönenberger KA, Reber E, Bally L, Geiser T, Lin D, Stanga Z. Nutritional assessment in adults with cystic fibrosis. Nutrition 2019;67.
[19] Bellini SG, Chapman P, Szendre K, McDonald C, Williams N, Hopkin L, et al. Changes in handgrip strength in children with cystic fibrosis compared to children without cystic fibrosis. Clin Nutr ESPEN 2021;42:206–11.
[20] Bouma SF, Iwanicki C, McCaffery H, Nasr SZ. The association of grip strength, body mass index, and lung function in youth with cystic fibrosis. In: Nutrition in clinical practice : official publication of the American society for parenteral and enteral nutrition, vol. 35; 2020. p. 1110–8.
[21] Contreras-Bolivar V, Olveira C, Ruiz-Garcia I, Porras N, Garcia-Olivares M, Sanchez-Torralvo FJ, et al. Handgrip strength: associations with clinical variables, body composition, and bone mineral density in adults with cystic fibrosis. Nutrients 2021;13:4107.
[22] Gibson HT, McDonald CM, Derrick JW, Eggett DL, Bellini SG. Evaluating changes in handgrip strength in children with cystic fibrosis: a pilot study. Nutr Clin Pract 2018;33:261–7.
[23] Papalexopoulou N, Dassios TG, Lunt A, Bartlett F, Perrin F, Bossley CJ, et al. Nutritional status and pulmonary outcome in children and young people with cystic fibrosis. Respir Med 2018;142:60–5.
[24] Souza RP, Donadio MVF, Heinzmann-Filho JP, Baptista RR, Pinto LA, Epifanio M, et al. The use of ultrasonography to evaluate muscle thickness and subcutaneous fat in children and adolescents with cystic fibrosis. Rev Paul Pediatr 2018;36:457–65.
[25] Alicandro G, Battezzati A, Bianchi ML, Loi S, Speziali C, Bisogno A, et al. Estimating body composition from skinfold thicknesses and bioelectrical impedance analysis in cystic fibrosis patients. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2015;14:784–91.
[26] Calella P, Valerio G, Thomas M, McCabe H, Taylor J, Brodlie M, et al. Association between body composition and pulmonary function in children and young people with cystic fibrosis. Nutrition 2018;48:73–6.
[27] Charatsi AM, Dusser P, Freund R, Maruani G, Rossin H, Boulier A, et al. Bioelectrical impedance in young patients with cystic fibrosis: validation of a specific equation and clinical relevance. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:825–33.
[28] Hauschild DB, Barbosa E, Moreira EA, Neto LL, Platt VB, Filho EP, et al. Nutrition status parameters and hydration status by bioelectrical impedance vector analysis were associated with lung function impairment in children and adolescents with cystic fibrosis. In: Nutrition in clinical practice : official publication of the American society for parenteral and enteral nutrition, vol. 31; 2016. p. 378–86.
[29] Hollander-Kraaijeveld FM, Lindeman Y, de Roos NM, Burghard M, van de Graaf EA, Heijerman HGM. Non-fasting bioelectrical impedance analysis in cystic fibrosis: implications for clinical practice and research. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:153–8.
[30] Bravo MP, Balboa P, Torrejon C, Bozzo R, Boza ML, Contreras I, et al. Bone mineral density, lung function, vitamin D and body composition in children and adolescents with cystic fibrosis: a multicenter study. Nutr Hosp 2018;35:789–95.
[31] Bellissimo MP, Zhang I, Ivie EA, Tran PH, Tangpricha V, Hunt WR, et al. Visceral adipose tissue is associated with poor diet quality and higher fasting glucose in adults with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:430–5.
[32] Chaves CR, Cunha AL, Costa AC, Costa Rde S, Lacerda SV. Nutritional status and body fat distribution in children and adolescentes with Cystic Fibrosis. Ciência Saúde Coletiva 2015;20:3319–28.
[33] Contreras-Bolivar V, Olveira C, Porras N, Garcia-Olivares M, Giron MV, Sanchez-Torralvo FJ, et al. Assessment of body composition in cystic fibrosis: agreement between skinfold measurement and densitometry. Nutr Hosp 2022;39:376–82.
[34] Owen E, Williams JE, Davies G, Wallis C, Grant RL, Fewtrell MS. Growth, body composition, and lung function in prepubertal children with cystic fibrosis diagnosed by newborn screening. Nutr Clin Pract 2021;36:1240–6.
[35] Hulst JM, Huysentruyt K, Gerasimidis K, Shamir R, Koletzko B, Chourdakis M, et al. A practical approach to identifying pediatric disease-associated undernutrition: a position statement from the ESPGHAN special interest group on clinical malnutrition. J Pediatr Gastroenterol Nutr 2022;74:693–705.
[36] Calella P, Valerio G, Brodlie M, Taylor J, Donini LM, Siervo M. Tools and methods used for the assessment of body composition in patients with cystic fibrosis: a systematic review. Nutr Clin Pract 2019;34:701–14.
[37] Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: a systematic review. Nutrition 2018;55–56:131–9.
[38] Phong RY, Taylor SL, Robinson BA, Jhawar S, Nandalike K. Utility of mid-upper arm circumference in diagnosing malnutrition in children with cystic fibrosis. Nutr Clin Pract 2020;35:1094–100.
[39] McDonald CM. Validation of a nutrition risk screening tool for children and adolescents with cystic fibrosis ages 2-20 years. J Pediatr Gastroenterol Nutr 2008;46:438–46.
[40] Souza Dos Santos Simon MI, Forte GC, da Silva Pereira J, da Fonseca Andrade Procianoy E, Drehmer M. Validation of a nutrition screening tool for pediatric patients with cystic fibrosis. J Acad Nutr Diet 2016;116:813–8.
[41] Moeeni V, Shojaee P, Kianifar H, Walls T, Pattemore P, Day AS. The prospective assessment of nutrition in children with cystic fibrosis. Int J Child Health Nutr 2015;4:129–34.
[42] Poulimeneas D, Grammatikopoulou MG, Petrocheilou A, Kaditis AG, Vassilakou T. Triage for malnutrition risk among pediatric and adolescent outpatients with cystic fibrosis, using a disease-specific tool. Children 2020;7:269.
[43] Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 2003;22:321–36.
[44] Tham A, Katz TE, Sutherland RE, Garg M, Liu V, Tong CW, et al. Micronutrient intake in children with cystic fibrosis in Sydney, Australia. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:146–52.
[45] Timmers N, Stellato RK, van der Ent CK, Houwen RHJ, Woestenenk JW. Vitamin D intake, serum 25-hydroxy vitamin D and pulmonary function in paediatric patients with cystic fibrosis: a longitudinal approach. Br J Nutr 2019;121:195–201.
[46] Woestenenk JW, Broos N, Stellato RK, Arets HG, van der Ent CK, Houwen RH. Vitamin A intake and serum retinol levels in children and adolescents with cystic fibrosis. Clin Nutr 2016;35:654–9.

[47] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018;17:153–78.
[48] Filigno SS, Robson SM, Szczesniak RD, Chamberlin LA, Baker MA, Sullivan SM, et al. Macronutrient intake in preschoolers with cystic fibrosis and the relationship between macronutrients and growth. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16:519–24.
[49] Goss CH, Sykes J, Stanojevic S, Marshall B, Petren K, Ostrenga J, et al. Comparison of nutrition and lung function outcomes in patients with cystic fibrosis living in Canada and the United States. Am J Respir Crit Care Med 2018;197:768–75.
[50] Szentpetery S, Fernandez GS, Schechter MS, Jain R, Flume PA, Fink AK. Obesity in Cystic fibrosis: prevalence, trends and associated factors data from the US cystic fibrosis foundation patient registry. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:777–83.
[51] Cystic Fibrosis Foundation Patient Registry. Annual data report. 2021. Bethesda, Maryland: Cystic Fibrosis Foundation; 2022.
[52] Ayoub F, Lascano J, Morelli G. Risk factors for hepatic steatosis in cystic fibrosis are distinct from risk factors for cystic fibrosis liver disease. Hepatology 2017;66:663A–4A.
[53] El Attar MM, Azab NM, El Dine Hamed DH, Tawfik ASA. Growth assessment in Egyptian children with cystic fibrosis: a single center study. In: Egyptian Pediatric Association Gazette, 65; 2017. p. 21–4.
[54] Bonhoure A, Boudreau V, Litvin M, Colomba J, Bergeron C, Mailhot M, et al. Overweight, obesity and significant weight gain in adult patients with cystic fibrosis association with lung function and cardiometabolic risk factors. Clin Nutr 2020;39:2910–6.
[55] Gonzalez Jimenez D, Munoz-Codoceo R, Garriga-Garcia M, Molina-Arias M, Alvarez-Beltran M, Garcia-Romero R, et al. Excess weight in patients with cystic fibrosis: is it always beneficial? Nutr Hosp 2017;34:578–83.
[56] Gobato AO, Vasques ACJ, Ribeiro AF, Yamada RM, Hessel G. Prevalence of hepatic steatosis among children and adolescents with cystic fibrosis and its association with nutritional status. Rev Paul Pediatr 2019;37:435–41.
[57] Gramegna A, Aliberti S, Contarini M, Savi D, Sotgiu G, Majo F, et al. Overweight and obesity in adults with cystic fibrosis: an Italian multicenter cohort study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:111–4.
[58] Harindhanavudhi T, Wang Q, Dunitz J, Moran A, Moheet A. Prevalence and factors associated with overweight and obesity in adults with cystic fibrosis: a single-center analysis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:139–45.
[59] Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al. A contemporary survival analysis of individuals with cystic fibrosis: a cohort study. Eur Respir J 2015;45:670–9.
[60] Sands D, Umlawska W, Zielinska A. A cross-sectional study of growth, nutritional status and body proportions in children and adolescents at a medical center specializing in the treatment of cystic fibrosis in Poland. Arch Med Sci 2015;11:155–63.
[61] Poulimeneas D, Petrocheilou A, Grammatikopoulou MG, Kaditis AG, Loukou I, Doudounakis SE, et al. High attainment of optimal nutritional and growth status observed among Greek pediatric cystic fibrosis patients: results from the GreeCF study. J Pediatr Endocrinol Metab 2017;30:1169–76.
[62] Bodnar R, Kadar L, Holics K, Ujhelyi R, Kovacs L, Bolbas K, et al. Factors influencing quality of life and disease severity in Hungarian children and young adults with cystic fibrosis. Ital J Pediatr 2014;40:50.
[63] Dhochak N, Jat KR, Sankar J, Lodha R, Kabra SK. Predictors of malnutrition in children with cystic fibrosis. Indian Pediatr 2019;56:825–30.
[64] Umławska W, Krzyzanowska M, Zielińska A. s D. Effect of selected factors associated with the clinical course of the disease on nutritional status in children with cystic fibrosis. Adv Clin Exp Med 2014;23:775–83.
[65] Tóth T, Mák E, Molnár S, Sinka M, Tóth F, Szabolcs I, et al. Nutrition status of adult patients with cystic fibrosis. New Med 2014;2014:63–6.
[66] Orenti A, Zolin A, Jung A, van Rens J, Fox A, Krasnyk M, et al. ECFSPR annual report 2020. 2022.
[67] Gaskin KJ. Nutritional care in children with cystic fibrosis: are our patients becoming better? Eur J Clin Nutr 2013;67:558–64.
[68] Centers for Disease Control and Prevention. About child & teen BMI. 2022.
[69] Ashkenazi M, Nathan N, Sarouk I, Aluma BEB, Dagan A, Bezalel Y, et al. Nutritional status in childhood as a prognostic factor in patients with cystic fibrosis. Lung 2019;197(3):371–6.
[70] Hanna RM, Weiner DJ. Overweight and obesity in patients with cystic fibrosis: a center-based analysis. Pediatr Pulmonol 2015;50:35–41.
[71] Munck A, Boulkedid R, Weiss L, Foucaud P, Wizla-Derambure N, Reix P, et al. Nutritional status in the first 2 Years of life in cystic fibrosis diagnosed by newborn screening. J Pediatr Gastroenterol Nutr 2018;67:123–30.
[72] Kilinc AA, Beser OF, Ugur EP, Cokugras FC, Cokugras H. The effects of nutritional status and intervention on pulmonary functions in pediatric cystic fibrosis patients. Pediatr Int 2021;63:316–22.
[73] Sheikh S, Zemel BS, Stallings VA, Rubenstein RC, Kelly A. Body composition and pulmonary function in cystic fibrosis. Front Ped 2014;2:33.
[74] Sanders DB, Emerson J, Ren CL, Schechter MS, Gibson RL, Morgan W, et al. Early childhood risk factors for decreased FEV1 at age six to seven years in young children with cystic fibrosis. Ann Am Thorac Soc 2015;12:1170–6.
[75] Sanders DB, Zhang Z, Farrell PM, Lai HJ, Wisconsin CFNSG. Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2018;17:528–35.
[76] Marks MP, Heltshe SL, Baines A, Ramsey BW, Hoffman LR, Stalvey MS. Most short children with cystic fibrosis do not catch up by adulthood. Nutrients 2021;13.
[77] Zysman-Colman ZN, Kilberg MJ, Harrison VS, Chesi A, Grant SFA, Mitchell J, et al. Genetic potential and height velocity during childhood and adolescence do not fully account for shorter stature in cystic fibrosis. Pediatr Res 2021;89:653–9.
[78] Martins JP, Forte GC, Simon M, Epifanio M, Pinto LA, Marostica PJC. The role of neonatal screening in nutritional evolution in the first 12 months after diagnosis of cystic fibrosis. Rev Assoc Med Bras 2018;64:1032–7. 1992.
[79] Papachristou E, Katsagoni CN, Roussou X, Tokou I, Moustaki M, Petrocheilou A, et al. Dietary intake, weight status, pulmonary function and metabolic profile in children with cystic fibrosis with or without pancreatic sufficiency. Nutrition 2023:112091.
[80] Nagy R, Gede N, Ocskay K, Dobai BM, Abada A, Vereczkei Z, et al. Association of body mass index with clinical outcomes in patients with cystic fibrosis: a systematic review and meta-analysis. JAMA Netw Open 2022;5:e220740.
[81] Panagopoulou P, Fotoulaki M, Nikolaou A, Nousia-Arvanitakis S. Prevalence of malnutrition and obesity among cystic fibrosis patients. Pediatr Int 2014;56:89–94.
[82] Trang T, Chan J, Graham DY. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency in the 21(st) century. World J Gastroenterol 2014;20:11467–85.
[83] Walkowiak J, Nousia-Arvanitakis S, Cade A, Kashirskaya N, Piotrowski R, Strzykala K, et al. Fecal elastase-1 cut-off levels in the assessment of exocrine pancreatic function in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2002;1:260–4.
[84] Konstan M, Wagener J, Wilschanski M, Gangal M, Martin RS, Pennington J. Phase 3 comparison of higher-dose liprotamase, a nonporcine pancreatic enzyme replacement therapy, to pancrelipase on fat and protein absorption in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. Pediatr Pulmonol 2018;53:230.
[85] Wooldridge JL, Schaeffer D, Jacobs D, Thieroff-Ekerdt R. Long-term experience with ZENPEP in infants with exocrine pancreatic insufficiency associated with cystic fibrosis. J Pediatr Gastroenterol Nutr 2014;59:612–5.
[86] Haupt ME, Kwasny MJ, Schechter MS, McColley SA. Pancreatic enzyme replacement therapy dosing and nutritional outcomes in children with cystic fibrosis. J Pediatr 2014;164:1110–1115 e1.
[87] Hetrick EM, Sperry DC, Nguyen HK, Strege MA. Characterization of a novel cross-linked lipase: impact of cross-linking on solubility and release from drug product. Mol Pharm 2014;11:1189–200.
[88] Woestenenk JW, van der Ent CK, Houwen RH. Pancreatic enzyme replacement therapy and coefficient of fat absorption in children and adolescents with cystic fibrosis. J Pediatr Gastroenterol Nutr 2015;61:355–60.
[89] Kashirskaya N, Kapranov N, Sander-Struckmeier S, Kovalev V. Safety and efficacy of Creon® micro in children with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2015;14:275–81.
[90] Layer P, Kashirskaya N, Gubergrits N. Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency. World J Gastroenterol 2019;25:2430–41.
[91] Ng C, Major G, Smyth AR. Timing of pancreatic enzyme replacement therapy (PERT) in cystic fibrosis. Cochrane Database Syst Rev 2021;8:CD013488.
[92] Calvo-Lerma J, Roca M, Boon M, Colombo C, de Koning B, Fornes-Ferrer V, et al. Association between faecal pH and fat absorption in children with cystic fibrosis on a controlled diet and enzyme supplements dose. Pediatr Res 2021;89:205–10.
[93] Calvo-Lerma J, Asensio-Grau A, Heredia A, Andres A. Lessons learnt from MyCyFAPP Project: effect of cystic fibrosis factors and inherent-to-food properties on lipid digestion in foods. Food Res Int 2020;133:109198.
[94] Calvo-Lerma J, Boon M, Colombo C, de Koning B, Asseiceira I, Garriga M, et al. Clinical evaluation of an evidence-based method based on food characteristics to adjust pancreatic enzyme supplements dose in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:e33–9.
[95] Somaraju URR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2020;8:CD008227.
[96] Ng SM, Moore HS. Drug therapies for reducing gastric acidity in people with cystic fibrosis. Cochrane Database Syst Rev 2021;4:CD003424.
[97] Ng C, Major G, Smyth AR. A systematic Cochrane Review of the timing of pancreatic enzyme replacement therapy (PERT) in cystic fibrosis. Paediatr Respir Rev 2021;40:44–5.
[98] Orel R, Benninga MA, Broekaert IJ, Gottrand F, Papadopoulou A, Ribes-Koninckx C, et al. Drugs in focus: proton pump inhibitors. J Pediatr Gastroenterol Nutr 2021;72:645–53.
[99] Zazzeron L, Alicandro G, Dacco V, Lanfranchi C, Bulfamante A, Sciarrabba CS, et al. Effects of prolonged proton pump inhibitor treatment on nutritional status and respiratory infection risk in cystic fibrosis: a matched cohort study. Dig Liver Dis 2022;55:360–5.
[100] Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:675–80.
[101] Schechter M, Michel S, Liu S, Seo B, Kapoor M, Khurmi R, et al. Relationship of initial pancreatic enzyme replacement therapy dose with weight gain in infants with cystic fibrosis. J Pediatr Gastroenterol Nutr 2018;67:520–6.

[102] Calvo-Lerma J, Hulst JM, Asseiceira I, Claes I, Garriga M, Colombo C, et al. Nutritional status, nutrient intake and use of enzyme supplements in paediatric patients with Cystic Fibrosis; a European multicentre study with reference to current guidelines. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16:510–8.
[103] Calvo-Lerma J, Hulst J, Boon M, Colombo C, Masip E, Ruperto M, et al. Clinical validation of an evidence-based method to adjust Pancreatic Enzyme Replacement Therapy through a prospective interventional study in paediatric patients with Cystic Fibrosis. PLoS One 2019;14:e0213216.
[104] Calvo-Lerma J, Fornes-Ferrer V, Peinado I, Heredia A, Ribes-Koninckx C, Andres A. A first approach for an evidence-based in vitro digestion method to adjust pancreatic enzyme replacement therapy in cystic fibrosis. PLoS One 2019;14:e0212459.
[105] Gelfond D, Heltshe SL, Skalland M, Heubi JE, Kloster M, Leung DH, et al. Pancreatic enzyme replacement therapy use in infants with cystic fibrosis diagnosed by newborn screening. J Pediatr Gastroenterol Nutr 2018;66:657–63.
[106] Gao WY, Mulberg AE. Dependence of PERT endpoint on endogenous lipase activity. Pancreas 2014;43:1232–8.
[107] Heubi J, Schaeffer D, Ahrens R, Sollo N, Strausbaugh S, Graff G, et al. Safety and efficacy of a novel microbial lipase in patients with exocrine pancreatic insufficiency due to cystic fibrosis: a randomized controlled clinical trial. J Pediatr 2016;176:156–161.e1.
[108] Calvo-Lerma J, Martinez-Barona S, Masip E, Fornes V, Ribes-Koninckx C. Pancreatic enzyme replacement therapy in cystic fibrosis: dose, variability and coefficient of fat absorption. Rev Esp Enferm Dig 2017;109:684–9.
[109] Lindkvist B, Phillips ME, Dominguez-Munoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: prevalence and diagnostic use. Pancreatology 2015;15:589–97.
[110] Mascarenhas M, Mondick J, Barrett J, Wilson M, Stallings V, Schall J. Malabsorption blood test: assessing fat absorption in patients with cystic fibrosis and pancreatic insufficiency. J Clin Pharmacol 2015;55:854–65.
[111] Drzymala-Czyz S, Krzyzanowska-Jankowska P, Dziedzic K, Lisowska A, Kurek S, Gozdzik-Spychalska J, et al. Severe genotype, pancreatic insufficiency and low dose of pancreatic enzymes associate with abnormal serum sterol profile in cystic fibrosis. Biomolecules 2021;11:313.
[112] Declercq D, Van Biervliet S, Robberecht E. Nutrition and pancreatic enzyme intake in patients with cystic fibrosis with distal intestinal obstruction syndrome. Nutr Clin Pract 2015;30:134–7.
[113] Perano SJ, Couper JJ, Horowitz M, Martin AJ, Kritas S, Sullivan T, et al. Pancreatic enzyme supplementation improves the incretin hormone response and attenuates postprandial glycemia in adolescents with cystic fibrosis: a randomized crossover trial. J Clin Endocrinol Metab 2014;99:2486–93.
[114] Barker DH, Quittner AL. Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. Pediatrics 2016;137:e20152296.
[115] Trapnell BC, Chen S, Khurmi R, Bodhani A, Kapoor M, Haupt M. Hospitalization rates among patients with cystic fibrosis using pancreatic enzyme replacement therapy. Chron Respir Dis 2020;17. 1479973119900612.
[116] Olsen MF, Kjoller-Svarre MS, Moller G, Katzenstein TL, Nielsen BU, Pressler T, et al. Correlates of pancreatic enzyme replacement therapy intake in adults with cystic fibrosis: results of a cross-sectional study. Nutrients 2022;14.
[117] van der Haak N, Boase J, Davidson G, Butler R, Miller M, Kaambwa B, et al. Preliminary report of the (13)C-mixed triglyceride breath test to assess timing of pancreatic enzyme replacement therapy in children with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:669–74.
[118] Raun AMT, Brekke G, Molgaard C, Jaudszus A, Mainz JG, Pressler T, et al. Impact of timing of PERT on gastrointestinal symptoms in Danish children and adolescents with CF. Acta Paediatr 2022;111:432–9.
[119] Sathe MN, Patel D, Stone A, First E. Evaluation of the effectiveness of in-line immobilized lipase cartridge in enterally fed patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2021;72:18–23.
[120] Hendrix SJ, Flume PA, First ER, Stone AA, Van Buskirk M. Improvements in anthropometric measures and gastrointestinal tolerance in patients with cystic fibrosis by using a digestive enzyme cartridge with overnight enteral nutrition. Nutr Clin Pract 2022;37:344–50.
[121] Freedman S, Orenstein D, Black P, Brown P, McCoy K, Stevens J, et al. Increased fat absorption from enteral formula through an in-line digestive cartridge in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2017;65:97–101.
[122] Stevens J, Wyatt C, Brown P, Patel D, Grujic D, Freedman SD. Absorption and safety with sustained use of RELiZORB evaluation (ASSURE) study in patients with cystic fibrosis receiving enteral feeding. J Pediatr Gastroenterol Nutr 2018;67:527–32.
[123] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol 2006;20:531–46.
[124] Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2002;1:51–75.
[125] Dorlöchter L, Aksnes L, Fluge G. Faecal elastase-1 and fat-soluble vitamin profiles in patients with cystic fibrosis in Western Norway. Eur J Nutr 2002;41:148–52.
[126] Rana M, Wong-See D, Katz T, Gaskin K, Whitehead B, Jaffe A, et al. Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis. J Clin Pathol 2014;67:605–8.
[127] Maqbool A, Stallings VA. Update on fat-soluble vitamins in cystic fibrosis. Curr Opin Pulm Med 2008;14:574–81.
[128] Daley T, Hughan K, Rayas M, Kelly A, Tangpricha V. Vitamin D deficiency and its treatment in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18(Suppl 2):S66–73.
[129] Mangas-Sánchez C, Garriga-García M, Serrano-Nieto MJ, García-Romero R, Álvarez-Beltrán M, Crehuá-Gaudiza E, et al. Vitamin D status in pediatric and young adult cystic fibrosis patients. Are the new recommendations effective? Nutrients 2021;13.
[130] Peng Y, Wu M, Alvarez JA, Tangpricha V. Vitamin D status and risk of cystic fibrosis-related diabetes: a retrospective single center cohort study. Nutrients 2021;13:4048.
[131] Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology 2011;140:153–61.
[132] Ramsey ML, Gokun Y, Sobotka LA, Wellner MR, Porter K, Kirkby SE, et al. Cystic fibrosis transmembrane conductance regulator modulator use is associated with reduced pancreatitis hospitalizations in patients with cystic fibrosis. Am J Gastroenterol 2021;116:2446–54.
[133] Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to< 24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med 2018;6:545–53.
[134] Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2–5 years (KLIMB). J Cyst Fibros 2019;18:838–43.
[135] Munce D, Lim M, Akong K. Persistent recovery of pancreatic function in patients with cystic fibrosis after ivacaftor. Pediatr Pulmonol 2020;55:3381–3.
[136] Saxby N, Painter C, Kench A, King S, Crowder T. In: Bell Scott C, editor. The Australian and New Zealand cystic fibrosis nutrition guideline authorship group. Nutrition guidelines for cystic fibrosis in Australia and New Zealand. Sydney: Thoracic Society of Australia and New Zealand; 2017.
[137] Bodewes FA, Verkade HJ, Taminiau JA, Borowitz D, Wilschanski M, Working group Cystic F. Cystic fibrosis and the role of gastrointestinal outcome measures in the new era of therapeutic CFTR modulation. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2015;14:169–77.
[138] Gerasimidis K, Bronsky J, Catchpole A, Embleton N, Fewtrell M, Hojsak I, et al. Assessment and interpretation of vitamin and trace element status in sick children: a position paper from the European society for paediatric gastroenterology Hepatology, and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr 2020;70:873–81.
[139] McDonald CM, Alvarez JA, Bailey J, Bowser EK, Farnham K, Mangus M, et al. Academy of nutrition and dietetics: 2020 cystic fibrosis evidence analysis center evidence-based nutrition practice guideline. J Acad Nutr Diet 2021;121:1591–15636 e3.
[140] Simoneau T, Bazzaz O, Sawicki GS, Gordon C. Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. Ann Am Thorac Soc 2014;11:205–10.
[141] Madde A, Okoniewski W, Sanders DB, Ren CL, Weiner DJ, Forno E. Nutritional status and lung function in children with pancreatic-sufficient cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:769–76.
[142] Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014;43:125–33.
[143] Caley L, Smith L, White H, Peckham DG. Average rate of lung function decline in adults with cystic fibrosis in the United Kingdom: data from the UK CF registry. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:86–90.
[144] Bailey J, Krick S, Fontaine KR. The changing landscape of nutrition in cystic fibrosis: the emergence of overweight and obesity. Nutrients 2022;14.
[145] Potter KJ, Boudreau V, Shohoudi A, Mailhot M, Tremblay F, Lavoie A, et al. Influence of pre-diabetic and pancreatic exocrine states on pulmonary and nutritional status in adults with Cystic Fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:803–9.
[146] Nowak JK, Wykretowicz A, Madry E, Krauze T, Drzymala-Czyz S, Krzyzanowska-Jankowska P, et al. Preclinical atherosclerosis in cystic fibrosis: two distinct presentations are related to pancreatic status. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:26–33.
[147] Sanders DB, Fink A, Mayer-Hamblett N, Schechter MS, Sawicki GS, Rosenfeld M, et al. Early life growth trajectories in cystic fibrosis are associated with pulmonary function at age 6 years. J Pediatr 2015;167:1081–1088 e1.
[148] Macdougall A, Jarvis D, Keogh RH, Bowerman C, Bilton D, Davies G, et al. Trajectories of early growth and subsequent lung function in cystic fibrosis: an observational study using UK and Canadian registry data. J Cyst Fibros 2023;22(3):388–94.
[149] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. 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;108:832–9.
[150] 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. Am J Clin Nutr 2013;97:872–7.

[151] Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, et al. European cystic fibrosis society standards of care: best practice guidelines. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13(Suppl 1):S23–42.
[152] Döring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2012;11:461–79.
[153] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med 2020;8:65–124.
[154] Scotet V, Gutierrez H, Farrell PM. Newborn screening for CF across the globe-where is it worthwhile? Int J Neonat Screen 2020;6:18.
[155] Leung DH, Heltshe SL, Borowitz D, Gelfond D, Kloster M, Heubi JE, et al. Effects of diagnosis by newborn screening for cystic fibrosis on weight and length in the first year of life. JAMA Pediatr 2017;171:546–54.
[156] Coffey MJ, Whitaker V, Gentin N, Junek R, Shalhoub C, Nightingale S, et al. Differences in outcomes between early and late diagnosis of cystic fibrosis in the newborn screening era. J Pediatr 2017;181:137–145.e1.
[157] Ong T, Onchiri FM, Britto MT, Heltshe SL, Kessler LG, Seid M, et al. Impact of guideline-recommended dietitian assessments on weight gain in infants with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:115–22.
[158] Freeman AJ, Huang R, Heltshe SL, Gelfond D, Leung DH, Ramsey BR, et al. Association between stool consistency and clinical variables among infants with cystic fibrosis: findings from the BONUS study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:830–6.
[159] Sathe M, Huang R, Heltshe S, Eng A, Borenstein E, Miller SI, et al. Gastrointestinal factors associated with hospitalization in infants with cystic fibrosis: results from the baby observational and nutrition study. J Pediatr Gastroenterol Nutr 2021;73:395–402.
[160] Fitzgerald C, Linnane B, George S, Ni Chroinin M, Mullane D, Herzig M, et al. Neonatal screening programme for CF: results from the Irish comparative outcomes study (ICOS). Pediatr Pulmonol 2020;55:2323–9.
[161] Hoen AG, Li J, Moulton LA, O'Toole GA, Housman ML, Koestler DC, et al. Associations between gut microbial colonization in early life and respiratory outcomes in cystic fibrosis. J Pediatr 2015;167:138–47. e1-3.
[162] Colombo C, Alicandro G, Daccò V, Consales A, Mosca F, Agostoni C, et al. Breastfeeding in cystic fibrosis: a systematic review on prevalence and potential benefits. Nutrients 2021;13.
[163] Miller T, Antos NJ, Brock LA, Wade T, Goday PS. Lactation consultation sustains breast milk intake in infants with cystic fibrosis. J Pediatr Gastroenterol Nutr 2019;69:358–62.
[164] Freedman SD. Breast milk fats and lipids: expanding benefits to fragile infant populations. Breastfeed Med 2018;13:S26–7.
[165] Smith C. Supporting optimal growth in infants with chronic conditions: how are we doing and what can we do? Breastfeed Med 2019;14:S18–9.
[166] Declercq D, Van Braeckel E, Marchand S, Van Daele S, Van Biervliet S. Sodium status and replacement in children and adults living with cystic fibrosis: a narrative review. J Acad Nutr Diet 2020;120:1517–29.
[167] Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al. Complementary feeding: a position paper by the European society for paediatric gastroenterology, Hepatology, and nutrition (ESPGHAN) committee on nutrition. J Pediatr Gastroenterol Nutr 2017;64:119–32.
[168] Dipasquale V, Romano C. Complementary feeding: new styles versus old myths. Minerva Med 2020;111:141–52.
[169] Brown A, Jones SW, Rowan H. Baby-Led weaning: the evidence to date. Curr Nutr Rep 2017;6:148–56.
[170] D'Auria E, Bergamini M, Staiano A, Banderali G, Pendezza E, Penagini F, et al. Baby-led weaning: what a systematic review of the literature adds on. Ital J Pediatr 2018;44:49.
[171] Tan SMJ, Coffey MJ, Ooi CY. Differences in clinical outcomes of paediatric cystic fibrosis patients with and without meconium ileus. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:857–62.
[172] Sathe M, Houwen R. Meconium ileus in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16(Suppl 2):S32–9.
[173] Padoan R, Cirilli N, Falchetti D, Cesana BM. Risk factors for adverse outcome in infancy in meconium ileus cystic fibrosis infants: a multicentre Italian study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:863–8.
[174] Jessula S, Van Den Hof M, Mateos-Corral D, Mills J, Davies D, Romao RL. Predictors for surgical intervention and surgical outcomes in neonates with cystic fibrosis. J Pediatr Surg 2018;53:2150–4.
[175] Long AM, Jones IH, Knight M, McNally J. Early management of meconium ileus in infants with cystic fibrosis: a prospective population cohort study. J Pediatr Surg 2021;56:1287–92.
[176] Powers SW, Mitchell MJ, Patton SR, Byars KC, Jelalian E, Mulvihill MM, et al. Mealtime behaviors in families of infants and toddlers with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2005;4:175–82.
[177] Morton AM. Symposium 6: young people, artificial nutrition and transitional care. The nutritional challenges of the young adult with cystic fibrosis: transition. Proc Nutr Soc 2009;68:430–40.
[178] Alicandro G, Bisogno A, Battezzati A, Bianchi ML, Corti F, Colombo C. Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:328–34.
[179] Barni GC, Forte GC, Forgiarini LF, Abrahao CLO, Dalcin PTR. Factors associated with malnutrition in adolescent and adult patients with cystic fibrosis. J Bras Pneumol 2017;43:337–43.
[180] Conrad DJ, Bailey BA. Multidimensional clinical phenotyping of an adult cystic fibrosis patient population. PLoS One 2015;10:e0122705.
[181] Kapnadak SG, Ramos KJ, Lopriore AM, Goss CH, Aitken ML. A survey identifying nutritional needs in a contemporary adult cystic fibrosis cohort. BMC Nutr 2019;5.
[182] Frankenfield DC, Ashcraft CM, Drasher TL, Reid EK, Vender RL. Characteristics of resting metabolic rate in critically Ill, mechanically ventilated adults with cystic fibrosis. J Parenter Enter Nutr 2017;41:601–6.
[183] Collins S. Nutritional management of cystic fibrosis - an update for the 21st century. Paediatr Respir Rev 2018;26:4–6.
[184] Connett GJ. Cystic fibrosis nutrition–chewing the fat. Paediatr Respir Rev 2016;17:42–4.
[185] Jain R, Kazmerski TM, Zuckerwise LC, West NE, Montemayor K, Aitken ML, et al. Pregnancy in cystic fibrosis: review of the literature and expert recommendations. J Cyst Fibros 2022;21(3):387–95.
[186] Geake J, Tay G, Callaway L, Bell SC. Pregnancy and cystic fibrosis: approach to contemporary management. Obstet Med 2014;7:147–55.
[187] Reynaud Q, Jablonski CR, Poupon-Bourdy S, Denis A, Rabilloud M, Lemonnier L, et al. Pregnancy outcome in women with cystic fibrosis and poor pulmonary function. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:80–3.
[188] Pontzer H, Yamada Y, Sagayama H, Ainslie PN, Andersen LF, Anderson LJ, et al. Daily energy expenditure through the human life course. Science 2021;373:808–12.
[189] Solomon M, Bozic M, Mascarenhas MR. Nutritional issues in cystic fibrosis. Clin Chest Med 2016;37:97–107.
[190] Lusman S, Sullivan J. Nutrition and growth in cystic fibrosis. Pediatr Clin 2016;63:661–78.
[191] Ramirez I, Filbrun A, Hasan A, Kidwell KM, Nasr SZ. Improving nutritional status in a pediatric cystic fibrosis center. Pediatr Pulmonol 2015;50:544–51.
[192] Smyth RL, Rayner O. Oral calorie supplements for cystic fibrosis. Cochrane Database Syst Rev 2017;5:CD000406.
[193] Victoria CB, Casilda O, Nuria P, Jose AF, Maria GO, Jose SF, et al. Oral nutritional supplements in adults with cystic fibrosis: effects on intake, levels of fat-soluble vitamins, and bone remodeling biomarkers. Nutrients 2021;13:1–9.
[194] Shaikhkhalil AK, Freeman AJ, Sathe M. Variations in nutrition practices in cystic fibrosis: a survey of the digest Program. Nutr Clin Pract 2021;36:1247–51.
[195] Hollander FM, van Pierre DD, de Roos NM, van de Graaf EA, Iestra JA. Effects of nutritional status and dietetic interventions on survival in Cystic Fibrosis patients before and after lung transplantation. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:212–8.
[196] Libeert D, Declercq D, Wanyama S, Thomas M, Van Daele S, De Baets F, et al. The effect of enteral tube feeding in cystic fibrosis: a registry based study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2018;17:264–70.
[197] Declercq D, Huysentruyt K, Hauser B, De Wachter E, Van Daele S, De Baets F, et al. Long-term use of tube feeding in children with cystic fibrosis: results from two Belgian CF centers. Eur J Clin Nutr 2021;75:620–7.
[198] Hollander FM, de Roos NM, Belle van Meerkerk G, Teding van Berkhout F, Heijerman HGM, van de Graaf EA. Body weight and body mass index in patients with end-stage cystic fibrosis stabilize after the start of enteral tube feeding. J Acad Nutr Diet 2017;117:1808–15.
[199] Ledder O, Oliver MR, Heine RG, Graham J, Volders E, Robinson PJ. Clinical audit results in earlier nutritional intervention in malnourished children with cystic fibrosis with improved outcome. J Paediatr Child Health 2015;51:988–93.
[200] Khalaf RT, Green D, Amankwah EK, Peck J, Carr V, Goldenberg NA, et al. Percutaneous endoscopic gastrostomy tubes may Be associated with preservation of lung function in patients with cystic fibrosis. Nutr Clin Pract 2019;34:290–6.
[201] Schwarzenberg SJ, Hempstead SE, McDonald CM, Powers SW, Wooldridge J, Blair S, et al. Enteral tube feeding for individuals with cystic fibrosis: cystic Fibrosis Foundation evidence-informed guidelines. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:724–35.
[202] Mulherin DW, Bensink J, Zuckerwise L, Murphree JN, Tolle J, Seidner DL. Long-term parenteral nutrition in a patient with cystic fibrosis during pregnancy. J Parenter Enter Nutr 2019;43:1065–8.
[203] Melville T, Vardy K, Milliner L, Angus R. Intradialytic parenteral nutrition improves nutritional status in a complex cystic fibrosis patient with redo double lung transplant and end-stage renal disease. BMJ Case Rep 2020;13.
[204] Sermet-Gaudelus I, Bianchi ML, Garabédian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2011;10(Suppl 2):S16–23.
[205] Moen IE, Nilsson K, Andersson A, Fagerland MW, Fluge G, Hollsing A, et al. Dietary intake and nutritional status in a Scandinavian adult cystic fibrosis-population compared with recommendations. Food Nutr Res 2011;55.
[206] Gordon CM, Anderson EJ, Herlyn K, Hubbard JL, Pizzo A, Gelbard R, et al. Nutrient status of adults with cystic fibrosis. J Am Diet Assoc 2007;107:2114–9.
[207] Poulimeneas D, Grammatikopoulou MG, Devetzi P, Petrocheilou A, Kaditis AG, Papamitsou T, et al. Adherence to dietary recommendations, nutrient intake adequacy and diet quality among pediatric cystic fibrosis patients: results from the GreeCF study. Nutrients 2020;12.

[208] Sands D, Mielus M, Umlawska W, Lipowicz A, Oralewska B, Walkowiak J. Evaluation of factors related to bone disease in Polish children and adolescents with cystic fibrosis. Adv Med Sci 2015;60:315–20.
[209] Haworth CS, Jones AM, Adams JE, Selby PL, Webb AK. Randomised double blind placebo controlled trial investigating the effect of calcium and vitamin D supplementation on bone mineral density and bone metabolism in adult patients with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2004;3:233–6.
[210] Hillman LS, Cassidy JT, Popescu MF, Hewett JE, Kyger J, Robertson JD. Percent true calcium absorption, mineral metabolism, and bone mineralization in children with cystic fibrosis: effect of supplementation with vitamin D and calcium. Pediatr Pulmonol 2008;43:772–80.
[211] Escobedo Monge MF, Barrado E, Alonso Vicente C, Redondo Del Rio MP, Marugan de Miguelsanz JM. Zinc nutritional status in patients with cystic fibrosis. Nutrients 2019;11.
[212] Bauer SE, Lai HJ, McDonald CM, Asfour F, Slaven JE, Ren CL. Zinc status and growth in infants and young children with cystic fibrosis. Pediatr Pulmonol 2021;56:3768–76.
[213] Damphousse V, Mailhot M, Berthiaume Y, Rabasa-Lhoret R, Mailhot G. Plasma zinc in adults with cystic fibrosis: correlations with clinical outcomes. J Trace Elem Med Biol 2014;28:60–4.
[214] Sankararaman S, Hendrix SJ, Schindler T. Update on the management of vitamins and minerals in cystic fibrosis. Nutr Clin Pract 2022;37:1074–87.
[215] Simon M, Dalle Molle R, Silva FM, Rodrigues TW, Feldmann M, Forte GC, et al. Antioxidant micronutrients and essential fatty acids supplementation on cystic fibrosis outcomes: a systematic review. J Acad Nutr Diet 2020;120:1016–10133 e1.
[216] Hurley MN, Smith S, Forrester DL, Smyth AR. Antibiotic adjuvant therapy for pulmonary infection in cystic fibrosis. Cochrane Database Syst Rev 2020;7:Cd008037.
[217] Ataee P, Najafi M, Gharagozlou M, Aflatounian M, Mahmoudi M, Khodadad A, et al. Effect of supplementary zinc on body mass index, pulmonary function and hospitalization in children with cystic fibrosis. Turk J Pediatr 2014;56:127–32.
[218] Sharma G, Lodha R, Shastri S, Saini S, Kapil A, Singla M, et al. Zinc supplementation for one year among children with cystic fibrosis does not decrease pulmonary infection. Respir Care 2016;61:78–84.
[219] Ciofu O, Smith S, Lykkesfeldt J. A systematic Cochrane Review of antioxidant supplementation lung disease for cystic fibrosis. Paediatr Respir Rev 2020;33:28–9.
[220] Nessel TA, Gupta V. Selenium. StatPearls. Treasure Island (FL): StatPearls Publishing copyright © 2022. StatPearls Publishing LLC.; 2022.
[221] Sagel SD, Khan U, Jain R, Graff G, Daines CL, Dunitz JM, et al. Effects of an antioxidant-enriched multivitamin in cystic fibrosis. A randomized, controlled, multicenter clinical trial. Am J Respir Crit Care Med 2018;198:639–47.
[222] Wood LG, Fitzgerald DA, Lee AK, Garg ML. Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung function. Am J Clin Nutr 2003;77:150–9.
[223] Uijterschout L, Nuijsink M, Hendriks D, Vos R, Brus F. Iron deficiency occurs frequently in children with cystic fibrosis. Pediatr Pulmonol 2014;49:458–62.
[224] Gettle LS, Harden A, Bridges M, Albon D. Prevalence and risk factors for iron deficiency in adults with cystic fibrosis. In: Nutrition in clinical practice : official publication of the American society for parenteral and enteral nutrition, vol. 35; 2020. p. 1101–9.
[225] von Drygalski A, Biller J. Anemia in cystic fibrosis: incidence, mechanisms, and association with pulmonary function and vitamin deficiency. Nutr Clin Pract 2008;23:557–63.
[226] Lee M, Smith EM, Ziegler TR, Alvarez J, Tangpricha V. Changes in micronutrient status during and after pulmonary exacerbation in adult cystic fibrosis. J Invest Med 2015;63:386–7.
[227] Reid DW, Withers NJ, Francis L, Wilson JW, Kotsimbos TC. Iron deficiency in cystic fibrosis: relationship to lung disease severity and chronic Pseudomonas aeruginosa infection. Chest 2002;121:48–54.
[228] Gifford AH, Alexandru DM, Li Z, Dorman DB, Moulton LA, Price KE, et al. Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis. J Cyst Fibros 2014;13:311–8.
[229] Khalid S, McGrowder D, Kemp M, Johnson P. The use of soluble transferrin receptor to assess iron deficiency in adults with cystic fibrosis. Clin Chim Acta 2007;378:194–200.
[230] Uijterschout L, Swinkels DW, Akkermans MD, Zandstra T, Nuijsink M, Hendriks D, et al. The value of soluble transferrin receptor and hepcidin in the assessment of iron status in children with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:639–44.
[231] Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011–23.
[232] Di Sant'Agnese PA, Darling RC, Perera GA, Shea E. Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas; clinical significance and relationship to the disease. Pediatrics 1953;12:549–63.
[233] Scurati-Manzoni E, Fossali EF, Agostoni C, Riva E, Simonetti GD, Zanolari-Calderari M, et al. Electrolyte abnormalities in cystic fibrosis: systematic review of the literature. Pediatr Nephrol 2014;29:1015–23.
[234] Coates AJ, Crofton PM, Marshall T. Evaluation of salt supplementation in CF infants. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2009;8:382–5.
[235] Ozcelik U, Gocmen A, Kiper N, Coskun T, Yilmaz E, Ozguc M. Sodium chloride deficiency in cystic fibrosis patients. Eur J Pediatr 1994;153:829–31.
[236] Declercq D, Peremans L, Glorieus M, Weygaerde YV, Van Braeckel E, Schaballie H, et al. Urinary sodium/creatinine ratio is a predictor for fractional sodium excretion and related to age in patients with cystic fibrosis. J Cyst Fibros2022 Mar 2022;21(2):e136–40.
[237] Sermet-Gaudelus I, Mayell SJ, Southern KW, European Cystic Finrosis Society NSWG. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2010;9:323–9.
[238] Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, et al., Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155:S73–93.
[239] Cystic Fibrosis Trust. Nutritional management of cystic fibrosis. 2nd ed. London: Cystic Fibrosis Trust; 2016.
[240] Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. Cochrane Database Syst Rev 2016;2016:CD002201.
[241] Wheelock CE, Strandvik B. Abnormal n-6 fatty acid metabolism in cystic fibrosis contributes to pulmonary symptoms. Prostaglandins Leukot Essent Fatty Acids 2020;160:102156.
[242] Strandvik B. Nutrition in cystic fibrosis-some notes on the fat recommendations. Nutrients 2022;14.
[243] Chinuck R, Dewar J, Baldwin DR, Hendron E. Appetite stimulants for people with cystic fibrosis. Cochrane Database Syst Rev 2014:Cd008190.
[244] Grunert J, van der Haak N, La Vanda C, Farrow N, Tai A. Cyproheptadine as an appetite stimulant in children with cystic fibrosis. Clin Nutr ESPEN 2021;42:407–9.
[245] McTavish D, Thornton J. Appetite stimulants for people with cystic fibrosis. Cochrane Database Syst Rev 2022;9:Cd008190.
[246] Sheikh S, Gemma S, Patel A. Factors associated with low bone mineral density in patients with cystic fibrosis. J Bone Miner Metabol 2015;33:180–5.
[247] Jakovska T, Mecevska-Jovcevska J, Petlickovski A, Fustik S, Zorcec T. Prevalence of low bone mass and vitamin D deficiency in pediatric and adult patients with cystic fibrosis in Republic of Macedonia. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2014;35:151–8.
[248] Chedevergne F, Sermet-Gaudelus I. Prevention of osteoporosis in cystic fibrosis. Curr Opin Pulm Med 2019;25:660–5.
[249] Braun C, Bacchetta J, Braillon P, Chapurlat R, Drai J, Reix P. Children and adolescents with cystic fibrosis display moderate bone microarchitecture abnormalities: data from high-resolution peripheral quantitative computed tomography. Osteoporos Int 2017;28:3179–88.
[250] Gensburger D, Boutroy S, Chapurlat R, Nove-Josser R, Roche S, Rabilloud M, et al. Reduced bone volumetric density and weak correlation between infection and bone markers in cystic fibrosis adult patients. Osteoporos Int 2016;27:2803–13.
[251] Baker JF, Putman MS, Herlyn K, Tillotson AP, Finkelstein JS, Merkel PA. Body composition, lung function, and prevalent and progressive bone deficits among adults with cystic fibrosis. Joint Bone Spine 2016;83:207–11.
[252] Stahl M, Holfelder C, Kneppo C, Kieser M, Kasperk C, Schoenau E, et al. Multiple prevalent fractures in relation to macroscopic bone architecture in patients with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2018;17:114–20.
[253] Nishiyama KK, Agarwal S, Kepley A, Rosete F, Hu Y, Guo XE, et al. Adults with cystic fibrosis have deficits in bone structure and strength at the distal tibia despite similar size and measuring standard and relative sites. Bone 2018;107:181–7.
[254] Mailhot G, Dion N, Farlay D, Rizzo S, Bureau NJ, Jomphe V, et al. Impaired rib bone mass and quality in end-stage cystic fibrosis patients. Bone 2017;98:9–17.
[255] Ciuca IM, Pop LL, Rogobete AF, Onet DI, Guta-Almajan B, Popa Z, et al. Genetic expression in cystic fibrosis related bone disease. An observational, transversal, cross-sectional study. Clin Lab 2016;62:1725–30.
[256] Chirita-Emandi A, Shepherd S, Kyriakou A, McNeilly JD, Dryden C, Corrigan D, et al. A retrospective analysis of longitudinal changes in bone mineral content in cystic fibrosis. J Pediatr Endocrinol Metab 2017;30:807–14.
[257] Swisher AK, Hebestreit H, Mejia-Downs A, Lowman JD, Gruber W, Nippins M, et al. Exercise and habitual physical activity for people with cystic fibrosis: expert consensus, evidence-based guide for advising patients. Cardiopulm Phys Ther J 2015;26:85–98.
[258] Tejero S, Cejudo P, Quintana-Gallego E, Sañudo B, Oliva-Pascual-Vaca A. The role of daily physical activity and nutritional status on bone turnover in cystic fibrosis: a cross-sectional study. Braz J Phys Ther 2016;20:206–12.
[259] Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, et al. Effects of exercise intervention Program on bone mineral accretion in children and adolescents with cystic fibrosis: a randomized controlled trial. Indian J Pediatr 2019;86:987–94.
[260] Atlas G, Yap M, Lim A, Vidmar S, Smith N, King L, et al. The clinical features that contribute to poor bone health in young Australians living with cystic fibrosis: a recommendation for BMD screening. Pediatr Pulmonol 2021;56:2014–22.
[261] Gur M, Bar-Yoseph R, Diab G, Hanna M, Rozen G, Daud F, et al. Understanding the interplay between factors that influence bone mineral density in CF. Pediatr Pulmonol 2020;55:2667–73.

[262] Robinson CA, Hofer M, Benden C, Schmid C. Evaluation of bone disease in patients with cystic fibrosis and end-stage lung disease. J Bras Pneumol 2019;45:e20170280.
[263] Fedewa MV, Bentley JL, Higgins S, Kindler JM, Esco MR, MacDonald HV. Celiac disease and bone health in children and adolescents: a systematic review and meta-analysis. J Clin Densitom 2020;23:200–11.
[264] Emiralioglu N, Ademhan Tural D, Hizarcioglu Gulsen H, Ergen YM, Ozsezen B, Sunman B, et al. Does cystic fibrosis make susceptible to celiac disease? Eur J Pediatr 2021;180:2807–13.
[265] Doulgeraki A, Petrocheilou A, Petrocheilou G, Chrousos G, Doudounakis SE, Kaditis AG. Body composition and lung function in children with cystic fibrosis and meconium ileus. Eur J Pediatr 2017;176:737–43.
[266] Ritchie H, Nahikian-Nelms M, Roberts K, Gemma S, Shaikhkhalil A. The prevalence of aberrations in body composition in pediatric cystic fibrosis patients and relationships with pulmonary function, bone mineral density, and hospitalizations. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:837–42.
[267] Silva Junior CCD, Marques Queiroz DJ, de Paiva MP, Lopes MT, da Cunha Costa M, de Matos Bezerra PG, et al. Evaluation of anthropometry as an alternative to DXA as predictor of low bone mineral density in children and adolescents with cystic fibrosis. Clin Nutr ESPEN 2021;45:229–35.
[268] Nodoushan AJ, Golzar A, Hassanzad M, Sayedi SJ, Velayati A. Low bone mineral density and associated factors in patients with cystic fibrosis: a cross-sectional study. Int J Pediatr 2017;5:5237–44.
[269] Cairoli E, Eller-Vainicher C, Morlacchi LC, Tarsia P, Rossetti V, Pappalettera M, et al. Bone involvement in young adults with cystic fibrosis awaiting lung transplantation for end-stage respiratory failure. Osteoporos Int 2019;30:1255–63.
[270] Engelen MP, Com G, Deutz NE. Increased whole body hydroxyproline production as assessed by a new stable isotope technique is associated with hip and spine bone mineral loss in cystic fibrosis. Clin Nutr 2014;33:1117–21.
[271] Ubago-Guisado E, Cavero-Redondo I, Alvarez-Bueno C, Vlachopoulos D, Martinez-Vizcaino V, Gracia-Marco L. Bone health in children and youth with cystic fibrosis: a systematic review and meta-analysis of matched cohort studies. J Pediatr 2019;215:178–86. e16.
[272] Solarino G, Vicenti G, Spinarelli A, Abate A, Carrozzo M, Cagnetta V, et al. Assessing bone mineral density in Italian adult cystic fibrosis patients: a cross sectional study. J Biol Regul Homeost Agents 2015;29:79–85.
[273] Putman MS, Anabtawi A, Le T, Tangpricha V, Sermet-Gaudelus I. Cystic fibrosis bone disease treatment: current knowledge and future directions. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18(Suppl 2):S56–65.
[274] Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, El-Hajj Fuleihan G, Kecskemethy HH, et al. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 2014;17:225–42.
[275] Bachrach LK, Gordon CM. Bone densitometry in children and adolescents. Pediatrics 2016:138.
[276] Putman MS, Haagensen A, Neuringer I, Sicilian L. Celiac disease in patients with cystic fibrosis-related bone disease. Case Rep Endocrinol 2017;2017:2652403.
[277] Anabtawi A, Le T, Putman M, Tangpricha V, Bianchi ML. Cystic fibrosis bone disease: pathophysiology, assessment and prognostic implications. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18(Suppl 2):S48–55.
[278] Brookes DS, Briody JN, Munns CF, Davies PS, Hill RJ. Cystic fibrosis-related bone disease in children: examination of peripheral quantitative computed tomography (pQCT) data. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2015;14:668–77.
[279] Ullal J, Kutney K, Williams KM, Weber DR. Treatment of cystic fibrosis related bone disease. J Clin Transl Endocrinol 2022;27:100291.
[280] Liu Y, Le S, Liu Y, Jiang H, Ruan B, Huang Y, et al. The effect of calcium supplementation in people under 35 years old: a systematic review and meta-analysis of randomized controlled trials. Elife 2022;11:e79002.
[281] Jeffery TC, Chang AB, Conwell LS. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database Syst Rev 2023;1:CD002010.
[282] Grassi G, Chiodini I, Cairoli E, Morlacchi LC, Rossetti V, Rosso L, et al. Impact of bone-active drugs and underlying disease on bone health after lung transplantation: a longitudinal study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:e100–7.
[283] Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database Syst Rev 2014;2014:CD002010.
[284] Wu M, Bettermann EL, Arora N, Hunt WR, McCracken C, Tangpricha V. Relationship between estrogen treatment and skeletal health in women with cystic fibrosis. Am J Med Sci 2020;360:581–90.
[285] Wu M, Hunt WR, Putman MS, Tangpricha V. Oral ethinyl estradiol treatment in women with cystic fibrosis is associated with lower bone mineral density. J Clin Transl Endocrinol 2020;20:100223.
[286] Battezzati A, Bedogni G, Zazzeron L, Mari A, Battezzati PM, Alicandro G, et al. Age- and sex-dependent distribution of OGTT-related variables in a population of cystic fibrosis patients. J Clin Endocrinol Metab 2015;100:2963–71.
[287] Olesen HV, Drevinek P, Gulmans VA, Hatziagorou E, Jung A, Mei-Zahav M, et al. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome; Olesen et al. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:321–7.
[288] Alves C, Della-Manna T, Albuquerque CTM. Cystic fibrosis-related diabetes: an update on pathophysiology, diagnosis, and treatment. J Pediatr Endocrinol Metab 2020;33:835–43.
[289] Mozzillo E, Franceschi R, Piona C, Passanisi S, Casertano A, Pjetraj D, et al. Diabetes and prediabetes in children with cystic fibrosis: a systematic review of the literature and recommendations of the Italian society for pediatric endocrinology and diabetes (ISPED). Front Endocrinol 2021;12:673539.
[290] Perrem L, Stanojevic S, Solomon M, Carpenter S, Ratjen F. Incidence and risk factors of paediatric cystic fibrosis-related diabetes. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:874–8.
[291] Prentice BJ, Chelliah A, Ooi CY, Hameed S, Verge CF, Plush L, et al. Peak OGTT glucose is associated with lower lung function in young children with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:305–9.
[292] Leclercq A, Gauthier B, Rosner V, Weiss L, Moreau F, Constantinescu AA, et al. Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:478–84.
[293] Ararat E, Sonawalla A, Berlinski A, Tas E. Nutritional status between 5-10 years is associated with cystic fibrosis-related diabetes in adolescence. Pediatr Pulmonol 2021;56:3217–22.
[294] Coriati A, Ziai S, Lavoie A, Berthiaume Y, Rabasa-Lhoret R. The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis. Acta Diabetol 2016;53:359–66.
[295] Lehoux Dubois C, Boudreau V, Tremblay F, Lavoie A, Berthiaume Y, Rabasa-Lhoret R, et al. Association between glucose intolerance and bacterial colonisation in an adult population with cystic fibrosis, emergence of Stenotrophomonas maltophilia. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16:418–24.
[296] Reynaud Q, Boudreau V, Touzet S, Desjardins K, Bourdy SP, Blond E, et al. Glucose tolerance in Canadian and French cystic fibrosis adult patients. Sci Rep 2019;9:4763.
[297] Nguyen CQT, Denis MH, Chagnon M, Rabasa-Lhoret R, Mailhot G. Abnormal glucose tolerance in a pediatric cystic fibrosis cohort: trends in clinical outcomes and associated factors in the preceding years. Nutr Metabol Cardiovasc Dis 2021;31:277–85.
[298] Granados A, Beach EA, Christiansen AJ, Patterson BW, Wallendorf M, Arbelaez AM. The association between body composition, leptin levels and glucose dysregulation in youth with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:796–802.
[299] Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: pathophysiology, screening and diagnosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18(Suppl 2):S3–9.
[300] Colomba J, Boudreau V, Lehoux-Dubois C, Desjardins K, Coriati A, Tremblay F, et al. The main mechanism associated with progression of glucose intolerance in older patients with cystic fibrosis is insulin resistance and not reduced insulin secretion capacity. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:551–6.
[301] Boudreau V, Coriati A, Hammana I, Ziai S, Desjardins K, Berthiaume Y, et al. Variation of glucose tolerance in adult patients with cystic fibrosis: what is the potential contribution of insulin sensitivity? J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:839–45.
[302] Wooldridge JL, Szczesniak RD, Fenchel MC, Elder DA. Insulin secretion abnormalities in exocrine pancreatic sufficient cystic fibrosis patients. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2015;14:792–7.
[303] Schmid K, Fink K, Holl RW, Hebestreit H, Ballmann M. Predictors for future cystic fibrosis-related diabetes by oral glucose tolerance test. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:80–5.
[304] Lavie M, Fisher D, Vilozni D, Forschmidt R, Sarouk I, Kanety H, et al. Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. Diabetes Res Clin Pract 2015;110:276–84.
[305] Clemente Leon M, Bilbao Gasso L, Moreno-Galdo A, Campos Martorrell A, Gartner Tizzano S, Yeste Fernandez D, et al. Oral glucose tolerance test and continuous glucose monitoring to assess diabetes development in cystic fibrosis patients. Endocrinol Diabetes Nutr (Engl Ed). 2018;65:45–51.
[306] Scully KJ, Sherwood JS, Martin K, Ruazol M, Marchetti P, Larkin M, et al. Continuous glucose monitoring and HbA1c in cystic fibrosis: clinical correlations and implications for CFRD diagnosis. J Clin Endocrinol Metab 2022;107:e1444–54.
[307] Racine F, Shohoudi A, Boudreau V, Nguyen CQT, Denis MH, Desjardins K, et al. Glycated hemoglobin as a first-line screening test for cystic fibrosis–related diabetes and impaired glucose tolerance in children with cystic fibrosis: a validation study. Can J Diabetes 2021;45:768–74.
[308] Gojsina B, Minic P, Todorovic S, Soldatovic I, Sovtic A. Continuous glucose monitoring as a valuable tool in the early detection of diabetes related to cystic fibrosis. Front Pediatr 2021;9:659728.
[309] Darukhanavala A, Van Dessel F, Ho J, Hansen M, Kremer T, Alfego D. Use of hemoglobin A1c to identify dysglycemia in cystic fibrosis. PLoS One 2021;16:e0250036.
[310] Boudreau V, Coriati A, Desjardins K, Rabasa-Lhoret R. Glycated hemoglobin cannot yet be proposed as a screening tool for cystic fibrosis related diabetes. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2016;15:258–60.
[311] Boudreau V, Reynaud Q, Bonhoure A, Durieu I, Rabasa-Lhoret R. Validation of a stepwise approach using glycated hemoglobin levels to reduce the number of required oral glucose tolerance tests to screen for cystic fibrosis-related diabetes in adults. Can J Diabetes 2019;43:161–2.
[312] Bonhoure A, Potter KJ, Colomba J, Boudreau V, Bergeron C, Desjardins K, et al. Peak glucose during an oral glucose tolerance test is associated with future diabetes risk in adults with cystic fibrosis. Diabetologia 2021;64:1332–41.

[313] Scheuing N, Berger G, Bergis D, Gohlke B, Konrad K, Laubner K, et al. Adherence to clinical care guidelines for cystic fibrosis-related diabetes in 659 German/Austrian patients. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:730–6.
[314] Franck Thompson E, Watson D, Benoit CM, Landvik S, McNamara J. The association of pediatric cystic fibrosis-related diabetes screening on clinical outcomes by center: a CF patient registry study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:316–20.
[315] Colomba J, Rabasa-Lhoret R, Bonhoure A, Bergeron C, Boudreau V, Tremblay F, et al. Dyslipidemia is not associated with the development of glucose intolerance or diabetes in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:704–11.
[316] Megias MC, Albarran OG, Vasco PG, Ferreiro AL, Carro LM. Influence of macrolides, nutritional support and respiratory therapies in diabetes and normal glucose tolerance in cystic fibrosis. A retrospective analysis of a cohort of adult and younger patients. Diabetes Metabol Syndr 2015;9:1–6.
[317] Potter KJ, Reynaud Q, Boudreau V, Racine F, Tremblay F, Lavoie A, et al. Combined indeterminate and impaired glucose tolerance is a novel group at high risk of cystic fibrosis-related diabetes. J Clin Endocrinol Metab 2021;106:e3901–10.
[318] Nielsen BU, Faurholt-Jepsen D, Oturai PS, Qvist T, Krogh-Madsen R, Katzenstein TL, et al. Associations between glucose tolerance, insulin secretion, muscle and fat mass in cystic fibrosis. Clin Med Insights Endocrinol Diabetes 2021;14. 11795514211038259.
[319] Ballmann M, Hubert D, Assael BM, Staab D, Hebestreit A, Naehrlich L, et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6:114–21.
[320] Kelly A, Sheikh S, Stefanovski D, Peleckis CRNPA, Nyirjesy S, Eiel J, et al. Randomized, controlled trial of Sitagliptin and islet function in cystic fibrosis with abnormal glucose tolerance. 2021.
[321] Kelly A, Sheikh S, Stefanovski D, Peleckis AJ, Nyirjesy SC, Eiel JN, et al. Effect of Sitagliptin on islet function in pancreatic insufficient cystic fibrosis with abnormal glucose tolerance. J Clin Endocrinol Metab 2021;106:2617–34.
[322] Onady GM, Stolfi A. Drug treatments for managing cystic fibrosis-related diabetes. Cochrane Database Syst Rev 2020;10:CD004730.
[323] Geyer MC, Sullivan T, Tai A, Morton JM, Edwards S, Martin AJ, et al. Exenatide corrects postprandial hyperglycaemia in young people with cystic fibrosis and impaired glucose tolerance: a randomized crossover trial. Diabetes Obes Metabol 2019;21:700–4.
[324] Stonestreet J, Ar A, Herd K, Matson A, Bell J. Carbohydrate counting accuracy in adults with cystic fibrosis related diabetes. Nutr Diet 2020;77:508–14.
[325] McFarlane C, Marshall K, Doola Re, Todd A. Nutritional management of cystic fibrosis and cystic fibrosis-related diabetes in Australia. Nutr Diet 2016;73:376–82.
[326] Ziai S, Coriati A, St-Pierre D, Chabot K, Desjardins K, Leroux C, et al. Glucose fluctuations are not modulated by the proportion of calories from macronutrients or spontaneous total energy expenditure in adults with cystic fibrosis. Can J Diabetes 2016;40:389–92.
[327] Armaghanian N, Atkinson F, Taylor N, Kench A, Brand-Miller J, Markovic T, et al. Dietary intake in cystic fibrosis and its role in glucose metabolism. Clin Nutr 2020;39:2495–500.
[328] Scheuing N, Thon A, Konrad K, Bauer M, Karsten C, Meissner T, et al. Carbohydrate intake and insulin requirement in children, adolescents and young adults with cystic fibrosis-related diabetes: a multicenter comparison to type 1 diabetes. Clin Nutr 2015;34:732–8.
[329] Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined exercise training improves glycemic control in adult with cystic fibrosis. Med Sci Sports Exerc 2017;49:231–7.
[330] Moheet A, Chan CL, Granados A, Ode KL, Moran A, Battezzati A. Hypoglycemia in cystic fibrosis: prevalence, impact and treatment. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18(Suppl 2):S19–24.
[331] Leung DH, Narkewicz MR. Cystic fibrosis-related cirrhosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2017;16(Suppl 2):S50–61.
[332] Shah ND, Limketkai BN. The use of medium-chain triglycerides in gastrointestinal disorders. Practical Gastroenterol 2017;160:20–5.
[333] Heuschkel RB, Gottrand F, Devarajan K, Poole H, Callan J, Dias JA, et al. ESPGHAN position paper on management of percutaneous endoscopic gastrostomy in children and adolescents. J Pediatr Gastroenterol Nutr 2015;60:131–41.
[334] Höroldt BS, Lee FK, Gleeson D, McAlindon ME, Sanders DS. Ultrasound guidance in the placement of a percutaneous endoscopic gastrostomy (PEG): an adjuvant technique in patients with abdominal wall varices? Dig Liver Dis 2005;37:709–12.
[335] Lowery EM, Afshar M, West N, Kovacs EJ, Smith B, Joyce C. Self-reported alcohol use in the cystic fibrosis community. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:84–90.
[336] Antosca KM, Chernikova DA, Price CE, Ruoff KL, Li K, Guill MF, et al. Altered stool microbiota of infants with cystic fibrosis shows a reduction in genera associated with immune programming from birth. J Bacteriol 2019;201:e00274. 19.
[337] Thavamani A, Salem I, Sferra TJ, Sankararaman S. Impact of altered gut microbiota and its metabolites in cystic fibrosis. Metabolites 2021;11:123.
[338] Espírito Santo C, Caseiro C, Martins MJ, Monteiro R, Brandão I. Gut microbiota, in the halfway between nutrition and lung function. Nutrients 2021;13:1716.
[339] Sullivan J, Hounchell J, Pecott-Grimm H, Cowan K, Lahiri T. Probiotic use and antibiotic associated gastrointestinal symptoms in pediatric patients with cystic fibrosis. In: Pediatr pulmonol: WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2015. p. 407.
[340] Gonzalez KD, Zuckerman JB, Sears EH, Prato BS, Guill M, Craig W, et al. Exploring probiotic use in a regional cystic fibrosis consortium. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2018;17:e20–1.
[341] Di Nardo G, Oliva S, Menichella A, Pistelli R, De Biase RV, Patriarchi F, et al. Lactobacillus reuteri ATCC55730 in cystic fibrosis. J Pediatr Gastroenterol Nutr 2014;58:81–6.
[342] del Campo R, Garriga M, Perez-Aragon A, Guallarte P, Lamas A, Maiz L, et al. Improvement of digestive health and reduction in proteobacterial populations in the gut microbiota of cystic fibrosis patients using a Lactobacillus reuteri probiotic preparation: a double blind prospective study. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2014;13:716–22.
[343] de Freitas MB, Moreira EAM, Oliveira DL, Tomio C, da Rosa JS, Moreno YMF, et al. Effect of synbiotic supplementation in children and adolescents with cystic fibrosis: a randomized controlled clinical trial. Eur J Clin Nutr 2018;72:736–43.
[344] Bruzzese E, Raia V, Ruberto E, Scotto R, Giannattasio A, Bruzzese D, et al. Lack of efficacy of Lactobacillus GG in reducing pulmonary exacerbations and hospital admissions in children with cystic fibrosis: a randomised placebo controlled trial. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2018;17:375–82.
[345] Bruzzese E, Callegari ML, Raia V, Viscovo S, Scotto R, Ferrari S, et al. Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial. PLoS One 2014;9:e87796.
[346] Bilan N, Marefat E, Nikniaz L, Abbasalizad Farhangi M, Nikniaz Z. Does synbiotic supplementation affect the quality of life in children with cystic fibrosis? A pilot randomized controlled clinical trial. BMC Nutr 2020;6:44.
[347] Van Biervliet S, Hauser B, Verhulst S, Stepman H, Delanghe J, Warzee JP, et al. Probiotics in cystic fibrosis patients: a double blind crossover placebo controlled study: pilot study from the ESPGHAN Working Group on Pancreas/CF. Clin Nutr ESPEN 2018;27:59–65.
[348] Tabori H, Arnold C, Jaudszus A, Mentzel HJ, Renz DM, Reinsch S, et al. Abdominal symptoms in cystic fibrosis and their relation to genotype, history, clinical and laboratory findings. PLoS One 2017;12:e0174463.
[349] Narayanan S, Mainz JG, Gala S, Tabori H, Grossoehme D. Adherence to therapies in cystic fibrosis: a targeted literature review. Expet Rev Respir Med 2017;11:129–45.
[350] Duckers J, Lesher B, Thorat T, Lucas E, McGarry LJ, Chandarana K, et al. Real-world outcomes of ivacaftor treatment in people with cystic fibrosis: a systematic review. J Clin Med 2021;10:1527.
[351] Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database Syst Rev 2020;12:CD010966.
[352] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med 2019;381:1809–19.
[353] Carnovale V, Iacotucci P, Terlizzi V, Colangelo C, Medio P, Ferrillo L, et al. Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease with the Phe508del/minimal function genotype. Respir Med 2021;189:106646.
[354] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet 2019;394:1940–8.
[355] Burgel P-R, Munck A, Durieu I, Chiron R, Mely L, Prevotat A, et al. Real-life safety and effectiveness of lumacaftor–ivacaftor in patients with cystic fibrosis. Am J Respir Crit Care Med 2020;201:188–97.
[356] Aalbers BL, de Winter-de Groot KM, Arets HGM, Hofland RW, de Kiviet AC, van Oirschot-van de Ven MMM, et al. Clinical effect of lumacaftor/ivacaftor in F508del homozygous CF patients with FEV(1) >/= 90% predicted at baseline. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:654–8.
[357] Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, et al. Effect of CFTR modulators on anthropometric parameters in individuals with cystic fibrosis: an evidence analysis center systematic review. J Acad Nutr Diet 2021;121:1364–13678 e2.
[358] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663–72.
[359] Borowitz D, Lubarsky B, Wilschanski M, Munck A, Gelfond D, Bodewes F, et al. Nutritional status improved in cystic fibrosis patients with the G551D mutation after treatment with ivacaftor. Dig Dis Sci 2016;61:198–207.
[360] King SJ, Tierney AC, Edgeworth D, Keating D, Williams E, Kotsimbos T, et al. Body composition and weight changes after ivacaftor treatment in adults with cystic fibrosis carrying the G551 D cystic fibrosis transmembrane conductance regulator mutation: a double-blind, placebo-controlled, randomized, crossover study with open-label extension. Nutrition 2021;85:111124.
[361] Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elexacaftor-tezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:265–71.

[362] Stallings VA, Sainath N, Oberle M, Bertolaso C, Schall JI. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. J Pediatr 2018;201:229–237 e4.
[363] Gelfond D, Heltshe S, Ma C, Rowe SM, Frederick C, Uluer A, et al. Impact of CFTR modulation on intestinal pH, motility, and clinical outcomes in patients with cystic fibrosis and the G551D mutation. Clin Transl Gastroenterol 2017;8:e81.
[364] Sommerburg O, Hammerling S, Schneider SP, Okun J, Langhans CD, Leutz-Schmidt P, et al. CFTR modulator therapy with lumacaftor/ivacaftor alters plasma concentrations of lipid-soluble vitamins A and E in patients with cystic fibrosis. Antioxidants 2021;10:483.
[365] Francalanci M, Terlizzi V, Fevola C, Di Rosa G, Pierattini V, Roselli E, et al. Nutritional status and circulating levels of fat-soluble vitamins in cystic fibrosis patients: a cohort study and evaluation of the effect of CFTR modulators. Basel, Switzerland: Children; 2023. p. 10.
[366] Wisniewski BL, Aylward SC, Jordan CO, Kopp BT, Paul GR. Hypervitaminosis A with fulminant secondary intracranial hypertension following personalized medicine-based Elexacaftor/Tezacaftor/Ivacaftor initiation in a preadolescent with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:e217–20.
[367] Hutchinson I, McNally P. Appearance of pancreatic sufficiency and discontinuation of pancreatic enzyme replacement therapy in children with cystic fibrosis on ivacaftor. Ann Am Thorac Soc 2021;18:182–3.
[368] Mainz JG, Zagoya C, Polte L, Naehrlich L, Sasse L, Eickmeier O, et al. Elexacaftor-tezacaftor-ivacaftor treatment reduces abdominal symptoms in cystic fibrosis-early results obtained with the CF-specific CFAbd-score. Front Pharmacol 2022;13.
[369] Ooi CY, Syed SA, Rossi L, Garg M, Needham B, Avolio J, et al. Impact of CFTR modulation with ivacaftor on gut microbiota and intestinal inflammation. Sci Rep 2018;8:17834.
[370] Tetard C, Mittaine M, Bui S, Beaufils F, Maumus P, Fayon M, et al. Reduced intestinal inflammation with lumacaftor/ivacaftor in adolescents with cystic fibrosis. J Pediatr Gastroenterol Nutr 2020;71:778–81.
[371] Dagenais RVE, Su VCH, Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: a systematic review. J Clin Med 2020;10.
[372] Scully KJ, Marchetti P, Sawicki GS, Uluer A, Cernadas M, Cagnina RE, et al. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:258–63.
[373] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:68–79.
[374] Nolley EP, Pilewski JM. Call for changes in lung allocation to reduce transplant wait-list mortality for cystic fibrosis. American Thoracic Society; 2019. p. 956–7.
[375] Lehr CJ, Skeans M, Dasenbrook E, Fink A, Fernandez G, Faro A, et al. Effect of including important clinical variables on accuracy of the lung allocation score for cystic fibrosis and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2019;200:1013–21.
[376] Jennerich AL, Pryor JB, Wai TYH, Kapnadak SG, Aitken ML, Goss CH, et al. Low body mass index as a barrier to lung transplant in cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2022;21:475–81.
[377] Belkin RA, Henig NR, Singer LG, Chaparro C, Rubenstein RC, Xie SX, et al. Risk factors for death of patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med 2006;173:659–66.
[378] Koutsokera A, Sykes J, Theou O, Rockwood K, Steinack C, Derkenne MF, et al. Frailty predicts outcomes in cystic fibrosis patients listed for lung transplantation. J Heart Lung Transplant 2022;41:1617–27.
[379] Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant 2001;20:288–96.
[380] Levine H, Prais D, Raviv Y, Rusanov V, Rosengarten D, Saute M, et al. Lung transplantation in cystic fibrosis patients in Israel: the importance of ethnicity and nutritional status. Clin Transplant 2017;31.
[381] Ramos KJ, Kapnadak SG, Bradford MC, Somayaji R, Morrell ED, Pilewski JM, et al. Underweight patients with cystic fibrosis have acceptable survival following lung transplantation: a united Network for organ sharing registry study. Chest 2020;157:898–906.
[382] Benden C, Ridout DA, Edwards LB, Boehler A, Christie JD, Sweet SC. Body mass index and its effect on outcome in children after lung transplantation. J Heart Lung Transplant 2013;32:196–201.
[383] Pryor JB, Bradford MC, Jennerich AL, Wai TYH, Pilewski JM, Kapnadak SG, et al. Body mass index recovery after lung transplant for cystic fibrosis. Ann Am Thorac Soc 2022;19:1130–8.
[384] Aaron SD, Stephenson AL, Cameron DW, Whitmore GA. A statistical model to predict one-year risk of death in patients with cystic fibrosis. J Clin Epidemiol 2015;68:1336–45.
[385] Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, et al. Lung transplant referral for individuals with cystic fibrosis: cystic Fibrosis Foundation consensus guidelines. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2019;18:321–33.
[386] Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. J Clin Transl Endocrinol 2021;26:100276.
[387] Beck CE, Lin A, Robbins RC, Dosanjh AK. Improvement in the nutritional and pulmonary profiles of cystic fibrosis patients undergoing bilateral sequential lung and heart-lung transplantation. Nutr Clin Pract 2016;12:216–21.
[388] Hollander-Kraaijeveld FM, van Lanen AS, de Roos NM, van de Graaf EA, Heijerman HGM. Resting energy expenditure in cystic fibrosis patients decreases after lung transplantation, which improves applicability of prediction equations for energy requirement. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2020;19:975–80.
[389] Kalnins D, Pencharz PB, Grasemann H, Solomon M. Energy expenditure and nutritional status in pediatric patients before and after lung transplantation. J Pediatr 2013;163:1500–2.
[390] Hollander FM, Kok A, de Roos NM, Belle-van Meerkerk G, van de Graaf EA. Prediction equations underestimate resting energy expenditure in patients with end-stage cystic fibrosis. Nutr Clin Pract 2017;32:116–21.
[391] Durette G, Jomphe V, Bureau NJ, Poirier C, Ferraro P, Lands LC, et al. Long-term bone mineral density changes and fractures in lung transplant recipients with cystic fibrosis. J Cyst Fibros : Off J Eur Cystic Fibr Soci 2021;20:525–32.
[392] Hubert G, Chung TT, Prosser C, Lien D, Weinkauf J, Brown N, et al. Bone mineral density and fat-soluble vitamin status in adults with cystic fibrosis undergoing lung transplantation: a pilot study. Can J Diet Pract Res 2016;77:199–202.
[393] Toledano MB, Mukherjee SK, Howell J, Westaby D, Khan SA, Bilton D, et al. The emerging burden of liver disease in cystic fibrosis patients: a UK nationwide study. PLoS One 2019;14:e0212779.
[394] Colombo C, Costantini D, Rocchi A, Romano G, Rossi G, Bianchi ML, et al. Effects of liver transplantation on the nutritional status of patients with cystic fibrosis. Transpl Int 2005;18:246–55.
[395] Cheng K, Rosenthal P, Roberts JP, Perito ER. Liver transplant in children and adults with cystic fibrosis: impact of growth failure and nutritional status. Am J Transplant 2022;22:177–86.
[396] Dowman JK, Watson D, Loganathan S, Gunson BK, Hodson J, Mirza DF, et al. Long-term impact of liver transplantation on respiratory function and nutritional status in children and adults with cystic fibrosis. Am J Transplant 2012;12:954–64.
[397] Flemming G, Baumann U, Richter N, Vondran F, Tummler B, Dittrich AM, et al. Survival benefits following liver transplantation: a matched-pair analysis in pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2021;73:385–90.
[398] Wahab AA, Hammoudeh M, Allangawi M, Al-Khalaf F, Chandra P. Bone mineral density in cystic fibrosis patients with the CFTR I1234V mutation in a large kindred family is associated with pancreatic sufficiency. Internet J Rheumatol 2014;2014:465395.