



Review

The nutritional status in CF: Being certain about the uncertainties

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SUMMARY

Background: Nutritional therapy is one of the cornerstones in cystic fibrosis (CF) therapy. There is a strong association between nutritional status and pulmonary function and thus longevity. Therefore nutritional therapy should be continuously adapted to preserve or improve the nutritional status. This narrative review was written to reconsider nutritional therapy in CF based on the latest evidence available since the publication of the ESPEN – ESPGHAN – ECFS guidelines on nutrition care for infants, children and adults with CF.

Methods: A literature search in Pubmed, Scopus and Web of Science was conducted to identify new research focusing on the use of growth charts, body composition, protein intake and pancreatic enzyme therapy (PERT) in CF between June 2014 and June 2017.

Results: The search strategy resulted in a total of 1810 hits across the databases. After reviewing title and abstract only 17 studies were included of which 2 animal studies. The use of growth charts was discussed in 3 studies, body composition in 6, protein intake and digestion in 4 and PERT in 4.

Conclusion: According to the current guidelines and the available evidence of the discussed topics, it is important that the nutritional therapy in CF is redefined according to age, pancreatic function and disease stage. Macronutrients balances are of importance and change over lifetime. As a consequence an accurate PERT intake is required and thus further research on timing and dosage is necessary. To improve the nutritional assessment a proper use of the growth charts and a consensus on body composition measurements, references and thresholds is advised.

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1. Introduction

Cystic fibrosis (CF) is a life-threatening autosomal recessive multisystem disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. A variety of organs, including lungs, pancreas, intestine and hepatobiliary tract are affected [1]. CF, first described in 1938 by Dorothy Andersen, was identified as a pancreatic disease with extensive acinar lesions on autopsy, possibly leading to pancreatic insufficiency. Clinical

characteristics as vitamin A deficiency, increased fibrous tissue in the liver, indeterminate glucose intolerance and chronic respiratory infections were also described in the analysed cases [2]. These gastro-intestinal and endocrine related challenges have a significant impact on the nutritional status and evolution of the disease. Today most of them, like cystic fibrosis related diabetes (CFRD) and cystic fibrosis related liver disease (CFLD), remain a challenge to diagnose and manage [1].

Since Corey et al. (1988) described the importance of a high fat, high calorie diet with sufficient pancreatic enzyme replacement therapy (PERT) for survival, improving nutritional status became one of the cornerstones of CF-therapy [3]. Today, based on registry results, merely half of the CF patients in Europe achieve a BMI according to the guidelines: $\geq 50^{\text{th}}$ percentile (P50) for children or $\geq 23 \text{ kg/m}^2$ or $\geq 22 \text{ kg/m}^2$ for male and female patients respectively [1,4].

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Abbreviations

CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductor
CFRD	cystic fibrosis related diabetes
CFLD	cystic fibrosis related liver disease
BMI	body mass index
FEV1	forced expiratory volume in one second
PERT	pancreatic enzyme replacement therapy
WFL:	weight for length
GC	growth charts
FFM	fat free mass
FFMI	fat free mass index
FM	fat mass
BIA	bioelectrical impedance analysis
DXA	dual-energy X-ray absorptiometry
RV	residual volume
TLC	total lung capacity
NWO	normal weight obesity
PCDR	percentage cumulative dose recovered
ST	skinfold thickness

With increasing life expectancy, the burden and prevalence of comorbidities has increased. Not only CFRD, CFLD, CF-related bone disease and kidney disease, but also obesity and overweight have made their entrance in the CF population [1,5,6].

Furthermore, in light of the current treatments targeting CFTR function a new area of nutritional management might be at our doorstep. CFTR modulator therapy has the potential to improve not only forced expiratory volume in one second (FEV1) but also BMI z-score [7], although this was not observed in all currently available trials [8]. In view of the evolution towards targeted therapies but also persistence of malnutrition in the CF population, it is appropriate to reconsider, reinvestigate and redefine the nutritional therapy and optimal nutritional status across the different life and disease stages. This narrative review, with limited scope, is an attempt to give direction to future research, screening and management of the nutritional status in CF. The authors are aware of other factors influencing the nutritional status in CF which fell out of the scope of this article [1,9].

2. Method

Pubmed and Cochrane databases were searched until 2014 for the update of the ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with CF [1]. The scope of this narrative review is limited to growth charts, body composition, PERT and protein intake and digestion. Within this scope only original research published in English was included. Reviews, short communications, case studies, abstracts, letters to the editor and invited commentaries were excluded. The search terms in various combinations were “cystic fibrosis”, “nutritional status”, “BMI”, “body composition”, “lean body mass”, “fat free mass”, “nutritional assessment”, “protein and nutrition” and “pancreatic enzymes”. The search was undertaken from June 2014 until June 2017 across 3 databases: Pubmed, Scopus and Web of Science. All hits were reviewed. Title and abstract were used to determine relevance for inclusion. No distinction was made between studies conducted in children or adults.

3. Results

A total of 1810 hits resulted in the inclusion of 17 studies. Three studies were included to discuss the use of growth charts as a method to evaluate nutritional status [10–12]. Six studies dealt with body composition as an essential part of nutritional assessment [13–18]. Four studies evaluated protein intake and digestibility [19–22] and 4 studies discussed PERT dosage and timing [23–26]. In the latter two groups, two animal studies were included. A summary of the included studies, according to their subject of research, is given in Tables 1–4. The tables are compiled to support the reading of the results section.

3.1. Growth charts

Based upon the available literature, guidelines advise to aim at a weight for length (WFL) or BMI \geq 50th percentile (P) to ensure optimal nutritional status and safeguard future pulmonary function [1]. Since 2010, Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics recommend the use of the 2006 WHO growth charts (GC) in patients until the age of 2 and the 2000 CDC GC in older patients. Three studies [10–12] focused on the consequences of this advice in the CF population. Zhang et al. (2015) reported an important discrepancy in WFL P between 2000 CDC and 2006 WHO GC at the age of 12–24 months. At the age of 24 months, 29% of the children with a WFL \geq 50th P on WHO GC fell <50th P on the CDC charts. For the BMI, the 50th P on CDC GC was equivalent to the 70th P for boys and the 67th P for girls on the WHO GCs. These differences in nutritional target have consequences on clinical outcomes as demonstrated by Machogu et al. (2015) and Usatin et al. (2017). CF patients with a WFL \geq 50th P on both curves at the age of 2 had a significant higher FEV1 at the age of 6 compared to those with WFL \geq 50th P on the WHO GC alone. Usatin et al. (2017) stratified patients in 3 groups based on their WFL at the age of 2: WFL < 50th P on both GCs, WFL \geq 50th P on WHO but < 50th P on CDC and WFL \geq 50th P on both GCs. At the age of 18 the highest FEV1 was observed in the group with WFL \geq 50th P on both GCs, which also comprised the highest lung-transplant-free proportion of patients. In a parallel analysis, the authors found a correlation between the CDC WFL category (WFL < 10th percentile, WFL 10th to 25th percentile, WFL 25th to 50th percentile and WFL > 50th percentile) and FEV1 at age 18.

3.2. Body composition

Since the 6 studies on body composition used different methods, comparison of the results between studies was impossible [13–18]. All studies suggested fat free mass (FFM) as a more sensitive parameter than BMI to evaluate nutritional status and predict deterioration in pulmonary function. Sands et al. (2015) studied body composition using skinfold thickness measurements. CF children had a lower FFM in limbs and upper part of the trunk compared to controls. The lower FFM was more pronounced in patients with chronic *P. aeruginosa* infection. The CF children were also shorter. Alicandro et al. (2015) studied the concordance between skinfold thickness, single frequency bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA). BIA and DXA displayed a good correlation in their mean FFM measurement. Skinfold thickness measurements, on the other hand, underestimated the body fat percentage (BF%) in children and adult males compared to DXA. There was, however, a poor intra-individual agreement between the 3 techniques. In adults FFM was over- and under-predicted at the respectively lower and upper DXA results. In children fat mass (FM)% and FFM% underestimation decreased during puberty.

Table 1
Overview of included studies on GC.

Growth charts						
Study	Participants N	Participants Age	Male/Female	PI	Study design	Results
[10]	1155	born 2001–2004	48%/52%	100%	retrospective, descriptive registry study	WFL P by age 2 yrs on WHO vs CDC (median (IQR)): 64,8 (41,7–84,9) vs 48,1 (23,7–75,7) $\geq 50^{\text{th}}$ P by age 2 yrs on both GC vs WHO: FEV1% 107% (96–117) vs 103% (94–115) by age 6 yrs
[12]	2587	born 2003–2006	50%/50%	92%	retrospective, descriptive registry study	Age: 24 months, 29% of children short on WHO GC and normal on CDC GC; 27% on WHO WFLp $> 50^{\text{th}}$ at CDC WFLp $< 50^{\text{th}}$; 30% WHO BMIp $> 50^{\text{th}}$ at CDC BMIp $< 50^{\text{th}}$.
[11]	3014	born 1990–1994	54%/46%	91%	retrospective, descriptive registry study	Age: 18 yrs, (mean and 95% CI): FEV1% A: 73,8%, (72,4–75,1); B: 76,7%, (74,4–78,9); C: 80,2%, (78,9–81,4) lung transplant free: A: 83,8%; B: 88,7%; C: 92,3%; pairwise comparisons between: WFL $< 10^{\text{th}}$ P (FEV1% 72.3) to 10th – 25th (FEV1% 73.7, $p = 0.348$), 10th – 25th to 25th – 50 th (FEV1% 76.8, $p = 0.04$), 25th – 50 th to $\geq 50^{\text{th}}$ (FEV1% 80.4, $p = 0.003$)

WFL $< 50^{\text{th}}$ P on both GCs (A); WFL $\geq 50^{\text{th}}$ P on WHO but $< 50^{\text{th}}$ P on CDC (B) and WFL $\geq 50^{\text{th}}$ P on both GCs (C).

Table 2
Overview of included studies on body composition.

Body composition							
Study	Participants N	Participants Age (mean (SD))	Male/Female	PI	Study design	Anthropometric technique	Results
[18]	89	12,3 (3,5)	41%/48%	89.9%	retrospective, cross-sectional reference: Polish subjects	Skinfold thickness (ST) (Holtain Caliper)	mean z-score (SD) range: ST: -0.34 (1.09) (-2.11; -5.52) UAMC: -0.75 (1.01) (-3.23; -1.81)
[13]	142	16 (6)	44%/56%	72%	Cross-sectional Reference DXA: Italian subjects	ST (Holtain Caliper) DXA (Waltham) BIA (50 Hz 800 μ A, BIA 101 RJL)	Mean z-score (SD) ST vs DXA: BF% < 17 yrs male: 15.6 (5.6) vs 19.4 (5.4) female: 20.4 (5.9) vs 24.2 (5.8)
[16]	56	12.2 (2.5)	43%/57%	64%	retrospective, cross-sectional	DXA (Lunar iDEXA Promodel)	52% BMI $> 25^{\text{th}}$ P median (min–max) DXA % torso fat: 17,6 (8.1–33.5)
[14]	32	26.1 (8.9)	44%/56%	97%	Pilot study, cross-sectional	BOD-POD (Concord)	NWO vs Lean vs Obese: FEV1% (mean (SD): 66,2% (19,2) vs 81,5% (19,4) vs 101,0% (12,3))
[15]	54	10.8 (5.8)	45%/55%	94%	2-step prospective study	DXA (Hologic QDR-4500 W) BIA (400–500 μ A 200 kHz, 50 kHz and 5 kHz, Aminostats Bio-ZM II) references BMI: Cole et al. (1990)	FFM depletion (n = 9) median (IQR) vs no FFM depletion (n = 31) Days AB: (155 (105; 222) vs 65 (35.3; 87) $p < 0.001$ FEV1%: 33 (31; 45) vs 91% (71.5; 106) $p < 0.001$
[17]	101	14 (3)	42%/58%	100%	Cross-sectional comparative	DXA (Lunar Prodigy Scanner) Reference: Greek children and adolescents	Association between history of MI and BMI or factors of body composition R^2 ; estimate; SE; p-value BMI: 0.298; -0.58; 0.15; < 0.01 TBLH aBMD: 0.177; -0.64; 0.28; 0.03 FM z-score: 0.280; -0.77; 0.26; < 0.01 FEV1%: 0.077; -0.13; 0.06; 0.04

BIA equations and technique should be validated for the population if used for body composition measurement. For CF patients, an equation was validated by Charatsi et al. (2016), with DXA as a reference method. A significant correlation for FFM ($r = 0.995$; $p < 0.001$) and FM ($r = 0.96$; $p < 0.001$) was found using both techniques. They further studied the relation between body composition measured by BIA and pulmonary function in 40 patients. FFM depletion, defined as FFM_{BIA} z-score ≤ -2 , was present in 9 (22.5%) patients of whom 7 had a BMI z-score > -1 . There was a strong association between FFM depletion and pulmonary outcome. A lower FEV1, longer periods of antibiotic treatment and more thorax hyperinflation (ratio of residual volume/total lung capacity) was noted in the group with FFM depletion. A decrease of 1 unit in FFM z-score resulted in a decrease of 9.3% in FEV1.

Two studies focused on FM in CF [14,16]. Chaves et al. (2015) observed in 9% of the patients an increased torso FM. FM increased in older male patients and correlated with BMI. The less active patients receiving tube feeding displayed the highest torso FM. Alvarez et al. (2016) observed in CF patients compared to controls a

lower BMI and fat free mass index (FFMI) but a similar fat mass index (FMI) and FM%. Normal weight obesity (NWO) defined as a BMI $< 25 \text{ kg/m}^2$ and a FM% $> 23\%$ in men and $> 30\%$ in women, was reported in one third of the CF patients. FEV1 was positively associated with FFMI and negatively with FMI and FM% after adjustment for age, sex and BMI. Patients with NWO had a lower mean FEV1 compared to lean patients (FM% ≤ 30 women, $\leq 23\%$ men) and obese patients (BMI $\geq 30 \text{ kg/m}^2$). Doulgeraki et al. (2017) studied meconium ileus as a possible predictor for impaired body composition and pulmonary function. Independent of the length of the excised small bowel, meconium ileus appeared to increase the risk for suboptimal BMI and FM. FEV1 was significantly lower in the meconium ileus group.

3.3. Macronutrient: protein intake and digestion

Research on macronutrient needs in CF patients is scarce. The current recommendation for protein intake is derived from other inflammatory conditions and set at 20 energy percent (EN%) [1].

Table 3
Overview of included studies on protein.

Protein							
Study	Participants N	Participants Age (mean (SD))	Male/Female	PI	Study design	Technique	Results
[20]	27	CF children n = 10: 14.9 (0.2) CF adults n = 9: 28.6 (0.8) Healthy adults n = 8: 29.2 (1.2)	–	100%	Prospective cohort study, controlled before and after	IV: citrulline (L-[5-13C-5,5-2H2]-Cit) Oral: 15N-spirulina and L-[ring-2H5]Phenylalanine	Protein digestibility as% of healthy subjects for adults vs children: 44.7% vs 48.3% (without PERT) between 340 and 420 min plateau was reached: 93.4% vs 87.4% (after PERT administration) mean (SD) daily intake energy: 1462 (329) kcal/day fat: 35.5 EN% (6,1); protein: 12.7 EN% (1,7) or 45.9 (12,1) grams; carbohydrates: 52 (6,1%) mean intake (EN%): protein 14, fat 34 and carbohydrates 51 PERT: 1520 to 7758 LU/g fat/meal ileal protein digestibility (%) (mean (SD)): C 89 (6) vs P0 29 (11) vs P1 58 (14) vs P2 74 (14)
[21]	75	3.8 (1.3)		100%	Baseline study from multisite RCT	7 day food record	
[19]	207	8.3 (1.2)	53%/47%	91%	prospective, cross-sectional, multicenter	4 day food record and PE registration references: CDC	
[22]	10 (piglets)			60%	Cross-over, controlled	2-levels of enzymes: LU 7500 and 75,000 and PU 388 and 3881	

LU = lipase units; PU = protease units; C = control; P0 = untreated group; P1 = lower dose group; P2 = higher dose group.

Table 4
Overview of included studies on PERT.

PERT							
Study	Participants N	Participants Age (mean (SD))	Male/Female	PI	Study design	Technique	Results
[26]	224	born 1988–2012	52%/48%	100%	Retrospective observational	CFA (n = 1373); 3-day dietary food records (n = 1719)	PERT administration: 2–9 years > 5000LU/KGBW/day; > 9 yrs < to around 3000 LU/kgBW/day; 16 children: >10,000 LU/kgBW/day EN: 1359 - 2043LU/g fat/day and 3959 -7627 LU/kgBW/day; CFA: 91%–96%. PERT: 5620 lipase units/g dietary fat; mean BW (SD): C 79.7 (5.03); P0 51.3 (4.36); P1 62.9 (3.03) GIT weight (g/kg BW): C 42.8 (2.79); P0 64.9 (4.37); P1 54.8 (3.21) PERT: 1333 LU/g fat/meal; 10 min before (A) or after meal (B) PCDR of 13CO ₂ at 360 min A 32.5 (10)% vs B 31.2 (13.7)%; individual basis: PERT B → A: 11 increased PCDR, PERT A → B: 7 increased PCDR.
[24]	12 (piglets)			100%	Animal study	7 day food record	median (IQR): CFA 89.7% (84.9; 93.3); LU/g fat: 719.4 (451.5; 1205); SD LU/g fat: 616.7 (308.1; 1516)
[25]	18	9.8 (4.2)	50%/50%	100%	randomised double blind, control trial	lipase activity: 13C-mixed triglyceride breath test; gastric emptying: 13C-octanoate breath test	
[23]	16	8.6 (4.1)	56%/44%	100%	Retrospective observational	CFA (n = 144); 4-day food records (n = 192)	

C = control; P0 = untreated group; P1 = treated group; GIT: gastrointestinal tract.

This recommendation seems difficult to reach [19,21]. Calvo-Lerma et al. (2017) observed a variable protein intake from 10 to 17 EN% with a mean intake of 14 EN% in a cross sectional study of paediatric patients from 6 different European CF centers. Young patients tended to have a high carbohydrate intake whereas this decreased with age in favour of an increased protein and lipid intake. The mean carbohydrate consumption decreased with 1.1–2.5%/year of life and the mean lipid and protein intake increased with respectively, 0.8–2.2% and 0.7–1.8%. Filigno et al. (2017) noted a mean daily protein intake of 12.7 EN% (1.7) in pre-schoolers. Dinner and lunch contributed to the fat and protein intake whereas snacks mainly contributed to the carbohydrate intake. A strong negative correlation between fat and carbohydrate intake was observed ($r = -0.97$, $P < 0.001$). The absolute energy intake increased with age but the macronutrient intake expressed as EN% did not. Over the 6 months study period the protein EN% intake decreased with

1%. A positive height for age z-score evolution correlated with protein but not with carbohydrate and fat intake.

Another issue is protein digestibility. Two studies focused on the digestibility of protein of which one was performed in an animal model [20,22]. Mary et al. (2017) measured ¹⁵N in the digestive and metabolic pools in pancreatic duct ligated minipigs with different enzyme replacement doses compared to controls. A PERT dose-dependent effect on protein digestion was shown. The PERT dose-dependent effect on plasma proteins could not be shown, possibly due to the high protein content in the test meal. The urinary excretion of ¹⁵N did not differ. The PERT treatment groups differed significantly when total amount of dietary ¹⁵N recovered in plasma protein and urine were pooled. Engelen et al. (2014) demonstrated a severely reduced protein digestion capacity using a continuous sip feeding with added ¹⁵N-labeled spirulina protein and L-[ring-²H₅]phenylalanine (PHE) and measuring the plasma

ratio [^{15}N]PHE to [$^2\text{H}_5$]PHE in pancreatic insufficient CF patients. Without PERT only 46% of protein digestion was reached in CF patients compared to controls. With PERT administration 90% of protein digestion was reached with a significant delay of 100 min. There was no difference between CF children and CF adults. The use of proton pump inhibitors in 85% (16/19) of CF patients had no impact on protein digestion.

3.4. Pancreatic enzymes

PERT is the utmost important factor to correct maldigestion and improve nutritional status in CF patients. In an animal model study, pancreatic insufficient piglets with or without PERT were significantly different compared to controls. Pancreatic insufficient piglets receiving PERT had a significant higher weight compared to those without PERT but did not reach the control weight. PERT dosage was constant and based on the fat content of the meal. Furthermore pancreatic insufficient piglets without PERT had a higher gastrointestinal tract weight [24].

In humans, studies were unable to demonstrate a correlation between BMI and PERT dosage [19,23,26]. Even the coefficient of fat absorption (CFA) could not be related to the PERT dosage [23,26]. 24% of the CF patients with a CFA <85% took comparable PERT dosage to patients with a CFA >85%. Patients using tube feeding (17%) had a higher CFA compared to those without, while PERT intake was not significantly different [26]. Calvo-Lerma et al. (2017) found that PERT dose variability was correlated with improved CFA. Van der Haak et al. (2016) studied PERT timing in relation to gastric emptying using a ^{13}C breath test. The percentage cumulative dose recovered (PCDR) by breath test in the total group did not change according to PERT timing (before or after the meal) and gastric emptying. However, there was a marked inter-individual variance. Changing the enzyme timing according to gastric emptying, improved the PCDR in patients with a low PCDR (6/8). Furthermore, a 10% increase in PCDR was achieved in patients with a fast gastric emptying by giving the enzymes before the meal.

4. Discussion

4.1. Nutritional assessment

Since the study of Corey et al. (1988), the nutritional status, evaluated as BMI, has markedly improved in the CF population. The persistent association between BMI and pulmonary function has led to continuing strategies to improve or maintain an adequate BMI. In the era of constantly evolving therapies targeting CFTR function, a significant number of patients need further nutritional interventions. As a consequence, a proper assessment of the nutritional status is necessary. In this review two aspects concerning the nutritional assessment were addressed: the use of growth charts and the measurement of body composition.

A significant difference between the CDC and WHO charts between the age of 12–24 months has been observed as well as its influence on long-term pulmonary function. Based on these studies, the Cystic Fibrosis Foundation released a recommendation to set the target for WFL \geq P 75th on the WHO GC for children aged 12–24 months. The use of national and ethnic appropriate growth charts is necessary to assess nutritional status, evaluate effect of interventions but also correlate to pulmonary function in CF patients. Machogu et al. (2015) reported, depending on the growth chart used, a difference of 4% in FEV1 in children with CF with a normal pulmonary function. The clinical relevance of this difference was debated. However, other commonly used therapies as dornase alfa (FEV1 difference 5.6%) and hypertonic saline (FEV1 difference 4.15%), had similar effects on FEV1 [10]. Both therapies

are now standards of clinical practice. A good nutritional assessment in the first years of life and proper nutritional therapy should be considered as an adjunct to pulmonary therapy. It should also be noticed that the European Cystic Fibrosis Patient Registry uses the CDC references in their annual report. Therefore the number of children achieving a BMI at the 50th percentile might differ when national or ethical appropriate growth charts are used. The observed differences between the growth charts are not a critique on the methodology of the used growth charts but might create a false sense of security for healthcare providers and thus result in a lesser aggressive nutritional therapy [10,11]. Redefining the use of the growth charts might be of value for the assessment of the nutritional status in CF. Therefore we are aware that more research is needed, e.g. comparing long term outcomes when CDC, WHO and national or regional growth charts are used.

Although measuring body composition is suggested as a more sensitive parameter to evaluate nutritional status and predict deterioration of pulmonary function, there is no consensus on the technique or the used equation, nor are there proper references available. As a consequence, consensus on thresholds for FFM and FFMI are lacking. The strong correlation between FFM and pulmonary function found by Charatsi et al. (2016) justifies the urge for more research concerning body composition. Especially in the era of an increasing incidence of obesity and the introduction of novel therapies, a consensus on the above-mentioned methodological issues is justified. Achieving an acceptable BMI is not always build on acquiring sufficient lean body mass nor does it result in a clinical benefit [14]. Although beyond the scope of this review, research on lean body mass and its influence on pulmonary outcome parameters, requires also insight in the presence of CFRD and physical activity. Insulin is an anabolic hormone therefore deficiency can alter the anabolic response. As a consequence the impaired glucose metabolism can result in energy losses and eventually deteriorate body composition [5]. Physical activity, a known factor to preserve or improve lean body mass has been insufficiently studied in CF [27]. With respect to the relation with pulmonary function, future studies on physical activity in CF should include body composition as an outcome parameter and vice versa.

4.2. Macronutrient: protein intake and digestion

Research on intake and recommendations of macronutrients in CF is scarce. Up to now, fat has been the macronutrient of interest with little attention to protein and carbohydrate. Digestion of these two neglected nutrients is, however, also jeopardized and might have clinical consequences [20,24]. The protein pool (18%) of the human body is constantly renewed. Therefore delivery of essential and non-essential amino acids is needed but an efficient protein use will only occur when other nutrient demands are met. CF patients have three conditions to tackle: a sufficient delivery of nutrients and protein, achieving an adequate digestion and assimilation. Currently there's no evidence available to deal with these conditions in depth. The European guidelines do not distinct protein recommendations according to age, disease stage or pancreatic function [1]. The average protein requirement for healthy children, however, decreases from 1,12 g protein/kg body-weight (BW)/day at the age of 6 months to 0,75 g protein/kg BW/day at the age of 10. From the age of 10 the requirement will differ slightly according to gender. Expressed in g/kg BW the demand for protein is the highest in the first years of life. Facing malnutrition and wasting an increase in protein (2,8–4,8 g/kg/day) and energy (126–167 kcal/kg/day) is needed to obtain weight gain (10–20 g/kg) and growth [28]. As demonstrated by Engelen et al. (2014) protein digestion is delayed by 2 h compared to healthy controls. For amino acids, mainly absorbed in the proximal small intestine,

gastric emptying and thus PERT timing might have an influence, independent of PERT dose. An impaired protein digestion can also result in an impaired anabolic response to a meal [20,22]. As little is known about protein metabolism in CF further research looking at different aspects is needed. Simply increasing protein intake might result in increased undigested protein in the colon influencing the gut microbiome. Alternative protein sources selected for their digestibility might be interesting. Finally, other factors influencing protein metabolism such as inflammation, CFRD and exercise can influence the assimilation of FFM and will have to be taken into account as well.

4.3. PERT

Currently PERT is mainly administered to correct steatorrhea and minimize gastro-intestinal complaints. The dosing guidelines, written as a response to several fibrosing colonopathy case reports, do not aim for optimal digestion and assimilation [1]. There is furthermore an inconsistency in denominators. For instance the denominator lipase units/kg BW/meal does only take into account body weight and not the amount of ingested macronutrients. This might result in under- or over supplementation based on the nutrient intake. Using lipase units/g fat seems physiological more correct but does not take into account the other macronutrients. Efficacy, compliance and influencing factors of PERT will also have to be addressed as up to now, no relation between PERT dose and BMI could be demonstrated [23,25,26]. Adapting PERT timing to gastric emptying might improve digestion [23,25]. Further on, hyperacidity and transit time variations might also influence PERT efficacy. Finally, nutrient absorption might also be altered in CF due to increased losses of bile salts, thickened mucus properties, small intestinal bacterial overgrowth or food factors such as physico-chemical characteristics of the food matrix or type of fat [1,23,26,29]. As demonstrated in PI piglets, the weight of the gastro-intestinal tract increases in absence of PERT. This increase might be a result of an attempt to correct the malabsorption by hypertrophy of the gastrointestinal tract. Therefore, insufficient PERT use might contradict a result in a small false positive evaluation of the body weight. Current research feeds the necessity to not only personalize the PERT dose but also the timing.

5. Conclusion

This review addressed some aspects of the nutritional management in CF since redefining nutritional therapy might be necessary as a consequence of the current evolution in the CF therapy and longevity. Research focusing on growth charts, body composition, protein intake and digestion and PERT was reviewed. Growth charts are not uniform in predicting long-term pulmonary outcomes. Measurement of body composition might be interesting but techniques, references and definitions of FFM and FFM depletion in CF need to be standardized. To improve FFM a balanced diet accounting for age, pancreatic function and disease stage seems necessary. Accurate PERT intake needs further study concerning the influencing factors. Preserving or improving FFM addresses challenges requiring a multidisciplinary approach. More research is needed to tackle the certainty about the uncertainties.

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DD and SVB worked on the concept and the design of the review. SVB did a critical revision of the manuscript. DD performed the literature search, analyzed the abstracts and titles and wrote the manuscript. SVM, SM, SVD, FDB and EVB did a critical review of the method and result section. All co-authors helped during the process with writing suggestions.

References

- [1] Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECSF guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clin Nutr* 2016;35(3):557–77.
- [2] Andersen D. Cystic Fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* 1938;56:344.
- [3] Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41(6):583–91.
- [4] Zolin A, McKone E, van Rens J, Fox A, Lansa P, Pypops U, et al. European cystic fibrosis society patient registry annual report. 2014.
- [5] Moheet A, Moran A. CF-related diabetes: containing the metabolic miscreant of cystic fibrosis. *Pediatr Pulmonol* 2017;52(S48):S37–43.
- [6] Berg KH, Ryom L, Faurholt-Jepsen D, Pressler T, Katzenstein TL. Prevalence and characteristics of chronic kidney disease among Danish adults with cystic fibrosis. *J Cyst Fibros* 2017;17(4):478–83.
- [7] Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstone MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med* 2013;187(11):1219–25.
- [8] Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *N Engl J Med* 2017;377(21):2013–23.
- [9] Engelen MP, Com G, Deutz NE. Protein is an important but undervalued macronutrient in the nutritional care of patients with cystic fibrosis. *Curr Opin Clin Nutr Metab Care* 2014;17(6):515–20.
- [10] 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(3):378–83.
- [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* 2017;16(4):503–9.
- [12] 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(5):1089–95.
- [13] 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* 2015;14(6):784–91.
- [14] 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(4):447–52.
- [15] 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* 2016;15(6):825–33.
- [16] Chaves CR, Cunha AL, Costa AC, Costa Rde S, Lacerda SV. Nutritional status and body fat distribution in children and adolescents with Cystic Fibrosis. *Cien Saude Colet* 2015;20(11):3319–28.
- [17] Doulgieraki 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(6):737–43.
- [18] 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(1):155–63.
- [19] 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* 2017;16(4):510–8.
- [20] Engelen MP, Com G, Anderson PJ, Deutz NE. New stable isotope method to measure protein digestibility and response to pancreatic enzyme intake in cystic fibrosis. *Clin Nutr* 2014;33(6):1024–32.
- [21] 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* 2017;16(4):519–24.

- [22] Mary F, Moessler A, Khodorova N, Foucault-Simonin A, Benamouzig R, Tome D, et al. Metabolic markers of protein maldigestion after a (15)N test meal in minipigs with pancreatic exocrine insufficiency. *Am J Physiol Gastrointest Liver Physiol* 2017;314(2):G223–30.
- [23] 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(10):684–9.
- [24] Mössler A, Schwarzmaier T, Gregory P, Piechotta M, Beyerback M, Kamphues J. Pancreatic exocrine insufficiency affects not only digestibility of nutrients and growth, but also body composition and endocrinological parameters – study on piglets used as a model for children. *Pancreat Disord Ther* 2015;5:003–12.
- [25] 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* 2016;15(5):669–74.
- [26] 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(3):355–60.
- [27] Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: etiology, clinical implications and response to therapeutic interventions. *J Cyst Fibros* 2017;16(5):538–52.
- [28] Joint WHOFAOUNUEC. Protein and amino acid requirements in human nutrition. *World Health Organ Tech Rep Ser* 2007;(935):1–265 [back cover].
- [29] Thorning TK, Bertram HC, Bonjour JP, de Groot L, Dupont D, Feeney E, et al. Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. *Am J Clin Nutr* 2017;105(5):1033–45.