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Nutritional assessment in adults with cystic fibrosis

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ABSTRACT

Objectives: Clinical experience with patients with cystic fibrosis (CF) suggests a nutritional risk in this population. In addition to the lung pathology, a main pathophysiologic concern is the viscous mucus blocking pancreatic ducts, leading to reduced production of pancreatic enzymes. Therefore, maldigestion and consequently malabsorption (particularly fat and fat-soluble vitamins) occur, resulting in steatorrhea, vitamin deficiencies, and subsequently manifest malnutrition. The aim of this study was to investigate the nutritional status and determine the prevalence of malnutrition in an adult Swiss CF cohort.
Methods: This was an observational cohort study in which the nutritional status and dietary habits of patients with CF and healthy controls were compared. Assessment was based on the nutritional risk screening (NRS-2002), dietary habits (7-d dietary record), body composition (bioelectrical impedance analysis), anthropometrics, resting energy expenditure (REE; indirect calorimetry), and physical or mental function (hand-grip strength, Short Form-36 v2).
Results: Nineteen patients (15 men, mean age 32 y) and 15 controls (8 men, mean age 49 y) were included. Eight patients (42%) were at nutritional risk (NRS-2002 $\geq$3). Patients had higher energy intake/body weight ($P = 0.021$) with lower body fat percentage ($P < .001$), body mass index ($P = 0.030$), and physical/mental health scores ($P < 0.001$) than controls. Energy intake was higher than REE in patients ($P = 0.003$), but not in controls ($P = 0.373$).
Conclusions: Prevalence of malnutrition was high in this CF cohort, coinciding with low body fat percentage and low body mass index despite high energy and protein intake. Energy requirements of patients with CF should be estimated as approximately twice the Harris–Benedict REE and 1.7 times indirect calorimetry REE, while ensuring adequate intake of pancreatic enzymes.

Introduction

Cystic fibrosis (CF), or mucoviscidosis, is an inheritable autosomal recessive disorder caused by mutations in a gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein [1,2]. The CFTR protein, an anion channel [3], regulates secretion and absorption in epithelial tissues including airways, gastrointestinal (GI) and reproductive tracts, and sweat and salivary glands [4]. CF is the most common genetically inherited disorder in white populations with ~1 in 3500 newborns affected in Europe [5]. In 1938, when CF was first identified, life expectancy was only a few months and death often was caused by malnutrition [6]. Nowadays, the major cause of death is a complication of the lung disease and most deaths occur between 21 and 30 y of age [7]. Life expectancy is continuously increasing with a median predicted survival age of 48 y for those born in 2016 [8].

The primary cause of morbidity and mortality in CF is the lung disease [8], in which thick, sticky mucus obstructs the airways and impedes mucociliary clearance [9]. Fibrosis and obstruction of the airways results in increased work of breathing [10]. These altered lung mechanics and the inflammatory response to chronic pulmonary infections lead to an increased metabolic rate and, hence, increased dietary energy requirements in patients with CF [10]. Nutritional support is crucial, as lung function correlates with nutritional status [11]. CF also affects the exocrine and the endocrine function of the pancreas. Most CF patients with severe mutations are affected by exocrine pancreatic insufficiency from birth

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but it may also develop later in life [12,13]. The lack of pancreatic enzymes leads to maldigestion and consequently to malabsorption of fat, protein, starch, and substances that are co-absorbed with fat, in particular the fat-soluble vitamins A, D, E, and K. Furthermore, malabsorption of fat causes the loss of an important energy source for the body, and may lead to steatorrhea [14]. Malabsorption, in combination with the increased nutritional requirements of patients with CF, can lead to protein-energy malnutrition with fat-soluble vitamin deficiencies.

The recommended therapy for patients with CF and exocrine pancreatic insufficiency is a high-fat diet with simultaneous administration of pancreatic enzyme replacement therapy (PERT) and substitution of fat-soluble vitamins [15]. Proton pump inhibition therapy may be required to increase pH of duodenal/jejunal chyme (pH >7.0) and thus optimize PERT efficacy [16,17]. Pancreas inflammation and fibrosis result in CF-related diabetes mellitus (CFRD), a distinct form of diabetes sharing features of both types 1 and 2 diabetes [18,19]. CFRD usually develops in late adolescence or adulthood and is highly prevalent in adult patients with CF (30%) [7,8]. Further GI consequences of CF are liver disease and cirrhosis caused by obstruction of the biliary ducts. Moreover, thickened intestinal secretions can lead to constipation and chronic, recurring intestinal obstruction, also called distal intestinal obstruction syndrome [20].

Very little data are available concerning the nutritional state of adult patients with CF. Studies on the nutritional status and prevalence of malnutrition in adult patients with CF, applying various definitions and diagnostic criteria of malnutrition, have found that nearly half of the patients showed symptoms of malnutrition. Korsinska et al. [21] found that 46% of their patients were malnourished using the Cole index to classify nutritional status. Dray et al. [22] found that 49.7% of their patients were malnourished, defining malnutrition as body mass index (BMI) <18.5 kg/m^2. However, some studies also show that the nutritional status of adult patients with CF has improved compared with the last century. Richardson et al. [23] found that 9% of their patients were malnourished, defining malnutrition as BMI <20 kg/m^2. The authors atributted this lower prevalence mainly to improved nutritional management including PERT, oral nutrition supplements, and enteral nutrition. The present study aimed to evaluate the nutritional risk and nutritional status in an adult CF population, using a simple screening tool and further clinical assessment. The findings are important to determine the prevalence of malnutrition and the nutritional needs in these patients.

Materials and methods

A single-center, prospective cohort study was conducted at the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism of the University Hospital of Bern, Switzerland, in collaboration with the Department of Pulmonary Medicine. The study was performed between April and July 2018, and all measurements were taken by the same investigator. All adult patients with CF treated at the Department of Pneumology were consecutively recruited. Patients were included in the study if they were age ≥18 y, of either sex, and diagnosed with CF. Patients were excluded if they were unable to follow the procedures, were pregnant, or were lactating. Historic control data from healthy volunteers [24] were used to compare nutrient intake, body composition, and energy expenditure.

The evaluation of the nutritional status on the basis of structured interviews and physical examination included demographic characteristics, current medication and intake of dietary supplements, nutritional screening, nutritional intake according to diet records, anthropometrics, measurements of body composition and energy expenditure, and laboratory blood analysis.

Nutritional screening

Patients were screened for nutritional risk with the nutritional risk screning 2002 (NRS-2002) [25]. The validated screening tool gives scores of different level of nutritional status to patients, based on weight loss, BMI in combination with general condition, and food intake. It also takes into account disease severity (stress metabolism) and age. NRS-2002 total score is obtained by adding impaired nutritional status score (0–3 points), severity of disease score (0–3 points), and age (1 point if age ≥70 y).

Nutritional assessment

Patients completed a 7-d dietary record before the investigations. Quantitative food intake data was converted into energy and macronutrient intake with the Prodi 6.6 expert dietetic software (Nutri-Science GmbH, Stuttgart, Germany). Resting energy expenditure (REE) was estimated with the Harris-Benedict equation (REE_{HB}) [26] and measured by indirect calorimetry (REE_{IC}; Quark RMR, COSMED srl, Rome, Italy) using the Weir equation [27]. The measurement was performed for 30 min and after an overnight fast (except for water and medication). The time point of measurement was not standardized with the menstrual cycle phase for premenopausal women.

Weight and height were measured with a Seca 707 column scale with a seca 220 telescopic measuring rod (Vogel & Halke GmbH & Co., Hamburg, Germany). Mid-upper arm circumference was measured at the midpoint between the acromion and olecranon of the dominant arm (±1 mm). Triceps skinfold was measured at the same place at the center of the back of the upper arm with a caliper (±1 mm; T. + R. Tüscher AG, Bern, Switzerland). Both measurements were taken three times and the average was used for the calculation of midupper arm muscle area (MAMA) according to Gurney and Jelliffe [28]. Hand-grip strength (HGS) was measured with a hydraulic hand dynamometer model SH5001 (Saehan Corporation, Masan, Korea).

Body composition was measured by bioelectric impedance analysis (BIA) with the Impedance Analysis Apparatus Nutriguard-MS (Data Input GmbH, Pöcking, Germany) at an operating frequency of 50 kHz. The BIA manager of the Geneva University Hospitals was used to calculate total body water, fat mass, and dry fat-free mass, as well as fat mass index and fat-free mass index. The formulae used are shown in Table 1.

Quality of life was assessed using the Optum 36-Item Short-Form Health Survey Version 2 (SF-36 v2).

Blood values were taken from the most recent (within 6 mo) routine blood analysis of the patients. Levels of vitamins A, D, and E, and international normalized ratio as a substitute for vitamin K were recorded. Blood values were not available for the control group.

Ethics

This study was conducted in accordance with the ethical guidelines of the 1957 Declaration of Helsinki and approved by the Bernese Cantonal Ethics committee, Bern, Switzerland.

Table 1
Formulae used by the BIA manager to calculate body composition

Parameter	Males BMI ≤ 26 kg/m^2	Males BMI > 26 kg/m^2	Females BMI < 30 kg/m^2	Females BMI ≥ 30 kg/m^2
FMI	FM/h^2	FM/h^2	FM/h^2	FM/h^2
FFMI	FFM/h^2	FFM/h^2	FFM/h^2	FFM/h^2
FM	$w \times (4.95/\rho - 4.5)$ [29], $\rho = 1.1554 - 0.0841 \times w \times R/h^2$ [30]	w − FFM	w − FFM	w − FFM
FFM	w − FM	$0.00088580 \times h^2 - 0.02999 \times R + 0.42688 \times w - 0.07002 \times a + 14;14.52435$ [31]	$0.398 \times h^2/R + 0.307 \times w + 0.095 \times (h - 100) + 0.741$ [32]	$0.00091186 \times h^2 - 0.01466 \times R + 0.29990 \times w - 0.07012 \times a + 9.37938$ [31]
Dry FFM	FFM − TBW	FFM − TBW	FFM − TBW	FFM − TBW
TBW	$0.396 \times h^2/R + 0.143 \times w + 8.399$ [33]	$0.73 \times FFM$	$0.382 \times h^2/R + 0.105 \times w + 8.315$ [33]	$0.73 \times FFM$

BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat-mass index; h, height; R, resistance; TBW, total body water; w, weight; ρ, density.

Table 2
Demographic characteristics of the study population

	Patient group			Control group		
	Sex	Age, y	BMI, kg/m^2	Sex	Age, y	BMI, kg/m^2
	M	47	23.1	m	31	22.5
	M	42	24.5	m	61	28.4
	M	25	20.7	f	65	24.0
	F	22	22.4	m	65	21.7
	F	25	18.0	m	33	20.3
	M	24	20.9	m	52	26.2
	M	32	19.4	f	69	20.7
	M	38	25.5	f	39	24.2
	M	32	21.9	m	39	23.9
	M	32	21.5	m	35	24.3
	F	33	19.9	m	44	23.4
	M	18	17.0	f	52	19.5
	M	33	22.0	f	54	25.0
	M	22	23.8	f	45	26.0
	M	20	25.6	f	55	27.4
	M	61	17.0			
	F	36	18.6			
	M	40	27.6			
	M	21	20.5			
n	19	n/a	n/a	15	n/a	n/a
Males, n (%)	15 (79)	n/a	n/a	8 (53)	n/a	n/a
Females, n *(%)* (%)	4 (21)	n/a	n/a	7 (47)	n/a	n/a
Mean ± SD	n/a	32 ± 11	21.6 ± 2.9	n/a	49 ± 12	23.8 ± 2.5
Median (min-max)	n/a	32 (18-61)	21.5 (17.0-27.6)	n/a	52 (31-69)	24 (19.5-28.4)

BMI, body mass index; n/a, not applicable.
P-value between patient and control group for sex $P = 0.151$, for age $P < 0.001$, for BMI $P = 0.030$.

Statistical analysis

Statistical analysis was performed with R (version 3.5.0, The R Foundation for Statistical Computing, 2018, Vienna, Austria). The nonparametric Wilcoxon–Mann–Whitney rank sum test for two separate sets of independent and not identically distributed samples was used for continuous variables and the Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant. Results are reported as mean ± SD, median (interquartile ratio) or as number (n) and percentage (%).

Results

Of 29 eligible patients treated at the University Hospital of Bern, 7 (25%) refused to participate for personal reasons and 3 (10%) were unable to participate due to cognitive deficits. Therefore, the study included 34 participants: 19 patients and 15 controls. Table 2 shows the demographic characteristics and BMI of patients and controls. Table 3 shows the CF-specific characteristics.

Nutritional screening and assessment

A significant difference in BMI was found between the two groups. Twelve patients (63%) had BMI below the recommendation for ideal BMI (≥22 kg/m^2 for women and ≥23 kg/m^2 for men), and 6 (32%) were even below the recommendation of >20 kg/m^2 (Table 2) [11,15]. The BMI of patients taking insulin did not significantly differ from that of patients not taking insulin (20.9 [2.4] versus 21.7 [3.9] kg/m^2; $P > 0.999$).

In the nutritional screening, eight patients (42%) but none of the controls were at nutritional risk (NRS-2002 total score ≥3; $P < 0.001$). NRS-2002 total score ranged from 1 to 4 in patients with CF.

Energy and macronutrient intake are shown in Table 4. Daily energy and protein intake per kilogram body weight was significantly higher in the patient group than in the control group, whereas carbohydrate and fat intake in percent energy intake were similar. Six patients (32%) took oral nutritional supplements and 1 (5%) received enteral nutrition.

Table 3
Cystic fibrosis–specific characteristics

Characteristic	n (%)
Family history of cystic fibrosis	6 (32)
Diagnosis during infancy	13 (68)
Genetic mutation F508 del homozygous	9 (47)
Lung transplant	2 (11)
Pancreatic enzyme replacement therapy	16 (84)
Proton pump inhibitors	4 (21)
Vitamin A supplements	16 (84)
Vitamin D supplements	18 (95)
Vitamin E supplements	16 (84)
Vitamin K supplements	16 (84)
Cystic fibrosis-related diabetes mellitus	10 (53)
Insulin therapy	5 (26)

Figure 1 shows REE_{HB}, REE_{IC}, and energy intake of the patient and control group. REE_{IC} tended to be higher in the patient group than in controls in (2010 [482] versus 1811 [226] kcal/d; $P = 0.451$). No significant differences were found in REE_{HB} (1628 [265] versus 1528 [427] kcal/d; $P = 0.891$). Energy intake was significantly higher than REE_{IC} in the patient group (+617 [397] kcal/d; $P = 0.003$), but not in the control group (+57 [804] kcal/d; $P = 0.373$). Physical activity level (PAL) was 1.6 (0.3) in the patients and 1.6 (0.2) in the control group ($P = 0.208$). PAL was excluded from calculations because it proportionally increases energy expenditure.

The MAMA of the patient group was higher than in the control group (52.8 [22.2] versus 55.0 [14.1] cm^2;$P = 0.215$). HGS was similar in the patient and control groups (43 [18] versus 44 [27] kg, respectively; $P = 0.917$). Comparing only men, HGS was significantly weaker in patients than in controls (45 [11] versus 54 [11] kg; $P = 0.024$).

Figure 2 shows the results of the BIA analysis. Fat mass index was significantly lower in the patient group than in the control group (4

Table 4
Nutrient intake in patients with CF and healthy controls

Nutrient		Patient group median (IQR)	Control group median (IQR)	*P*-value
Energy	Absolute, kcal/d	2678 (1049)	1899 (893)	0.059
	Body weight adjusted, kcal·kg·d^{-1}	35 (14)	28 (10)	0.008
Carbohydrate	Absolute, g/d	286 (186)	223 (91)	0.088
	% energy intake	47 (17)	46 (7)	0.564
Fat	Absolute, g/d	90 (29)	86 (36)	0.232
	% energy intake	32 (11)	35 (7)	0.412
Protein	Absolute, g/d	115 (85)	77 (35)	0.016
	Body weight adjusted, kcal·kg·d^{-1}	1.6 (1.1)	1.1 (0.4)	0.004

CF, cystic fibrosis; IQR, interquartile ratio

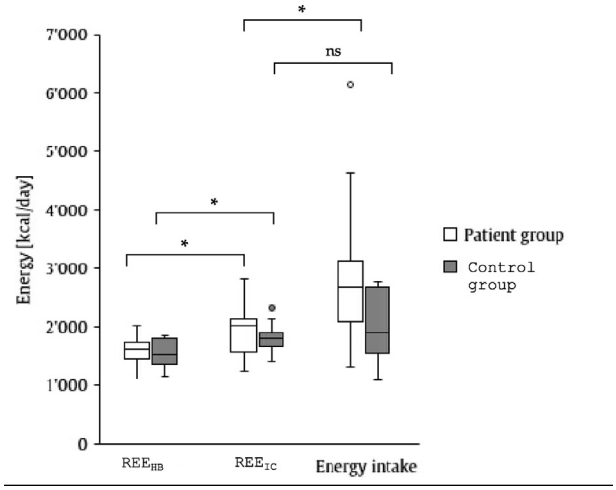

Fig. 1. Energy expenditure and intake of patients with cystic fibrosis and healthy controls. * $P < .050$. ns, not significant; REE$_{HB}$, resting energy expenditure estimated with Harris-Benedict equations; REE$_{IC}$, resting energy expenditure measured with indirect calorimetry.

[2.4] versus 7.3 [1.8] kg/m^2; $P < 0.001$); fat-free mass index did not differ significantly (17.3 [3.4] versus 17 [2] kg/m^2; $P < 0.636$).

Figure 3 displays the results of the quality-of-life (QoL) analysis. Significant differences in QoL were found in every category between the patient and control groups, except for the social functioning and role emotional categories. The mean physical component summary score was 68 ± 15 in the patient group versus 92 ± 7 in the control group ($P < 0.001$). The mean mental component summary score was 70 ± 13 in the patient group versus 90 ± 7 in the control group ($P < 0.001$).

Blood values revealed that three patients (16%) had vitamin A deficiency (normal value: 1.05–2.80 μmol/L), five (26%) had vitamin D deficiency (normal value: 50–135 nmol/L), and two (11%) had vitamin E deficiency (normal value: 12–42 μmol/L). None of the patients had an international normalized ratio >1.2 (indicator for vitamin K deficiency). However, one patient (5%) had increased vitamin A and D levels.

Discussion

The present study aimed to evaluate the nutritional risk and nutritional status in an adult CF population, using the validated NRS-2002 screening tool [25] and comprehensive clinical assessment. Determining the prevalence of malnutrition and the special nutritional needs in patients with CF is especially important because adequate nutritional therapy can substantially improve the clinical outcome of those who are malnourished [34,35]. Eight patients (42%) were at nutritional risk according to the NRS-2002. Eight patients (42%) were malnourished according to the European Society of Clinical Nutrition and Metabolism definition [36], including lack of intake or uptake of nutrition, altered body composition (decreased fat-free mass) and body cell mass, diminished physical and mental function, and impaired clinical outcome. Applying the European Society of Clinical Nutrition and Metabolism diagnostic criteria for malnutrition (combination of BMI, unintentional weight loss, age, and fat-free mass index) [37], only five patients (26%) were malnourished. The high prevalence of malnutrition is in line with previous studies [21,22]. The NRS-2002 lacked sensitivity in two cases and specificity in two others. Chronic low weight with BMI just above the NRS-2002 cutoff of 20.5 kg/m^2, and little or no weight loss despite low muscle mass may explain the lack of sensitivity. Specificity was decreased owing to stable BMI slightly below the cutoff and acute weight loss in the past month owing to surgery. Because CF is a chronic disease, only 1 point was allocated for the severity of disease score (stress metabolism). However, CF causes numerous GI impairments, additionally influencing the nutritional status. In half of the malnourished patients, the disorder was not diagnosed before the study. Hence, there is a need for screening, assessment, and adequate treatment of malnutrition in patients with CF. Nutritional screening with the NRS-2002 should be extensively implemented in all departments treating patients with CF. Additionally, simple measurements such as HGS or BIA could be performed annually to detect a decline in muscle mass and malnutrition in patients who were missed by the NRS-2002.

The median energy intake of patients with was ~700 kcal/d higher than in healthy controls, with great interindividual variations (1332–6140 kcal/d). Patients diagnosed in childhood had a higher energy intake than those diagnosed in adulthood (median difference 752 kcal/d). This might be attributed to the fact that patients with higher disease severity are more likely to be diagnosed in childhood [22], whereas a significant relationship between the type of mutation and nutritional status has been demonstrated [21].

Comparing energy intake with REE$_{IC}$ revealed a positive energy balance in patients (about +600 kcal/d), whereas it was neutral in controls. REE was not multiplied with the PAL value becuase it proportionally increases energy expenditure, which might not be accuarate for patients with CF owing to the increased breathing work under physical load. REE$_{IC}$ was ~200 to 500 kcal/d higher than in previous studies [38–43]; however, some of the patients in these studies were adolescents, with less advanced CF disease and smaller body size. Furthermore, there were more males in the present cohort, which might also account for higher REE$_{IC}$. Then again, in a study reporting REE$_{IC}$ adjusted for fat-free mass, a much higher REE$_{IC}$ than in the present study was found (57 versus 37 kcal/kg fat-free mass daily), and the patients had a considerably lower fat-free mass than in the present cohort [44].

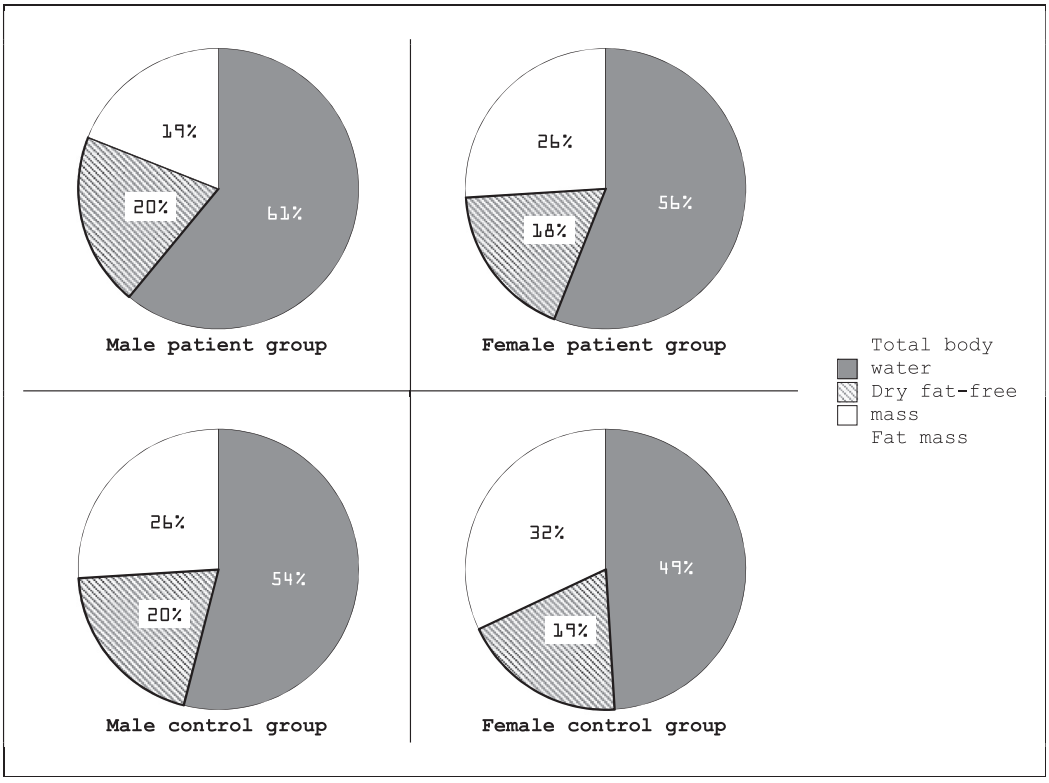

Fig. 2. Body composition of patients with cystic fibrosis and healthy controls.

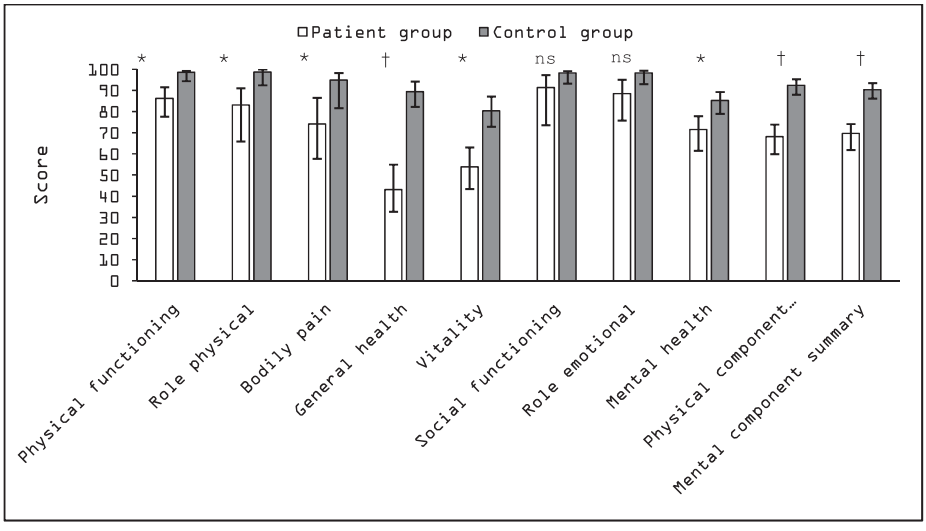

Fig. 3. Quality-of-life scores of patients with cystic fibrosis and healthy controls. *$P < .050$ between patient and control group. †$P < 0.001$ between patient and control group. ns, not significant.

Despite the high nutritional energy intake and positive energy balance, patients with CF had a lower BMI than healthy controls, with 32% below the recommendation of 20 kg/m^2 [11,15]. This is substantially more than found by Richardson et al. [23], probably caused by hypermetabolism as a result of increased work of breathing, systemic inflammation, recurring infections, and malabsorption [10]. Other possible influencing factors include severity of disease, the use of dornase alfa (a mucocytic agent), and tobramycin (an inhaled antibiotic) [23]. A BMI below the recommended values is associated with decreased lung function and higher risk for complications [11], whereas BMI also has been shown to have a significant influence on survival rate in patients with CF [45].

REE_{HB} was 23% lower than REE_{IC}; hence, this weight-, sex-, and age-adapted equation underestimates energy requirements in patients with CF. One previous study compared REE_{IC} to REE_{HB} in patients with CF and found similar results [46]. Patients with CF need 100% REE for basic physiologic function and homeostasis, an extra 20% to 50% to account for malabsorption, and a further 30% should be added in case of malnutrition [47]. Additional energy is needed for physical activity, whereas the increased energy

requirements of patients with CF presumably come into effect even more under physical load owing to the increased work of breathing. In the present study, patients needed an energy intake of 160% REE_{HB} to maintain a stable low BMI with low average physical activity. Thus, it can be concluded that patients with CF need approximately twice the energy calculated with the Harris-Benedict equation or the formula established in practice of 25 kcal/kg body weight daily. On average, this corresponds to 1.7 times the result obtained with the indirect calorimetry measurement.

Protein intake was twice the recommended daily amount for healthy people of 0.8 g/kg body weight [48], which can be attributed to the increased quantity of food consumed and oral nutritional supplements. Nevertheless, patients with CF had reduced fat reserves and five (26%) had a low fat-free mass index, which has been associated with decreased lung function [49]. Because the control group was significantly older, age-related decrease in muscle mass may be seen [50]. The present results showed similar muscle mass in both groups despite the significant age difference, meaning that patients may have lower muscle mass than healthy individuals of the same age. Therefore, fat storage and muscle buildup are impaired in malnourished patients with CF (catabolic metabolic state). Because patients with CF are prone to low insulin levels and CFRD, an oral glucose tolerance test (OGTT) is routinely performed annually. Even before a pathologic OGTT, anabolic hormone insulin and, for male patients, testosterone, might be administered to support muscle buildup and fat storage.

Despite the high rate of vitamin supplementation (95% of the patients) and energy intake, fat-soluble vitamin A, D, and E deficiencies occurred. Possible reasons for this are inadequate substitution or supplementation of fat-soluble vitamins and suboptimal PERT dosage or timing.

QoL assessed by the summary scores was lower in patients with CF than in healthy controls. This was generally reflected in a lower physical health of patients with CF, although social life was not restricted. CF is a degenerative disease that limits patients physically and, to a lesser degree, mentally. Compared with previous studies, patients with CF in the present study had higher or similar scores [51–54].

Strength and limitations of the study

To our knowledge, this was the first study to perform an extensive nutritional assessment using a validated screening tool (NRS-2002) for adults, performed by the same investigator, in an adult population of patients with CF. One limitation of the study was its small sample size. Because this was designed as a single-center study, only adult patients with CF treated at the Department of Pulmonary Medicine of the University Hospital of Bern were recruited. The imbalance between the patient and the historical control group was a further limitation, especially the significant age difference, because it may confound the muscle mass comparison. Additionally, methodological limitations (e.g., errors in measuring the inspiratory and end-tidal oxygen concentration) leading to magnified errors in the calculations or underreporting of the nutritional intake, can be suspected in the control group because intake was lower than REE.

Conclusions

The prevalence of malnutrition is high among patients with CF. The NRS-2002 is a useful tool to detect malnutrition in this population, despite its reduced sensitivity and specificity in few cases. Regular comprehensive nutritional assessments should be performed to ensure optimal nutritional support as patients need twice the energy estimated requirement (and 1.7 times the requirements measured by indirect calorimetry). Accurate use of PERT regarding dosage and timing of intake must be ensured as well.

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