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Use of body mass index percentile to identify fat-free mass depletion in children with cystic fibrosis☆

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SUMMARY

Background & aims: Nutritional failure in children with cystic fibrosis (CF) has a negative effect on their morbidity and survival. It is unknown if determination of fat-free mass is a better screening method for nutritional failure than the currently recommended body mass index (BMI) alone.
Methods: This cross-sectional study in 77 children with CF (age: 14.8 ± 2.9 y) measured fat-free mass, fat mass, bone mineral content and density using dual-energy X-ray absorptiometry. Nutritional failure was defined as BMI <10 percentile and/or fat-free mass index <5th percentile. Statistics were done using ANOVA and *t*-tests.
Results: Thirty-one percent (31%) of the patients with CF was characterized by nutritional failure, and 14% had low fat-free mass index with preserved values for BMI (hidden depletion). Only 52% of the patients with fat-free mass depletion was detected when using the criteria BMI <10 percentile. Patients with fat-free mass depletion had reduced values for forced expiratory volume in 1 s (FEV_1), independent of body mass index ($P < 0.05$), and lower values for bone mineral density in whole body, spine and hip, and spine bone mineral apparent density ($P < 0.01$). BMI ≤20 percentile was associated with a large drop in fat-free mass, a reduced FEV_1, and in bone mineral loss.
Conclusions: Depletion of fat-free mass enhances morbidity in children with CF and is undetected in many of these children when only BMI percentile is used as screening method. BMI percentile of 20 should be considered as the new critical threshold for nutritional failure in CF if body composition techniques are not available.

1. Introduction

Cystic fibrosis (CF) is one of the most common life-threatening inherited disorders in the Caucasian population. In the past decades, the median predicted survival of patients with CF has increased from 10–12 to over 37 years.[1] One of the major factors contributing to this increased survival has been the understanding of the role of optimal nutrition on the overall health status of individuals with CF. Studies showed that in children with CF, better nutritional status was associated with improved linear growth, better pulmonary functions, and exercise tolerance,[2–4] and interventions to establish weight gain led to improvements in pulmonary functions.[5] Since there is a strong association between BMI and overall health metrics, especially lung health,[6] the Cystic Fibrosis Foundation recommends that children with CF maintain a body mass index (BMI) ≥50th percentile. However, malnutrition is still prevalent in children with CF.[7]

BMI is currently the universally accepted method to determine malnutrition in children. However, low body weight and BMI do not differentiate between fat mass (FM) and fat-free mass (FFM), and weight-for-height measurements underestimated the prevalence of malnutrition defined after body composition measurement using total body potassium[8] or skinfold thickness measurements.[9] FFM depletion commonly occurs in adults with CF.[10–14] Previous studies showed that while FFM was low, FM was maintained in 40% of these patients (hidden depletion of FFM),[10,11] and 54% of the patients with a normal body weight for height had low values for lean body mass.[15] Apparent or hidden FFM depletion rather than

Abbreviations: BA, bone area; BMAD, bone mineral apparent density; BMC, bone mineral content; BMCI, bone mineral content index; BMD, bone mineral density; BMI, body mass index; BMIp, body mass index percentile; CF, cystic fibrosis; CFF, cystic fibrosis foundation; CFRD, cystic fibrosis-related diabetes; DXA, dual-energy X-ray absorptiometry; FEV_1, forced expiratory volume in 1 s; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index.

☆ The work was performed at Arkansas Children's Hospital and University of Arkansas for Medical Sciences, Little Rock, AR, USA.

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low body weight in CF was associated with overall disease severity as indicated by decreased lung function, respiratory muscle weakness, increased systemic inflammatory activity, low bone mineral density, and increased frequency of exacerbations.[10,11,15]

Studies in pediatric subjects with CF[16–18] found differences in body composition between young and post-pubertal children with CF. Limited studies are available examining the prevalence of (hidden) FFM depletion in pediatric subjects with CF. A study in 22 children with CF reported that 45% of the patients with FFM had *z*-scores below −2 and half of the normal-weight patients (% ideal weight for height >85%) had FFM *z*-scores below −2.[19] Furthermore, it is unclear at what age, changes in tissue distribution occur in CF and whether FFM depletion in children with CF is associated with increased morbidity (lung function, bone loss, disease severity) as previously observed in adults with CF.[10–14]

The hypotheses for this cross-sectional study were that FFM measurement in children with CF is a better method to screen for malnutrition than the use of BMI percentiles alone, and that depletion of FFM is associated with increased morbidity and worsening of lung health. In this study, we examined a group of randomly selected children with CF to determine (1) the prevalence of underweight and (hidden) FFM depletion, (2) whether (hidden) FFM depletion was associated with changes in body composition on whole body and subregional (trunk and extremities) level, and increased morbidity (reduced lung function, loss of bone mineral density), and (3) whether specific BMI percentiles can be used to predict FFM depletion and increased morbidity.

2. Methods and materials

2.1. Study population

Seventy-seven children, age 8–21 years, with CF who received care at Arkansas Children's Hospital CF Care Center from June 2002 through March 2010 were consecutively enrolled and studied retrospectively. Data were obtained from the electronic medical records of children presenting for routine clinical visits and before hospital discharge when they were admitted for an exacerbation. Approval from the Institutional Review Board of the University of Arkansas for Medical Sciences (IRB # 110166) and patient consent for inclusion in the study was obtained prior to data extraction.

2.2. Anthropometric data and body composition

Body weight was measured by a digital beam scale and height by a stadiometer. BMI was calculated by dividing body weight by squared height. Height, weight and BMI percentiles were calculated in accordance with the CF consensus report.[20]

Whole body soft lean mass (SLM), fat mass (FM), bone mineral content (BMC) and density (BMD), and fat-free mass (FFM) were obtained by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500/Version 12.7.3.1 (Bedford, MA)) when the patients were in supine position. Between-group comparisons were done by adjusting weight, FFM, and FM for differences in body height. For this purpose, these parameters were divided by squared height (kg/m^2), as suggested by VanItallie[21] to obtain BMI, FFMI, and FMI. Body composition was determined in the whole body as well as in the arms, legs, and trunk. The anthropometric and body composition data were compared to published reference data.[22–25] In nearly all patients, a separate regional DXA scan was done to measure BMD of the lumbar spine and hip and values were expressed in g/cm^2 and in *z*-scores. Furthermore, to adjust for size, the bone mineral apparent density (BMAD) was calculated for the lumbar spine from the BMC and bone area (BA) as follows: $BMAD = BMC/BA^{1.5}$.[26]

2.3. Definition of malnutrition

As there is no universally accepted cut-off point for FFM depletion in CF that predicts clinical outcome or survival, FFM depletion was defined as FFMI <5th percentile in accordance to previously published studies in CF.[10–14] Furthermore, the Cystic Fibrosis Foundation selected BMI cut-off points were used for nutritional failure (age ≤20 years: BMIp <10th and age >20 years: BMI <19 kg/m^2).[5] Assessment of puberty was done by the study physician using Tanner staging and growth assessment for girls and boys. Patients were grouped in 3 categories: Pre-pubertal patients (Tanner stage 1), Pubertal patients (Tanner 2, 3 and 4); and Post-pubertal patients (Tanner 5).

2.4. Lung function

Forced expiratory volume in 1 s (FEV_1) was measured by spirometry (nSpire Health, Longmont, CO) in all participants and reference equations[27] were used to calculate FEV_1% predicted values. Lung function data as close to the day of the DXA scan were obtained. Lung function and DXA data were obtained on average 2.3 ± 4.1 days apart. The severity of pulmonary disease was defined as: Normal lung function (FEV_1 >99% pred, $n = 17$), mild lung disease (FEV_1: 70–99% pred, $n = 47$), moderate lung disease (FEV_1: 40–69% pred, $n = 10$); severe disease (FEV_1 <40% pred, $n = 3$).[28]

2.5. Laboratory data

Biochemical blood parameters of fat-soluble vitamins (A, D, and E), serum calcium, HbA1C, albumin, creatinine, blood urea nitrogen, fasting glucose, and liver enzymes and complete blood count differentials were collected. The laboratory data obtained closest to the day of the DXA scan were used in this study. Time difference between lab data and DXA was for fat-soluble vitamins: 43 ± 11 days, serum calcium, HbA1C, albumin, creatinine, blood urea nitrogen, and fasting glucose: 46 ± 5 days, liver enzymes: 52 ± 17 days, and for complete blood count differentials: 9 ± 1 days.

2.6. Statistical analysis

Statistical analysis was performed using Microsoft® 2007 Excel (Microsoft Corporation, Redmond, WA), SPSS Version 17.0, and GraphPad Prism® Version 5.04 (GraphPad Software, Inc. La Jolla, CA) Data were presented as mean ± standard error. For comparison between the groups with a different nutritional status (low BMIp and FFMI, normal BMI and low FFMI, low BMIp and normal FFMI), analysis of covariance (ANCOVA). ANCOVA was done with body composition as the dependent variable, with group as independent variable, and with Tanner score, height (only for absolute body composition values), gender and age as covariates to control for their potential confounding effects. Pearson's rank correlation test and regression analysis were used to determine correlations between variables. $P < 0.05$ was considered statistically significant. Sensitivity of BMIp was calculated as number of patients recognized by BMIp as FFM depleted divided by the total number of depleted patients. Specificity was calculated as number of non-depleted patients recognized by BMIp as non-depleted divided by the total number of non-depleted patients.

3. Results

3.1. Patients characteristics

The study group consisted of 77 children with CF (40 females, 37 males), with a mean age of 14.8 ± 2.9 years. Characteristics were as

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Table 1
Body composition characteristics of the CF group stratified by nutritional status.

		Low BMIp and FFMI $n = 12$	Normal BMIp and Low FFMI (Hidden FFM depletion) $n = 11$	Normal BMIp and FFMI $n = 54$
Males/females		8/4	4/7	25/29
Age	yr	15.4 ± 2.2	15.1 ± 2.3	14.6 ± 3.1
	range yr	11–19	12–18	8–19
FEV_1	%pred	69.3 ± 29.1**	73.4 ± 14.4*	87.6 ± 15.8
FVC	%pred	82.1 ± 19.4**	86.8 ± 14.1*	98.3 ± 19.4
Tanner stage				
Pre-pub/Pub/ Post-pub	*n*	0/9/3	1/7/3	12/26/16
BMI	percentile	4.3 ± 1.7***,##	34.3 ± 22.5*	50.2 ± 22.4
Height	percentile	23.4 ± 21.0	23.4 ± 30.0	34.7 ± 24.7
Weight	percentile	7.3 ± 11.6***,##	23.8 ± 18.4*	42.9 ± 23.1
FFM total	kg	34.4 ± 10.3***	33.8 ± 7.1**	39.8 ± 12.0
FFM trunk	kg	16.7 ± 4.8***	16.8 ± 3.5***	19.6 ± 5.8
FFM extremities	kg	14.5 ± 5.6***	13.6 ± 3.8***	16.8 ± 5.9
FFM extremities/ trunk	ratio	0.86 ± 0.05	0.81 ± 0.04	0.85 ± 0.01
FM total	kg	6.7 ± 2.0**,##	12.8 ± 4.5	10.6 ± 5.3
M trunk	kg	2.4 ± 0.8**,p=0.09	4.2 ± 1.7	4.0 ± 2.3
FM extremities	kg	3.5 ± 1.4*,##	7.7 ± 3.0	5.8 ± 3.1
FM extremities/ trunk	ratio	1.48 ± 0.12#	1.86 ± 0.17**	1.51 ± 0.05

Results expressed as mean ± standard deviation and number of patients (n). FEV_1 (Forced expiratory volume in 1 s), FVC (Forced vital capacity), Pre-pubertal: Tanner stage 1, Pubertal: Tanner stage 2–4, Post-pubertal: Tanner stage 5, BMI (body mass index), FFM (fat-free mass), FM (fat mass). Significance of difference as compared to the normal BMIp (body mass index percentile) + FFMI group: *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, Significance of difference as compared to the hidden FFM depletion group: ##: $P < 0.01$. Statistical analysis was done after adjustment for differences in gender, age, height and Tanner Stage between the groups.

follows: 63% homozygote for ΔF508, 26% heterozygote for ΔF508, 11% gene combination without ΔF508, 97% pancreatic insufficient, 13% Cystic Fibrosis-related diabetes, 27% liver disease, 30% received nocturnal enteral nutrition, and 6% had a history of short bowel syndrome.

3.1.1. Prevalence of malnutrition

Twenty-four children (31%) were characterized by malnutrition as defined by the FFMI and/or BMIp criteria; 16% had low BMIp and FFMI; 14% had normal BMI and low FFMI (hidden depletion); and 1% had low BMIp and normal FFMI. Overall, 30% of patients were characterized by FFM depletion. The sensitivity of BMIp for detecting FFM depletion was 52% and the specificity was 98%. Age and Tanner stage were not different between the 3 groups (Table 1).

3.1.1.1. Body composition (Table 1, Fig. 1). Body weight, height and composition of the subjects with hidden FFM depletion was compared to that of the group with low BMIp and FFMI, and with a normal BMIp and FFMI. Body weight and BMIp were reduced in the low BMIp and FFMI group ($P < 0.001$) as well as in the hidden FFM depletion group ($P < 0.05$), the lowest values being present in the low BMI and FFMI group ($P < 0.01$). No significant differences were found in height (percentile) and Tanner stage between the 3 groups.

FFMI as % of normal (Fig. 1, upper left panel) was reduced in both the low BMIp and FFMI, and the hidden FFM depletion group as compared to the normal BMI and FFMI group ($P < 0.001$). FFM of whole body, trunk and extremities were all lower in both the low BMIp and FFMI, and the hidden FFM depletion group after adjustment for age, gender, Tanner stage and height (Table 1, $P < 0.01$). FMI as % of normal (Fig. 1, upper right panel) was reduced in the low BMIp and FFMI group ($P < 0.05$). FM of whole body and extremities were lower in the low BMIp and FFMI group as compared to the hidden FFM depletion group ($P < 0.01$) and the normal BMI and

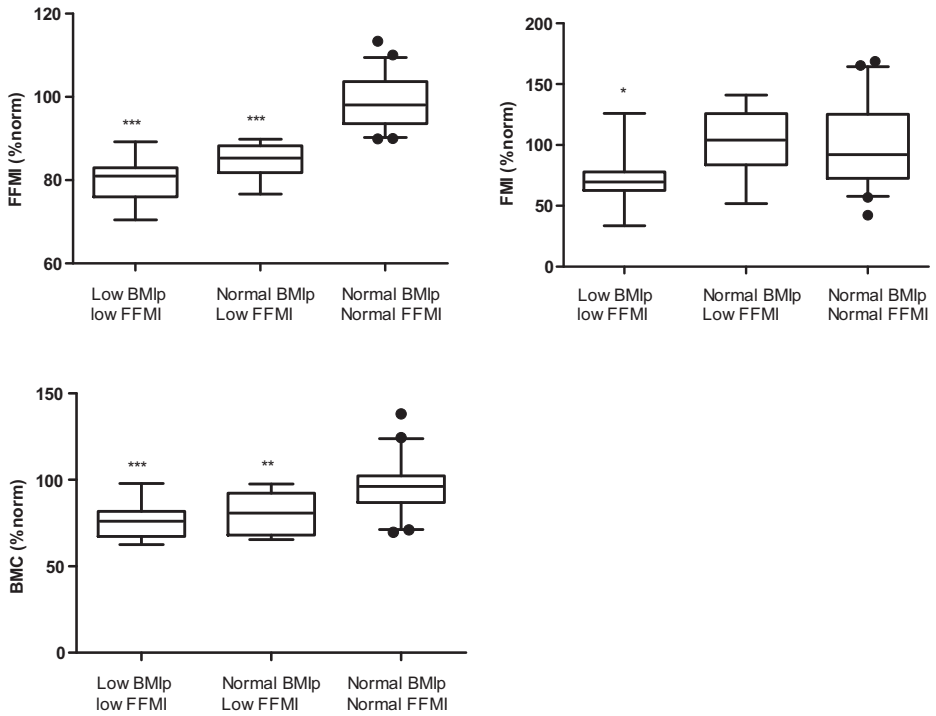

Fig. 1. Box plots (Fat-free mass index (FFMI), upper left panel), Fat mass index (FMI, upper right panel) and Bone mineral content (BMC, lower left panel) in % of normal values of the total body after stratification of the CF group into the subgroups: (1) Low BMIp + low FFMI, (2) Normal BMIp + low FFMI (hidden FFM depletion), and (3) Normal BMIp + normal FFMI. The dark black dots represent individual values outside the 5–95 percentile interval (outliers). Significance of difference as compared to group with Normal BMIp + normal FFMI: ***: $P < 0.001$, **: $P < 0.01$.

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FFMI group (Table 1, $P < 0.05$). FM of the trunk was also lower in the low BMIp and FFMI group ($P < 0.01$) and a tendency toward lower values for FM trunk was found as compared to the hidden FFM depletion group ($P = 0.09$) after adjustment for age, gender, Tanner stage and height. FM extremities-to-trunk ratio was higher in patients with hidden FFM depletion than in the low BMIp and FFMI group ($P < 0.01$) and the normal BMIp and FFMI ($P < 0.05$) group.

3.1.1.2. Bone mineral characteristics (Table 2, Fig. 1). BMC as percentage of normative data (Fig. 1, lower left panel) was reduced in the group with low BMIp and FFMI ($P < 0.001$) and in the hidden FFM depletion group ($P < 0.05$) as compared to the normal BMIp and FFMI group, and BMCI (Table 2) was reduced in the low BMIp and FFMI group ($P < 0.05$). BMD of whole body and spine were lower (in *z*-score ($P < 0.01$)) in those with low BMIp and FFMI as compared to normal BMIp and FFMI. There were no significant differences found in BMAD spine between the 3 groups although significant lower values were found when the group with hidden FFM depletion was combined with the low BMI and FFMI ($p < 0.01$, data not shown). No significant differences were found in BMD hip (in g/cm^2) between the 3 groups but in *z*-score the values were reduced in both the group with low BMIp and FFMI and in the hidden FFM depletion group ($P < 0.05$).

FFMI (%norm) was significantly related to BMD (*z*-scores) of whole body (r: 0.41, $P < 0.001$), hip (r: 0.46, $P < 0.001$), and spine (r: 0.40, $P < 0.001$) as well as to BMAD (r: 0.38, $P < 0.001$). FMI (%norm) was not significantly related to any of the bone mineral markers (data not shown). The findings did not significantly change when using FFMI or LBMI (both as absolute values as normal values are not present for LBM) in the relationship with bone mineral markers (data not shown).

3.1.1.3. Lung function and clinical status. FEV_1 and forced vital capacity (FVC) (Table 1) were reduced in both the hidden FFM depletion group ($P < 0.05$) and the low BMIp and FFMI group ($P < 0.01$). There were no differences in disease characteristics (% pancreatic insufficiency, liver disease, short bowel syndrome, CFRD, number of antibiotic use or hospitalizations within past or last 3 years) and biochemical values between the 3 groups (data not shown). Only plasma albumin ($P < 0.001$) and serum calcium ($P < 0.05$) levels were reduced in the low BMI and FFMI group. FEV_1 was significantly correlated with FFMI %norm (r: 0.39, $P < 0.001$) and FMI %norm (r: 0.30, $P < 0.01$) but not with FM/FFM (r: 0.21). Stratification by gender resulted in a significant correlation between FEV_1 and FFMI %norm (r: 0.59, $P < 0.001$), FMI %norm (r: 0.45, $P < 0.01$) and FM/FFM (r: 0.34, $P = 0.05$) in males but no significant correlation was observed in females. Correlation coefficients were comparable when using FFMI or LBMI (both as absolute values) in the relationship with FEV_1 even after stratification for gender (data not shown).

Table 2
Body mineral characteristics of the CF group stratified by nutritional status.

		Low BMIp and FFMI $n = 12$	Normal BMIP and Low FFMI (Hidden FFM depletion) $n = 11$	Normal BMIp and FFMI $n = 54$
BMC Index total	kg/m^2	0.59 ± 0.07*	0.64 ± 0.14	0.68 ± 0.12
BMD whole body	g/cm^2	0.94 ± 0.13	0.97 ± 0.15	1.01 ± 0.15
BMD whole body	*z*-score	−1.23 ± 1.04**	−0.70 ± 1.12	−0.03 ± 1.17
BMD spine	g/cm^2	0.75 ± 0.12	0.79 ± 0.18	0.85 ± 0.17
BMD spine	*z*-score	−1.32 ± 0.68**	−0.90 ± 1.06	−0.23 ± 1.12
BMAD spine	g/cm^3	0.109 ± 0.013	0.117 ± 0.019	0.121 ± 0.181
BMD hip	g/cm^2	0.79 ± 0.12	0.76 ± 0.15	0.86 ± 0.21
BMD hip	*z*-score	−1.46 ± 0.73*	−1.63 ± 1.01*	−0.55 ± 1.17

Results expressed as mean ± standard deviation. BMC (bone mineral content), BMD (bone mineral density), BMAD (Bone mineral apparent density). Significance of difference as compared to the normal BMIp (body mass index percentile) + FFMI group: *: $P < 0.05$, **: $P < 0.01$.

3.2. Re-evaluation of the currently used cut-off point for nutritional failure

As the sensitivity of the BMIp cut-off point of <10th to predict FFM depletion was low (52%), we investigated whether a specific BMIp cut-off point exists that would predict FFM depletion and poor clinical outcome. The study population was stratified in BMIp categories of 10 percentiles, and in each subgroup body composition, bone mineral density, and lung function was assessed. The number of subjects in each group was 13 (BMIp <10), 7 (BMIp: 10–20), 11 (BMIp: 20–30), 6 (BMIp: 30–40), 13 (BMIp: 40–50), 27 (BMIp ≥50).

3.2.1. Body composition

Fig. 2 shows a gradual reduction in FFMI% with the decline in BMIp. Below the 20th BMI percentile, there was a drop in FFMI% below 90% of normative values which agrees with a FFMI <5th percentile. Fifty-seven percent (57%) of the patients in the category 10–20th BMI percentile had FFM depletion, compared to 18% in the category 20–30th BMI percentile (Fig. 3, left panel). Nearly all patients (92%) with BMIp <10 were FFM depleted. Whereas FM remained relatively stable until BMIp <10, at BMIp <10 there were lower values for both FM and FFM (Fig. 2). BMIp ≥50 was associated mainly with higher values for FM.

3.2.2. Lung functions and bone mineral density

With the decline in BMIp, there was also a gradual reduction in mean FEV_1 (Fig. 3, right panel). Below 20th BMI percentile mean FEV_1 dropped below 80%pred, a threshold for abnormal lung function in children with CF. Comparable observation was also found for total BMD (Fig. 4). Below the 20th BMIp the percentage of patients with a BMD *z*-score ≤−1.0 increased steeply whereas no differences were found in the percentage of patients with a reduced BMD in the group BMIp: 20–49.

4. Discussion

In the present study, we found that FFM depletion in children with CF was poorly detected when using the 10% BMIp cut-off

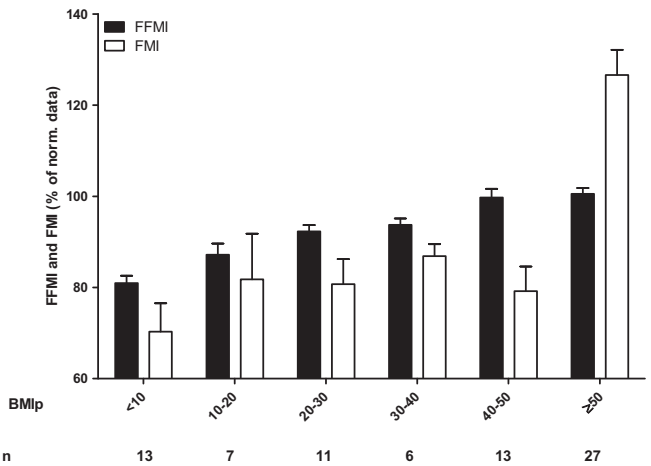

Fig. 2. FFMI (%) and FMI (%) after stratification of the CF group in BMIp groups of 10 percentiles.

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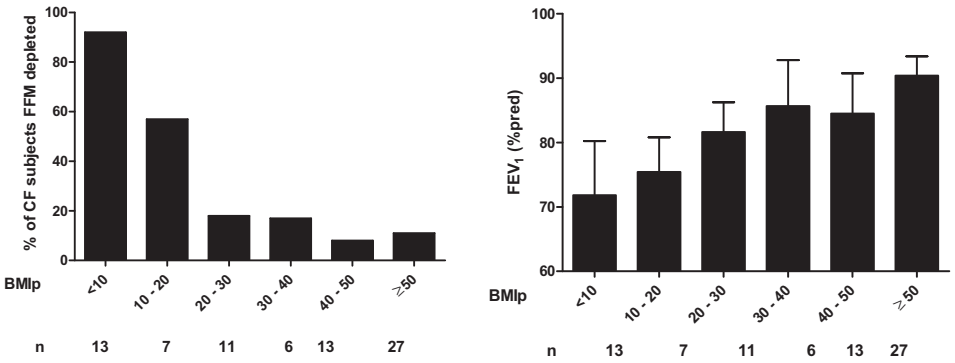

Fig. 3. Percentage of pediatric CF patients with FFM depletion (left panel), and mean FEV_1 (right panel) after stratification of the CF group in BMIp groups of 10 percentiles.

criteria defined by the CFF as nutritional failure, and the results support the CFF recommendations for a good nutritional status with a BMIp ≥50. Fifty-eight percent (58%) of the CF patients with FFM depletion had BMIp larger than 10% (hidden FFM depletion), indicating that a large portion of patients would have been missed when malnutrition was purely defined by these criteria. Low FFM values were associated with reduced lung function and bone mineral loss indicating the clinical importance of measuring body composition in children with CF.

4.1. Prevalence of malnutrition and changes in whole body and subregional body composition in CF

In this study, 17% of the patients were characterized by nutritional failure (BMIp <10) which was comparable to a previous study in children with CF (14%)[29] but lower than that of another smaller study (31%).[30] Thirty percent (30%) of our patients had low FFM values, assessed by DXA independent of their BMI values. Until now, prevalence of low FFM in children with CF has been studied using total body potassium to determine body cell mass, finding comparable values.[8] In a more recent study,[30] 52% of the pediatric patients with CF had low FFM according to mid-arm muscle circumference (<5th percentile), which is a less accurate method of measurement. Most of these body composition studies in children with CF used 2-component models to assess FM and fat-free mass FFM. A recent study using the gold-standard 4-component model (4CM),[31] showed that although shorter than healthy children, boys with CF were heavier and had a body composition within the normal range; whereas girls with CF had lower fat mass than did healthy girls. However in that study a much younger group of children with CF was studied with a tighter age range (6–12 y).

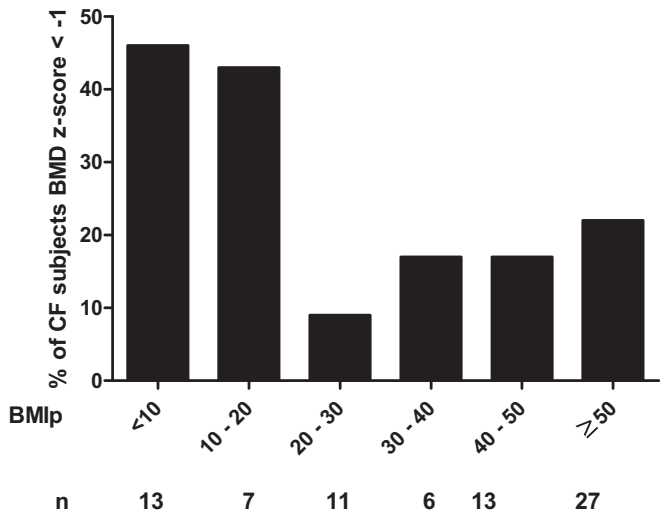

Fig. 4. Percentage of pediatric CF patients with a BMD *z*-score ≤−1.0 after stratification of the CF group in BMIp groups of 10 percentiles.

DXA has been used to study prevalence of FFM depletion in adults with CF with a prevalence of FFM depletion around 60%,[10–14] suggesting that aging is associated with a higher occurrence of FFM depletion. As patients with CF get older, a gradual decline in lung function associated with chronic inflammation and an increased number of pulmonary exacerbations contribute to their low FFM levels. However, overestimation of FFM depletion might be present in most of the CF adult studies[11–13] as FFM was not standardized for the individual's body height which is important as CF is associated with stunting. Furthermore, these adult patients had a high prevalence of severe lung impairment (35%–41%) and a significant correlation was found between FFM depletion and FEV_1 (%).[10–14] A significant correlation was also found between FFMI %norm and lung function in the present study, which was due to a significant relationship in boys but not in girls. The available studies in children and young adults with CF using DXA observed a weak correlation between FFM and FEV_1 (%),[17,18,32,33] but most of the studied patients had mild lung disease. A strong association was found between the severity of pulmonary disease and reduced levels for total body bone mineral,[33] BMI[17,18] and FM,[31] the last was in line with our data indicating that FMI %norm itself also has a large influence on lung function in boys but not in girls with CF. The apparent gender difference in the relationship between lung function and body composition needs further investigation. Despite improvement in survival and lung function in patients with CF, the rate of decline in FEV_1 that starts in the adolescent years has not changed. Poor compliance with chronic medications is common in most adolescents with CF, negatively affecting clinical status.[34–36]

4.2. Hidden FFM depletion

Fourteen percent (14%) of the subjects had hidden FFM depletion. Despite FFM depletion, half of them had an adequate (BMIp: 25–50) or recommended (BMIp >50) nutritional status as defined by the Cystic Fibrosis Foundation.[7] The available studies in children with CF observed slightly higher prevalence of hidden FFM depletion; however, different techniques to measure FFM (TBK[8] and MAMC[30]) or different definitions for FFM depletion or underweight[15] were used. The prevalence of hidden FFM depletion was higher in adults with CF (25–38%),[10,11,14] probably related to the increased disease severity.

FFM was evenly reduced among the extremities and trunk in the patients with hidden FFM depletion as compared to the normal BMI

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and FFMI group after adjustment for differences in gender, age, height and puberty. There was a tendency toward elevated FM values in the hidden depletion group as compared to the normal BMIp/normal FFMI group due to higher FM values in the extremities. Spine and hip BMD, as well as total BMD, assessed by DXA, which is known for its relative high precision for bone measurement,[37] were lower in patients with FFM depletion, as well as FEV_1. Although the difference in BMAD did not reach significance between the 3 groups, BMAD was significantly lower in the total group of patients with low FFMI (independent of FMI). The group with hidden FFM depletion had lower values for FEV_1 and BMC (as % of normal) than the normal BMIp and FFMI group and comparable values as those with low BMIp and FFMI. This indicates that low FFM values in pediatric CF are associated with reduced lung function and bone loss. In line, FEV_1 (%) was also lower in adults with CF characterized by hidden FFM depletion.[11] Preferential FFM depletion suggests a catabolic state and chronic inflammation. In the study by King,[14] patients that received enteral nutrition were overrepresented in the hidden FFM group, suggesting that nutritional support may not restore FFM but that weight gain is mostly FM in patients with ongoing chronic inflammation. In addition, factors like negative energy balance, malabsorption for fat and/or protein, corticosteroid therapy, reduced levels of sex hormones and hypoinsulinemia also contribute to preferential FFM depletion in CF.[13] In CF, reduced FFM was associated with impaired inspiratory muscle function,[38] activity level of the patient, number of exacerbations in the previous year and inflammatory mediators.[11–13] In the present study, there was no difference in the number of hospitalizations and exacerbations in the preceding 3 years before the DXA measurement between CF patients with or without FFM depletion, suggesting that FFM depletion in children with CF does not immediately result in advanced clinical impairment. Since most of our patients were adolescents, FFM depletion may represent delayed puberty and hormone release like androgens that help build FFM. The hidden FFM depletion in CF could be explained by enhanced use of body proteins for energy production as a result of a negative energy balance.

Patients with FFM depletion had reduced values for FEV_1, BMD in whole body, spine and hip, and total BMAD. This indicates that FFM depletion starts early in life in CF and is associated with clinical impairment such as reduced lung function and bone loss.

4.3. BMI percentiles to predict FFM depletion

BMIp failed to detect FFM depletion in 58% of the FFM depleted patients indicating that the current BMIp threshold of nutritional failure (BMIp <10) needs to be re-evaluated. Stratification of the study population in BMIp categories of 10 percentiles showed that mean FFMI% was normal at and above the threshold of 40th BMIp, suggesting that above this threshold only FM increase is expected. FEV_1 values $<90\%$ were reached at BMIp <50th, confirming that BMIp of 50 remains the recommended cut-off point for good nutritional status. The BMIp <20 group had more patients with low FFMI, low BMD, and reduced lung function than the BMIp ≥ 20 group. Furthermore, the number of patients with total BMD and BMD in the hip z-score ≤ -1.0 also increased steeply at BMIp <20th. The results suggest that nutritional failure can be redefined as BMIp <20 and children with CF are at nutritional risk with a BMIp in the 20–50th percentile. This study also shows that FFM depletion can still be present in children with a BMIp in the 20–50th and ≥ 50th percentile. Using BMIp <20 as the cut-off point for nutritional failure covered 63% of the patients with FFM depletion, indicating that 37% was still not recognized by use of this BMIp cut-off point alone.

4.4. Limitations of the study

The present study was using DXA as body composition method. DXA is a valuable tool for assessing pediatric bone health as the precision of the DXA for bone is good but the accuracy is variable particularly in assessment of soft tissue. Errors in body composition measurement by DXA occur because body fat and fat-free mass are not distributed uniformly,[37] and the bias in FFM and FM varies according to the sex, size, fatness, and disease state of the subjects.[39] DXA is not able to accurately evaluate FM and the nature of FFM (water, protein and mineral) like the gold-standard 4-component model (4CM).[31] In the present study, references for body composition were used that were generated by a different method than that used in the present study (hydrodensitometry vs. DXA). Furthermore, lung function data were not always obtained on the same day as the DXA but as close to the day of the DXA scan (on average 2.3 ± 4.1 days apart). In 61% of the patients, the lung function measurement was done on the same day, the following or previous day. The maximal time frame between DXA and lung function was 51 days. The fact that no differences in clinical endpoints were found between the groups might be caused by lack of power of the study due to the relative small number of patients in some of the groups. Furthermore, the large age range may mask differences between the studied groups due to growth and puberty. Stratification into pre-pubertal group (Tanner 1), pubertal (Tanner 2–4) and post-pubertal (Tanner 5) (data not shown) showed that in the pre-pubertal group 93% of the subjects had normal BMIp and FFMI, whereas in the pubertal (Tanner 2–4) and post-pubertal (Tanner 5) group these percentages were 61 and 69% respectively. In the pubertal group relatively more patients had reduced BMIp and FFMI as compared to hidden depletion (23 vs. 15%), whereas in the post-pubertal group this was more equally divided (13% vs. 17%). Although nearly all CF patients were included of the CF Center ACH, which is considered a middle to large size center, studies in larger or multiple centers are needed to analyze in a larger study population the differences in body composition in detail between these pre-, post- and pubertal groups, taking into account a potential gender effect, and to confirm our newly proposed cut-off point for BMI.

In conclusion, the present study shows that FFM depletion is present in many children with CF independent of their BMI, and that the currently used BMIp cut-off point does not recognize FFM depletion in a large percentage of this group. BMI percentile of 20 should be considered as the new critical threshold for nutritional failure in CF, although this new cut-off point still does not recognize all cases of malnutrition and therefore can only be used if body composition techniques are not available. Furthermore, longitudinal studies are needed examining whether a change in nutritional status in patients with CF with nutritional failure and those with hidden FFM depletion in time is associated with changes in outcome parameters like exacerbation rate, quality of life, muscle function, and hospitalization rate.

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Conflict of interest

There is no conflict of interest to declare.

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