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Original Article

Bioelectrical impedance in young patients with cystic fibrosis: Validation of a specific equation and clinical relevance

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Abstract

Background: Body composition (BC) analysis based on bioelectrical impedance analysis (BIA) provides conflicting results. The purpose of the study was to validate an equation specific for young patients with cystic fibrosis (CF), describe their BC and investigate its association with lung function.
Methods: Fifty-four young CF patients were evaluated by BIA and dual X-ray absorptiometry (DXA). An empirically derived CF-specific equation for fat-free mass (FFM) estimation by BIA was elaborated after stepwise multivariate regression and the agreement between BIA and DXA was assessed by Bland–Altman plots. The association between BC and lung function was investigated by regression analysis.
Results: The mean difference between the BIA and DXA assessment was close to zero. A total of 22.5% of patients ($n = 9$) presented a FFM z-score ≤ -2. They had a worse pulmonary function and diaphragmatic impairment. Among these 9 patients, 7 had a normal BMI z-score > -1.
Conclusions: BIA, based on a CF-specific equation, is a reliable method for BC assessment and allows the identification of patients at risk of nutritional degradation and bad respiratory prognosis.

Keywords: Cystic fibrosis; Body composition; Bioelectrical impedance analysis; Fat-free mass; Lung function; Diaphragm

1. Introduction

The crucial role of nutritional status in the survival of cystic fibrosis (CF) patients has been identified from first identifications of the disease [1]. This was further demonstrated by Corey et al. with the comparison between patients followed in Boston and in Toronto [1]. The latter were administered pancreatic enzyme replacement therapy with unrestricted fat diet in contrast to a low-fat diet in Boston and had a consequently better nutritional status with a significantly

Abbreviations: CF, cystic fibrosis; BMI, body mass index; FM, fat mass; FFM, fat-free mass; BC, body composition; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; BIA, bioelectrical impedance analysis; DXA, dual x-ray absorptiometry; PFT(s), pulmonary function test(s); Cl, chloride; NIV, non-invasive ventilation; TS, Tanner stage; Z, impedance; PA, phase angle; RE, resistance; X, reactance; IGF-1, insulin growth factor-1; FRC-He, forced residual capacity by helium dilution; RV, residual volume; TLC, total lung capacity; PI max, maximal inspiratory pressure; PE max, maximal expiratory pressure; IQR, interquartile range; BI, bias; LOA, limits of agreement.

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better survival rate. The independent correlation between nutritional status and prognosis on the one hand and lung disease on the other hand was further confirmed by other studies [2–5].

Nutritional status can be assessed by anthropometric methods, such as weight and height, expressed to normal values for age, and weight-for-stature assessments, such as body mass index (BMI) [6]. BMI represents a widely used indicator of nutritional status and has proved to be independently correlated to lung function in CF [7,8]. However, not all BMI is equal, given that individuals with the same BMI may have different distributions of fat (FM) and fat-free mass (FFM) and patients with normal BMI may lack FFM [9,10]. Indeed, BMI is imprecise, and can overestimate adiposity in people who are very muscular and underestimate adiposity in those who are very unfit (normal weight obesity). On the other hand, body composition (BC) has proved to be correlated to CF respiratory disease, mainly in adult cohorts [10–13]. In children, different studies have shown positive correlations between FFM and percent predicted forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and Shwachman score [12,14–16]. Thus, BMI is an imprecise measure for the assessment of nutritional status in CF and direct measurement of BC needs to be included in the routine follow-up of patients.

BC can be evaluated by anthropometric methods such as the measurement of 4 skinfold thickness and arm circumference [17] or more sophisticated methods including total body potassium [18], total body water by isotope dilution, total body electrical conductivity, bioelectrical impedance analysis (BIA) [19] and dual energy X-ray absorptiometry (DXA) [20]. DXA, initially developed in the 1980s for the measurement of mineral bone mass, has been established as the method of reference for the BC study [21]. However, its limited availability, the radiation production and the long duration of the examination (10–20 min) preclude its use routinely for longitudinal follow-up of patients.

BIA is a bedside, non-irradiating method of BC evaluation, which is simpler and less expensive than DXA. This measure allows the quantification of FFM with a validated equation that is appropriate with regard to physiopathology, age and race [22]. In CF, the use of a specific equation is important, because the altered sodium content in the sweat of patients may modify the impedance [19]. Previous studies [23–30] led to conflicting results. Very recently, Alicandro et al. [31] observed poor intra-individual agreement between body composition data provided by DXA and FFM estimated from BIA and concluded that this latter technique could not be part of the standard nutritional assessment of CF patients. In order to further assess the agreement between the two methods, we hypothesized that they would provide the same results of FFM and FM on the condition that the BIA equation is adapted to the CF population. We present here the results of a 2-step study aiming to implement an equation specific for young CF patients. This allowed us to describe the BC in this population and to investigate the association between BC, lung function and diaphragmatic force.

2. Materials and methods

2.1. Population

We conducted a two-step prospective study, as shown in Fig. A, Supplemental material. During the first phase, CF patients (CF1, $n = 54$) were assessed by DXA and BIA in order to validate a specific FFM_{BIA} equation, using DXA as a reference method. Thirty-one patients (CFA) of the first phase who did not have reliable pulmonary function tests (PFTs) were excluded in the second phase. The remaining patients of the first phase with reliable PFTs (CFB, $n = 23$) in addition to seventeen other patients (CFC, $n = 17$) were assessed by BIA, PFTs and blood sampling.

CF patients were all followed in the CF clinic of "Necker-Enfants Malades" Hospital in Paris, France. The diagnosis of CF was confirmed by positive sweat test (Cl > 60 mmol/L) and the presence of two CF-causing mutations for all patients. They were all in a stable condition without respiratory exacerbation (defined by Fuchs criteria [32]) within the last 2 weeks and without signs of oedema or dehydration. The overall CF respiratory disease was assessed by collecting history of chronic oxygen supplementation, non-invasive ventilation (NIV), the number of days under antibiotic treatment during the previous year (with the exclusion of inhaled antibiotics, anti-viral and anti-mycotic agents) and sputum microbiology. Chronic infection by *Staphylococcus aureus* or *Pseudomonas aeruginosa* was defined by at least 3 positive cultures in 6 months. History of pancreatic insufficiency, CF liver disease, CF diabetes and enteral nutrition were also collected.

Height was measured to the nearest 0.1 cm using a calibrated stadiometer and weight was measured to the nearest 0.1 kg using an electronic scale (Seca, Hamburg). Weight and height *z*-scores were calculated according to the CDC growth charts [33]. BMI was calculated and expressed in kg/m^2 and *z*-score, according to Cole's reference data [34]. Pubertal status was assessed using Tanner stages (TS); patients were considered pre-pubertal when Tanner stage was 1 (TS 1), pubertal when TS was equal or above 2 (TS 2–5). All participants were informed about the purpose of the study and consented to participate, according to the Helsinki rules.

2.2. DXA

The DXA scanning technique measures the differential attenuation of two different energy level x-rays as they pass through the body and allows the determination of soft tissue mass on a pixel-per-pixel basis [20]. Participants underwent whole-body DXA scans performed by Hologic QDR-4500 W (Hologic Inc., Waltham, MA, USA), using the Hologic software version 21.6.1:5. The manufacturer's precision of measures is reported to be 1%. After DXA scans and within an interval of maximum 2 h, patients were evaluated by BIA. They were not allowed to eat, drink or urinate between the two tests in order to avoid modification of hydration.

2.3. BIA

BIA is based on the assumption that the body is a cylindrical-shaped ionic conductor; tissues that contain large amounts of water and electrolytes, such as muscles, present the lowest impedance, in contrast to fat tissue and bone [35,36]. Measurements were carried out with the patient lying at a supine position on a flat, non-conductive bed using a multiple-frequency tetra-polar technique, with one of the two available devices for each patient: Aminostats Bio-ZM II, Aminogram, La Ciotat, France or Spengler IBE, IMPB04, Caen, France. A low-voltage alternative electrical current (400–500 μA) was applied through two electrodes placed on the right hand (intermediate phalanx of the middle finger) and foot (proximal phalanx of hallux). Two voltage sensor electrodes were placed on the right wrist and ankle. This allowed to assess impedance at three frequencies (200 kHz, 50 kHz and 5 kHz; Z200, Z50 and Z5, respectively), phase angle (PA), resistance and reactance at 50 kHz (RE50; X50). FFM_{BIA} and FM_{BIA} were evaluated using the equations described below and *z*-scores for age and sex were estimated based on reference data for healthy children published by Wells et al. [37].

2.4. Biological evaluation

Blood samples were taken on the day of BIA assessment. Albumin (g/l), urea (mmol/l), IGF-1 (ng/ml) and 25-hydroxy vitamin D (ng/ml) were analyzed. IGF-1 was adjusted for pubertal status and expressed as a percentage of the median predicted value according to patients' TS.

2.5. Pulmonary function tests (PFTs)

PFTs were performed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [38]. FEV1, functional residual capacity by helium dilution (FRC-He), FVC and the ratio of residual volume to total lung capacity (RV/TLC) are expressed as percentages of reference values for age by Knudson [39]. Maximal inspiratory and expiratory pressures (PI max, PE max) were obtained from a maximal effort against a closed shutter at FRC or TLC, respectively, and performed according to current recommendations [40].

2.6. Statistical analysis

All statistical analyses were performed using "R Statistical software" (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as medians [interquartile range (IQR)]. Categorical variables were presented as frequencies and percentages.

Differences between populations of CF patients were assessed using univariate analysis. Differences in medians were tested using non-parametric Mann–Whitney *U* tests. The independence of categorical variables was tested using Chi-squared tests or Fisher's exact tests, when necessary. A bilateral p-value ≤ 0.05 was considered as statistically significant.

Stepwise regression analysis was performed for the implementation of the FFM_{BIA} equation. Simple regressions were calculated to test correlations of FFM and FM between BIA and DXA. Bland and Altman analysis was performed to assess the agreement between assessments of FFM and FM by BIA (FFM_{BIA}, FM_{BIA}) and DXA (FFM_{DXA}, FM_{DXA}). In Bland and Altman plots, the difference between the values is plotted against their mean. This analysis allows for the calculation of bias (BI), estimated by the mean differences, and the limits of agreement (95% LOA = ±1.96 standard deviations, SD).

Associations between clinical and biological determinants and FFM depletion were analyzed in univariate analysis. Determinants with a p-value <0.05 were included in the final multivariate logistic regression. A systematic research of interaction between determinants with a p-value <0.20 on univariate analysis was performed.

3. Results

3.1. Implementation of a FFM_{BIA} equation specific for young CF patients

A total of 54 CF patients (CF1) were assessed by DXA and BIA. The clinical characteristics of the patients are shown in Table 1 and Table I, Supplemental material. Ages varied from 5 to 21 years with a median age of 12 years [IQR 9.4; 15.1] and 39% of patients were pre-pubertal. The patients had a wide range of CF pulmonary disease severity as assessed by median FEV1 of 86% of predicted values [IQR 68.5; 106]. The CFA patients, who were then excluded from the second step of the study because of unreliable PFTs, were significantly younger than the 2 other groups of patients (CFB and CFC), which explains the low absolute value for weight, height, BMI and BC; however, their BMI *z*-score was not significantly different (Table 1).

A specific equation was established by a stepwise multivariate regression for calculation of the FFM by BIA (FFM_{BIA} equation). The variables included in the initial model were patients' age, sex, weight and height, the BIA device and BIA measures (reactance at 50 kHz, X50; and the resistance index, RI = height^2/RE50). The type of device, the age and the sex were not included in the final equation because they were not significant (Table II, Supplemental material).

The retained FFM_{BIA} equation was the following:

$$FFM_{BIA}(kg) = (0.54 * RI) + (0.25 * W) + (0.07 * H) + (0.04 * X50) - 11.91$$

(RI: resistance index = height^2/RE50, cm^2/Ω; RE50: resistance at 50 kHz, Ω; W: weight, kg; H: height, cm; X50: reactance at 50 kHz, Ω).

FM was then deducted from the patient's weight: FM_{BIA} (kg) = W − FFM_{BIA}.

FFM_{BIA} and FFM_{DXA} were significantly correlated ($r = 0.995$; $p < 0.001$) (Fig. 1). The Bland and Altman analysis showed a

Table 1
Clinical characteristics of study population

	CF1 (CFA + CFB)		CF2 (CFB + CFC)	*p*-value		
	CFA (*N* = 31)	CFB (*N* = 23)	CFC (*N* = 17)	CFA-CFB	CFB-CFC	CFA-CFC
Age (years)	10.8 [5.8]	13.9 [4.9]	14.3 [6.8]	**0.03**	NS	**0.04**
Male sex (*n*, %)	14 (45.2)	15 (65.2)	10 (58.8)	NS	NS	NS
Anthropometric data						
Weight (kg)	29 [17.1]	41.8 [20.1]	43.2 [20.0]	**0.01**	NS	**0.01**
Weight (*z*-score)	−1 [2.1]	−0.7 [1.2]	−0.9 [1.5]	NS	NS	NS
Height (cm)	136.5 [26.6]	155.0 [25.0]	147.8 [20.0]	**0.01**	NS	**0.04**
Height (*z*-score)	−1 [1.5]	−0.4 [1.2]	−0.7 [2.2]	NS	NS	NS
BMI (kg/m^2)	16 [3]	18.1 [3.7]	18.5 [2.7]	**0.01**	NS	**0.01**
BMI (*z*-score)	−0.3 [1.4]	−0.3 [1.0]	−0.4 [1.6]	NS	NS	NS
Pubertal status (*n*, %)				NS	NS	NS
Pre-pubertal	15 (48.4)	6 (26.1)	6 (35.3)			
Pubertal	16 (51.6)	17 (73.9)	11 (64.7)			
CFTR mutations (*n*, %)				NS	NS	NS
F508del homozygous	16 (51.6)	12 (52.2)	7 (41.2)			
F508del heterozygous	11 (35.5)	9 (39.1)	8 (47)			
No F508del mutations	4 (12.9)	2 (8.7)	2 (11.8)			
FEV1 (% predicted)	85 [41]	88.5 [36]	68 [53.5]	NS	NS	NS
Pancreatic insufficiency (*n*, %)	29 (93.6)	21 (91.3)	15 (88.2)	NS	NS	NS
CF liver disease (*n*, %)	8 (25.8)	7 (30.4)	3 (17.6)	NS	NS	NS
CF diabetes (*n*, %)	1 (3.2)	1 (4.4)	1 (5.9)	NS	NS	NS
FFM						
DXA (kg)	22.5 [10.3]	31.3 [16.7]	NA	**0.006**	NA	NA
BIA (kg)	22 [12.1]	32.3 [15.6]	32.7 [18.1]	**0.003**	NS	**0.02**
BIA (*z*-score)	−1.8 [1.8]	−0.9 [0.8]	−1.3 [1.9]	**0.04**	NS	NS
FFM depletion* (*n*, %)	14 (45.2)	3 (13.0)	6 (35.3)	**0.01**	NS	NS
FM						
DXA (kg)	5.7 [4.2]	8 [4]	NA	NS	NA	NA
BIA (kg)	7.2 [4.3]	8.6 [4.6]	10.1 [2.9]	NS	NS	**0.04**
BIA (*z*-score)	−0.2 [0.9]	−0.09 [0.7]	−0.01 [0.9]	NS	NS	NS
FM depletion* (*n*, %)	0 (0)	0 (0)	0 (0)	NA	NA	NA

Categorical variables are expressed as number (*n*) of observations and percentages of frequency (%). Quantitative variables are expressed as medians and interquartile range [IQR]. BMI, body mass index; FFM, fat-free mass; DXA, dual X-ray absorptiometry; BIA, bioelectrical impedance analysis. *FFM and FM depletion are defined by FFM_{BIA} and FM_{BIA} *z*-scores ≤ −2, respectively. NA, not applicable; NS, not significant.

mean difference (bias, BI) of FFM_{BIA} − FFM_{DXA} very close to zero (BI = −4.87e-15 kg) with 95% limits of agreement (95% LOA) [−2.25; 2.25]. The two assessments of FM (FM_{BIA} and FM_{DXA}) were also well correlated ($r = 0.96$; $p < 0.001$) with a mean difference of 0.6 kg (BI = 0.6 kg); 95% LOA [−1.82; 3.02] (Fig. 1).

3.2. BC assessment in young CF patients

The clinical characteristics of the CF patients assessed in the second phase of the study (CF2) are shown in Table I, Supplemental material. Median age was 14 years [IQR 11.3; 16.7].

FFM_{BIA}, calculated with the above validated FFM_{BIA} equation, and deduced FM_{BIA} were compared to reference data of BC from healthy children [37] according to age and sex, and *z*-scores were calculated. Median FFM_{BIA} *z*-score was −1.0 [IQR −1.8; −0.6] whereas median FM_{BIA} *z*-score was near normal at −0.07 [IQR −0.56; 0.2].

Twenty-two percent of patients ($n = 9$) had a FFM depletion, defined by a FFM_{BIA} *z*-score ≤ −2. As shown in Fig. B, Supplemental material, patients' FFM_{BIA} *z*-scores present a distribution slightly skewed to the right (skewness 0.7; kurtosis 5.2) with a median of −1 [IQR −1.8; −0.6]. Interestingly, as shown in Fig. 2, among the 9 patients with FFM depletion, only 2 (22.2%) had a BMI *z*-score < −1; 5 patients had BMI *z*-scores between −1 and −0.5 and 2 patients had BMI *z*-scores above 0 (0.13 and 0.62).

FM_{BIA} *z*-scores presented a more symmetrical distribution (skewness 0.3; kurtosis 3.3) with a median of −0.1 [IQR −0.6; 0.2] (Fig. B, Supplemental material). FFM_{BIA} and FM_{BIA} *z*-scores were correlated with a Pearson's product moment correlation coefficient of 0.42 [95% CI 0.13; 0.65], $p = 0.007$ (Fig. 3). However, patients with FFM depletion did not have a defective FM. This was reflected by the fact that there was no statistical difference between FM_{BIA} *z*-scores of patients with and without FFM depletion.

3.3. Relation between BC and CF disease parameters

There was no statistical difference between patients with FFM depletion and those with a normal FFM_{BIA} for sex and pubertal status nor for incidence of extra-respiratory CF-related disease (pancreatic insufficiency, CF liver disease, CF diabetes or enteral nutrition; Table 2).

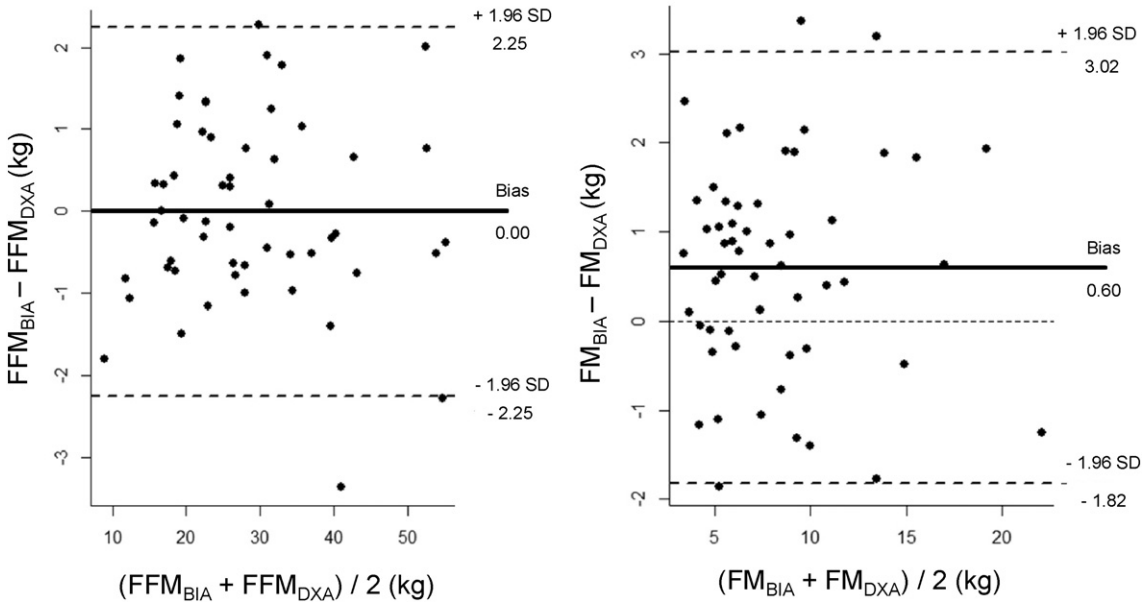

Fig. 1. On the left: Bland–Altman plot showing the difference of FFM (kg) between the BIA and DXA assessments in CF1 population (N = 54). On the right: Bland–Altman plot showing the difference of FM (kg) between the BIA and DXA assessment in CF1 population (N = 54). FFM_{BIA}, fat-free mass by bioelectrical impedance analysis; FFM_{DXA}, fat-free mass by dual X-ray absorptiometry; FM_{BIA}, fat mass by bioelectrical impedance analysis; FM_{DXA}, fat mass by dual X-ray absorptiometry; Bias, mean difference; SD, standard deviation.

Patients with FFM depletion (median age 16.6 years [IQR 14.8; 17.7]) were significantly older than patients without FFM depletion (median age 12.5 years [IQR 10.2; 15.7]) (p = 0.025). These patients had also lower levels of albumin (p = 0.004; Table 2).

Patients with FFM depletion had a more severe respiratory disease compared to patients without FFM depletion, as assessed by longer antibiotic treatment (median 155 days [IQR 105; 222] versus 65 days [IQR 35.3; 87], $p < 0.001$), although no statistical difference was found in terms of chronic infection by *S. aureus* or *P. aeruginosa* between the two groups (Table 2).

They also had lower FEV1 (median 33% [IQR 31; 45] versus 91% [IQR 71.5; 106] of predicted values; $p < 0.001$), lower FVC (57% [IQR 51; 61] versus 93% [IQR 82; 101.5]; p = 0.001) and more pulmonary distension expressed by a higher ratio of RV/TLC (217% [IQR 140; 228] versus 114% [IQR 83.5; 145]; p = 0.003) (Table 2). They also presented significantly lower PI max (79.5% [IQR 55.6; 108.3] versus 111.4% [IQR 80.8; 118.4]; p = 0.05), an indirect assessment of respiratory muscle function (Table 2). This severity was reflected by the fact that more than 50% of the FFM-depleted patients required oxygen supplementation and/or NIV (p = 0.001; 0.003, respectively).

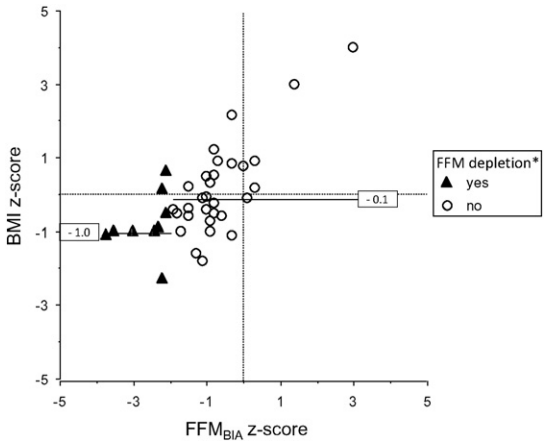

Fig. 2. Scattergram depicting BMI z-scores for patients with FFM depletion (black triangle; n = 9) and without FFM depletion (white circle; n = 31). Horizontal lines represent median values of BMI z-scores for the two FFM conditions. *FFM depletion is defined by a FFM_{BIA} z-score ≤ −2. BMI, body mass index; FFM, fat-free mass.

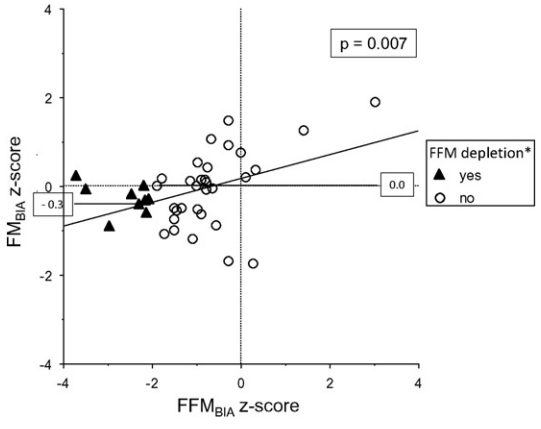

Fig. 3. Scattergram depicting FM_{BIA} z-scores for patients with FFM depletion (black triangle; n = 9) and without FFM depletion (white circle; n = 31) and correlation between FFM_{BIA} and FM_{BIA} z-scores. Horizontal lines represent median values of FM_{BIA} z-scores for the two FFM conditions. Pearson's product moment correlation coefficient = 0.42 [95% CI, 0.13; 0.65] (p = 0.007). *FFM depletion is defined by a FFM_{BIA} z-score ≤ −2. FM, fat mass; FFM, fat-free mass.

Table 2
Anthropometric, respiratory and nutritional parameters according to FFM depletion

	FFM depletion * (N = 9)	No FFM depletion * (N = 31)	p-value
Age (years)	16.6 [2.9]	12.5 [5.5]	0.025
Male sex (*n*, %)	6 (66.7)	19 (61.3)	NS
Anthropometric data			
Weight (kg)	43.3 [11.0]	41.8 [22.3]	NS
Weight (*z*-score)	−1.9 [0.9]	−0.5 [1.2]	< 0.001
Height (cm)	150.5 [17.5]	155.0 [26.2]	NS
Height (*z*-score)	−1.8 [0.9]	−0.3 [1.4]	< 0.001
BMI(kg/m^2)	18.1 [2.0]	18.3 [3.7]	NS
BMI (*z*-score)	−1.0 [1.5]	−0.1 [1.3]	0.025
Pubertal status (*n*, %)			
Pre-pubertal	1 (11.1)	11 (35.5)	NS
Pubertal	8 (88.9)	20 (64.5)	
Body composition (BIA)			
FFM (kg)	29.8 [13.0]	32.3 [17.9]	NS
FFM (*z*-score)	−2.3 [0.8]	−0.8 [0.9]	< 0.001
FM (kg)	10.4 [2.1]	8.9 [4.9]	NS
FM (*z*-score)	−0.3 [0.3]	0.0 [1.0]	NS
PFTs (% predicted)			
FEV1	33.0 [14.0]	91.0 [34.5]	< 0.001
FRC-He	101 [22]	95 [21.6]	NS
FVC	57 [10]	93 [19.5]	0.001
RV/TLC	217 [88]	114[61.5]	0.003
PI max	79.5 [52.7]	111.4 [37.6]	0.05
PE max	82.8 [24.5]	101.4 [58.7]	NS
Chronic respiratory insufficiency			
O_2 supplementation (*n*, %)	5 (55.6)	1 (3.23)	0.001
NIV (*n*, %)	5 (55.6)	2 (6.45%)	0.003
Sputum microbiology			
Staphylococcus aureus (*n*, %)	7 (77.8)	28 (90.3)	NS
Pseudomonas aeruginosa (*n*, %)	6 (66.7)	10 (32.3)	NS
Antibiotic treatment (d)	155 [117]	65 [51.8]	<0.001
Biological assessment			
Albumin (g/l)	34.3 [3.5]	40.1 [4.5]	0.004
Urea (mmol/l)	3.8 [1.3]	5.1 [1.7]	NS
25-hydroxy vitamin D (ng/ml)	38 [14]	27 [9.5]	NS
IGF1 (% predicted)	50.3 [26.7]	64.5 [34.5]	NS
Pancreatic insufficiency (*n*, %)	9 (100)	27 (87.1)	NS
CF liver disease (*n*, %)	1 (11.1)	9 (29)	NS
CF diabetes (*n*, %)	1 (11.1)	1 (3.2)	NS
Enteral nutrition (*n*, %)	3 (33.3)	2 (6.5)	NS

Categorical variables are expressed as number (*n*) of observations and percentages of frequency (%). Quantitative variables are expressed as medians and interquartile range [IQR].
BMI, body mass index; BIA, bioelectrical impedance analysis; FFM, fat-free mass; FM, fat mass; PFTs, pulmonary function tests; NS, not significant.
* FFM depletion is defined by a FFM_{BIA} *z*-score ≤ −2.

To assess the specific correlation between FEV1 and FFM, we performed a stepwise multivariate logistic regression, including age, FFM_{BIA} *z*-score, BMI *z*-score and chronic infection by *P. aeruginosa* in the initial model. The only remaining factors for FEV1 modelization were FFM_{BIA} *z*-score ($p = 0.011$) and age ($p = 0.033$), according to the following equation: FEV1 (%) = (9.3 * FFM_{BIA} *z*-score) − (2.4 * age) + 118.5. This means that a decrease of FFM_{BIA} *z*-score of 1 unit results in a decrease of FEV1 by 9.3% (absolute change), assuming all other variables constant.

4. Discussion

Our study shows that BIA can reliably measure body composition in CF patients. We have validated a CF-specific equation, using DXA as a reference method, which proved to be accurate for FFM and FM estimation in children adolescents and young adults with CF. This is, to our knowledge, the first study with validation of an equation specific for children, adolescents and young adult CF patients. This provides high clinical relevance of our findings about BC in CF. We observed FFM defect in a substantial proportion of our CF patients, which was not detected by routine nutritional assessment such as weight or BMI, as assessed by the fact that 22% of the patients investigated presented FFM depletion, whereas only a quarter of them had a decreased BMI *z*-score. Those patients had a more severe respiratory disease and decreased respiratory muscle function, which underlines the relationship between BC and CF lung disease.

4.1. Limits of the study

The weakness of our study is related to the relatively small sample size. This is, however, comparable to other previously published studies. CFA patients were younger than CFB and CFC patients and this is probably the reason why the PFTs performed by these patients were unreliable. The other difference concerns a lower FFM_{BIA} *z*-score of the CFA population compared to CFB population but no such difference was seen between the CFA and CFC populations. However, there was no statistical difference for weight, height and BMI when these values were expressed as *z*-scores. Furthermore, the populations CF1 (=CFA + CFB) and CF2 (=CFB + CFC) did not have significant differences in terms of age, anthropometric characteristics and FFM, as presented in Table I, Supplemental. Based on these arguments, we believe that the equation elaborated on CF1 population can also be used for the CF2 population.

We enrolled children, adolescents and young adults, paying attention to puberty because BC largely varies during sexual maturation. We did not find any statistical difference for BC according to pubertal status. As a result, the proposed FFM_{BIA} equation should be further evaluated in older CF patients, before its application on a larger scale. We hope that ongoing studies in adults will allow us to generalize the use of this equation for all the CF patients.

Due to the lack of reference data for paediatric normal BC values with BIA, we used published data of FFM and FM *z*-scores based on a 4-component model for BC analysis (air-displacement plethysmography, deuterium dilution, DXA scans and anthropometric evaluation) in 565 healthy British children and young adults [37].

4.2. Implementation of a specific equation

DXA and BIA represent two different methods for BC assessment. DXA measures FM and deduces FFM, which corresponds to non-fatty tissues: muscle mass, water and organs, assuming a constant value for FFM hydration of 73.2%

[21]. This may result in FFM over or underestimation in case of respectively oedema or dehydration [41]. In the present study, modification of hydration status between DXA and BIA assessments was prevented by performing the two tests within a very short time interval.

BIA allows direct determination of the FFM in subjects and deduces FM. This is obviously more appropriate in our case where we aim to measure the FFM. The main difficulty of BIA relies on the fact that it is based on the use of age- or disease-specific BIA equations [36].

We therefore implemented a specific FFM_{BIA} equation in comparison to the DXA which is considered to be the gold standard method. This equation provides very reliable results in comparison to the previously validated ones [30,41,42]. Indeed, the difference between the DXA and BIA measurements for the FFM assessment is very close to 0 (SD 1.15), and the 95% LOA are [−2.25; 2.25]. In comparison, the Kotler formula for FFM_{BIA} estimation in adults with CF had a mean difference of 2.7 kg (SD 2) and the Geneva formula had a mean difference of −2.3 kg (SD 2.9), when compared to DXA [42]. King et al. [41] reported 2 different equations of FFM assessment and respective 95% LOA of [−8.3; 1.7] and [−4.8; 3.6] for male and [−6.4; 4.8] and [−3.1; 8.9] for female adult CF patients.

A very recent study [31] provided very poor agreement between DXA and BIA assessment. This might be explained by 2 reasons. The first is that this group used single-frequency BIA analyzer (a 50 kHz oscillating current of 800 μA) whereas multi-frequency devices have been demonstrated to be more accurate [43,44]. The second one is that other studies used equations validated in healthy subjects. Our study highlights that a CF-specific equation is mandatory because of the specific pattern of BC in CF, and possibly abnormal intracellular cell water content which might modify bioelectrical impedance [19].

Importantly, our equation proved to be independent of the devices that we used. This suggests that the equation can be used for the BC assessment in CF with different tetra-polar multiple frequency BIA devices. The implementation of this equation is therefore a step forward to more accurate nutritional assessment in CF.

4.3. FFM depletion is frequent and underestimated by BMI

In the present study, we found that 22.5% of the paediatric and young adult patients were depleted in FFM (defined by a FFM_{BIA} z-score ≤ −2). This confirms previous studies in paediatric CF patients which also reported FFM depletion [12,16,45–47]. Very interestingly, among the 9 patients with FFM depletion, 7 had a normal BMI z-score equal or above −1 and who therefore would have not been classified as patients with abnormal nutritional status. This is explained by the fact that FFM depleted patients were not depleted in FM and more generally that the BC defect involves only FFM in our patients. This probably explains why BMI fails to identify patients with low FFM and is not a reliable indicator of BC and of overall nutritional status [9,10,13,45].

4.4. Correlation between FFM and specific disease parameters

In the second part of the study, we used the specific FFM_{BIA} equation for BC assessment of 40 CF patients and investigated the relationship between FFM_{BIA} and the CF phenotype. We found a strong association between FFM depletion and respiratory disease severity, as assessed by PFT parameters, chronic oxygen supplementation or NIV, and longer antibiotic treatment during the year preceding the evaluation. Furthermore, decrease in FFM translates to FEV1 deterioration, as assessed by the multivariate model of FEV1, which shows that a decrease of FFM_{BIA} z-score of 1 unit results in a decrease of FEV1 by 9.3% (absolute change), assuming all other variables are constant.

This association between BC and FEV1 has already been reported by other authors in adult and paediatric CF patients [10,12,15,48]. Pedreira et al. have found a correlation between FFM_{DXA} and FEV1 in children with CF, although it was less strong than that between FEV1 and BMI [48]. Alicandro et al. have demonstrated a relationship between reduced appendicular FFM and recurrent pulmonary exacerbations in young male patients with CF [13]. A French study performed in lung transplant candidates has shown a correlation between low FFM (assessed by the creatinine-height index) and more severe hypoxemia, reduced 6-min walking distance and higher mortality [49].

The strong association between FFM depletion and respiratory disease severity is further assessed by the fact that FFM depletion was also associated with a more important pulmonary distension, expressed by higher RV/TLC and lower respiratory muscle force, evaluated indirectly by PI max. This latter has been suggested in 2 studies of adult CF patients which demonstrated that patients with low FFM had lower diaphragmatic thickness [50] and lower PI max [50,51]. In a paediatric study [52], twitch trans-diaphragmatic pressure, a non-volitional test of diaphragm strength, was correlated to FFM (calculated by skinfold thickness) in young patients with CF. Altogether, these results suggest that FFM depletion results in diaphragmatic force impairment. This impairment should then in turn potentiate CF respiratory disease by decreasing efficient mucus clearance during cough and physiotherapy. Therefore, we advocate that follow-up of BC should be a target of CF care. This should focus on enhancement of FFM based on specific exercise training and/or anabolic therapies on a case-by-case basis, such as growth hormone therapy after endocrinological assessment. Our patients are now becoming less symptomatic and most of them display a normal BMI. We demonstrate here that we do not have to rely solely on these measurements but need more accurate ones, such as BC, to identify patients at risk of malnutrition and probably respiratory degradation. It is now time to upgrade FFM to a surrogate biomarker for CF nutritional disease and possibly respiratory disease.

5. Conclusion

We demonstrate in the present study that BIA is a helpful and reliable method for BC assessment on the condition that an

age- and disease-specific equation is used. We provide here for the first time an equation specific for young people with CF. Implementation of this specific equation is a step forward to more accurate nutritional status assessment in CF patients at the individual level. We also advocate for its use in multicenter studies and clinical trials in clinical research. Indeed, patients with preserved BMI and weight may have FFM depletion and be at risk of severe pulmonary disease. Overall, BIA assessment allows clinicians to identify patients who are not recognised by the usual anthropometric methods at risk of nutritional degradation and possibly bad respiratory prognosis. We recommend longitudinal BC assessment to adjust nutritional care and potentially improve the respiratory outcome of CF patients.

Conflict of Interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2016.05.004.

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