Original Article

Non-fasting bioelectrical impedance analysis in cystic fibrosis: Implications for clinical practice and research

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A R T I C L E   I N F O

Article history:
Received 27 December 2018
Revised 23 May 2019
Accepted 26 May 2019
Available online 5 June 2019

Keywords:
Cystic fibrosis
Single frequency bioelectrical impedance analysis
Body composition
FEV1%pred
Non-fasting
Anthropometry

A B S T R A C T

Background: Nutritional status affects pulmonary function in cystic fibrosis (CF) patients and can be monitored by using bioelectrical impedance analysis (BIA). BIA measurements are commonly performed in the fasting state, which is burdensome for patients. We investigated whether fasting is necessary for clinical practice and research.

Methods: Fat free mass (FFM) and fat mass (FM) were determined in adult CF patients (n = 84) by whole body single frequency BIA (Bodystat 500) in a fasting and non-fasting state. Fasting and non-fasting BIA outcomes were compared with Bland-Altman plots. Pulmonary function was expressed as Forced Expiratory Volume at 1 s percentage predicted (FEV1%pred). Comparability of the associations between fasting and non-fasting body composition measurements with FEV1%pred was assessed by multiple linear regression.

Results: Fasting FFM, its index (FFMI), and phase angle were significantly lower than non-fasting estimates (−0.23 kg, p = 0.006; −0.07 kg/m², p = 0.002; −0.10°, p = 0.000, respectively). Fasting FM and its index (FMI) were significantly higher than non-fasting estimates (0.22 kg, p = 0.008; 0.32%, p = 0.005, and 0.07 kg/m², p = 0.005). Differences between fasting and non-fasting FFM and FM were <1 kg in 86% of the patients. FFMI percentile estimates remained similar in 83% of the patients when measured after nutritional intake. Fasting and non-fasting FFMI showed similar associations with FEV1%pred (β: 4.3%, 95% CI: 0.98, 7.70 and β: 4.6%, 95% CI: 1.22, 8.00, respectively).

Conclusion: Differences between fasting and non-fasting FFMI and FM were not clinically relevant, and associations with pulmonary function remained similar. Therefore, BIA measurements can be performed in a non-fasting state.

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1. Introduction

Slowing the progression of lung disease severity is the primary aim in cystic fibrosis (CF) patient care, as a deterioration in pulmonary function impairs health-related quality of life and survival [1,2]. Nutritional status is related to lung disease severity in CF patients [1–4]. Body mass index (BMI) is often used to determine nutritional status [2,3], but does not distinguish between the amount of fat free mass (FFM) and fat mass (FM) [5,6]. The amount of FFM and FM is important, because CF patients with a higher FFM (in kg) have a better pulmonary function than patients with a higher FM (in kg and %) [6,7]. This indicates the need for a more detailed assessment of body composition in this patient group, because CF patients may have a normal BMI, but can still have an unfavorable proportion of FFM and FM characterized by a higher amount of FM than FFM [6,7].

Bioelectrical impedance analysis (BIA) is a quick and portable method [8,9], which estimates the amount of FM and FFM from measured impedance and resistance [8,10,11]. Being in a non-fasting state has been shown to increase FFM and decrease FM estimates [9,12,13], and is therefore avoided in scientific studies. However, it is unclear whether this strict condition is needed in clinical practice [12,14]. Currently, patients are asked to refrain
from eating and drinking until BIA measurements have been performed, which can be experienced as burdensome. Therefore, this study assessed whether the differences between fasting and non-fasting BIA results are clinically relevant in adult CF patients. Researchers may use data registered in electronic patient records for studies. Thus, for applicability in clinical research, this study additionally investigated whether associations between BIA results with pulmonary function are different when using fasting or non-fasting data.

2. Subjects and methods

2.1. Study participants and design

An observational cross-sectional study was conducted among adult CF patients. Patient recruitment was done at the outpatient clinic of the CF center at the University Medical Center Utrecht from September 2017 until July 2018. Measurements were performed as part of routine CF care at their annual check-up, as this was the convenience of the activities being undertaken at the outpatient clinic visit. The annual check-up includes an oral glucose tolerance test (OGTT) for screening for CF-related diabetes in all patients not previously diagnosed with CFRD. Patients were assigned to a private room at the outpatient clinic at 7.45 AM, and remained there during all undertaken measurements and visits of the different specialists until 12.00 PM. Inclusion criteria were: ≥18 years of age, diagnosed with CF by genotyping [15], registered at CF center Utrecht. Exclusion criteria included: pregnancy and wearing a biosensor for treatment of cystic fibrosis related diabetes (CFRD). Patients provided written informed consent. The Medical Ethical Committee of the University Medical Center Utrecht approved the study protocol (research protocol 17–915/C).

2.2. Patient characteristics

Height was measured with a wall-mounted measuring tape (SECA 206, Hamburg, Germany) to the nearest 0.1 cm without shoes. Weight was measured to the nearest 0.1 kg on a digital scale (SECA 770, Hamburg, Germany) with patients dressed in light clothes and without shoes.

Other patient characteristics were obtained from electronic medical records and included: age, BMI (kg/m²), genotype of the disease (homozygote ΔF508, heterozygote ΔF508, or other), CFRD, pancreatic insufficiency (PI), presence of chronic Pseudomonas aeruginosa (P aeruginosa) infection, and use of CFTR modulator therapy (ivacaftor and combination lumacaftor/ivacaftor). Patients were categorized based on the ESPEN BMI target value (for men ≥23 kg/m², for women ≥22 kg/m²) [5].

2.3. Non-fasting energy and fluid intake

Nutritional intake was registered before the non-fasting BIA measurements were performed and missing values were present in only six patients. Patients who were not diagnosed with CFRD had to perform an OGTT during their check-up for diagnosis of CFRD [2]. Therefore, intake included 75 g of glucose (300 kcal) plus 200 mL of water in 71 patients who had to perform an OGTT for diagnosis of CFRD [2]. The OGTT was performed after patients underwent fasting BIA measurements. Nutrition and fluid intake by patients was only allowed after OGTT result and before non-fasting BIA performance. Calculation of energy (kcal) and fluid (mL) intake was performed in eMagister (version V28.2.2.14R1.15, Pink Roccade Healthcare, Den Bosch, NL), by using food composition data of NEVO2010 (version June 2010, National Institute for Public Health and Environment, Bilthoven, NL).

2.4. Pulmonary function

Pulmonary function was expressed as Forced expiratory volume at 1 s percentage predicted (FEV1%pred). FEV1%pred was assessed by spirometry tests (Geratherm, Geschwenda, Germany) [3], using Global Lung Function Initiative reference equations [16].

2.5. Bioelectrical impedance analysis

Whole-body single frequency (SF) (50 kHz) BIA measurements were performed according to Standard Operating Procedures by trained personnel, using Bodystat 500 (Bodystat Ltd., Isle of Man, British Islands). Patients laid in supine position on the examination table, and had their right hand and foot cleaned with alcohol. For each patient two new electrodes were placed on the right hand, and two new electrodes on the right foot [17]. Fasting measurements were performed between 8 and 9 AM. Patients were asked to void before fasting measurements. Non-fasting measurements were between 10 and 11 AM with no restrictions regarding caffeine intake and emptying the bladder. All patients performed both fasting and non-fasting measurements.

Raw BIA data (impedance, resistance, reactance, and phase angle) were registered in electronic medical records. Estimates of FFM (in kg, %, and kg/m²), and FM (in kg, %, and kg/m²) were obtained, using the Kyle equation [18].

Percentile estimates for the fat free mass index (FFMI) (kg/m²), and fat mass index (FMI) (kg/m²), based on Schutz et al. [19], were used to compare anthropometric outcomes of patients to healthy people of similar age, and gender in clinical practice. Values between the 5th and 95th percentile were considered as normal [19,20]. Values at the 5th percentile were considered as critical values for risk of malnutrition.

2.6. Statistical analyses

Descriptive statistics were used for the population characteristics, which were presented as means ± standard deviation (SD) or number (%), unless stated otherwise. The differences between fasting and non-fasting measurements with their limits of agreement (LOA, means ± 1.96SD) were presented in Bland-Altman graphs [21]. Clinically acceptable ranges, determined using Kyle et al. [20], and Schutz et al. [19] percentiles, were used to define clinical relevance of the differences: −1.50 to 1.50 kg for FFM (kg), −1.40 to 1.40 kg for FM (kg), −2.0 to 2.0% for FM (%), −0.42 to 0.42 kg/m² for FFMI, and −0.50 to 0.50 kg/m² for FMI. Clinical acceptable ranges were based on the differences between the 5th and 10th percentile values for the age categories 18–34 years, 35–54 years, and 55–74 years. Next, a grand mean was calculated for the differences of all age categories together. Also, to indicate significant differences between fasting and non-fasting measurements, p-values were generated with the paired t-test.

Multiple linear regression assessed effects of using fasting or non-fasting BIA outcomes (BMI, FFMI, FMI) on associations with pulmonary function. Outcome variable was FEV1%pred. FMI was in the model with FFMI. Age was dichotomized based on the median value for regression analyses (≤ and ≥26.0 years), which decreased the residual sums of squares. Covariates were progressively entered in the models, and remained present if the regression coefficients changed >10%. Covariates considered were: age, sex [4,7], presence of chronic P aeruginosa infection, PI, genotype of the disease, CFRD [4], and CFTR modulator therapy use [22,23]. Ultimately, age, gender and presence of chronic P aeruginosa infection remained present as covariates.

Because nutritional intake between measurements was different between patients, intake-related bias was assessed by stratification,
based on the calculated median energy (≤ or >638 kcal) and fluid intake (≤ or >390 mL).

All tests were two-sided and the significance level was set at 5%. Statistical analyses were performed using IBM SPSS Statistics (version 25.0.0; IBM Corp., Armonk, NY).

3. Results

The annual check-up included 128 patients. We excluded 44 patients from the study population, due to no consent given (n = 2), measurement errors (phase angle >10° [10,11]) (n = 2) or because they did not have both fasting and non-fasting measurements (n = 40). Ultimately, 84 patients were included for analyses. Missing data for nutritional intake were only present in six patients, and were imputed using the median value.

Median (IQR) age was 26.0 years (22.0–33.8), and about half of the patients were men (61%) (Table 1). Most patients (57%) were homozygous for ΔF508 mutation, and 42% of the patients met the ESPEN BMI target value [2]. Nutritional intake before non-fasting BIA measurements was 662 kcal ± 255, and fluid intake was 420 mL ± 183. FEV1%pred was 67.7 ± 22.4 (Table 1).

3.1. Differences between fasting and non-fasting BIA outcomes

On average, fasting FFM (kg), FFMI (kg/m²), and phase angle (°) were lower than non-fasting estimates (mean difference: −0.23 kg, LOA: −2.67, 2.22, −0.07 kg/m², LOA: −0.51, 0.37, and −0.10°, LOA: −0.56, 0.36, respectively) (Fig. 1, A, B, F, Table 2). Fasting FM (in kg and %), and FFMI (kg/m²) were higher than non-fasting estimates (mean differences: 0.23 kg, LOA: −1.10, 1.55, 0.32%, LOA: −1.65, 2.28, and 0.07 kg/m², LOA: −0.38, 0.52, respectively) (Fig. 1, C, D, E, Table 2). All mean differences were significantly different from zero (FFM p = 0.002, FFMI p = 0.006, FM p = 0.003 for kg and p = 0.005 for %, FMI p = 0.005) (Table 2). However, the mean differences were within the clinically acceptable range (Fig. 1), and LOA were similar to the clinically acceptable range (Fig. 1).

The LOA for FFM (kg) go out of the clinically acceptable range (1.50 kg, LOA: −2.67, 2.22) (Fig. 1, A), but the majority of the patients (95%) showed a clinically acceptable difference (difference <1.50 kg) between fasting and non-fasting FFM (kg). Moreover, 86% of the patients showed a difference <1 kg between fasting and non-fasting FM (kg) and FFMI (kg), and in 60% of the patients the difference was <0.5 kg. The LOA for phase angle also go out of the clinically acceptable range (0.25°, LOA: −0.56°, 0.36°), which relates to only 70% of the patients showing a clinically acceptable difference between fasting and non-fasting measurements (Fig. 1F).

Approximately 80% of the patients showed normal FFMI percentile estimates (fasting 79% and non-fasting 83%), and normal FMI percentile estimates (fasting 89% and non-fasting 90%). Percentile estimates remained similar in 83% of the patients in both fasting and non-fasting states. These results indicate that most patients showed a similar nutritional status classification in both the fasting and non-fasting states. In 24% of the patients, a lower FMI was observed in the non-fasting state. Furthermore, 15 patients (18%) showed a FFMI ≤5th percentile and three of these 15 patients (20%) showed normal FFMI in non-fasting state (data not shown).

3.2. Comparison associations between fasting and non-fasting BIA results with FEV1%pred

Our study showed that for each 1.0 kg/m² increase in fasting FFMI, FEV1%pred was 4.34% higher (β: 4.34, 95% CI: 0.98, 7.70). This was similar to the beta coefficient for non-fasting FFMI values (β: 4.61, 95% CI: 1.22, 8.00). For FMI similar results were found between using fasting FMI values and non-fasting FMI values (β: −0.35, 95% CI: −2.82, 2.31, β: −0.30, 95% CI: −2.76, 2.17, respectively), as well as between fasting and non-fasting phase angle (β: 7.10%, 95% CI: 1.45, 12.74, β: 7.00%, 95% CI: 1.07, 12.92, respectively). These results indicate that non-fasting BIA measurements can be registered in electronic patient records and that researchers may use non-fasting BIA data in observational studies.

3.3. Stratification analyses

Stratification for energy (≤638 kcal n = 44 and >638 kcal n = 40) and fluid intake (≤ 390 mL n = 45 or >390 mL n = 39) showed no intake-related bias (Fig. 2). Mean differences between fasting and non-fasting data were similar between patients with a low and high energy (Fig. 2, A, C, E) and fluid intake (Fig. 2, B, D, E). Patients with a higher nutritional intake (≥638 kcal and >390 mL) showed larger LOA than patients with a low energy or low fluid intake, indicating that individual differences were larger in patients with a higher nutritional intake than patients with a lower nutritional intake. Still, even in >90% of the patients with a high intake the differences between fasting and non-fasting BIA measurements were clinically acceptable (≤0.42 kg/m² for FFMI and ≤0.50 kg/m² for FMI) (Fig. 2).

4. Discussion

Differences between fasting and non-fasting body composition parameters in adult CF patients were not clinically relevant in >95% of the patients, except for phase angle, and the differences were close to zero. The associations between BIA outcomes and pulmonary function were comparable when using fasting and non-fasting BIA data.

Limited studies have investigated meal effects on BIA measurements [13,14,24–26], but none of these studies were performed in CF patients. Three of these studies reported increases in FM% after nutritional intake [14,24,25], which was different from our results. In contrast to our study, those previous studies used other BIA methods (segmental, multi frequency [14] and leg to leg [14,24]), had subjects remain in supine position for 12 h [25], included different time points for non-fasting measurements (20, 40, and 60 min after eating) [14], or provided a higher energy intake (919 kcal [14], and 869 kcal [24]). Only two studies used whole-body SF BIA outcomes; one among healthy subjects [13] and one

Table 1

<table>
<thead>
<tr>
<th>Characteristics of included adult cystic fibrosis patients (n = 84) and excluded adult cystic fibrosis patients (n = 40).</th>
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<tbody>
<tr>
<td>Included patients</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
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<tr>
<td>Male, number (%)</td>
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<tr>
<td>Height (cm), mean ± SD</td>
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<tr>
<td>Weight (kg), median (IQR)</td>
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<tr>
<td>BMI (kg/m²), mean ± SD</td>
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<tr>
<td>ESPEN BMI target*, number (%)</td>
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<tr>
<td>PL, number (%)</td>
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<tr>
<td>CFRD, number (%)</td>
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<tr>
<td>ΔF508 homozygous, number (%)</td>
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<tr>
<td>ΔF508 heterozygous, number (%)</td>
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<tr>
<td>Other, number (%)</td>
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<tr>
<td>CFTR modulator therapy user, number (%)</td>
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<tr>
<td>FEV1%pred (mean ± SD), N = 84</td>
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</tbody>
</table>

n = number of subjects. IQR = interquartile range. SD = standard deviation. BMI = body mass index. PI = pancreas insufficiency. CFRD = cystic fibrosis related diabetes. CFTR = cystic fibrosis transmembrane conductance regulator. CFTR modulator therapy includes ivacaftor and lumacaftor/ivacaftor use. Normally distributed data presented as mean ± SD, not normally distributed data as median (IQR). * ESPEN BMI target: ≥23 kg/m² for men and ≥22 kg/m² for women.
among elderly [26], and their results studies were similar to our study. The study among healthy participants observed decreases in impedance (−18 Ω) and FM% (−2%) 2–4 h after a mean intake of 652 kcal [13]. The study among elderly observed non-significant increases in FFM (+0.2 kg) and decreases in FM (−0.05 kg) one hour after standardized meal consumption (299 kcal) in the morning [26]. As in our study, differences were small and negligible on both the individual and group level.

Not just the mean differences between fasting and non-fasting outcomes were clinically acceptable, but also the individual differences were within the clinically acceptable range, as shown by the LOA of the Bland-Altman plots. Consequently, BIA measurements can be performed in a non-fasting state to assess anthropometric outcomes in clinical practice with CF, preferably with similar testing conditions in order to increase reproducibility [9]. Except for phase angle, for which >5% of the observations were observed to be clinically unacceptable. An explanation is that phase angle is

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**Table 2**

Anthropometric outcomes from fasting and non-fasting bioelectrical impedance analysis measurements in adult cystic fibrosis patients (n = 84).

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Non-fasting</th>
<th>Mean difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat free mass (kg)</td>
<td>52.1 ± 9.5</td>
<td>52.3 ± 9.6</td>
<td>−0.02 ± 0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>Fat free mass index (kg/m²)</td>
<td>17.0 ± 2.1</td>
<td>17.1 ± 2.1</td>
<td>−0.07 ± 0.23</td>
<td>0.006</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>16.0 ± 6.8</td>
<td>15.8 ± 6.8</td>
<td>0.22 ± 0.67</td>
<td>0.003</td>
</tr>
<tr>
<td>Fat mass index (kg/m²²)</td>
<td>5.3 ± 2.4</td>
<td>5.2 ± 2.4</td>
<td>0.07 ± 0.23</td>
<td>0.005</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>23.3 ± 7.7</td>
<td>23.0 ± 7.7</td>
<td>0.31 ± 1.00</td>
<td>0.005</td>
</tr>
<tr>
<td>Phase angle (degree, °)</td>
<td>6.5 ± 1.0</td>
<td>6.6 ± 1.0</td>
<td>−0.01 ± 0.23</td>
<td>0.000</td>
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</table>

Data presented as mean ± SD, n = number of subjects. SD = standard deviation. P-values indicate significant difference between fasting and non-fasting values at 5%, and were calculated using the paired t-test.

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**Fig. 1.** Bland and Altman plots showing differences between fasting and non-fasting bioelectrical impedance analysis outcomes in adult cystic fibrosis patients (n = 84). Red line indicates mean difference, thick dashed lines limits of agreement, thin dashed lines 95% confidence intervals, and green lines the clinically acceptable range. FFM = fat free mass, FM = fat mass, FFMI = fat mass index, FMI = fat mass index, A is FFM, B is FFMI, C is FM (kg), D is FMI, E is FM (%), F is phase angle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
directly related to shifts in body water, which slightly occurs after nutritional intake [13].

In clinical practice, body composition measures are usually compared to reference values to determine malnutrition. In this study, meal consumption did not affect classification of malnutrition. Percentile estimates remained similar in 85% of the patients, indicating that the risk of malnutrition would remain the same for most patients when using non-fasting values. Fifteen patients (18%) showed a FFMI <5th percentile, and 3 of these 15 patients showed normal FFMI after energy and fluid intake. However, these 3 patients showed values close to the critical value for risk of malnutrition in both a fasting and non-fasting state (difference from critical value (0.2 kg/m²)). This indicates that close monitoring of patients showing values close to the critical value of malnutrition is warranted. These results substantiate that non-fasting BIA measurements can be implemented in CF patient care.

Furthermore, this study assessed effects of using fasting and non-fasting BIA measurements on associations between body composition outcomes with pulmonary function. No differences in estimates or directions were observed between fasting and non-fasting associations with pulmonary function. This means that other observational studies that used either fasting or non-fasting values can be combined for use in meta-analyses.

Strengths of this study were the limited missing values in our dataset of the included patients. Secondly, our study population was representative of other CF study populations in terms of demographic and disease characteristics [4,5,7]. Also, high prevalence of normal values for FFMI, FMI, and phase angle were observed [10,19], which can be related to inclusion of clinically stable patients. Another explanation is that 50% of the patients used CFTR modulators, which is associated with improved nutritional status [22]. Moreover, CF center care is recommended to provide an adequate treatment of CF patients and improve quality of life [27]. Despite that not all patients who visit the outpatient clinic were included for analyses (n = 244 in the study sample versus n = 128 in the study population), most patient and disease characteristics were similar between the study population and study sample. There was a difference between the prevalence of CFRD, our

![Fig. 2. Bland and Altman plots showing differences between fasting and non-fasting Bioelectrical Impedance Analysis outcomes in adult cystic fibrosis patients (n = 78), stratified for low (<664, n = 45, blue squares) and high (≥664 kcal, n = 33, orange triangle) energy intake (A, C, E), and low (<423 mL, n = 44, blue squares), and high (≥423 mL, n = 34, orange triangle) fluid intake (B, D, F). Solid lines indicate mean differences (blue for low intake and orange for high intake), and dashed lines limits of agreement. FFMI = fat-free mass index. FMI = fat mass index. A = FFMI (energy), B = FMI (fluid), C = FMI (energy), D = FMI (fluid), E = phase angle (energy), F = phase angle (fluid). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
study population mainly included patients without CFRD. Patients who had been diagnosed with CFRD before were not invited for the OGTT and therefore not eligible for our study. Although this is a form of selection bias, we do not think that having CFRD or not will affect the difference in body composition before and after a meal. Patients for whom we did not have both measurements (fasting and non-fasting) were not clinically different from the ones we used in our analysis. For that reason, we think that the results can be extrapolated to the general CF population.

This study had some limitations. First, the Kyle equation to estimate body composition [18] has not been validated in CF patients, but showed good precision (coefficient of variation 3.6%, standard error of the estimate of FFM 1.72 kg) when validated against Dual-energy X-ray absorptiometry among healthy individuals, as compared to other BIA equations [9]. Secondly, SF BIA measurements may be less accurate than Multi Frequency BIA measurements [8], but meal effects on impedance changes have shown to be similar between SF and Multi frequency BIA in healthy participants [13,14]. Nonetheless, the results of this study should cautiously be interpreted when applied to MF BIA or BIS due to differences in the techniques [9]. Also, it is important to acknowledge that performing BIA measurements in a non-fasting state can increase potential errors of the estimate [9], and should therefore still be cautiously interpreted. Moreover, we cannot draw conclusions regarding measuring changes over time as data were collected cross-sectionally. Though using similar testing conditions increases reproducibility [9]. Another limitation of this study is that patients could ingest caffeine and were not asked to void their bladder before non-fasting measurements, which might influence the results [9]. Only 6 (7%) patients performed physical exercise between measurements, which is due to the patients schedule at the outpatient clinic. Still, none of the patients with a clinically unacceptable difference performed exercise between measurements or showed similarities in factors known to influence BIA results.

In conclusion, differences between fasting and non-fasting FFMI and FMI were not clinically relevant. Also, associations between anthropometric outcomes with pulmonary function remained similar between using fasting and non-fasting data. Therefore, assessment and monitoring of the nutritional status by using BIA measurements can be performed in a non-fasting state in adult CF patients visiting the outpatient clinic.

Competing interests

No conflict of interest was reported.

Funding

None.

Acknowledgements

The authors thank the patients for their participation.

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