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Evaluación de la composición corporal en adultos con fibrosis quística: concordancia entre la densitometría y la antropometría

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ABSTRACT

Introduction: few studies have evaluated body composition (BC) through different techniques, and the degree of agreement between them in adults with cystic fibrosis (CF).

Objectives: to describe BC using techniques to assess nutritional status and to test their concordance in CF.

Methods: a cross-sectional study in CF patients in a clinically stable situation. Nutritional assessment was performed using skinfold measurement (SM) and densitometry (DXA). Fat-free mass index (FFMI) was also determined. The diagnosis of malnutrition was established if body mass index (BMI) $< 18.5 \text{ kg/m}^2$. Fat-free mass (FFM) malnutrition was diagnosed when FFMI was $< 17 \text{ kg/m}^2$ in males and $< 15 \text{ kg/m}^2$ in females (FFMI: fat-free mass in kg/height in m^2).

Results: forty-one patients were studied (twenty-two females, 53.7 %); median age was 29.8 (interquartile range, 20.9-33.7); BMI was 21.6 (19.8-23.0). Only four (9.8 %) patients had a BMI < 18.5 . By DXA, FFM (kg) results were: median, 52.8 (47.8-56.9) with FFMI of 17.9 (16.7-19.3) in males and 36.7 (33.1-38.9) in females, FFMI of 14.7 (14.2-15.8). Twenty (48.6 %) patients presented FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected. By SM, the FFMI was 18.7 (17.2-20.0) in males and 14.9 (14.2-15.8) in females; moreover, sixteen (39.1 %) patients presented malnutrition of FFM, with 20.8 % of males and 61.8 % of females being affected.

For FFM (kg), a high concordance was obtained between SM and DXA (intraclass correlation coefficient of 0.950); likewise when they were compared by applying the ESPEN criteria for FFM malnutrition. However, when the techniques were compared to classify malnutrition according to FFMI, the kappa coefficient was only moderate ($k = 0.440$). The mean difference between FFM by DXA and SM was $+1.44 \pm 0.62 \text{ kg}$ in favor of SM, with greater dispersion as FFM increased.

Conclusions: the prevalence of FFM malnutrition is high in adult CF patients, despite a normal BMI, especially in females. Notwithstanding the good statistical agreement between SM and DXA, concordance was moderate. Therefore, DXA remains the technique of choice, and SM may be used when the former is not available.

Keywords: Cystic fibrosis. Malnutrition. Nutritional assessment. Dual energy X-ray densitometry (DXA). Skinfold measurement (SM).

RESUMEN

Introducción: pocos estudios han evaluado la composición corporal (BC) mediante diferentes técnicas y el grado de concordancia entre ellas en adultos con fibrosis quística (FQ).

Objetivos: describir la BC mediante técnicas de evaluación nutricional y comprobar su concordancia en la FQ.

Métodos: estudio transversal de adultos con FQ en situación de estabilidad clínica. La evaluación nutricional se realizó mediante medición de pliegues cutáneos (SM) y densitometría (DXA). También se determinó el índice de masa libre de grasa (FFMI). El diagnóstico de desnutrición se estableció si el índice de masa corporal (IMC) era $< 18,5 \text{ kg/m}^2$. Se diagnosticó desnutrición por masa libre de grasa (FFM) cuando el FFMI era $< 17 \text{ kg/m}^2$ en los hombres y $< 15 \text{ kg/m}^2$ en las mujeres (FFMI: masa libre de grasa en kg/estatura en m^2).

Resultados: se estudiaron cuarenta y un pacientes (veintidós mujeres (53,7 %), con una edad media de 29,8 años (rango intercuartílico, 20,9-33,7) y un IMC de 21,6 (19,8-23,0). Solo cuatro (9,8 %) pacientes tenían un IMC $< 18,5$. Mediante DXA, los resultados de FFM (kg) fueron (mediana y RIC): 52,8 (47,8-56,9) con FFMI de 17,9 (16,7-19,3) en los varones y 36,7 (33,1-38,9) en las mujeres con FFMI de 14,7 (14,2-15,8). Veinte (48,6 %) pacientes presentaban desnutrición del FFM, con el 16,7 % de varones y el 59,1 % de mujeres afectados. Mediante el SM, el FFMI fue de 18,7 (17,2-20,0) en los varones y de 14,9 (14,2-15,8) en las mujeres; además, dieciséis (39,1 %) pacientes presentaban malnutrición del FFMI, con el 20,8 % de varones y el 61,8 % de mujeres afectados.

En el caso de la FFM (kg), se obtuvo una alta concordancia entre el SM y la DXA (coeficiente de correlación intraclase de 0,950); igualmente cuando se compararon las técnicas aplicando los criterios ESPEN para la desnutrición de la FFM. Sin embargo, cuando se compararon las técnicas para clasificar la malnutrición según el FFMI,

el coeficiente kappa fue solo moderado (coeficiente kappa = 0,440). La diferencia media entre el FFM por DXA y el SM fue de $+1,44 \pm 0,62$ kg a favor del SM, con mayor dispersión a medida que aumenta el FFM.

Conclusiones: la prevalencia de la malnutrición por FFM es elevada en los pacientes adultos con FQ, a pesar de presentar un IMC normal, especialmente en el caso de las mujeres. A pesar de existir una buena correlación estadística entre el SM y la DXA, la concordancia fue moderada. Por lo tanto, la DXA sigue siendo la técnica de elección y el SM puede ser una alternativa cuando la DXA no esté disponible.

Palabras clave: Fibrosis quística. Desnutrición. Valoración nutricional. Densitometría de doble energía X (DXA). Antropometría (SM).

INTRODUCTION

Cystic fibrosis (CF) is an inherited multisystemic disease caused by the alteration of a gene located on chromosome 7 (CFTR: cystic fibrosis transmembrane conductance regulator) (1). Alterations in CFTR lead to an impaired transport of chloride, bicarbonate, and sodium ions across epithelial cell membranes (2). In healthy subjects, mucus is mainly composed of mucins and water. Hydration and pH regulate mucus viscosity, and both functions are controlled by CFTR on the apical surface of epithelial cells. Chloride movement dictates the degree to which mucus retains water, while CFTR-mediated bicarbonate efflux plays a key role in defining pH, which is critical for a healthy antibacterial response. When the CFTR protein is altered, thick mucus secretions are produced (1). These thickened secretions are produced predominantly in the pancreas and lungs. This disturbance at the pulmonary level may cause decreased pulmonary function. In addition, malabsorption and maldigestion of nutrients,

particularly fat-soluble vitamins and fats, can lead to poor nutritional status. Until a few years ago, malnutrition was considered to be associated with CF because it was practically always present at the time of diagnosis and a vast majority of patients suffered from deterioration of their nutritional status and died deeply malnourished. The interaction between lung function and nutrition has a great importance, as a parallel worsening in both would affect prognosis and quality of life. Thus, malnutrition behaves as a risk factor predictor of morbidity and mortality in CF (1-6). Although the prevalence of malnutrition has decreased considerably, figures close to 25 % continue to be reported in both children and adults (7).

Guidelines on endocrine-nutrition care for patients with CF at different stages of life (infants, children, and adults) have been developed by the *ESPEN*, *ESPGHAN*, and *ECFS*. These guidelines recommend periodic nutritional assessments as a primary step to achieve the best therapeutic and prognostic outcomes as possible (4). At every visit, patient's weight, height, body mass index (BMI), and weight loss over time are recorded (8). BMI is used in the clinical setting to quantify the nutritional status of CF patients. BMI targets are used in clinical practice; however, although the relationship between BMI and lung function in CF patients is well established, the exclusive use of BMI as an indicator of nutritional status can be misleading (9). In clinical practice, individuals with the same BMI may have different distributions of fat (FM) and fat-free mass (FFM); besides, patients with normal BMI may lack of FFM. Measuring the proportion of FFM and lean body mass may help to describe better the nutritional status in CF. In CF, one of the most important determinants of morbidity and mortality related to malnutrition is the decrease in fat-free mass (FFM); therefore, it is important to measure it accurately (10). Different methods can be used to assess whole-body and segmental BC: dual energy X-ray densitometry (DXA), bioimpedanciometry (BIA), skinfold measurement (SM), or deuterium dilution (DD). In addition, imaging methods such as computed tomography (CT) or magnetic

resonance imaging (MRI) can also be used for evaluating nutritional status. However, there has been great variability among the studies that assess body composition (BC) by different methods in CF patients (11). Therefore, clear conclusions to propose an evidence-based algorithm to assist in the assessment of BC cannot be drawn. Currently, DXA represents the preferred option for assessing and monitoring BC changes in this population, and is the most frequently applied method (10). Furthermore, in clinical practice DXA is considered the technique of choice (12). Thus, it is necessary to know the degree of agreement between the values obtained by DXA and other techniques more easily implemented in routine care, such as SM, which is more accessible for health care teams. In addition, increasingly accurate equations are available for the assessment of BC, which would support the use of SM (13). However, few studies have assessed BC using different techniques and evaluated their agreement in adults with CF.

We hypothesize that SM has both an adequate correlation and concordance for measuring FFM with respect to DXA in adults with CF. The objective of our study was to describe BC using different techniques to evaluate nutritional status (DXA vs SM), and to assess their concordance in adults with CF.

MATERIALS AND METHODS

This was a cross-sectional, observational study in patients with CF in situation of clinical stability. A sequential recruitment was carried out when patients attended the CF adult's outpatient consulting room for their annual examination.

Anthropometric and body composition parameters

Height was obtained by a stadiometer (Holtain limited, Crymch, UK) and weight was assessed through a scale (SECA 665). With these two values, BMI was calculated. The diagnosis of malnutrition was established when BMI was $< 18.5 \text{ kg/m}^2$.

Skinfold thickness measurement (SM)

The skinfolds assessed were the triceps, biceps, subscapularis, and supra-iliac. A Holtain constant pressure caliper (Holtain Limited) was used to assess skinfolds. The same investigator performed the measurements in triplicate for each of the skinfolds assessed and the mean was calculated according to the recommendations by the Spanish Society of Endocrinology and Nutrition (SEEN) (14). The values for the healthy Spanish population were taken as a reference for the estimation of percentiles (15). Percentages and kilograms of FM and FFM were estimated according to the formulas of Siri (16) and Durnin and Womersley (17). Age, sex, weight, and the sum of four skinfolds (triceps, biceps, supra-iliac, and subscapular) were taken into account in the formula.

Dual-energy X-ray absorptiometry (DXA)

A General Electric Healthcare Lunar Prodigy Advance densitometer was used to scan the patients and the software used was EnCore 12.3 (18). All the scans were performed according to the manufacturer's standard scan and positioning protocols. Weight, total and regional fat, and FFM were recorded.

In addition, FFM index (FFMI) was calculated (FFMI: fat-free mass in kg/height in m²) and the prevalence of FFM malnutrition was determined according to the European Society for Clinical Nutrition and Metabolism (ESPEN) criteria: < 17 (men) kg/m² or < 15 kg/m² (women) (8).

Assessment of respiratory status

Recorded exacerbations were assessed at the annual review appointment. Exacerbations occurring in the year preceding the assessment were considered. Exacerbations were divided into mild/moderate (suggestive symptoms and concordant blood test results, treated on an outpatient basis and resolved with oral antibiotics) or severe (suggestive symptoms presenting clinical

worsening and requiring hospital admission and/or intravenous antibiotics on an outpatient basis) (19). In addition, following the recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), respiratory function tests were performed using forced spirometry with a JAEGER pneumotachograph (Jaeger Oxycon Pro® Erich Jaeger, Würzburg, Germany), and forced vital capacity (FVC), maximal expiratory volume in the first second (FEV₁), and the ratio between both (FEV₁/FVC) were determined for all patients. The values obtained were expressed in absolute terms in ml and as a percentage of the theoretical value for subjects of age, weight and height, according to a reference population (20). Bronchorrhoea was defined as the amount of sputum produced per day and was expressed in milliliters. To assess bronchorrhea, the patient made an estimate during the last three days before the visit (19).

Data analysis

The SPSS version 22.0 was used for the data analysis (21). The Kolmogorof-Smirnoff test was used to evaluate the distribution of quantitative variables. The paired-samples t-test (or Wilcoxon's test in the absence of normality) was used to compare quantitative variables. Statistical significance was set at $p < 0.05$ for all statistical analyses performed.

The intraclass correlation coefficient (ICC) (22) was used to study the degree of agreement between the BC using the different techniques, and Bland-Altman plots were used to analyze the individual differences. The kappa coefficient was calculated in order to assess the concordance between the different methods to classify individuals with a low FFMI.

Ethics

All subjects gave their informed consent before being included in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics Committee of the Malaga Province (27/04/2017).

RESULTS

Forty-one patients with CF were recruited. Of these patients, nineteen were males (46.3 %) and twenty-two (53.7 %) were females. Their median age was 29.8 (20.9-33.7) (Table I).

Only four (9.8 %) patients had a BMI lower than 18.5 kg/m². By DXA, FFM (kg) results were median: 52.8 (interquartile range, 47.8-56.9) kg with FFMI 17.9 (16.7-19.3) kg/m² in men, and 36.7 (33.1-38.9) kg in women with FFMI 14.7 (14.2-15.8) kg/m². Using this technique, twenty (48.6 %) patients presented FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected. By SM, FFMI was 18.7 (17.2-20.0) kg/m² in males and 14.9 (14.2-15.8) kg/m² in females; moreover, sixteen (39.1 %) patients presented FFM malnutrition, with 20.8 % of males and 61.8 % of females being affected. The general characteristics of the patients are summarized in table I. All patients designated as malnourished by FFM according to SM were found to be malnourished according to DXA.

Figures 1A and B show body composition as assessed by DXA and SM. They show that the prevalence of FFM malnutrition is higher for DXA than for SM. In addition, the prevalence of malnutrition was higher in females than in males in the nutritional assessment by both techniques.

Concordance was high between SM and DXA for the FFM in kg (ICC of 0.950; $p < 0.001$) and also in % (Table II). Concordance was also high for FM as expressed both in kg and %. When the techniques were compared by applying the ESPEN criteria for FFMI malnutrition, concordance was moderate: kappa coefficient of 0.440 when comparing SM with DXA ($p = 0.006$).

By analyzing individual differences using the Bland-Altman plot analysis, the degree of agreement between baseline BC data obtained with DXA and SM was assessed (Fig. 2). The mean overestimation with respect to DXA was $+1.44 \pm 0.62$ kg, with a tendency to greater dispersion in higher FFM.

DISCUSSION

In our study we found a high prevalence of FFM malnutrition, especially in females, according to the different nutritional assessment techniques used. In addition, we found a high statistical agreement between DXA and SM for FM and FFM values. However, the concordance when we assessed malnutrition according to FFMI was moderate. It was observed that SM tends to overestimate FFM and to underestimate FM, compared to DXA.

According to the Cystic Fibrosis Foundation (CFF), a BMI ≥ 22 kg/m² in females and a BMI ≥ 23 kg/m² in males is recommended as a target for adults, as it is associated with improved lung function (23). However, despite the improvement in disease progression and nutritional status, according to the latest European Cystic Fibrosis Registry the prevalence of malnutrition determined by BMI (below 18.5 kg/m²) is approximately 30 % of adults (23). In our study, the mean BMI is slightly higher than the one published in the 2014 European CF registry (22.2 vs 21 kg/m²) for a similar mean age (24). In addition, the rate of malnutrition determined by BMI in our CF population was 9.8 %, lower than the one published in other series (24,25). However, BMI measurement alone in adults with CF should not be the only parameter used to assess nutritional status. Engelen et al. have warned about the increased prevalence of overweight and obesity in this population (even in association with severe mutations), and BMI may therefore be a confounding factor for nutritional status. It has been observed that between 25-38 % of adult CF patients with a normal or high BMI have low lean mass levels (26). Thus, guidelines on nutrition care for patients with CF recommend evaluating BC as part of the nutritional assessment (3,4).

In CF, one of the most important determinants of morbidity and mortality in relation to malnutrition is the decrease in FFM (10,27). It is therefore useful to measure BC, using different techniques, to estimate FFM; in this sense, the calculation of FFMI is particularly

useful (4). In the review by Calella et al. they conclude that the results showed great variability in the methods used to evaluate BC in patients with CF (10). In the review by Gomes et al. they conclude that further studies are needed to identify and determine which FFM measurements are associated with improved lung function and nutritional status in CF patients (5). The use of DXA-derived FFM measurements in clinical practice among CF patients shows great potential utility and value. Furthermore, together, FFM and BMI may provide a more comprehensive picture of nutritional status during the nutritional evaluation of CF patients (5).

In the present study, we have performed a comparison of simpler techniques as SM with DXA. Some of the potential advantages of DXA for assessing BC are the high accuracy of SM and DXA (28), the good agreement with the results obtained using the 4-compartment model (29), good short-term reproducibility (30), and the possibility of assessing total and segmental BC. On the other hand, the limitations of DXA are the lack of portability of the equipment, the radiation exposure associated with the scan, or the fact that it requires the patient to be in a decubitus position for a few minutes (which may be difficult for patients with severe lung disease) (28). For this reason, several studies have questioned whether DXA could be replaced by other measures of BC (31). A recent study of children with CF found, using DXA, estimated a prevalence of malnutrition of 38.6% based on FFM deficit (defined as FFMI < 10th percentile) (27). In our work, the median and IQR for FFMI determined by DXA were 17.9 (16.7-19.3) kg/m² in males and 14.7 (14.2-15.8) kg/m² in females, being slightly higher when determined by SM. By DXA, we found a prevalence of FFM malnutrition of 48.6 %, which was much higher in females (68.4 %) compared to males (27.8 %) and using the criteria recommended by ESPEN (17 kg/m² in males and 15 kg/m² in females) (8). It is possible that the ESPEN criterion for females is too high in this population, overestimating the prevalence of FFM malnutrition. According to the Spanish population data, the FFMI cut-off point for

males would remain at 17 kg/m²; however, in females it would be 14.4 kg/m² (32,33). If we consider 14.4 kg/m² as the cut-off point for FFM in females to diagnose FFM malnutrition, the prevalence of malnutrition in females in our study would drop to 47.4 % using DXA. Assuming that subcutaneous adipose tissue represents a constant proportion of total body fat, and that measurement sites are representative of the average subcutaneous adipose tissue thickness, skinfold thickness measurements are useful to estimate FFM and FM (29). This may vary depending on race, age, gender, and disease (29). Inter- and intra-observer variability are other limitations of this technique (30). The use of SM in CF has been evaluated in several studies (27,30,34-40). The same researcher always performed the anthropometric measurements in our study. We observed that 39.1 % of patients had FFM malnutrition, with 16.7 % of males and 59.1 % of females being affected, estimated by SM. This prevalence is slightly lower, especially in females, which could classify malnourished people as normonourished. In this sense, if we used the cut-off point 14.4 kg/m² (32,33) to detect malnutrition according to FFMI, the prevalence of FFM malnutrition would decrease considerably to 13.6 % according to SM.

Chomtho et al. evaluated the use of upper arm anthropometry compared to DXA in healthy children and children with CF, concluding that upper arm anthropometry is less accurate than DXA for determining segmental and total FFM. The results were better for FM determination (35). In the work by Alicandro et al. using DXA as a reference method, they conclude that BC estimation obtained by SM or BIA cannot be part of the standard nutritional assessment of CF patients due to low precision at the individual level, at least until reliable CF-specific equations become available (36). King et al. also compared BIA and SM with DXA in adults with CF (37). SM overestimated lean mass by almost 2.4 kg on average compared to DXA. In a study of our group in people with non-CF BQ, SM also overestimated lean mass with very similar values (2.35 kg on

average) and was homogeneously distributed across lean mass values (38). The study by de Meer et al. that assessed changes in lean mass by skinfold measurement in malnourished children with CF after a physical exercise program concluded that regardless of disease severity this technique is applicable to detect changes in lean mass (39). Stettler et al. also assessed prospectively body composition in children with CF using various techniques such as double watermarking, SM and BIA; the study showed high concordance for lean mass but not for FM (40). In our study, there was good statistical agreement between SM and DXA for assessing FM and FFM. However, the concordance was moderate for detecting malnutrition according to FFMI. Using Bland-Altman plot analysis, the mean overestimation with respect to DXA was $+1.44 \pm 0,62$ kg, thus, the degree of agreement showed a greater dispersion as FFM increased.

The limitations of our study are mainly due to the fact that it is a single-center study, which prevented us from having a larger sample size. Furthermore, the study design was cross-sectional. These limitations hamper drawing causal conclusions, and therefore, we can only speculate about different associations.

In conclusion, the prevalence of FFM malnutrition is high in CF patients, despite presenting a normal BMI, especially in females. The cut-off point for FFM proposed by the ESPEN may be high in our population. There was good statistical agreement between SM and DXA for assessing FM and FFM. However, the concordance was moderate for detecting malnutrition according to FFMI, and the degree of agreement showed a greater dispersion as FFM increased. Therefore, DXA remains the technique of choice for nutritional assessment in CF, and SM can be used in cases in which it is not available.

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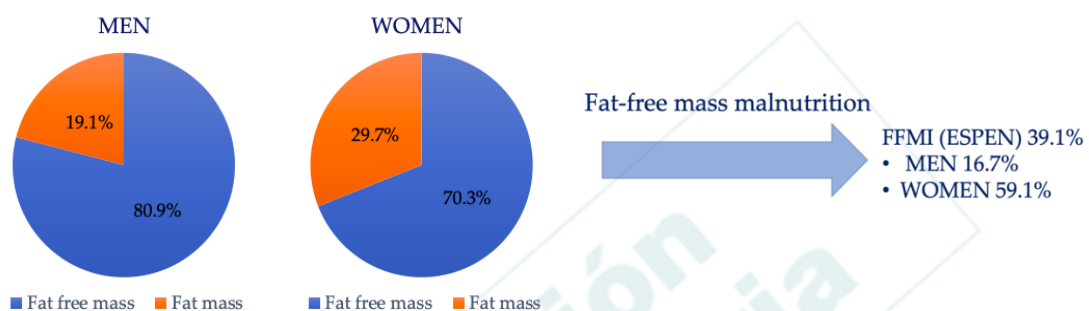
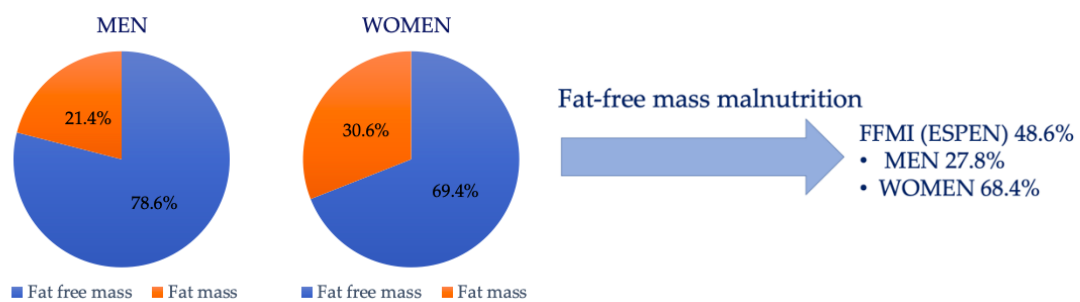


Fig. 1. A) Body composition according to sex by DXA (%). B) Body composition according to sex by SM (%).

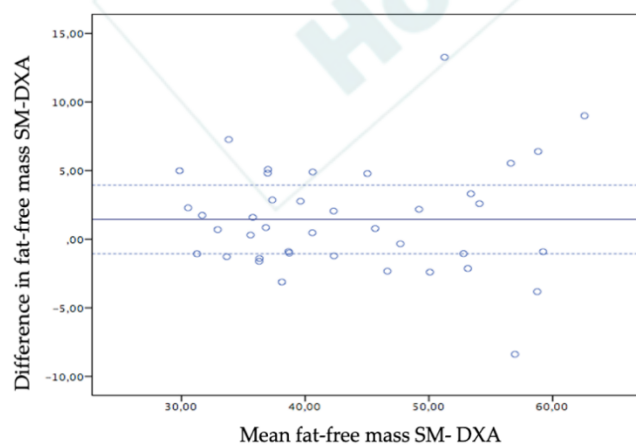


Fig. 2. Comparison between FFM by SM and DXA.



Table I. General characteristics

	CF
	(41)
	Median (Interquartile range)
Age	29.8 (20.9-33.7)
Sex, n (%)	n (%)
Female	22 (53.7)
Male	19 (46.3)
Respiratory	
Bronchorrhea (mL)	10.0 (10.0-20.0)
Annual exacerbation	2.0 (1.0-4.0)
FEV ₁ (%)	60.6 (48.5-87.9)
FVC (%)	74.6 (67.2-96.2)
FEV ₁ /FVC (%)	65.6 (53.7-65.6)
Nutritional status	
BMI (kg/m ²)	21.6 (19.8-23.0)
BMI ≥ 18.5 kg/m ² , n (%)	37 (90.2)
BMI < 18.5 kg/m ² , n (%)	4 (9.8)
DXA	
<i>FM (kg)</i>	
Male	14.9 (11.8-17.9)
Female	14.8 (13.8-15.2)
<i>FFM (kg)</i>	
Male	52.8 (47.8-56.9)
Female	36.7 (33.1-38.9)
<i>FFMI (kg/m²)</i>	
Male (Normal ≥ 17 kg/m ²)	17.9 (16.7-19.3)
Female (Normal ≥ 15 kg/m ²)	14.7 (14.2-15.8)
SM	
<i>FM (kg)</i>	
Male	11.6 (8.5-19.3)
Female	15.3 (11.5-17.9)
<i>FFM (kg)</i>	
Male	52.1 (47.5-59.1)
Women	36.9 (33.8-40.5)

FFMI (kg/m^2)

Male (Normal ≥ 17 18.7 (17.2-20.0)

kg/m^2) 14.9 (14.2-15.8)

Female (Normal ≥ 15

kg/m^2)

BMI: body mass index; FEV₁: forced expiratory volume in 1 second;
FVC: forced vital capacity; DXA: dual-energy X-ray absorptiometry;
FM: fat mass; FFM: fat-free mass; FFMI: fat-free mass index; SM:
skinfold measurement.

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Table II. Comparison of measurements and agreement between BC values by SM and DXA

	DXA		SM		p¹	ICC	p²
	medians (IQR values)		medians (IQR values)				
FM	14.8	(9.6-	14.7	(10.3-	0.136	0.926	< 0.001
(kg)	18.9)		17.9)				
FFM	40.8	(36.0-	43.2	(36.6-	0.054	0.950	< 0.001
(kg)	52.5)		52.5)				
FM (%)	27.7	(18.6-	27.6	(17.9-	0.056	0.912	< 0.001
	33.5)		33.7)				
FFM	72.3	(66.5-	72.4	(66.3-	0.057	0.912	< 0.001
(%)	81.4)		82.1)				

Medians. IQR: interquartile range; ICC: intraclass correlation coefficient; DXA: dual-energy X-ray absorptiometry; SM: skinfold measurement; FM: fat mass; FFM: fat-free mass. p¹: statistical significance of the comparison of DXA and SM measures; p²: statistical significance of CCI.

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