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Review

Cystic fibrosis, body composition, and health outcomes: a systematic review

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ABSTRACT

Objectives: Patients with cystic fibrosis are characterized by an increased risk of nutrient malabsorption and inflammation, which may influence body composition. We examined the differences in body composition between patients with cystic fibrosis and healthy controls and how body composition differences may impact disease risk and mortality.
Methods: Three different electronic databases (PubMed, Web of Science, and Embase) were used to find articles from inception until March 2017. The search strategy excluded articles that reported data on anthropometric measures only such as body weight, height, or waist circumference. Information on the characteristics of the study populations (e.g., age, sex, body mass index), type of study design, body composition methods, body compartments, and health outcomes was extracted.
Results: Thirty-nine articles were included in the systematic review. The total number of patients with cystic fibrosis and controls that were included in these studies was 1839 and 2178, respectively. Only one study explored the association between body composition and risk of mortality whereas the majority of the studies examined the association between body composition and respiratory function (33%). Patients with cystic fibrosis had less fat-free mass and bone mineral density compared with the controls and fat-free mass was associated with decreased inspiratory muscle strength.
Conclusions: Patients with cystic fibrosis may be at an increased risk of sarcopenia and osteopenia. The measurement of body composition could improve the assessment of nutritional status and reduce the risk for respiratory and metabolic complications in patients with cystic fibrosis.

Introduction

Cystic fibrosis (CF) is an inherited disease that is caused by recessive mutations in the cystic fibrosis transmembrane conductance regulator gene, which cause altered transport of chloride, bicarbonate, and sodium ions across the epithelial cell membranes [1]. The phenotypic manifestations of this dysfunction are abnormal fluid transport and accumulation of thick mucus in different organs such as the liver, pancreas, intestines, and lungs [2].

Patients with CF are affected by a range of respiratory and gastrointestinal problems including airway inflammation and increased susceptibility to repeated infections, exocrine pancreatic insufficiency and malabsorption, and a chronic inflammatory status that leads to general malaise and a poor quality of life [3]. Patients with CF may have a reduced level of physical activity (PA) and increased resting energy expenditure, which is often exacerbated by pulmonary complications, increased fecal energy loss, and reduced food intake that is caused by inflammation-related

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anorexia. All these factors may contribute to the increase in risk of malnutrition [4].

The mechanisms that explain the increase in resting energy expenditure are still unclear and could be associated with the severity of pancreatic insufficiency and lung inflammation [5]. The risk of malnutrition could also be increased by fecal energy losses as a result of malabsorption. The incremental transit of unprocessed food in the intestine may further intensify the malabsorptive syndrome as a consequence of bacterial intestinal overgrowth and low bicarbonate output [6]. The resulting negative energy balance that is derived from a reduced appetite and increased energy needs contributes to the risk of deterioration of the nutritional status of patients with CF [7].

Body composition can be assessed using various methods that provide quantitative and qualitative information on various tissue components such as fat-free mass (FFM), fat mass (FM), total body water (TBW), bone mineral density (BMD), and bone mineral content (BMC). These methods are all characterized by advantages and disadvantages that can affect the precision and accuracy of the body composition assessment, the applicability in clinical or research settings, and most importantly the provision of specific information on body components.

In 2015 the UK CF Trust Registry Report found that 12.4% of children and adolescents with CF were below the 10th percentile weight-for-age and sex and the median body mass index (BMI) in adults age 18 to 40 y was 22.4 kg/m^2 [8]. The careful monitoring of growth trajectories and nutritional status is a key priority in the multidisciplinary care of patients with CF. The poor nutritional status of patients with CF is associated with a deterioration of their quality of life and may accelerate the clinical progression of the disease [9]. Several studies have shown a close association between malnutrition and a decline in lung function [10,11].

There is a growing body of literature in support of the importance of the assessment of nutritional status in patients with CF to improve diagnostic and therapeutic health care pathways [12,13]. This systematic review aims to examine the differences in body composition between patients with CF and healthy controls and discuss how these differences may impact survival and clinical endpoints such as impaired lung function and recurrent infections.

Methods

Search strategy

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14]. The PubMed, Web of Science, and Embase databases were searched by one researcher (PC) from their inception to March 2017.

The following terms were included in the search strategy: (cystic fibrosis OR cftr) AND (body composition OR nutritional status); AND (fat mass or fat free mass OR adiposity OR lean body mass OR muscle mass OR hydration OR body water OR body cell mass OR bone mineral content OR bone mineral density OR osteopenia OR osteoporosis). Only articles in the English language and studies that were conducted in humans were selected. In addition, a manual search of the reference lists was carried out to find additional studies.

Two investigators (MS and PC) independently reviewed the titles and abstracts to identify eligible studies and any doubts over eligibility were resolved by discussion until a consensus was reached between the authors.

Inclusion criteria and data extraction

The inclusion criteria that were applied to this systematic review were: 1) Research that was published in the English-language; 2) assessment of body composition in patients with CF; and 3) comparison of the body composition of patients with CF with those of healthy controls. Duplicate publications were excluded from the review. We also excluded studies that evaluated body composition by measuring only weight, height, or waist circumference.

Data from eligible studies were independently extracted using a standardized form. The following information was collected: First author, year of publication, type of study, sample size, description of study population (i.e., age, sex, race, and country of study), method of body composition measurement, description of body composition (i.e., weight, height, BMI, FFM, FM, TBW, BMD, and BMC), pulmonary function (forced expiratory velocity in 1 s [FEV_1] or percent of predicted values [FEV_1%]), main aims, and findings of the selected studies.

Study quality assessment

The quality of the studies was measured using the Downs and Black item checklist [15], which is a recommended instrument by the Cochrane Collaboration for use in observational and non-randomized studies [16]. We omitted seven questions from the original checklist because these items were specific to interventional trials. Two extra items (#14 and #15) were added because they reviewed the quality of the methods that were used to evaluate body composition and the body compartments that were analyzed. The final checklist included 15 items with a maximum score of 15 points (range, 0–15) with the higher points indicating superior quality (Supplementary Table S1). The tool assesses quality criteria such as a clear description of the aims, interventions, participants, outcome measurements, and quality of the statistical analyses. Studies were independently appraised by two reviewers (LMD and PC). A cutoff point of nine was adopted in this systematic review to categorize studies as high (≥9) or low (<9) quality.

Results

Search results

The search of the electronic databases identified 8788 potentially relevant studies. After removing duplicate studies, 1850 studies were initially reviewed on the basis of an assessment of the titles and abstracts against the eligibility criteria. A total of 1523 articles failed to meet the inclusion criteria and were excluded from the review. The remaining 327 full-text articles were assessed for eligibility and 39 studies were included in the final review. Figure 1 summarizes the screening and selection process.

Description and quality of the studies

Among the 39 included studies, two were longitudinal [17,18] and the remaining 36 studies had a cross-sectional design (Table 1). All studies included a healthy control group. The total number of patients with CF and controls was 1839 and 2178, respectively. The age range of the subjects was different between the studies: Nine studies recruited subjects age <10 y [18,22,40] and 10 studies included subjects age 10 y to 20 y [17,39,49] but the majority of the studies were conducted in adult populations (18 studies: age ≥20 y; Table 1). Only one study recruited both children and adults [26].

The studies that were included in the systematic review had different aims: 1) Evaluation of the relationship between body composition and clinical outcomes (lung function [19,22,39,48,54], inflammation [4,21,23,45], clinical parameters [21,25–27,32], or disease severity [28,34,36,38,47]; and 2) validation or comparison of different techniques to evaluate the differences in body composition between patients with CF and healthy controls [17,20,41,50,51,53] or comparison of changes in growth and/or nutritional status between subjects with and without CF [18,33,37,42,52]. Finally, two studies explored the association between resting energy expenditure and body composition in patients with CF (Table 1) [40,49].

The average value from the Downs and Black quality evaluation was 8.8 ± 2.1. A total of 21 studies had a score ≥9 and 18

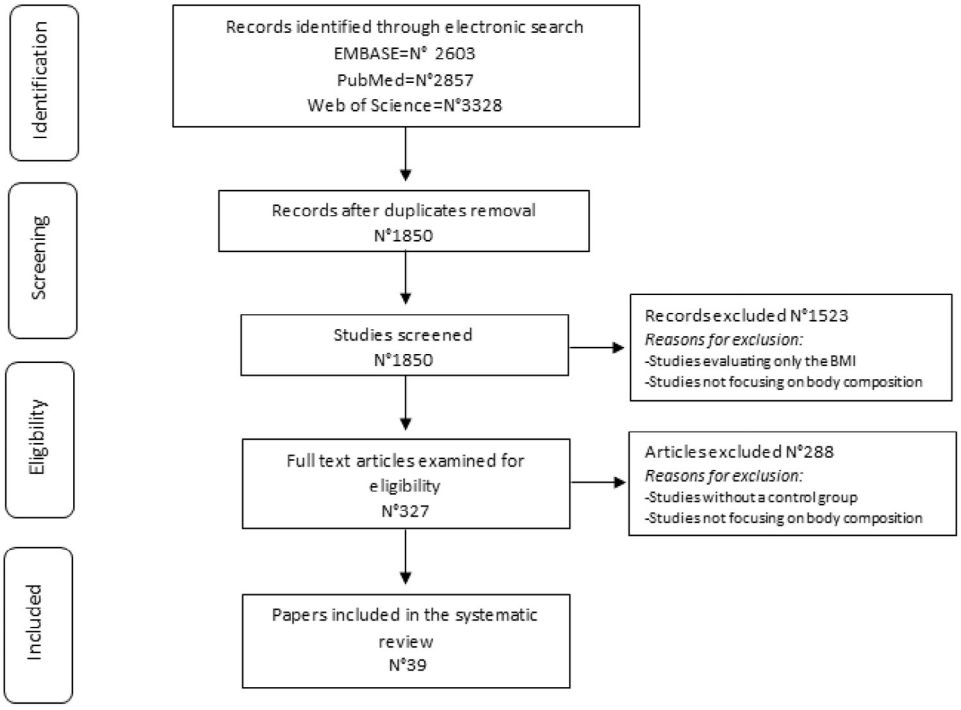

Fig. 1. Flow diagram for Preferred Reporting Items for Systematic Reviews and Meta-Analyses systematic review.

studies had a score <9. The minimum and maximum total scores were 5 and 12, respectively (Supplementary Table S2).

Body composition differences between subjects with and without cystic fibrosis

Fat-free mass

Six studies showed a lower FFM, lean body mass (LBM), or muscle mass in patients with CF compared with healthy subjects [19,33,36,38,42,44] but four papers did not find a significant difference between the two groups [43,45,47,52]. Two studies in children concluded that patients with CF gained less FFM during the follow-up period than the controls [18,21] but four studies found no significant difference between the two groups [43,45,47,52]. A significant association was reported between low LBM, loss of diaphragm muscle mass [29], and impaired inspiratory muscle function [34]. One study also found that patients with CF who had low FFM were less active than those with normal FFM (Table 2) [35].

Fat mass

Four studies reported a similar FM in patients with CF compared with healthy controls [19,36,43,45,52] but two studies reported a comparable FM% in the presence of an increased central fat accumulation in patients with CF [43,45]. Seven studies reported a lower FM in patients with CF compared with healthy controls [18,23,30,33,42,44,54], but only two of these studies were in adult populations [30,44] (Table 3).

Total body water

Three studies measured TBW and reported that a large proportion of children with CF were considered dehydrated [22]. One study compared bioelectric impedance analysis measurements of TBW to deuterium dilution and found a significant agreement between the two methods in subjects with and without CF [20] but another study found that bioelectric impedance analysis overestimated TBW in patients with CF but not in controls [46] (Table 4).

Bone mineral density/content

A reduced BMD or BMC was found in patients with CF compared with controls: Two studies reported a low BMD at all sites (i.e., lumbar spine [L2-L4], femoral neck, Ward's triangle) [30,33] and two studies evaluated the differences of tibial and radial BMD [25,27], but one study reported that hip BMD was reduced in patients with a normal BMI and low FFM [36]. Kelly et al. [37] concluded that the BMC deficit was related to an altered body size (i.e., short stature and low LBM) because the differences between patients and controls disappeared if BMC was corrected for these two variables [28]. On the other hand, three studies did not find any difference in BMD and BMC between patients with CF and controls who were matched for age, sex, height, and LBM [21,26,32]. All these studies used dual-energy x-ray absorptiometry or peripheral quantitative computed tomography to assess body composition (Table 5).

Body composition and clinical endpoints

Respiratory function

Thirteen studies analyzed the relationship between pulmonary function and body composition. Three studies found a higher impairment of lung function in patients with CF who had lower BMD [35,36,39]. Nine studies reported a significant association between low FEV_1 and low FFM or LBM [4,19,38,43,48], which was exacerbated by a low BMI [34,36] or poor inspiratory muscle work capacity [29]. The association between FEV_1 and FM was

Table 1
Main characteristics and aim of the of 39 studies that were selected for the systematic review

Reference	Study design	CF/healthy controls	Age (y)	Aim of the study
Alvarez et al. [19]	Pilot CS	32/20	CF: 26.1 ± 8.9 C: 30.9 ± 8.8	Evaluate the relationship between lung function and body composition and examine the presence of normal weight obesity.
Azcue et al. [20]	CS	20/21	CF: 21.2 ± 9.1 C: 21.5 ± 8.6	Validate BIA as a measure of TBW.
Bai et al. [21]	CS	12/24	CF: 11.8 ± 0.9 C: 12.4 ± 0.9	Examine BMC and BMD and investigate geometric bone properties of children with CF compared with healthy controls.
Barbieri et al. [22]	CS	46/24	CF: 8.5 C: 8.8	Examine the association of nutrition and hydration status with lung function.
Boguszewski et al. [23]	CS	26/33	CF: 8.52 ± 2.98 C: 8.76 ± 1.75	Evaluate the relationships between disease activity, body composition, IGF-1, and leptin concentrations
Borowitz et al. [24]	Pilot CS	10/10	CF: 27 C: 27.5	Compare BIA to isotope dilution in patients with CF and control.
Brookes et al. [25]	CS	53/53	CF: 12.5 ± 1.6 C: 11.8 ± 1.58	Assess volumetric BMD as well as bone and muscle parameters using pQCT.
Buntain et al. [26]	CS	153/149	CF: Range, 5.3–55.8 C: Range, 5.6–48.3	Examine the relationship between BMD and clinical parameters including physical activity, nutrition, and vitamin D levels.
De Meer et al. [17]	L	26/13	CF: 14.7 ± 2 C: 15.2 ± 1.9	Study applicability of the SFt method to measure changes in body composition after home exercise training and assess the validity of SFt compared with DD
Donovan et al. [27]	CS	30/30	CF: 30 ± 2 C: 32 ± 2	Examine the relationships between BMD, anthropomorphic variables, pulmonary status, glucocorticoid therapy, and vitamin D concentrations.
Elkin et al. [28]	CS	25/25	CF: 28 ± 8 C: 28 ± 7	Determine the relationship between muscle mass and strength, muscle, and bone mass and the quality of CF muscle.
Enright et al. [29]	CS	40/30	CF: 22.4 C: 21.7	Investigate the effect of loss of FFM on pulmonary function, physical activity, and diaphragm thickness.
Gray et al. [30]	CS	22/65	CF: 23 ± 8 C: 26 ± 6	Determine whether osteopenia occurs in adults with CF and delineate clinical and biochemical predictors of BMD.
Gruet et al. [31]	CS	15/15	CF: 28 ± 6 C: 28 ± 5	Determine whether patients with CF with mild-to-moderate lung disease have altered skeletal muscle contractility and greater muscle fatigability compared with healthy controls.
Hardin et al. [32]	CS	28 adults, 16 children/17 adults	CF: 25 ± 5 adults; 11 ± 1 children C, 25 ± 4 adults	Measure BMD in non-acutely ill adults and BMC in children with CF.
Henderson and Madsen [33]	CS	47/40	CF: 11.9 ± 4.0 C: NR	Assess the interrelationships between various measures of growth including height, weight, and bone density and the bone mineral, lean, and fat body compartments.
Ionescu et al. [34]	CS and survival	49/25	CF: 22.9 ± 3.8 C: NR	Determine the effect of BMI and LBM depletion on handgrip force and inspiratory muscle function.
Ionescu et al. [35]	CS	22/22	CF: 23.6 C: 23.8	Determine the relationships between host inflammatory response, body composition, bone protein turnover, and catabolic status.
Ionescu et al. [4]	CS	40/22	CF: 23.1 C: 23.8	Study the relationships between severity of lung disease, body composition, host inflammatory response, dietary intake, and evidence of cellular and connective tissue protein breakdown.
Ionescu et al. [36]	CS	56/20	CF: 23 C: 23.6	Determine the occurrence and distribution of hidden FFM loss and its relationship to indicators of disease severity.
Kelly et al. [37]	CS	82/322	CF: 13.2 ± 2.9 C: 12.9 ± 2.9	Characterize BMC in children with CF and determine the relationship to growth, body composition, and disease severity.
King et al. [38]	Prospective CS	86/156	CF: 30.0 ± 7.7 C: NR	Determine the prevalence of FFM depletion, compare FFM index with BMI, and identify predictors of FFM depletion.
Lucidi et al. [39]	CS	82/82	CF: 13.5 ± 5.6 C: 12.9 ± 5.9	Investigate the correlation between severity of the clinical condition, bone status, and body composition parameters.
Marin et al. [40]	CS	15/15	CF: 8.2 ± 3.8 C, 7.9 ± 3.2	Assess REE, nutrition status, and body composition of clinically stable outpatients with CF.
McNaughton et al. [41]	CS	226/140	CF: 8.76 ± 5.54 C: NR	Compare standard anthropometric measurements and TBK as indicators of malnutrition.
Miller et al. [42]	CS	9/8	CF: 9.3 C: 10.3	Investigate nutritional growth retardation, body composition, and muscle protein catabolism.
Moriconi et al. [43]	CS	24/24	CF: 30.4 ± 9.4 C: 30.5 ± 8.8	Compare body composition and serum adiponectin levels of patients with CF with those of healthy controls and examine whether LBM or serum concentrations of inflammatory mediators are associated with disease severity.
Newby et al. [44]	CS	8/8	CF: 27.3 ± 3.4 C: 28.4 ± 3.5	Contrast body composition as estimated by densitometry, BIA, TOBEC, SFt, and DD of patients with CF with the body composition of individuals without CF.
Panagopoulou et al. [45]	CS	43/27	CF: 20.2 ± 8.4 C: 19.9 ± 9.4	Examine serum adiponectin levels and the association with nutritional status and body composition.
Richards et al. [46]	CS	36/42	CF: 25.5 ± 5.6 C: 25.4 ± 4.8	Compare the measurement of TBW by DD and BIA and determine the intraindividual differences between methods for both groups.
Salamoni et al. [47]	CS	14/14	CF: 12.2 ± 3.5 C: 12.3 ± 3.5	Assess BMC in well-nourished patients and seek a correlation with FFM.
Sheikh et al. [48]	CS	208/390	CF: 12.4 ± 3.85 C: 11.9 ± 3.55	Assess associations of BMI and DXA-derived measures of LBM and FM with lung function.
Shepherd et al. [49]	CS	30/18	CF: 13.07 ± 0.55 C: 12.56 ± 1.25	Determine whether REE is related to either nutritional status or pulmonary function.
Spicher et al. [50]	CS	39/39	CF: 12.9 ± 4.4 C: 12.1 ± 4.3	Compare BIA values to other values obtained by anthropometry and the urinary creatinine excretion method.
Stettler et al. [18]	L	25/26	CF: 7.8 ± 1.3 C: 7.7 ± 1.3	Compare changes in growth, body composition, and nutritional status between children with and without CF.
Swisher et al. [51]	Pilot CS	10/10	CF: 22.2 ± 8.5 C: 21.5 ± 2.0	Compare skinfold and NIR measurements of body composition with ADP measurements.
Tomezsko et al. [52]	CS	23/24	CF: 7.8 ± 1.3 C: 7.7 ± 1.1	Compare body composition by various methods and identify patterns of growth, FFM, and FM.
Williams et al. [53]	CS	26/122	CF: 9.84 ± 0.9 C: 11 ± 3.06	Evaluate the level of agreement between DXA and the 4CM reference method.
Williams et al. [54]	CS	85/85	CF: 9.41 ± 1.27 C: 9.43 ± 1.43	Compare healthy children and children with CF using the 4CM and examine associations between body composition and lung function.

4CM, four-component model; ADP, air displacement plethysmography; BIA, bioelectric impedance analysis; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; C, controls; CF, cystic fibrosis; CS, cross-sectional design; DD, deuterium dilution; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; L, longitudinal design; IGF-1, insulin-like growth factor 1; LBM, lean body mass; NIR, near-infrared reactance; NR, not reported; pQCT, peripheral quantitative computed tomography; REE, resting energy expenditure; SFt, skinfolds thickness; TBK, total body potassium; TBW, total body water; TOBEC, total body electrical conductivity.

Table 2
Main findings about FFM in case-control studies on CF

First author name	Techniques	Results on FFM	Main findings of the study
Alvarez et al. [19]	ADP	FFM index was lower in patients with CF with respect to the reference group ($P < 0.01$). FEV_1% predicted was positively associated with FFM index ($\beta = 6.31 \pm 2.93$; $P = 0.04$).	Excess adiposity, particularly in the form of NWO, was inversely associated with lung function in CF.
Bai et al. [21]	pQCT	CF group had a trend of lower LBM per height ($P < 0.08$).	
Boguszewski et al. [23]	DXA	Shwachman-Kulczycki score was the strongest predictor of LBM.	Children with CF remain at a high risk of malnutrition and growth failure.
De Meer et al. [17]	SFt	SFt measurements are applicable to monitor FFM irrespective of clinical severity of the disease.	Repeated SFt measurements at intervals of 6 mo are applicable to monitor changes in FFM during exercise training.
Elkin et al. [28]	DXA SFt	Both muscle strength and muscle mass (total body and leg) were decreased in CF with respect to controls.	Adults with CF are significantly weaker than controls due to lower muscle mass and not to a reduced force-generating capacity of the muscle.
Enright et al. [29]	DXA	Loss of FFM is associated with loss of diaphragm muscle mass.	There is a relationship between loss of inspiratory muscle work capacity, FFM, PAS, and pulmonary function.
Henderson and Madsen [33]	DXA SFt	LBM was reduced with a mean deficit of 11.9 ± 2.4%.	
Ionescu et al. [35]	DXA	Subjects with a low FFM were more catabolic and less active than those with a normal FFM.	Chronic pulmonary infection in adults with CF may be a contributory factor in the long-term complications of low weight and bone disease.
Ionescu et al. [36]	BIA DXA	Patients had a lower total FFM than healthy subjects ($P < 0.01$).	Hidden depletion of FFM was associated with increased loss of BMD and systemic inflammatory activity.
Ionescu et al. [34]	SFt	There was a significant association between low LBM, impaired inspiratory muscle function, and reduced HG force.	A clear relationship between body composition and impairment of inspiratory muscle function was observed.
Kelly et al. [37]	DXA	BMC deficit was related to reduced LBM.	BMC deficit was related to reduced pulmonary function.
King et al. [38]	DXA	FFM depletion was found in 14% of adults with CF but undetectable by BMI in 58% of these patients.	One association of FFM index with FEV_1% was found.
Miller et al. [42]	SFt	Children with CF had a significant deficit of FFM.	Children with CF had a significant deficit of body mass ($P < 0.001$) including in muscle mass ($P < 0.005$).
Moriconi et al. [43]	DXA	FFM% was similar in patients and controls.	Decreased LBM and increased highly sensitive C-reactive protein levels were independently associated with worse lung function.
Newby et al. [44]	BIA DD SFt TOBEC UWW	Densitometry and BIA suggested that reduced CF weights were due to LBM (10.7, 9.5, and 10.4 kg). TOBEC SFt and DD indicated that patients with CF had less LBM than controls and less fat (5.4 kg and 3.6 kg) and less lean (5.2 kg and 7 kg) tissue.	Densitometry by underwater weighing is unsuitable to assess the body composition of patients with CF.
Panagopoulou et al. [45]	BIA CT	Patients with CF and controls had comparable FFM%.	Patients with malnutrition tended to have a more central fat distribution with increased visceral adipose tissue.
Salamoni et al. [47]	BIA DXA	Anthropometry, BIA, and DXA showed that FFM was similar both groups.	Bone mineral content was strongly correlated with fat-free mass.
Sheikh et al. [48]	DXA	LBM index was more strongly associated with pulmonary function than BMI (particularly in male subjects).	
Spicher et al. [50]	BIA SFt	FFM was linearly correlated to the resistance index.	Regression equations of BIA were similar for both patients with CF and healthy subjects.
Stettler et al. [18]	DD SFt TOBEC	FFM increases were slower in boys with CF than in controls.	Statural growth of boys with CF was slower than that of the control subjects ($P = 0.004$) but the differences were less striking for girls.
Tomezsko et al. [52]	DD SFt TOBEC	FFM not differ significantly between the two groups.	The majority of the methods demonstrated that the CF group achieved normal growth and body composition with a possible trend of fat depletion.

ADP, air displacement plethysmography; BIA, bioelectric impedance analysis; BMC, bone mineral content; BMD, bone mineral density; CF, cystic fibrosis; CT, computer tomography; DD, deuterium dilution; DXA, dual-energy x-ray absorptiometry; FEV_1%, forced expiratory volume in 1 s percentage; FFM, fat-free mass; HG, handgrip; LBM, lean body mass; NWO, normal weight obesity; SFt, skinfolds thickness; PAS, physical activity status; pQCT, peripheral quantitative computed tomography; TOBEC, total body electrical conductivity; UWW, densitometry by underwater weighing.
Shwachman-Kulczycki score to assess disease severity in CF.

examined in two studies: One study found a significant positive association in girls only [54] but the second study reported an inverse association between lung function and FM (adjusted for age, sex, and BMI) [19].

Physical activity level

Nine articles evaluated PA level using different tools such as the Wilson questionnaire [55], which was used in three studies [30,35,36]; Baecke questionnaire [56], which was used in two studies [31,38]; and Crocker questionnaire [57], which was used in one study [26]. One study asked parents about their child's PA level [54].

One study showed no significant correlation between PA levels and BMD [30]. One study reported a lower PA level in adults with CF than healthy controls [26] but no differences between the two groups were observed in another study [31]. The prevalence of sedentary behavior was 86.6% in patients with CF [40] and patients with less FFM were less physically active than those with normal FFM [4,35,36]. However, two studies reported a lack of correlation between body composition and PA level [38,54].

Muscular strength

One study tested the quadricep and hamstring isometric and isokinetic strength in adults with CF and matched healthy

Table 3
Main findings about FM in case-control studies on CF

First author name	Techniques	Results on FM	Main findings of the study
Alvarez et al. [19]	ADP	FM index and FM% did not differ between patients with CF and the reference group. FEV_1% predicted was inversely associated with FM index ($\beta = -6.44 \pm 2.93$; $P = 0.04$).	Excess adiposity, particularly in the form of NWO, was inversely associated with lung function in CF.
Boguszewski et al. [23]	DXA	FM standard deviation score, leptin concentration, and IGF-1 SDS were lower in children with CF compared with controls.	Children with CF remain at a high risk of malnutrition and growth failure.
Gray et al. [30]	DXA	FM was reduced by 30% compared with normal young adults.	BMI was positively correlated with BMD at four sites and disease severity negatively correlated with BMD at two sites.
Henderson and Madsen [33]	DXA SFt	The deficit in FM was nearly as great, averaging 18.1% ± 5.3%.	
Ionescu et al. [36]	BIA DXA	Patients had similar FM as healthy subjects.	In adults with CF, apparent or hidden loss of FFM rather than weight loss was related with overall disease severity. Hidden depletion of FFM was associated with increased loss of BMD and systemic inflammatory activity.
Miller et al. [42]	SFt	Children with CF had a significant deficit of FM.	Children with CF had a significant deficit of body mass ($P < 0.001$) including muscle mass ($P < 0.005$).
Moriconi et al. [43]	DXA	FM% was similar but central fat accumulation was increased (trunk to extremity fat; $P = 0.01$) in patients compared with controls.	Decreased LBM and increased highly sensitive C-reactive protein levels were independently associated with worse lung function.
Newby et al. [44]	BIA DD SFt TOBEC UWW	TOBEC SFt, and DD indicated that patients with CF had less FM than controls. Densitometry estimates of FM were not correlated ($r < 0.74$; $P > 0.05$) with any other method for patients with CF but correlated with all other methods for control subjects.	Densitometry by underwater weighing is unsuitable to assess the body composition of patients with CF.
Panagopoulou et al. [45]	BIA CT	Patients with CF and controls had comparable FM%.	Patients with malnutrition tended to have a more central fat distribution with increased visceral adipose tissue.
Sheikh et al. [48]	DXA	FM index was not associated with pulmonary function.	
Stettler et al. [18]	DD SFt TOBEC	FM increase was slower in boys with CF than in controls.	Over the 3 y of the study, the statural growth of boys with CF was slower than that of control subjects ($P = 0.004$). The differences in the pattern of changes in growth and body composition were less striking for girls.
Tomezsko et al. [52]	DD SFt TOBEC	FM does not differ significantly between the two groups when only using DD. FM% differed between the groups ($P < 0.05$).	The majority of the methods demonstrated that the CF group achieved normal growth and body composition with a possible trend of fat depletion.
Williams et al. [54]	ADP DD DXA SFt	Girls with CF had significantly less FM than healthy girls even after adjustment for height and pubertal status.	FM in girls was positively associated with FEV_1%.

ADP, air displacement plethysmography; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BIA, bioelectric impedance analysis; CF, cystic fibrosis; CT, computer tomography; DD, deuterium dilution; DXA, dual-energy X-ray absorptiometry; FEV_1%, forced expiratory volume in 1 s percentage; FFM, fat-free mass; IGF-1, insulin-like growth factor 1; LBM, lean body mass; NWO, normal weight obesity; pQCT, peripheral quantitative computed tomography; SDS, standard deviation scores; SFt, skinfolds thickness; TOBEC, total body electrical conductivity; UWW, densitometry by underwater weighing.

controls [28]. Patients with CF were significantly weaker than the controls due to a lower muscle mass but the force-generating capacity of the muscle appeared similar. Indices of muscle contractility appeared reduced in patients with CF compared with the controls but the difference disappeared after adjustment for muscle area, which explained a similar tolerance to fatigue in both groups [31].

Mortality

One study analyzed the association of body composition in patients with CF and mortality over a 20-mo follow-up period [34]. The study assessed body composition using skinfolds and BMI and showed that a lower baseline BMI was associated with a greater risk of mortality.

Discussion

Summary of main findings

The majority of the studies reported significant differences in body composition (i.e., FFM, TBW, and BMD) between patients with CF and healthy controls. A consistent, significant associa-

Table 4
Main findings about TBW in case-control studies on CF

First author name	Techniques	Results on TBW	Main findings of the study
Azcue et al. [20]	BIA $H_2{}^{18}O$	MRA of $H_2{}^{18}O$ space versus anthropometric measurements in both patients with CF and C subjects showed that weight and height were significant predictors of TBW.	The BIA predictive equation used in healthy controls cannot be used for patients with CF.
Barbieri et al. [22]	BIA SFt	43% of patients with CF were severely/mildly dehydrated but none were in the controls ($P = 0.007$).	Patients with CF exhibited a compromised nutrition status as assessed by anthropometric and BIA parameters that were also associated with lung function.
Richards et al. [46]	BIA DD	TBW predicted from BIA was significantly different from TBW as measured using ^2H_2O in patients with CF ($P < 0.05$) but not in controls.	In CF, BIA overpredicted TBW as determined by ^2H_2O dilution to an increasing extent at larger TBW volumes.

[2] H_2O, heavy water; BIA, bioelectric impedance analysis; C, controls; CF, cystic fibrosis; DD, deuterium dilution; $H_2{}^{18}O$, water isotope; MRA, multiple regression analysis; SFt, skinfolds thickness; TBW, total body water.

Table 5
Main findings about BMD/BMC in case-control studies

First author name	Techniques	Results on BMD/BMC	Main findings of the study
Bai et al. [21]	pQCT	Children with CF have similar tBMC relative to lean mass as controls.	Cortical bone area and bone strength were less in the CF group compared with controls.
Brookes et al. [25]	pQCT	At puberty, the CF cohort had less BMC at 4% tibia. Pubertal female patients with CF had a lower bone strength (SSI) at the tibia ($P = 0.00$) and radius ($P = 0.05$) sites.	Bone strength parameters were not compromised before puberty in this CF cohort. At puberty, several deficits were present compared with the controls; however, bone strength adapted to the mechanical demands of the muscle.
Buntain et al. [26]	DXA TBK	BMD was not significantly different in children age 5 y to 10 y with CF compared with controls.	In children/adolescents, BMD was weakly associated with nutritional status and disease severity.
Donovan et al. [27]	DXA	Patients with CF had significantly reduced BMD at the lumbar spine, total hip, and femoral neck. The radius was significantly less demineralized than the other sites.	Vertebral fractures were present in 19% of subjects and 41% had a confirmed history of previous fracture.
Elkin et al. [28]	DXA SFt	BMD is reduced in patients with CF compared with controls. When corrected for height, the differences disappeared.	Adults with CF were significantly weaker than controls, mainly due to lower muscle mass rather than a reduced force-generating capacity of the muscle.
Gray et al. [30]	DXA	Patients with CF had significantly reduced tBMD at all sites compared with normal young adults.	BMI was positively correlated with BMD at four sites and disease severity was negatively correlated with BMD at two sites.
Hardin et al. [32]	DXA	There was no difference in tBMD and BMC between adults with CF and controls matched for LBM, height, age, and sex.	There was no correlation between pulmonary function results and BMC.
Henderson and Madsen [33]	DXA SFt	There were significant deficits in tBMD with a mean deficit of 19.1 ± 3.0% in patients with CF relative to the matched controls.	
Ionescu et al. [36]	BIA DXA	BMD at hip sites were less in patients with normal BMI and low FFM compared with those with a normal BMI and FFM (all $P < 0.01$).	Hidden depletion of FFM was associated with increased loss of BMD and systemic inflammatory activity.
Kelly et al. [37]	DXA	BMC deficit was related to altered body size.	BMC deficit was related to reduced pulmonary function.

BIA, bioelectric impedance analysis; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; CF, cystic fibrosis; DXA, dual-energy x-ray absorptiometry;FM, fat mass; FFM, fat-free mass; LBM, lean body mass; pQCT, peripheral quantitative computed tomography; SFt, skinfolds thickness; SSI, stress-strain index; TBK, total body potassium; tBMC, total bone mineral content; tBMD, total bone mineral density.

tion was found between low FFM (or LBM) and impaired respiratory function in patients with CF. Lower PA levels and muscular strength were associated with lower LBM and associations were stronger in patients with CF compared with the controls. All studies were cross-sectional except for one longitudinal study that found a significant association between low BMI and increased risk of mortality in patients with CF.

Lean body or fat-free mass

Dual-energy x-ray absorptiometry was the most frequently applied method to measure LBM and showed that patients with CF have a significantly reduced LBM compared with controls. This may have important diagnostic and prognostic implications in patients with CF at risk or with signs of malnutrition [5]. Malnutrition is commonly assessed using simple measurements such as body weight or BMI and is closely associated with impaired pulmonary function and muscle performance, which emphasize the importance of an early identification of patients at risk of malnutrition [34,58,59]. Enright et al. [29] found a significant association between low FFM in patients with CF and the severity of pulmonary disease, which was related to a loss of diaphragm muscle mass. Recent criteria by the European Society of Clinical Nutrition and Metabolism for patients with chronic obstructive pulmonary disease advocate for a more integrated diagnostic approach that combines weight loss with either age-adjusted BMI or FFM index [60]. Specifically, adults with a normal BMI and low FFM have a lower predicted FEV_1% than adults with both normal BMI and FFM [36]. This finding underlines once again the limits of BMI as a marker of nutritional status in complex diseases such as CF [38].

Impaired pulmonary function was consistently associated with lower FFM in the studies that were included in the systematic review. Two interpretations are possible, both realistic and not mutually exclusive: 1) Patients with a worse pulmonary function and a more severe stage of the disease are characterized by a reduced appetite, which increases the risk of malnutrition and FFM loss; or 2) poor nutritional status in patients with CF may contribute to the deterioration of pulmonary function due to the inadequate performance of respiratory muscles and an increased risk of infections. However, longitudinal studies are clearly needed to clarify the relationship between FFM and pulmonary function in patients with CF.

Bone health

Studies have consistently reported a deficit of BMC and BMD in patients with CF compared with healthy controls. Factors that may affect bone health in patients with CF are still largely unknown but possible causes may include a dysregulation of the calcium-vitamin D metabolism and glucocorticoid-induced bone mobilization, which could be exacerbated by the presence of chronic inflammation.

The loss of LBM and bone could be mitigated in patients with CF by PA [61]. However, only a small number of studies that were included in this systematic review had evaluated PA levels in patients with CF. One study revealed a lower level of PA in patients with CF than controls [26] and the other three studies found that patients with CF and a lower FFM were less active [4,35,36].

The relationship between BMD and physical activity was evaluated only by one study and showed no significant correlation between PA levels and BMD [30]. In addition, these studies used self-reported questionnaires to evaluate PA, which may not be entirely appropriate because they have not been validated in populations with CF.

Finally, a recent position statement [62] highlighted this lack of evidence because no studies have evaluated physical fitness

and exercise performance using more accurate instruments such as accelerometers or standardized exercise tests to date.

Fat mass

The evidence gathered from the systematic review was not able to provide a coherent message across the studies on the differences and roles of FM in patients with CF. The majority of the studies were conducted in children and reported a lower FM in children with CF compared with healthy controls; however, studies that were conducted in adult populations found no differences for FM between the two groups. These discrepant results could be due to differences in sample size, age, and body composition techniques that were used to evaluate FM.

Another explanation could be the energy cost of growth that may account for the reduced FM in children with CF. The energy that is expended in the synthesis of new tissues is a substantial component of the total requirement for energy (5–6 kcal/g of body weight gained), which results in large variations in growth rate and also the composition of the accrued tissue [63]. Two studies reported an increased central fat accumulation in patients with CF despite that FM% was comparable with those of the healthy controls [43,45].

Limitations

The systematic review included only studies that had a control group as part of the study design; hence, studies that evaluated body composition in patients with CF only were not included. Our primary aim was to understand the changes in body composition in patients with CF, which could only and precisely be assessed if compared with a reference healthy group of individuals.

Finally, the large heterogeneity of the study designs, subject characteristics, and application of body composition techniques has to be taken into account for the interpretation of the results and validity of the associations between body composition and clinical outcomes.

Conclusions

Patients with CF, in this study, both adults and children, appeared to be characterized by a decrease in FFM and BMD. In addition, a decrease in FFM was consistently associated with impaired pulmonary function. The role of FM in patients with CF was left undefined because inconsistent results were found between the studies.

The results of the present review confirm the role of body composition in predicting the health outcomes of patients with CF. However, this evidence is predominantly from cross-sectional studies and longitudinal studies are clearly needed to provide more robust evidence on the causal associations between body composition and health outcomes in patients with CF.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.nut.2018.03.052.

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