Body composition in individuals with cystic fibrosis

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ABSTRACT

Because nutritional status is intimately linked with pulmonary function and survival, nutrition has been at the mainstay of cystic fibrosis (CF) care. Body Mass Index (BMI) is traditionally used to define nutritional status because of the ease with which it can be calculated, but it has a number of limitations including its inability to differentiate fat mass (FM) from lean body mass (LBM), the latter thought to confer health advantage. A number of tools are available to quantify body composition including dual-energy x-ray absorptiometry (DXA), bioelectrical impedance, MRI, CT, air displacement plethysmography, and stable isotopes, and these have been used to varying degrees in studies of CF. In CF, LBM tends to be lower for a given BMI, particularly at lower BMI. In adults, lower fat-free mass (FFM) correlates with greater CF disease severity, lower pulmonary function and higher inflammatory markers. FFM is also positively associated with greater bone mineral density, while greater FM is associated with greater loss of lumbar spine bone mineral density over 2 years. In youth, LBM is positively associated with pulmonary function. The predictive value of body composition for functional and clinical outcomes and the role of improving LBM on these outcomes remain undefined. With improvements in BMI accompanying highly-effective modulator therapy, closer evaluations of body composition may inform risk for more traditional, non-CF adult outcomes in CF.

Introduction

Cystic fibrosis (CF) arises from recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a channel for chloride, bicarbonate, and other molecules. Loss of CFTR function leads to thickened mucus secretions that affect multiple organs including the lungs, pancreas, intestine, and liver. Malabsorption, especially of fat and fat-soluble vitamins, poor appetite, and increased energy expenditure contribute to the frequent occurrence of undernutrition in the affected population [1].

A seminal study by Corey et al in 1988 found that individuals with CF with higher weight and height had better survival, a finding that was independent of pulmonary function. This finding translated into a focus on nutrition in people with CF [2]. The emphasis of nutritional counseling shifted from a low-fat, high protein diet designed to control symptoms of steatorrhea and abdominal pain, to a high-energy, high fat diet with the goal of promoting weight gain [1].

Body mass index (BMI = weight in kilograms divided by the square of height in meters) has traditionally been used to define nutritional status because of its association with multiple health outcomes. BMI is a composite of multiple tissue types (fat mass (FM) and fat-free mass (FFM), the latter composed of bone mass and lean body mass (LBM)), and this surrogate for healthy body composition serves as a screening tool. Sex-, age-, developmental stage, and racial differences in body composition challenge the use of BMI in this capacity. Additionally, BMI, fat-free mass (FFM)/LBM, and FM are not always aligned, and the differences can have health implications [3,4].

Assessment of body composition is considered an important part of the nutrition status evaluation in CF and is recommended in professional guidelines [1]. This review is intended to provide a greater

Abbreviations: CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; BMI, Body mass index; FM, Fat mass; LBM, Lean body mass; FFM, Fat-free mass; BC, Body composition; %BF, Percentage body fat; DXA, Dual-energy X-ray absorptiometry; BIA, Bioelectrical impedance; MRI, Magnetic resonance imaging; CT, Computed tomography; FFMi, Fat-free mass index; FMi, Fat mass index; HEMT, Highly Effective Modulator Therapy.

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understanding of the tools used to measure body composition and the relationship of BMI to body composition. It will also review what is known about body composition in the CF population.

**Body composition assessment tools**

Body composition assessment considers the *functional* role in energy metabolism played by muscle, bone, and fat. It is often described by five different levels – atomic, molecular, cellular, tissue, and whole body. In general, body composition is subdivided into 2-compartment (FM + FFM), 3-compartment (FM, LBM + bone mass) or multicompartment (FM + ≥ 3 components of FFM) [5].

In the general population, BMI has largely been used as a surrogate for FM and has been focused on defining overweight/obesity and associated comorbidities – such as Type 2 diabetes mellitus, Polycystic Ovary Syndrome, hypertension, dyslipidemia, and cardiovascular disease. Conversely, increased subcutaneous adipose tissue in the hip and thigh areas is not associated with increased risk for cardiovascular disease – and in fact, may be protective [6]. In contrast, in the general population, FFM is inversely associated with mortality [3]. Adjusting skeletal mass for adiposity improves its correlation with physical performance and prediction of incident disability [7]. Moreover, the location of LBM may have implications for health. For example, appendicular LBM is most associated with disability in patients with rheumatoid arthritis [8]. Adjusting appendicular LBM for adiposity may further improve the correlation with physical functioning [9]. Weber et al have developed a practical framework for this adjustment to define deficits in appendicular LBM relative to FM [10].

A number of clinical and research methods are available to assess body composition including dual-energy X-ray absorptiometry (DXA), bioelectrical impedance (BIA), magnetic resonance imaging (MRI), computed tomography (CT), air displacement plethysmography, and stable isotopes. Each modality has advantages and disadvantages (Table 1), and no single method is considered the gold standard for body composition assessment in CF [4,11–14]. In 2019, Calella et al published a systemic review of body composition analysis in individuals with CF that included 124 studies. They reported that 34% of the studies utilized DXA as the only method of body composition assessment, 10% of studies used only BIA for body composition analysis, and 31% of studies utilized mixed methods of body composition assessment. In terms of validating body composition assessment methods in individuals with CF, this same paper nicely summarized 10 studies drawing discordant conclusions about the agreement between the various methods [13].

An advantage of using DXA in individuals with CF is that it is already recommended for routine monitoring of bone density in the CF population starting in childhood [13]. The latest densitometers allow body composition assessment with a single whole-body scan [14]. Visceral adipose tissue can also be determined [15]. Fig. 1 is an example of a postprocessed DXA image [16]. Reference data for LBM, FM, and appendicular LBM in DXA are becoming increasingly available [7,9,10,17–19].

BIA is a quick, inexpensive, portable and simple-to-use technology that is commonly used in both research and clinical practice [4,14]. BIA directly measures the impedance of the human body, whereas the parameters related to body composition (water content, FFM and FM) are calculated [13]. A study using a CF-specific equation for BIA was validated by Charatsi et al using DXA as a reference method [20]. CT and MRI are currently considered the gold standard for determining the muscle mass quality and quantity. They allow for quantification of total adipose tissue as well as further division into subcutaneous, intramuscular and visceral adipose tissue. Peripheral quantitative computed tomography is cheaper, easier to obtain, and requires less radiation than traditional CT. However, it has lower accuracy, only analyzes peripheral anatomical sites, and provides only limited data on muscle and fat content [13]. The quantitative magnetic resonance (QMR) EchoMRI system is a newer body composition acquisition system that has been validated in healthy adults and children. The measurement acquisition time is only 2–4 min and does not require the participant to lie completely still [4].

Occasionally, studies on patients with CF have assessed body composition using other less commonly used methods including air displacement plethysmography, stable isotopes, and skin fold measurements. Non-CF studies have also utilized ultrasonography, NMR spectroscopy, PET/CT and PET/MR to quantify body composition.

### Table 1

| BC Assessment Tool | Advantages | Disadvantages |
|--------------------|------------|---------------|
| Dual-energy X-ray absorptiometry | Already obtained frequently in the CF population to monitor bone density [13] | Requirement for certified radiology technician |
| Bioelectrical impedance | Portable | Changes in hydration or skin temperature will alter results [13] |
| CT/MRI | Gold standard for determining muscle mass quality and quantity | High cost |
| Air displacement plethysmography | Noninvasive | May be less accurate in children |
| Stable isotopes | Noninvasive [11] | Indirect calculation of body fat that depends on hydration status [12] |

**Body composition differences across adult populations**

Body composition naturally differs amongst populations. For example, men and women have different body composition. Women have more FM while men have more LBM. Men more often accumulate fat around the trunk and abdomen, while women tend to accumulate it around the hips and thighs [21]. Body composition also varies significantly between individuals of different races [22,23]. For instance, African Americans have more LBM, specifically appendicular muscle mass, for a given BMI compared to Caucasians [24]. In addition, body composition in an individual naturally changes over time. Normal aging in adults is characterized by an increase in FM and decrease in LBM [4].

**Pediatrics/Growth/Puberty and changes in body composition**

Interpretation of body composition analysis in the pediatric population is inherently more challenging due to normal physiologic changes occurring throughout various developmental stages (i.e., infancy, early childhood, prepubertal, pubertal, and post-pubertal stages). The normal
onset of puberty has a wide range of 5 years; it varies from age 8–13 years old in females, and 9–14 years old in males. The tempo of progression in secondary sexual characteristics as well as peak growth velocity also vary amongst individuals [25].

The normal BMI range fans out during infancy and is highest in late infancy, then narrows by 5–6 years of age. Starting at age 6–8 years, growth rates and weight/BMI gains increase, with a widening of the normal age-specific BMI range over time [5]. Prior to puberty, sex-specific differences in FM and fat distribution as well as paraspinoxus musculature are already operative. Arfai et al. performed quantitative

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Fig. 1. An example of a post-processed whole body DXA scan. Fat is represented in yellow, bone in blue, and muscle in red [16]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
CT on 31 pairs of age-, height-, and weight-matched healthy white prepubertal boys and girls 5–10 years old and found that girls had 28% more total body fat and 30% more subcutaneous fat than males. Girls had 10% lower amount of paraspinous musculature and 15% lower vertebral cross-sectional measurements [26].

During puberty, both males and females have acceleration in linear growth as well as body weight gain. Sex-specific differences in body composition become more apparent. Just prior to the onset of puberty, males tend to have increases in FM. During puberty, they have a rapid increase in growth velocity along with increases in FFM and lower adipose tissue in the extremities. Females, however, experience greater increases in FM than LBM. Ultimately, a sexually dimorphic adult pattern in fat distribution emerges with central/visceral adiposity more typically observed in males whereas greater subcutaneous adipose tissue is more typically observed in females. These generalizations cannot be reliably made across pediatric populations given normal physiologic differences in body composition at different developmental stages driven by hormonal and environmental factors [5]. Further, maximal bone density accrual (both cortical and trabecular bone) also occurs during puberty [27]. Fig. 2 by Wells illustrates changes in body composition adjusted for height in each sex over time using reference data [28].

Given these normal physiologic changes throughout childhood, body composition in pediatric patients needs to be compared to age- and sex-matched references [29]. BMI is thus interpreted as percentile (or Z-score) relative to chronologic age and sex. In many patients, the BMI percentile may be an accurate marker of their body habitus. However, the clinical utility may be more limited in patients with predominantly abdominal obesity (such as children who were born with low birth weight / small for gestational age), patients with elevated BMI due to a large amount of muscle tissue, and patients with untreated endocrinopathies (growth hormone deficiency, hypothyroidism, cortisol excess) [30,31]. Despite these limitations, Taylor et al found that higher BMI values correlate with higher %BF determined via DXA. Amongst males, those just prior to the onset of puberty were found to have a higher %BF (34–36%) as opposed to younger prepubertal males (24–30%) and older pubertal/post-pubertal males (27–30%). In females, increasing chronologic age was associated with increasing %BF. For example, an 18 year-old male with BMI 30 kg/m<sup>2</sup> was predicted to have 27% BF, while a female of the same age and BMI was predicted to have a significantly higher %BF of 42% [32]. Ultimately, BMI is an efficient and cost-effective tool to use in the clinical setting: 1) Low BMI values are associated with lower adipose tissue in most patients, 2) Elevated BMI relative to chronologic age corresponds to increased risk of obesity-associated comorbidities, and 3) the trend in BMI percentiles remains useful for assessing an individual patient’s nutritional progress and risk factors [32,33].

Many of the body composition studies in the pediatric population include white children. Additional studies in other ethnic groups are needed to determine the generalizability of the findings.

### Body composition in individuals with CF

Most studies have reported that adults with CF have lower FFM, LBM, and skeletal muscle mass compared to the general population [13,34–36]. As a notable exception, a recent study by Bellisimo et al using DXA to assess body composition did not find a significant difference in LBM between adult subjects with CF and controls [37], the extent to which this difference reflects the overall better health status of adults with CF is not clear. Studies are more conflicted with respect to FM in patients with CF. Some studies have reported lower FM in patients with CF, while some found similar FM [34–39]. Most, but not all, of the studies reporting lower FM are in children. Some studies have reported comparable FM but higher central or visceral fat [37,40].

### Body composition vs. BMI in the CF population

In the CF population, evaluating only BMI as a marker of nutritional status may overlook other complex factors that contribute to poor nutritional status and ultimately poorer lung function. King et al reported that using a BMI cutoff of <18.5 kg/m<sup>2</sup> to identify malnutrition missed 58% of FFM depletion [41]. Similarly, Bolton et al assessed body composition in 51 adult CF patients vs. 18 normal controls by DXA and found that using a cutoff of BMI <19.9 kg/m<sup>2</sup> missed 43% of patients with a low fat-free mass index (FFMI; FFM divided by height in m<sup>2</sup>). Interestingly, of the 28 patients with a low BMI, 7 had a normal FFMI [36]. BMI measurements alone may also miss CF patients with normal-weight obesity, which is defined as a normal BMI but elevated %BF. This “normal weight obesity” condition may increase the risk for metabolic complications. Alvarez et al assessed body composition via air displacement plethysmography and found that 31% of participants had normal-weight obesity, defined as a BMI under 25 kg/m<sup>2</sup> with a %BF >30% in women and >23% in men [42].
Body composition and CF outcomes

Pulmonary function

Excess fat has been inversely associated with pulmonary function in CF [42], while LBM is hypothesized to positively impact respiratory strength and pulmonary function [37,43]. Fig. 3 illustrates the finding from Sheikh et al that in CF youth, LBM adjusted for height and age is positively associated with FEV1% predicted [43]. A study assessing FFM, diaphragm parameters, and spirometry in 40 adults with CF found that individuals with CF and low FFM have lower respiratory markers, with the lower FFM associated with lower diaphragm muscle mass [44]. Lower LBM has also been associated with worse lung function in individuals with cystic fibrosis [40]. A study published this year in 114 pediatric CF patients found that patients with a FFMI < 10th percentile had 9.5% lower FEV1% than patients with FFMI > 10th percentile [45]. In a study of 85 young adults with CF, male patients with frequent exacerbations (>2 per year) were found to have lower whole body and appendicular FFM compared to patients with infrequent exacerbations [46].

Bone mineral density

In a study of 64 adults with CF, greater FFMI was associated with greater BMD. In contrast, greater FMI was associated with greater lumbar spine BMD loss over 2 years [47]. The recent study in 114 pediatric patients with CF referenced above also found that individuals with a FFMI < 10th percentile had a lower BMD Z-score compared to patients with FFMI > 10th percentile. In this study both FMI and FFMI correlated with BMD [45].

Inflammatory markers

Studies in adults with CF have found higher concentrations of the inflammatory markers IL-6 and CRP in patients with lower FFM/LBM [48,49]. IL-6 levels have been associated with FFM loss in adults with CF over time [50]. It is hypothesized that chronic inflammation and pulmonary infections are a contributory factor to the altered body composition seen in CF patients, specifically the reduction in LBM and BMD [46,48].

Glucose

A study of 24 adults with CF found that visceral adipose tissue was positively associated with fasting blood glucose [37]. A 2021 study examining 59 adolescents and young adults with CF found that FMI z-score correlated positively with higher insulin resistance and lower insulin sensitivity [39].

Impact of sex steroids in men

In a cross-sectional study of 40 men with CF compared to healthy controls, men with CF were noted to have lower serum testosterone. However, these lower testosterone concentrations were not correlated with weight, total or regional LBM, or FM. This same study noted that men with CF did show a shift from FM to LBM when compared to healthy controls. Since adipose is a site of conversion of testosterone to estradiol, lower FM may compensate for the lower testosterone to favor LBM over FM [51].

Impact of highly effective modulator therapy (HEMT) on body composition

The introduction of CFTR modulation therapy has revolutionized cystic fibrosis care, and these therapies are expected to result in longer lifespan, less-severe symptoms, and less risk for undernutrition for many patients. A few studies have reported on the impact of HEMT upon anthropometric outcomes i.e. height, weight and BMI, but little is known about their effects on body composition. King et al recently reported on body composition changes in 20 adults with CF from a single-center double-blind, placebo-controlled 28-day crossover study of ivacaftor followed by an open-label extension for 5 months. Eleven of the patients on ivacaftor underwent body composition measurements 2 years later. Weight, BMI and FFM all increased significantly during the 28-day intervention, but were notably not different in the ivacaftor vs placebo groups. After the 5-month open-label extension period in ivacaftor users, weight and FM increased from baseline, but not FFM. For the 11 patients who were measured after

Fig. 3. The association between FEV1%-predicted and LBMI-Z adjusted for age among males and female youth with CF. LBMI-Z is positively associated with FEV1%-predicted in males (p < 0.0001) and females (p < 0.0001) [43].
an additional 2 years, no further changes in weight, BMI or body composition were observed as compared to measurements at 6 months [52].

Another recently published manuscript by King et al examined body composition in 24 adults with severe CF who were treated with clinically prescribed lumacaftor/ivacaftor for at least 1 year. No changes in body composition were observed during the first month of therapy. By 6 months, patients had gained significant FM which plateaued by 1 year. In the group as a whole no significant change in FFM or FFMI was found over the year. However, 20% of patients gained > 5% of baseline FFM in 1 year of treatment. Baseline BMI was inversely correlated with change in FFM, indicating that those with the poorest baseline nutritional status experienced the greatest gains in FFM. Changes in FFM by 1 year correlated with greater reduction in the number of both hospitalization days and IV antibiotic days in the year following clinically prescribed therapy started compared with the year prior [53].

While elixacaftor/tezacaftor/ivacaftor has been shown to significantly increase weight and BMI in the “short-term,” body composition outcomes have not been published [54]. The CFP Promise study is examining body composition by DXA at 0, 12–18 months, and 24–30 months following clinically prescribed therapy in individuals aged ≥ 12 years.

Knowledge gaps

The predictive value of body composition for functional and clinical outcomes remains undefined, and current evidence is insufficient to recommend one method of accessing body composition over others in clinical care. While the landscape of CF is changing with HEMT, consideration of nutritional status and LBM deficits remains crucial for the subset of patients with established severe disease or CFTR mutations unresponsive to current therapies. With increasing rates of overweight and obesity in the CF population, more traditional adult outcomes including cardiometabolic risk and vascular disease may need to be considered in the context of body composition.

Conclusion

The majority of studies have identified differences in body composition in adults with CF compared to the general population. Utilizing only BMI to quantify nutritional status may miss a significant portion of CF patients with abnormal body composition who are at risk for adverse health effects. These considerations are highlighted by associations of low FFM/LBM with impaired respiratory function and decreased bone mineral density in CF. The impact of modulators upon body composition and downstream implications for health remain undefined. Looking forward, assessing body composition changes over time may become an important mechanism to monitor therapy and guide treatment decisions in the CF population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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