Growth, body composition and lung function in pre-pubertal children with cystic fibrosis diagnosed by newborn screening

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Abstract

Background: Children with cystic fibrosis (CF) are at risk of altered body composition (BC): fat mass (FM) and fat-free mass (FFM). Newborn screening (NBS) may lead to improved BC outcomes. We investigated BC and its relationship with lung function in pre-pubertal children with CF diagnosed by NBS. Secondary aims explored predictors of FFM and lung function.

Methods: Thirty seven screened (non-meconium ileus) children with CF (20 boys) born 2007-2012, had a dual-energy X-ray absorptiometry scan at 5-8 years, to determine whole body (WB) and appendicular BC. Anthropometry was performed and routine spirometry recorded. Results were converted to z-scores, height-adjusted (fat mass index (FMI) and fat-free mass index (FFMI)), and compared to population mean values. Predictors of forced expiratory volume in one second ($FEV_{1)}$ were assessed.

Results: Height, body mass index (BMI) and FEV_1 were within normal limits, however weight and BC were significantly low compared to reference data (weight p= 0.03; WB FMI p= 0.001; WB FFMI p=0.009). Gender differences were detected with lower appendicular BC in boys and lower weight, BMI, and BC in girls. The association between FEV_1 and WB FFMI (r: 0.38; p=0.02) was stronger than with BMI (r: 0.29; p=0.08). WB FFMI was the only significant predictor of FEV_1 in a multivariable model (95% CI: 0.11 to 0.99; p=0.016).

Conclusions: In this NBS CF population, gender differences in growth and BC were apparent despite preserved lung function. These results support BC assessment in pre-pubertal children, particularly girls, with an opportunity to direct interventions to optimise FFM.

Keywords

Body composition; cystic fibrosis; dual-energy x-ray absorptiometry; fat-free mass; newborn screening; paediatrics

Introduction

Optimal growth in cystic fibrosis (CF) is defined using anthropometric markers such as body mass index (BMI) and percentiles, however BMI is unable to distinguish between the body tissues of fat mass (FM) and fat-free mass (FFM) which impact differentially on disease status.[1] Over the last decade, there has been increasing interest in the role of body composition and the relationship with clinical outcomes in CF, notably pulmonary function. A recent systematic review highlighted that people with CF are at risk of altered body composition.[2] This is particularly associated with increasing age and disease severity, but abnormalities have also been reported in children.[3-8] Many body composition studies have had wide age ranges, some including both children and adults [4,5] or crossing puberty [3,6,8,] making it difficult to identify when these tissue changes start. FFM has a positive association with forced expiratory volume in one second (FEV_1) independent of BMI, and is more sensitive than BMI in detecting malnutrition [5,6] thereby identifying patients at nutritional risk earlier. Importantly, loss of FFM is associated with reduced pulmonary function.[2] Hidden FFM depletion has also been reported; patients may have seemingly adequate nutritional status with acceptable BMI, but have low FFM stores.[5,6,9]

International nutrition guidelines suggest *'consideration'* of body composition assessment, in addition to anthropometric markers,[10,11] but more evidence is needed to support timing, benefits, and interpretation of routine measurements for all patients with CF. Dual energy X-ray absorptiometry (DXA) has advantages over bio-electrical impedance analysis or magnetic resonance imaging[12] and is recommended as the method of choice in CF as it combines: *'the accuracy of a 3-component model with the opportunity to obtain information on bone health, lean body mass and adiposity'.*[13] Measurements of FM and FFM from DXA compare favourably with those from the gold-standard 4-component model in children[1] where FFM is divided into protein, mineral (bone) and water, whilst appendicular (limb) analyses may provide greater accuracy than whole body as they assess more soft tissue by excluding the trunk, thereby minimising bias.[1]

Previously reported results using DXA as part of the 4-component model in clinically diagnosed children with CF born pre-screening, demonstrated gender differences - with girls having lower FM and lung function.[8] In healthy children, gender differences in body composition pre-puberty are modest compared to puberty when girls accrue more FM and boys gain more FFM, and in early childhood girls and boys have comparable FM and FFM.[14]

Newborn screening (NBS) for CF was introduced nationwide in the UK in 2007. Diagnosis by NBS allows earlier nutritional intervention leading to better growth indices through childhood into adulthood than diagnosis following symptomatic presentation,[15,16] or those with a history of meconium ileus (MI).[17] Age at diagnosis may also influence body composition but it is unknown if body composition changes are still apparent in young children diagnosed by NBS. FM has been shown to be lower in children with a history of MI than those without.[18]

The primary aim of this study was to investigate whether body composition abnormalities are apparent in a contemporary UK cohort of pre-pubertal children with CF diagnosed by NBS and to examine associations of anthropometry and body composition with lung function. Secondary aims were to explore potential predictors of FFM and FEV_1, including genotype and pancreatic status.

Materials and Methods

Study population

This cross-sectional study was conducted at a UK paediatric CF centre. Children aged 5 to 8 years with CF born 2007 to 2012, who had been diagnosed within the first two months of life following NBS or antenatal screening were recruited between January 2016 and December 2017. We excluded children with a history of MI due to different presentation at diagnosis, and also any child physically unable to perform a DXA assessment. Measurements were conducted when children were clinically stable, either at a routine CF clinic appointment or at the end of an elective hospital admission for routine intravenous (IV) antibiotics. Ethical

approval was granted by a national ethics committee (15/LO/2117). Informed written consent was obtained from parents and written assent from children at the time of the DXA scan.

Baseline demographic and clinical data

Baseline data collection included gender, ethnicity, age at diagnosis, genotype, pancreatic status, and any prescription of the CF transmembrane conductance regulator (CFTR) modulator ivacaftor. Genotype was classified according to whether subjects had ΔF508 homozygosity, ΔF508 heterozygosity, or other. Pancreatic status was assessed by noting the use of pancreatic enzymes (based on stool elastase <200ug/g). Clinical data collection included lung colonisation of chronic *Pseudomonas aeruginosa (PsA)* status and number of courses of IV antibiotic treatments in the previous year to measurements. CF-related co-morbidities, which could affect body composition such as diabetes, were noted.

Anthropometry and body composition

Subjects had a single whole body DXA scan, using a GE Lunar Prodigy machine (GE Medical Systems, Madison, USA) to measure FM, FFM, and bone mineral apparent density (BMAD), in conjunction with Encore software version 12.1. Local standard operating procedures were followed and the machine calibrated daily using a phantom. Total (whole) and appendicular body composition was determined. Appendicular measurements were calculated by combining those from arms and legs. Subjects lay supine and wore light clothing with metal objects removed. The radiation dose was <0.1 microsieverts per whole body scan, which was well below normal daily environmental radiation. The typical scan duration was 4 to 5 minutes depending on the child's height. Anthropometric measurements (weight and height) were taken at the time of the scan in light clothing with shoes removed. Weight in kilograms was measured to the first decimal place using calibrated SECA Class III electronic scales. Height was measured to the nearest millimetre using a wall mounted height measure. Measurements were undertaken by one of two trained operators (first or second author). Height-adjusted indices for FM and FFM, fat mass index (FMI) and fat-free mass index (FFMI), were used to

account for differences in body size as recommended.[8] Measures were converted to z-scores using UK reference data for growth[19] and body composition,[20] which included appendicular reference data from the same group (unpublished data, 2009). BMAD was used as a measure of bone mass adjusted for (bone) size.

Lung function

Data for FEV_1 were obtained from the routine clinic appointment on the same day, or the closest day to anthropometry and body composition measurements (within 3 weeks). Results were converted to z-scores using Global Lung Initiative reference equations which adjust for height, sex, age and ethnicity.[21]

Statistical analyses

Convenience sampling was used and cases measured consecutively. All potential eligible children aged 5 to 8 years were approached except one (no routine clinic appointment within the available timeframe). Three children declined to participate.

Statistical analysis was performed using SPSS version 23. Sexes were analysed separately for comparisons with reference data, due to known gender differences in body composition changes shown in previous studies.[5,8] All anthropometric, body composition and bone mass measurements were analysed as z-scores. Data was checked for normality.

Optimal BMI z-score was defined as ≥0 as per national and international guidelines.[22,11,23] In the absence of universally accepted definitions or thresholds for normal or low FFM, z-score ≥0 was used to define optimal FFM and z-score <-1.64 for FFM depletion as per other studies derived from adult populations.[6,24] Normal spirometry was classified as FEV_1 z-score >-1.96.

One sample *t*-tests were used to compare variables to reference population mean values as per previous research.[8] Independent *t*-tests were used to explore differences in anthropometric measures, body composition and lung function between groups. Relationships between variables were assessed using Pearson correlation. P <0.05 was considered

statistically significant for all analysis. Optimal BMI z-score was defined as ≥0 as per national and international guidelines.[22,11,23] In the absence of universally accepted definitions or thresholds for normal or low FFM, z-score ≥0 was used to define optimal FFM and z-score <-1.64 for FFM depletion as per other studies derived from adult populations.[6,24] Normal spirometry was classified as FEV_1 z-score >-1.96.

Predictors of FEV_1 were assessed using a general linear model, with FEV_1 as the dependent variable, and age, pancreatic status, genotype and one of BMI, FFMI or FMI as independent variables. All independent variables were entered into the regression together. Body composition values were height-adjusted in all analyses. For all analyses, p <0.05 was considered statistically significant.

Results

Thirty seven children (20 boys) were recruited. Baseline characteristics are summarised in Table 1. Three had been diagnosed with CF via antenatal screening, all others via NBS within the first 2 months of age. Over half (54%) were homozygous ΔF508, and 86% had exocrine pancreatic insufficiency. The majority of children (92%) had FEV_1 z-scores above the lower limit of normality. Ten children required IV antibiotic courses in the preceding year, including one who had regular 3 monthly IVs and two who had 6 monthly IVs. Two were chronically infected with *PsA*. None of the children had been diagnosed with CF-related diabetes (CFRD) and three were prescribed ivacaftor. All children were pre-pubertal, with ages ranging from 5.3 to 8.8 years, and girls were significantly younger than boys at the time of measurements.

Growth and body composition of children with CF compared to reference populations

Children had linear growth, BMI, bone density and FEV_1 which were not significantly different to reference population values, but weight and body composition values for the total sample were significantly lower (Table 2).

When analysed according to gender, although boys had normal anthropometry (weight, height and BMI) and whole body composition values including bone density significantly higher than reference data, limb analysis highlighted abnormalities in body tissues: FMI and FFMI were significantly lower than the reference population. Girls however had growth parameters significantly lower than reference data (weight and BMI), and like the boys - also had body composition changes: lower whole body and limb FMI, and limb FFMI. There were no significant differences between the sexes for weight, height, BMI, FEV_1, whole body and limb FMI, whole body and limb FFMI, and BMAD (data not shown).

Relationship between growth, body composition and lung function

There was a statistically significant but weak correlation between whole body FFMI and FEV_1 for the total sample (Table 3). There was no significant association between BMI or FMI and FEV_1.

There was a strong correlation between BMI and FFMI for the total sample (r 0.71, p <0.001). Two children (both boys) had FFMI values between -1 and -2 despite having optimal BMI values (Figure 1, circled), one of whom also had low FEV_1.

Factors affecting fat-free mass

FFMI was not significantly different in children grouped by genotype (ΔF508 homozygous (n=20) -0.24 (0.71) versus any other (n=17) -0.54 (0.94), p = 0.28); or pancreatic status (insufficient (n=32) -0.33 (0.85) versus sufficient (n=5) -0.69 (0.65) p = 0.36).

Predictors of lung function

Whole body FFMI was the only significant predictor of FEV_1 (Table 4). A 1SD increase in FFMI was associated with a 0.54SD increase in FEV_1 (95% CI: 0.11 to 0.99, p = 0.016).

Discussion

In this single centre group of clinically stable children with CF diagnosed via NBS, we detected significant differences from population reference data in body composition,

although there were no such differences in linear growth or bone density, highlighting the fact that BMI may mask tissue abnormalities. Gender differences in body composition were also evident. FFMI was found to be a predictor of lung function, but FMI was not.

This group of children was demographically representative of a contemporary Northern European population. Clinical characteristics were similar to the wider geographical area for NBS non-MI infants born at this time in terms of genotype and pancreatic status.[25] All children recruited had been diagnosed before two months of age and therefore had benefited from starting nutritional treatment earlier than children with a clinical diagnosis. They had mild pulmonary disease and few clinical complications. Age at the time of body composition measurement was younger than in previous studies. Linear growth and lung function were similar to reference data, however body composition variables were significantly lower. This was shown in whole body analysis for the total cohort and appendicular analysis for sexes separately, with girls having both lower whole body and limb FMI and limb FFMI, and boys having lower limb FMI and FFMI. This highlights that reduced FM and FFM accretion is apparent even in a well, pre-pubertal cohort as young as 5 years of age. Possible explanations for low FFM may be due to the CFTR protein dysfunction, which affects fat and protein absorption, or catabolism caused by infection and chronic inflammation.[26] *PsA* infection and IV antibiotic courses were relatively low in this group (27% had IV antibiotics in the preceding year), but may have been contributory factors. Low FM has been found in other paediatric studies in girls[8] and, as suggested by Calella *et al.,* low FM in children may be due to the energy cost of growth.[2] Abnormal body composition in boys would not have been identified using whole body DXA analysis, showing that limb analysis is more informative. Overall, boys had better nutritional status than girls when compared to the reference populations, similar to previous findings in unscreened cohorts.[8] The mechanism underlying this difference in pre-pubertal children remains unknown.

Five percent of this cohort had optimal BMI z-score >0 but with FFMI z-score <1, close to hidden depletion. This is similar to Engelen *et al.* who found that 93% of their smaller sub-

group of pre-pubertal children in the US had normal BMI and FFMI, using the same thresholds.[6] In a large US cohort of patients (n=208) aged 5 to 21 years, males with lower lean body mass had lower FEV_1 irrespective of BMI, whereas lower lean mass was associated with lower FEV_1 in females with sub-optimal BMI.[5]

The cut-off of z-score -1.64 to define FFM depletion stemmed from adult CF studies with different disease severity and nutritional status,[9] therefore this may be too low for children. Thresholds for FFM depletion that predict clinical outcomes in CF are yet to be defined, however low FFMI would have been undetected by using BMI alone as a marker of nutritional status. Additionally, although the number of children with abnormal lung function was low in this population (n=3), we did observe FFMI depletion in one patient with lung function near the lower limit of normal. In time this could worsen and impact on other clinical outcomes such as bone density.

In accordance with other studies using DXA, FFMI was more strongly correlated with FEV_1 than BMI.[3,5] There was no association between genotype or pancreatic status and FFMI, which is similar to other recent studies. Calella *et al.* also did not find any association between ΔF508 homozygous and body composition.[3] They found that (total and appendicular) lean mass was the only significant predictor of FEV_1 in a UK adolescent population with CF. Our results are in agreement, showing that FFMI was a significant predictor of FEV_1 in this younger NBS paediatric cohort.,

Strengths of this study include the narrow age range and the fact that all children were pre-pubertal, thereby minimizing the effect of age and avoiding the confounding effect of puberty on changes in body composition which differ in boys and girls. Body composition reference data were from a paediatric population from a similar geographical area, measured on the same DXA scanner minimizing variability and ensuring greatest compatibility. Measurements were converted to age and sex specific z-scores, therefore making the results more clinically applicable.

One of the main limitations of this study was the small sample size. Like most other studies this was cross-sectional and ideally changes over time should be explored. Pubertal status was not formally assessed, in line with our usual clinical practice for this age group (our maximum age at recruitment was 8.8 years). A further limitation is that comparisons were made between children with CF and reference data, albeit a large dataset, rather than healthy contemporaneous controls. Use of UK1990 reference data for growth has limitations given secular changes in adiposity and if compared to a more contemporary UK population this cohort may have lower values than non-CF peers. Physical activity was not assessed objectively, but as chronic disease may affect activity levels and therefore lean tissue development, future body composition studies should explore the relationship between diet, exercise and FFM. Finally, we made no adjustment for multiple testing and this should be considered when interpreting the findings. A crude Bonferroni would likely be too harsh an adjustment and would not change any of the conclusions.

Conclusions

In this NBS population, gender differences in growth and body composition were apparent in pre-pubertal CF children despite preserved FEV_1. This study provides further evidence to support a recommendation to consider routine body composition assessment as a marker of nutritional status in children, especially girls with CF. Further work is required on the interpretation of FFM measurements in children, including consensus on what thresholds for FFM should be used to best predict lung function, frequency of measuring body composition and interventions to optimise FFM.

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Conflicts of interest:

Elizabeth Owen received a grant from the British Dietetic Association Paediatric Group, related to the conduct of the study. Dr Gwyneth Davies has given lectures at meetings sponsored by Chiesi, unrelated to the current study. Dr Colin Wallis has given lectures at meetings sponsored by Vertex, unrelated to the current study.

Statement of Authorship

Elizabeth Owen, Jane E Williams and Robert L Grant contributed to the conception and design of the study; Elizabeth Owen and Jane E Williams contributed to the acquisition, analysis and interpretation of the data; Mary S Fewtrell contributed to the analysis and interpretation of the data; Elizabeth Owen drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Table 1: Clinical characteristics of newborn screened children with cystic fibrosis

Characteristics	**Total sample (n=37)**	**Boys (n=20)**	**Girls (n=17)**
Age at diagnosis, weeks: mean (sd)	3.94 (1.95)	3.75 (2.06)	3.99 (1.82)
Genotype: n (%) ΔF508 homozygous ΔF508 heterozygous Other	 20 (54) 13 (35) 4 (11)	 11 (55) 5 (25) 4 (20)	 9 (53) 8 (47) 0
Pancreatic insufficiency: n (%)	32 (86)	18 (90)	14 (82)
Ethnicity: n (%) Caucasian Asian Black	 33 (89) 3 (8) 1 (3)	 17 (85) 3 (15) 0	 16 (94) 0 1 (6)
CFRD: n	0	0	0 (1 type 1 diabetes)
IV antibiotic courses previous 12 months: n (%) None 1 2 3 or more	 27 (73) 2 (5.4) 5 (13.5) 3 (8.1)	 16 (80) 1 (5) 2 (10) 1 (5)	 11 (64.7) 1 (5.9) 3 (17.6) 2 (11.8)
CFTR modulator: n	3	2	1
Chronic *Pseudomonas aeruginosa:* n	2	1	1
FEV_1 z-score: mean (sd)	-0.32 (1.09)	-0.39 (1.23)	-0.25 (0.92)
Age, years: Mean (sd)	6.66 (1.06)	7.04 (1.07)	6.19 (0.87)

CFRD, cystic fibrosis related diabetes; FEV_1, forced expiratory volume in one second; IV, intravenous; CFTR, cystic fibrosis transmembrane conductance regulator

Table 2: Anthropometry, body composition and FEV_1 of newborn screened children with cystic fibrosis compared to UK paediatric reference data for growth and body composition, and GLI reference data for lung function

Variable z-score	**Total sample n=37 Mean (sd)**	***p***	**Boys n=20 Mean (sd)**	***p***	**Girls n=17 Mean (sd)**	***p***
Weight	-0.29 (0.79)	0.03*	-0.11 (0.72)	0.498	-0.50 (0.82)	0.023*
Height	-0.21 (0.83)	0.13	-0.11 (0.74)	0.523	-0.34 (0.93)	0.156
BMI	-0.25 (0.76)	0.06	-0.08 (0.76)	0.634	-0.44 (0.75)	0.028*
FEV_1	-0.32 (1.09)	0.08	-0.39 (0.17)	0.17	-0.25 (0.92)	0.28
Whole body FMI	-0.58 (0.72)	0.001*	-0.32 (0.70)	0.053	-0.89 (0.64)	0.000**
Limb FMI	-0.62 (0.68)	0.000**	-0.37 (0.64)	0.019*	-0.92 (0.62)	0.000**
Whole body FFMI	-0.38 (0.83)	0.009*	-0.40 (0.91)	0.062	-0.35 (0.74)	0.068
Limb FFMI	-0.69 (0.64)	0.000**	-0.66 (0.70)	0.000**	-0.72 (0.60)	0.000**
BMAD	0.32 (1.21)	0.12	0.67 (1.05)	0.01*	-0.12 (1.29)	0.7

*p <0.05, **p <0.001

BMAD, bone mineral apparent density; BMI, body mass index; FEV_1, forced expiratory volume in one second; FMI, fat mass index; FFMI, fat-free mass index; GLI, Global Lung Initiative

Table 3: Correlations between anthropometry, body composition and FEV_1 for the total sample (n=37)

Variable z-scores	**R**	***p***
Weight	0.25	0.13
Height	0.09	0.60
BMI	0.29	0.08
Whole body FMI	0.05	0.77
Limb FMI	0.08	0.63
Whole body FFMI	0.38	0.02*
Limb FFMI	0.31	0.06
BMAD	0.13	0.43

*p <0.05

BMAD, bone mineral apparent density; BMI, body mass index; FEV_1, forced expiratory volume in one second; FMI, fat mass index; FFMI, fat-free mass index

Table 4: Predictors of FEV_1

Variable	**ß**	**95% CI**	***p***
FFMI z-score	0.55	0.11 to 0.99	0.016
Age (years)	0.004	-0.33 to 0.34	0.98
Pancreatic status[1]	0.75	-0.38 to 1.87	0.19
Genotype[2]	0.008	-0.77 to 0.78	0.98

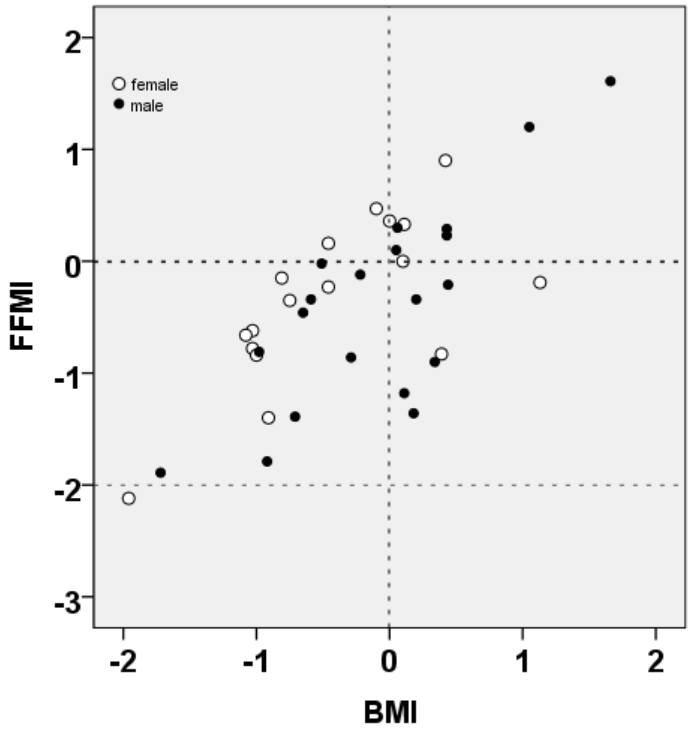
Model adjusted R^2 0.1

[1] Pancreatic status: 0=sufficient, 1=insufficient

[2] Genotype: 1=ΔF508 homozygous, 2=ΔF508 heterozgyous and other

FFMI, fat-free mass index; FEV_1, forced expiratory volume in one second

Figure 1: Correlation between FFMI and BMI z-scores. Black dotted lines crossing through zero indicate optimal BMI and FFMI. Dotted line crossing through -2 FFMI indicates low FFMI. Results circled indicate children with optimal BMI but approaching FFMI depletion



BMI, body mass index; FFMI, fat-free mass index