Journal of Cystic Fibrosis 13 (2014) 328–334

www.elsevier.com/locate/jcf

Original Article

Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis ☆

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Received 2 July 2013; received in revised form 30 October 2013; accepted 5 November 2013
Available online 28 November 2013

Abstract

Background: In cystic fibrosis (CF), systemic inflammation and pulmonary infections sustain a catabolic response leading to fat free mass (FFM) depletion.
Objectives: To investigate the association between recurrent pulmonary exacerbations and alteration in body composition in young adults with CF.
Methods: In a retrospective study we collected body composition data, obtained by DXA scan, on 85 young adults with CF (44 males, mean age 23 ± 4 years). Whole body and appendicular FFM were divided by height squared to obtain FFM indices (FFMI). Number of pulmonary exacerbations occurred in the year preceding DXA scan were computed and patients were defined as frequent exacerbators if they experienced more than 2 pulmonary exacerbations/year. Body composition data were compared between frequent and infrequent exacerbators.
Results: Male patients classified as frequent exacerbators had lower total body bone mineral density (Z-score −1.44 ± 1.22 vs. −0.66 ± 0.92, $P = 0.033$), whole body FFMI (18.0 ± 1.9 kg/m^2 vs. 19.3 ± 1.4 kg/m^2, $P = 0.024$) and appendicular FFMI (7.8 ± 1.0 kg/m^2 vs. 8.8 ± 0.8 kg/m^2 $P = 0.004$) compared to infrequent exacerbators. The reduced FFM found in frequent exacerbators was not uniformly distributed and involved mainly appendicular FFM (mean difference: −11% compared to infrequent exacerbators, $P = 0.016$), whereas trunk FFM was not significantly affected by pulmonary exacerbations (mean difference −3% compared to infrequent exacerbators, $P = 0.34$). These differences were not found in female patients.
Conclusions: Recurrent pulmonary exacerbations are associated with reduced appendicular FFM and bone mineral density in young male adults with CF. The gender-dependent relationship between pulmonary exacerbations and body composition alteration needs to be further investigated.

Keywords: Cystic fibrosis; Pulmonary exacerbations; Body composition; DXA

1. Background

Cystic fibrosis (CF) is an inherited disease caused by mutations of the CF Transmembrane Conductance Regulator gene. These mutations cause alterations in electrolyte transport and increased mucus thickness that damages various organs, particularly the pancreas and lung. Over 80% of patients have pancreatic insufficiency and are treated with pancreatic enzyme replacement therapy. Lung disease is the leading cause of death and is characterized by chronic bacterial infections and systemic inflammation.

Achievement of an optimal nutritional status is universally recognized as a relevant therapeutic goal in CF patients due to its association with better pulmonary function [1].

Despite significant improvement in nutritional status over the last decades, undernutrition remains an open issue in CF.

☆ The authors did not receive any sources of funding for research reported in this manuscript.

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1569-1993/$ -see front matter
http://dx.doi.org/10.1016/j.jcf.2013.11.001

International guidelines recommend the use of BMI to evaluate nutritional status of adult patients [1]. Nevertheless, BMI is considered a good surrogate of adiposity in overweight patients, but does not provide information on body composition in patients with normal body size or lean subjects [2,3].

Fat free mass (FFM) depletion was reported in CF patients and attributed to a catabolic state induced by low energy intake, insulin deficiency and chronic inflammation that may impair FFM and lead to a reduction in skeletal muscle mass, inspiratory muscle wasting and loss of inspiratory muscle function [4–8].

The aim of the study was to evaluate the relationship between recurrent acute pulmonary exacerbations (APEs) and altered body composition in young adults with CF. In addition we verified if body composition indices obtained by soft tissue analysis by DXA are associated with pulmonary function.

2. Methods

In a retrospective study we collected body composition, clinical and sputum microbiology data from medical records of 85 young adults with CF who had performed a DXA scan between January 2007 and June 2012. Patients who underwent lung transplantation were excluded. The local ethics committee approved the study. Patients were informed about the purpose of the study and gave permission to include their clinical data in this research.

2.1. Pulmonary exacerbations

The number of APEs that had occurred during the year preceding the DXA scan was derived from the clinical report of each patient. Patients were defined as frequent exacerbators if they had experienced more than 2 APEs the year before DXA scan.

APE was defined as the need for additional antibiotic treatment due to at least two of the following: change in sputum volume or colour, increase in cough, dyspnea, malaise, fatigue or lethargy, anorexia or weight loss, decrease in pulmonary function by 10% or more or radiographic changes [9].

2.2. Dual energy X-ray absorptiometry (DXA)

Participants underwent whole-body DXA scanning (DXA Hologic Discovery, Hologic, Waltham, USA), a technique that is able to estimate fat mass (FM) and FFM by measuring the X-ray attenuation of different tissue components. All DXA scans were performed in the outpatient setting with the patients in clinically stable condition (no symptoms suggesting APE). Body composition was assessed by the three compartment model (version 12.3), including FM, bone mineral content, and lean tissue mass. FFM was calculated using the sum of the estimates of lean tissue mass and bone mineral content. Bone mineral density (BMD) was determined on total body.

Instrument calibration was obtained with a phantom (including six fields of lucite and aluminium of varying thickness and known absorptive properties) scanned as an external standard. The whole-body DXA scans were performed and analysed by the same operator (MLB) according to the same protocol throughout the whole study. The coefficients of variation (CV) for total body FM and FFM were 2.9% and 1.7%, respectively. The CVs for FM and FFM of the main subregions of total body were respectively: 2.4% and 1.6% for trunk, 2.6% and 1.7% for legs and 3.1% and 2.6% for arms. CVs were calculated in vivo with repositioning of subjects.

Age and gender-specific Z-scores of BMD were obtained with reference to the BMD of a population of healthy age- and sex-matched Italian young people. Whole body and appendicular FFM were divided by height squared to obtain FFM index (FFMI). FFM depletion was defined as having whole body FFMI below the 5th centile for age and gender matched healthy subjects [10].

2.3. Anthropometry

Weight and height at the time patients had the DXA scan were used to obtain the BMI. Patients were defined underweight if they had a BMI < 18.5 kg/m^2. Males with a BMI < 23 kg/m^2 or females with a BMI < 22 kg/m^2 were considered below the CF Foundation (CFF) nutritional goal [1].

2.4. Sputum microbiology

Sputum microbiology data in the year preceding DXA scan were collected. Chronic lung infections by *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex and Methicillin Resistant *Staphyloccus aureus* were registered. Patients having at least 4 cultures per year, at least half of which positive for one of the previous mentioned bacteria were considered chronically infected [11].

2.5. Pulmonary function

Pulmonary function tests were performed according to the American Thoracic Society and European Respiratory Society guidelines [12]. Forced expiratory volume in one second (FEV1) was expressed as percentage of reference values.

2.6. Statistical analysis

Whole body and sub-regional body FFMI and BMD were the primary outcomes of the study. We estimated that 72 patients (36 for each group) would be adequate to detect a difference of 1 kg/m^2 in whole body FFMI between frequent and infrequent exacerbators (assumed SD = 1.5 kg/m^2, power = 80%, two-sided, $\alpha = 0.05$).

Continuous data are presented as mean and SD, whereas categorical data as counts and percentages. Comparisons between groups were performed by means of Mann–Whitney U test or Fisher exact test when appropriate. Spearman's rank correlation coefficients were calculated to evaluate the association between APEs and body composition, while Pearson's correlation coefficients were computed to evaluate the association between FEV1 and body composition data.

Multiple linear regression analysis was used to analyze the association between variables controlling for potential