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Body composition and lung function in cystic fibrosis and their association with adiposity and normal-weight obesity

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ABSTRACT

Objectives: This study aimed to evaluate the relationship between lung function and body composition in cystic fibrosis (CF) and examine the presence of normal-weight obesity (NWO), a high body fat percentage with a normal body mass index (BMI), in this population.
Methods: In a pilot, cross-sectional study, 32 subjects with CF and a reference group of 20 adults without CF underwent body composition analysis with air displacement plethysmography. NWO was defined as a BMI <25 kg/m^2 and body fat >30% (for women) or >23% (for men). Lung function in subjects with CF was determined by the percentage of predicted forced expiratory volume in 1 s (FEV_1% predicted).
Results: Despite lower BMI and fat-free mass index ($P < 0.01$), fat mass index and percent body fat did not differ between subjects with CF and the reference group. Among subjects with CF, FEV_1% predicted was positively associated with fat-free mass index ($\beta = 6.31 \pm 2.93$, $P = 0.04$) and inversely associated with fat mass index ($\beta = -6.44 \pm 2.93$, $P = 0.04$), after adjusting for age, sex, and BMI. Ten subjects with CF (31%) had NWO, which corresponded with lower fat-free mass index and FEV_1% predicted compared with overweight subjects ($P = 0.006$ and 0.004, respectively).
Conclusions: Excess adiposity, particularly in the form of NWO, was inversely associated with lung function in CF. Larger prospective studies should be undertaken to confirm these findings and determine the long-term metabolic and clinical consequences of excess adiposity in CF. As the lifespan of individuals with CF increases, nutrition screening protocols, which primarily rely on BMI, may require reassessment.

Introduction

As the median survival rate in patients with cystic fibrosis (CF) increases, it becomes increasingly important to identify targets for maintenance of optimal health in this aging population. Given the key role of malnutrition in the progression of CF lung disease, maintenance of adequate nutritional status, typically defined as a body mass index (BMI) goal, has been a conventional target for improved health outcomes in CF [1]. However, BMI simply reflects body size (kg/m^2) and does not distinguish between the major metabolically active components of body composition (fat mass and fat-free mass). Independent of BMI or body weight, numerous

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studies in individuals with CF have described a preferential depletion of fat-free mass, which is associated with indexes of disease severity, including reduced lung function, increased pulmonary exacerbations, and increased inflammation [2–5]. Therefore, studies of body composition in CF may be more informative than use of BMI alone as a measure of optimal health.

Nutritional interventions in CF are often targeted at increasing or maintaining BMI with high-fat and/or high-protein diets. However, the impact of such unrestricted, high-calorie diets on body composition in adults with CF is unclear. Aggressive nutrition support in CF primarily restores fat mass, as opposed to fat-free mass [5]. As inflammation and an oxidative environment have been shown in vitro to promote adipogenesis [6,7], it is possible that there is preferential energy partitioning toward fat mass gain in CF driven by concomitant systemic inflammation and/or redox imbalance.

In non-CF populations, adiposity is inversely associated with lung function [8,9]. Reports of obesity within CF populations are beginning to emerge [10–12]. For example, an analysis of BMI trends over the past three decades found an increase in the prevalence of overweight and obesity (from 7% to 18%) in a Toronto adult CF center [12], with a Pittsburgh pediatric CF center reporting a prevalence of up to 23% [11]. Whether the increase in obesity prevalence has negative effects on CF morbidity is unknown; however, both overweight status and obesity are associated with increased lipid concentrations in CF [12]. Furthermore, there may be a threshold above which BMI is not positively associated with lung function [12]. Recently, the term “normal-weight obesity” (NWO) has been introduced to describe the paradoxical presence of a normal-weight BMI classification with a concomitant high body fat percentage [13]. This NWO phenotype is associated with increased cardiometabolic risk in the general population [14,15]; however, the prevalence and clinical impact of NWO in CF are unknown.

This pilot study aimed to examine the relationship between body composition and lung function in older adolescents and adults with CF, with a specific focus on characterizing NWO in this population.

Subjects and methods

Study subjects

Participants were recruited as part of a parent study designed to investigate potential causes of cystic fibrosis–related diabetes [16]. Participants in the present cross-sectional analysis were 32 clinically stable subjects with CF and a reference group of 20 subjects without CF with available body composition data. The Emory Institutional Review Board approved the study; all participants provided written informed consent or assent, as applicable. Participants with CF were recruited during Emory CF clinic visits. Inclusion criteria for subjects with CF were age ≥16 y, confirmed CF diagnosis, and no pulmonary exacerbations within the past month. Exclusion criteria were use of systemic glucocorticoids, pregnancy, chronic illness other than CF requiring chronic medications, chronic oxygen therapy, or lung transplant. Participants in the reference group were recruited as part of the parent study and consisted of healthy, non-CF volunteer students and employees at the CF center. Exclusion criteria for the reference group were chronic illness requiring prescription medications and no acute illness in the prior 3 wk of the study. Testing was conducted in the Emory University Hospital Clinical Research Network unit of the Atlanta Clinical and Translational Science Institute (formerly General Clinical Research Center).

Body composition

Body composition was assessed using the two-component model using air displacement plethysmography (BOD-POD; Life Measurement Instruments, Concord, CA, USA) with subjects wearing a bathing suit and a swim cap. Thoracic gas volume was directly measured and used for the calculation of total body volume and subsequent body density (density = mass/total body volume). Percent body fat was calculated using the Siri equation [17], and subsequently used to determine fat mass (kg) and fat-free mass (kg). To account for variations in stature, height-normalized indexes were determined for fat mass and fat-free mass (fat mass or fat-free mass in kg/height in m^2) [18].

Height was measured without shoes to the nearest 0.1 cm with a manual stadiometer. Weight was measured to the nearest 0.1 kg with the BOD-POD system. BMI was calculated as kg/m^2. Participants with a BMI <25, 25 to 29.9, and ≥30 kg/m^2 were classified as normal weight, overweight, and obese, respectively. NWO was defined as a normal-weight BMI (<25 kg/m^2) and percent body fat >30% in women and >23% in men, according to published cut-points [14]. Normal-weight participants with a percent body fat ≤30% and 23% in women and men, respectively, were classified as lean.

Clinical, analytical, and dietary outcomes

Clinical data, such as genotype and exocrine pancreatic sufficiency status, were obtained from the CF Patient Registry maintained by the Cystic Fibrosis Foundation. Lung function in subjects with CF was assessed on the day of the study visit using conventional spirometry methods and American Thoracic Society standards. We report the percentage of predicted forced expiratory volume in 1 s (FEV_1% predicted) using the National Health and Nutrition Examination Survey as the reference population [19]. Lung function status was categorized based on FEV_1% predicted as moderate (<59%), mild (60% to 79%), or normal (≥80%). Dietary supplement intake was obtained through self-report or extracted from electronic medical records.

Glucose tolerance was determined with an oral glucose tolerance test after an overnight fast. After a fasted blood draw, an oral glucose solution was administered (1.75 g/kg body weight to a maximum of 75 g), and subsequent blood drawn 2 h later. Plasma glucose assays were performed using a standard glucose analyzer (Cardiovascular Specialty Laboratories, Atlanta, GA, USA). According to American Diabetes Association guidelines, subjects were categorized as having normal glucose tolerance (fasting plasma glucose [FPG] <5.56 mmol/L and 2 h plasma glucose <7.78 mmol/L), prediabetes (impaired fasting glucose with FPG 5.6 to 6.9 mmol/L, and/or impaired glucose tolerance with 2 h plasma glucose 7.8 to 11.0 mmol/L), or diabetes (FPG ≥7.0 mmol/L and/or 2 h plasma glucose ≥11.1 mmol/L). Fasting plasma interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) were assayed using a Bio-Plex multiplex system (Bio-Rad Laboratories Inc., Hercules, CA, USA).

Three-day food records, consisting of two weekdays and one weekend day, were analyzed by a registered dietitian using the Nutrition Data System for Research software (Nutrition Coordinating Center, University of Minnesota, MN, USA; database version 2013). Reported food intake was evaluated as a percentage of the Institute of Medicine’s Dietary Reference Intakes (DRI) for energy (calculated based on a physical activity coefficient of 1.0 and individual sex, age, height, and weight) and protein (0.85 g/kg for adolescents and 0.8 g/kg for adults) [20]. Dietary data were not available for two subjects with CF. Detailed diet intake data of subjects with CF are provided in the Supplementary Data.

Statistical methods

Descriptive statistics were performed on all variables. Differences between the CF and reference groups were determined with a two-group *t* test or Fisher's exact test, as appropriate. The relationship of FEV_1% predicted (dependent variable) with individual body composition factors (independent variable) was assessed, in separate models, using multiple linear regression analysis with age (as a continuous variable) and sex as covariates. BMI, as a continuous variable, was added as a covariate in the models for fat mass, fat-free mass, and their respective indices. Clinical and metabolic differences between the weight categories among subjects with CF were determined using analysis of variance with Tukey's post-hoc comparisons or the Kruskal-Wallis test if the data were not normally distributed (IL-6, IL-8, and TNF-α). Analyses were performed in JMP version 10 (SAS, Cary, NC, USA) using two-sided tests with an alpha significance value of 0.05.

Results

Demographic, clinical, and body composition characteristics of subjects with CF and the non-CF reference group are shown in Table 1. Among the subjects with CF, 44% had normal glucose tolerance, 19% had prediabetes, and 38% had CF-related diabetes. All but one subject with CF had pancreatic insufficiency, 84% had at least one ΔF508 mutation, and 82% were supplemented with a general multivitamin or a multivitamin with a water-miscible formulation. The majority of subjects with CF were classified as having normal lung function (62.5%); 25% of subjects had moderate or severe lung function, and 12.5% of subjects had mild lung function. The CF and reference groups did not differ in age or