Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study

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ABSTRACT

Background: A high-calorie diet has been a standard of care in cystic fibrosis (CF) for >3 decades. However, energy requirements may have changed with new treatments and milder genotypes.

Objectives: The objectives of this study were to describe longitudinal trends in nutritional status and to evaluate the relation between nutritional status and lung function.

Design: This longitudinal cohort study included 909 individuals followed at the Adult CF Clinic in Toronto from 1985 to 2011. Nutritional status was classified on the basis of WHO BMI guidelines. Multivariable linear regression with the use of generalized estimating equations was applied to evaluate the relation between BMI and lung function.

Results: The proportion of underweight individuals decreased from 20.6% before 1990 to 11.1% in the most recent decade, whereas the proportion of overweight and obese subjects increased from 7.0% to 18.4% (P < 0.001). Overweight and obese subjects were older, had better lung function, had milder genotypes, and were more often male and pancreatic sufficient. Multivariable regression analyses showed that within the underweight group, an increase in BMI resulted in improved lung function, whereas this effect was half of that in overweight individuals. The greatest advantage of improved nutrition on lung function was observed in the underweight group and in pancreatic-insufficient patients.

Conclusions: Modification to a high-fat diet may be required in some individuals with CF to optimize nutritional health. Higher BMI is associated with improvements in lung function, although the lung function benefit of increasing one’s BMI (in kg/m²) to >25 is small and needs to be balanced against the known health risks of obesity. Am J Clin Nutr 2013;97:872–7.

INTRODUCTION

Cystic fibrosis (CF)⁴ is a genetic disorder characterized by high resting energy expenditure and malnutrition secondary to fat malabsorption and impaired nutrient intake. Decreased lung function and chronic pulmonary infection result in increased caloric requirements and decreased appetite, which worsens nutritional status further (1). Fat restriction was standard therapy across North America for CF, although in the early 1970s the Toronto CF clinic advocated a high-fat, high-calorie diet with up to 20 or 30 pancreatic enzyme capsules per meal. With the use of data from Toronto, a pivotal study published in 1988 showed that patients in Toronto had a 9-y survival advantage compared with a similar clinic in the United States that prescribed fat restriction (2). The authors concluded that the improved growth and nutrition seen in Toronto patients contributed to the survival advantage. Since this publication, a high-fat, high-calorie diet has become the standard of care for individuals with CF worldwide to prevent malnutrition (3, 4).

The impact of correcting severe malnutrition in CF so that normal growth and weight is achieved has had a significant impact on many clinical outcomes. Several studies published in the 1980s and 1990s showed that aggressive nutritional supplementation with gastrostomy tube feeding in malnourished patients with CF could improve nutritional outcomes and was associated with a slower rate of decline in lung function and prolonged survival (5–10). What is less clear is whether there is an advantage to continuing to increase weight over and above the normal range in CF. Furthermore, since the discovery of the CF gene in 1989, mild CF mutations have been identified. These individuals, who are more likely to be pancreatic sufficient (PS), may have lower energy requirements compared with those with severe genotypes, and the impact of a high-fat, high-calorie diet is less clear in these circumstances. The current adult and pediatric CF guidelines on nutrition focus on nutritional failure with no recommendations on the management of individuals who are overweight or obese. Furthermore, the recommendations do not specify that a high-fat, high-calorie CF diet should be limited to pancreatic-insufficient (PI) individuals.

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4 Abbreviations used: BCC, Burkholderia cepacia complex; CF, cystic fibrosis; CFLD, cystic fibrosis–associated liver disease; CFRD, cystic fibrosis–related diabetes; FEV₁, forced expiratory volume in 1 s; GEE, generalized estimating equation; PI, pancreatic insufficient; PS, pancreatic sufficient; TCF, Toronto Cystic Fibrosis (registry).

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Limited published data that evaluate trends in BMI over time or characterize the current nutritional status of the CF population exist. In a cross-sectional study, researchers from the United Kingdom found that the prevalence of overweight and obese adults, homozygous for ΔF508, was 9.4% and 1%, respectively, in 2002 (11). By using a scatterplot of forced expiratory volume in 1 s (FEV₁) compared with BMI, the authors showed that FEV₁ increased with increasing BMI to a threshold BMI (in kg/m²) of 23, beyond which the increase in FEV₁ was marginal. The 2010 Canadian CF Patient Data Registry Report showed that the proportion of adults with a BMI >30 reached 3.4%, which was unheard of in earlier decades.

The objectives of this study were to describe clinical characteristics and longitudinal trends in nutritional status in adult Toronto patients with CF over the past 25 y and to evaluate the relation between nutrition and lung function in this population. Given the spectrum of CF disease and that a high-fat diet is standard therapy regardless of severity of disease, we hypothesized that the prevalence of overweight and obese individuals with CF has increased over time, that overweight and obese subjects will have milder CF disease, and a BMI threshold exists above which there is little gain in lung function.

SUBJECTS AND METHODS

This cohort study included all individuals followed at the Adult CF Clinic at St Michael’s Hospital in Toronto between 1 January 1985 and 31 December 2011, inclusive. All subjects had previously been diagnosed with CF on the basis of sweat chloride testing, genotyping, or both. Demographic data as well as clinical information obtained at each clinic visit were available from the Toronto CF (TCF) registry. TCF registry data are collected prospectively in all individuals attending the CF clinic in Toronto. Data obtained after lung transplantation, during pregnancy and in the 6 mo postpartum were excluded from the analysis. Informed consent was obtained from each subject for his or her information to be entered into the TCF registry. The use of the TCF registry for research purposes was approved by the Research Ethics Board at St Michael’s Hospital. All ethical procedures followed were in accordance with the ethical standards of our institution.

Clinical measurements

FEV₁ was measured at each clinic visit according to American Thoracic Society criteria (12). FEV₁ was expressed as a percentage of the normal predicted values for height and sex (FEV₁% predicted) by using the Hankinson reference norms (13). This is consistent with the US and Canadian CF registries and allows for meaningful comparisons with existing literature. Pancreatic status was determined by pancreatic enzyme usage, 3-d fecal fat measurements, serum trypsinogen, clinical evidence of steatorrhea, or all 3 measures. CF-related diabetes (CFRD) was defined as persistently elevated blood sugars and/or a positive oral-glucose-tolerance test consistent with CFRD on the basis of the CF Consensus Conference Report on CFRD (14). Fasting lipid profiles were measured every 1 or 2 y as part of routine care. The lipid profile recorded closest to and within 2 y of the most recent clinic visit at which both BMI and FEV₁ were recorded was used. Cholesterol and triglycerides were analyzed by using enzymatic methods (UniCel DxC 800; Beckman Coulter). Hypercholesterolemia was defined as total cholesterol ≥5.2 mmol/L, and hypertriglyceridemia was defined as plasma triglycerides ≥1.7 mmol/L on the basis of recommendations from the National Cholesterol Education Program (15) and the Canadian Cardiovacular Society (16). Subjects were classified as Burkholderia cepacia complex (BCC) positive if they had ever provided sputum samples containing BCC and Pseudomonas aeruginosa positive if they had ever provided a sputum sample containing P. aeruginosa.

Height (cm) and weight (kg) were recorded for each subject at each clinic visit. Height was measured by using a wall stadiometer, and weight was measured by using a calibrated balance beam scale. BMI was calculated by using weight (in kg)/height (in m)². Subjects were classified into 1 of 4 BMI categories on the basis of WHO guidelines (17): underweight (<18.5), adequate weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30).

Statistical analysis

To evaluate changes in BMI over time, we used longitudinal data from 1985 to 2011. Individuals older than 70 y were excluded. Four cohorts, based on the subjects’ year of birth (<1960, 1960–1969, 1970–1979, >1979), were derived. In addition, the sample was categorized into 3 measurement periods on the basis of the year the clinical measurements were taken (<1990, 1991–1999, ≥2000). Due to the skewed distribution of BMI and age, these variables were log transformed. To determine whether there had been a shift in the distribution of BMI, we drew a random sample of 1000 observations from each measurement period.

To characterize a contemporary CF cohort, the last recorded measurement for each subject between 2000 and 2011 was analyzed in each of the BMI categories. ANOVA for continuous variables and the chi-square test for categorical variables were used to evaluate differences between the BMI groups.

Relation between BMI and FEV₁

To characterize the relation between BMI and lung function (FEV₁% predicted), we further excluded subjects born before 1970 and subjects >50 y of age to avoid survivor bias. Individuals measured before 1990 were used as the reference group to calculate BMI z score. BMI was split into 3 categories (overweight and obese categories were combined because of limited sample size), and linear regression with the use of generalized estimating equation (GEE) models were applied to maximize the longitudinal data, with adjustment for the correlated nature of the repeated measures. An autoregressive correlation structure was used. In the multivariable model, we adjusted for sex, age, pancreatic status, CFRD, and birth cohort. Interactions were evaluated between BMI category and pancreatic status and sex.

For all analyses, P < 0.05 (2-tailed) was used as the criterion for significance. Statistical analysis was performed by using SAS software (version 9.2; SAS Institute Inc).

RESULTS

Complete adult CF cohort: 1985–2011

Analyses were based on a sample of 908 adult patients with CF who had 23,434 clinical measurements between 1985 and 2011. A random sample of 1000 measurements was taken from each of 3 decades (<1990, 1991–1999, ≥2000). There was clear shift
in the distribution of BMI over time, with the most recent cohort having the highest average BMI (Figure 1); the average BMI increased from 20.7 ± 2.7 before 1990 to 22.3 ± 3.4 in the most recent decade (2000–2011). The proportion of underweight individuals has also decreased from 20.6% before 1990 to 11.1% in the most recent decade. The proportion of adequate-weight subjects slightly decreased (72.4% in the 1980s, 72.6% in the 1990s, to 70.5% in the 2000s), whereas the proportion of overweight/obese subjects increased from 7.0% in the 1980s to 15.8% in the 1990s and to 18.4% in the most recent cohort ($P$-trend < 0.001).

Multivariable GEE models showed that, overall, BMI increased by 0.4%/y from 1985 to 2011. Analysis was repeated for PS and PI patients separately. The rate of BMI increase in PS subjects was much greater than in PI subjects (3.8% compared with 0.4%/y, respectively; $P$ < 0.001).

**Contemporary adult CF cohort: 2000–2011**

Descriptive characteristics, with the use of the last recorded measurement, of the 651 subjects measured between 2000 and 2011 are shown in Table 1. According to WHO classifications, 17% of CF subjects were underweight, 60% had adequate weight, 18% were overweight, and 3.8% were obese. Subjects in the overweight and obese categories were older, had higher lung function, had milder genotypes, were less likely to have *P. aeruginosa* and BCC, and were more often male and PS (Table 1). The prevalence of diabetes in the obese category was low (4%) compared with that in the underweight category (25%) ($P$ = 0.08). Lipid profiles ($n$ = 249 subjects; 38% of the contemporary cohort) differed between the BMI categories, with higher triglycerides and cholesterol observed in the overweight and obese subjects (Table 2). In addition, the proportion of individuals with triglycerides ≥1.7 mmol/L and cholesterol concentrations ≥5.2 mmol/L increased with increasing BMI categories ($P$-trend < 0.0001).

To address potential survival bias, subjects born after 1970 and who were between the ages of 20 and 50 y were analyzed ($n$ = 426). With the use of 7968 clinical measurements, multivariable GEE models, adjusted for age, height, sex, CFRD, pancreatic status, and birth cohort, showed that lung function improved as BMI increased. The magnitude of this improvement was not consistent across all BMI categories, with results similar to those reported for the complete CF cohort (Figure 2). Within the underweight group, a 10% increase in BMI resulted in a 4% relative increase in FEV1, individuals with a BMI in the adequate range had a 5% relative increase in FEV1, and those in the overweight category had a 2% increase in FEV1. The increase in lung function was similar in the underweight and adequate-weight groups ($P$ = 0.06), whereas the magnitude of the increase in FEV1 was significantly less in the obese group than in the adequate-weight reference group ($P$ < 0.001). Other significant independent predictors identified in the multivariable GEE model included age (older age was associated with lower FEV1; $P$ = 0.001), pancreatic status (PS subjects had higher FEV1; $P$ = 0.002), and the presence of CFRD (CFRD subjects had lower FEV1; $P$ = 0.002). Although women had slightly lower lung function than did men, this was not significant within the multivariable model. We observed an interaction between BMI and pancreatic status, whereby PI subjects had a 4.3% relative increase in FEV1 with each 10% increase in BMI compared with 2.7% in PS subjects ($P$ = 0.002).

By evaluating the decline in FEV1 over time, we found that, on average, FEV1 decreased at a rate of 1%/y, and there were no significant differences in the rate of FEV1 decline in the 3 BMI categories.

**DISCUSSION**

To our knowledge, this is the first study to characterize changes in nutritional status over time and to quantify the relation between nutrition and lung function across the spectrum of BMI categories. Our study showed a significant shift in the distribution of BMI in adults with CF over a 25-y period. Within a contemporary cohort of individuals with CF, fewer individuals were malnourished and more individuals were overweight compared with 20 y earlier. Our data suggest that improvements in nutritional status are associated with improvements in lung function, although this was not consistent across BMI categories or subgroups of the CF population.

There have been remarkable developments in the treatments for patients with CF, most notably improved nutrition, which have led to substantial improvements in survival. In our study we identified individuals who were overweight or obese who were older and had milder CF disease on the basis of lung function, pancreatic status, and genotype. A recently published Canadian cross-sectional study showed similar results in that overweight adult subjects with CF were more likely to be PS and have milder mutations (18). Thus, increasing obesity appears to be driven by a survivor effect whereby overweight subjects had milder disease. Regardless of what specific factors have played a role in the increase in overweight and obese subjects, paradoxically the recommendation of a high-fat, high-calorie diet in CF may now have negative consequences in certain individuals living with CF today. Such a diet may be disadvantageous for PS individuals who are overweight, particularly if they have elevated lipid profiles. Although heart disease has been distinctly uncommon in CF to date,
Burkholderia cepacia

Pseudomonas aeruginosa

Lung function

Genotype

Pancreatic insufficiency

fibrosis; FEV1, forced expiratory volume in 1 s.

et al (18) who showed that overweight subjects with CF exhibited

general population. Our findings are similar to those of Coderre

PS patients may be at the same risk of hyperlipidemia as the

tients have normal-to-low serum lipids but showed evidence that

lesterol. A 1994 study by Slesinski et al (22) found that PI pa-

other BMI categories had elevated triglycerides and total cho-

study a higher proportion of obese individuals compared with

factors for dyslipidemia (19). In CF, recent studies have sug-

a significant role in maintaining one’s health. For example, in the

may arise and modifiable risk factors such as weight could play

as patients live longer complications not previously recognized

higher concentrations of total and LDL cholesterol. Similar to

these findings, in our study obese subjects with high tri-

glycerides or high total cholesterol were PS. Medications that

could interfere with lipid profiles were not recorded for this

study; however, <1% of our patient population are taking lipid-

lowering medications; therefore, this is unlikely to affect our

In contrast to Kastner-Cole et al (11), we found that the

prevalence of being overweight and obese in our CF population

was much higher than they reported on the basis of 2002 UK

registry data. In addition to the 10 y between the 2 studies, the

difference observed in the estimates is likely explained by the fact

that Kastner-Cole et al limited their analysis to homozygous

ΔF508 subjects, which is a severe genotype associated with

TABLE 1

Descriptive statistics by BMI (in kg/m²) category

|                  | Underweight (BMI <18.5) | Adequate weight (BMI 18.5–24.9) | Overweight (BMI 25–29.9) | Obese (BMI ≥30) | P value
<table>
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<tbody>
<tr>
<td>n</td>
<td>109</td>
<td>397</td>
<td>120</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>27.1 ± 9.4</td>
<td>32.6 ± 10.6</td>
<td>35.5 ± 11.1</td>
<td>41.0 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td>54 (49.5)</td>
<td>219 (55.2)</td>
<td>90 (75.0)</td>
<td>16 (64.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CF-related diabetes [n (%)]</td>
<td>27 (24.8)</td>
<td>97 (24.4)</td>
<td>23 (19.2)</td>
<td>1 (4.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.2 ± 1.1</td>
<td>21.6 ± 1.7</td>
<td>26.8 ± 1.4</td>
<td>33.9 ± 4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁ (%) predicted</td>
<td>34.3 ± 18.9</td>
<td>53.4 ± 25.2</td>
<td>66.9 ± 26.7</td>
<td>76.6 ± 19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genotype [n (%)]</td>
<td>Homozygous ΔF508</td>
<td>46 (42.2)</td>
<td>170 (42.8)</td>
<td>38 (31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate (FEV₁ 40–70%)</td>
<td>25 (22.9)</td>
<td>144 (36.3)</td>
<td>39 (32.5)</td>
<td>10 (40.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe (FEV₁ &lt;40%)</td>
<td>77 (70.6)</td>
<td>143 (36.0)</td>
<td>22 (18.3)</td>
<td>0 (0.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pancreatic insufficiency [n (%)]</td>
<td>98 (89.9)</td>
<td>319 (80.4)</td>
<td>68 (56.7)</td>
<td>3 (12.0)</td>
<td>&lt;0.001</td>
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<td>0.008</td>
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</table>

TABLE 2

Total cholesterol and triglycerides by BMI (in kg/m²) category

|                  | Underweight (BMI <18.5) | Adequate weight (BMI 18.5–24.9) | Overweight (BMI 25–29.9) | Obese (BMI ≥30) | P value
<table>
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<tbody>
<tr>
<td>n</td>
<td>33</td>
<td>149</td>
<td>54</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.89 ± 0.49</td>
<td>0.94 ± 0.47</td>
<td>1.17 ± 0.71</td>
<td>1.74 ± 1.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>High (≥1.7 mmol/L)</td>
<td>3 (9.1)</td>
<td>13 (8.7)</td>
<td>7 (13.0)</td>
<td>5 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal (&lt;1.7 mmol/L)</td>
<td>30 (90.9)</td>
<td>136 (91.3)</td>
<td>47 (87.0)</td>
<td>8 (61.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.24 ± 0.82</td>
<td>3.78 ± 0.91</td>
<td>4.25 ± 1.20</td>
<td>4.70 ± 1.59</td>
<td>&lt;0.001</td>
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<tr>
<td>Total cholesterol [n (%)]</td>
<td></td>
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<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>High (≥5.2 mmol/L)</td>
<td>0 (0.0)</td>
<td>13 (8.7)</td>
<td>10 (18.5)</td>
<td>5 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal (&lt;5.2 mmol/L)</td>
<td>33 (100.0)</td>
<td>136 (91.3)</td>
<td>44 (81.5)</td>
<td>8 (61.5)</td>
<td>&lt;0.001</td>
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1 ANOVA for continuous variables and the chi-square test for categorical variables were used to evaluate differences between the BMI groups.

2 Mean ± SD (all such values).
had diabetes compared with 5% of nonobese adults (25). Previous studies have shown either small but significant associations between CFRD and lower height- and weight-for-age (26) or no significant associations between CFRD and BMI (27, 28).

The strengths of our study include the following: the large sample size; the longitudinal nature of the data, which was prospectively collected; the comprehensiveness of the TCF data registry; and the spectrum of disease severity included in the study cohort, which increases the generalizability of the study results. The limitations of our study merit discussion. As with any study that uses BMI as an indicator of nutritional status, information on body composition was lacking. Previous studies have linked lung function to body composition, specifically to fat-free mass depletion, which was not captured within the TCF database (29). Certain complications, such as CF-associated liver disease (CFLD), may affect the interpretation of nutritional status as measured by BMI. Along with the metabolic complications associated with liver disease, the presence of ascites in this subset of the population can falsely elevate body weight and place an individual in a higher BMI category than their nutritional status reflects. Although we were unable to accurately identify and exclude individuals with CFLD, we feel this minimally affects our conclusions because CFLD affects <5% of the CF population (30).

In conclusion, there has been a shift in nutritional status in the Toronto CF population over a 25-y period. Older individuals who are PS are at highest risk of obesity. In general, emphasis should be placed on preventing malnutrition to improve health outcomes in CF, although dietary recommendations may need to be modified when one’s BMI exceeds 25. Further study is needed to better define nutrition requirements for those with milder CF disease to prevent excess weight gain, which might be detrimental to health.

The authors’ responsibilities were as follows—ALS, MB, RR, LAM, SW, PBD, and SS: designed the research; ALS, MB, RR, LAM, SW, and PBD: conducted the research; ALS, RN, JM, SS, LAM, and SW: performed the statistical analysis and interpreted the data; ALS, MB, RR, LAM, PBD, JM, and SS: wrote the manuscript; ALS and PBD: supervised the study; and ALS and SS: had primary responsibility for the final content. None of the authors had any conflicts to declare.

REFERENCES


