Body Composition, Inflammation, Physical Exercises and Food Intake in Cystic Fibrosis: Cross-Sectional Study

Abstract

Introduction: The body composition detects earlier impairment of the nutritional status and it may be altered by chronic inflammation, physical activity and energetic imbalance.

Methods: It is a cross-sectional study with 46 patients from 8 to 18 years old with CF aged 11.9 ± 2.83 years. We evaluated the arm muscle area, ratio of the subscapular and triceps skinfolds, body fat percentage, 24 h dietary recall, physical activity, C-reactive protein, and cytokines. It was made descriptive statistics, univariate and multiple linear regressions.

Findings: Among the patients studied, 52.2% were undernourished, 26.1% owned low body fat percentage and 55.6% increase in abdominal fat. The physical inactivity, inadequate intake, increased age and interleukin 8 contribute to the increase of body fat (p<0.05). The prevalence of malnutrition was 1.9 times higher in those with high C-reactive protein. The prevalence of malnutrition was 1.9 times higher in those with high C-reactive protein. There was a positive association of Interleucine-8 with body fat percentage and ratio of skinfolds.

Conclusions: The C-reactive protein may be considered a prognostic indicator of malnutrition. The total energetic intake and level of physical activity are factors of preservation of lean body mass. The positive association of interleukins 8 with the percentage of body fat seems to be more associated with obesity.

Keywords: Cystic fibrosis; Nutritional assessment; Mediators of inflammation; Exercises

Introduction

Association of the body composition with inflammatory markers, physical exercises, and food intake in children and adolescents with cystic fibrosis

Patients with cystic fibrosis (CF) suffer from chronic infections and severe inflammation, which lead to progressive pulmonary disease [1]. Chronic suppurative lung disease, pancreatic insufficiency and anorexia are interrelated complications that have negative impacts on food intake and may affect the energy balance, contributing to the malnutrition [2]. Nutritional status is a prognostic marker of survival of patients with FC [3]. Body composition evaluation detects changes earlier than the anthropometrics indices [4].

The patient’s body composition with CF can be changed by the interaction of several factors, such as chronic inflammatory state, energetic imbalance and physical inactivity [2].

The characteristic chronic inflammatory condition in these patients may also be due to the imbalance in fatty acid metabolism between long chain omega-3 polyunsaturated (n-3 PUFA) and omega-6 (n-6 PUFA) [5]. Exercise is beneficial and is known to play a vital role in overall health. Most CF patients including those with severe pulmonary disease (40% predicted FEV-1) are capable of engaging in strength and aerobic exercises [6].

Regular physical exercise with muscle endurance training increases weight gain and lean body mass [5]. Furthermore, regular aerobic exercise has been shown to limit inflammation in diseases associated with low-grade inflammation [7].
Despite the importance of nutritional diagnosis, there are few international studies and no national on the association of the factors that interfere with the body composition of CF patients [6-9]. Thus, the aim of this study was to evaluate the association between nutritional status assessed by body composition, the inflammatory profile, food intake and level of physical activity of children and adolescents with CF. The results of this study can contribute to early intervention strategies designed to interrupt or reverse changes in body composition and improve patient survival.

**Methods**

It is a cross-sectional study with secondary database, which included all patients enrolled in a reference center of Rio de Janeiro/Brazil, between 2010 and 2011, of both sexes, eight to 18 years. All children and adolescents had two positive sweat test (chlorine >60 mEq/L) and/or two mutations in the gene CFTR [10].

We were included in the present study patients who had these information available in patient record: identification, type of genetic mutation, dietary data, C-reactive protein (CRP), tumor necrosis factor (TNF-α) and interleukins (IL-1β, IL-6 and IL-8), weight, height, arm circumference (AC), triceps skinfold (TSF) subscapular skinfold (SSF) and arm muscle circumference (AMC), sexual maturity and ethnicity and physical activity. Exclusion criteria were: Patients who did not have all this information available, liver disease and CF-related diabetes and those using steroids, NSAIDS and azithromycin.

The nutritional assessment was conducted by the Nutrition Clinic of professionals (doctors and nutritionists), previously trained for this activity. For the assessment of body composition was used to arm circumference (AC), the triceps skinfold (TSF) and subscapular skinfold (SSF). The skinfolds were measured according to the standards proposed by Lohman et al. with Cescorf® adipometer of 0.1 mm accuracy, by three times, considering the mean value [11].

The arm muscle circumference (AMC) was calculated by the formula: (cm) = AC (cm) – (TSF (mm) × 0.314), and the arm muscle circumference (AMC), sexual maturity and ethnicity and physical activity. Exclusion criteria were: Patients who did not have all this information available, liver disease and CF-related diabetes and those using steroids, NSAIDS and azithromycin.

The 5th percentile was used as cutoff point to define malnutrition [12].

The weight was measured with digital weight balance (LiderR) to nearest 0.1 kg. Heights were measured with stadiometer (WelmyR) to nearest 0.5 cm. Both were held according to Lohmann et al. [11]. Height was adjusted for age (H/A) using the Anthropus software by Word Health Organization (WHO) [13].

The body fat percentage was calculated by the Slaughter equation, which considers gender, ethnicity and level of the sexual maturity according to Tanner Stages [14]. The subscapular/triceps skinfolds ratio (SST/TSF) was calculated and considered as an indicator of higher risk of abdominal obesity, between 0.76 and 0.99, and as an abdominal obesity [15].

The 24 h recall method was used to assess the patients’ usual dietary intake. The method was applied in three non-consecutive days, with maximum interval of three months. The data were obtained by means of visual aids and photos of utensils. The calculation of the total energy intake (TEI) average and macronutrients was held using NutWin® version 1.5 (UNIFESP, 2002), by double entry. The study used data from the Brazilian Table of Food Composition in this analysis (TACO) [16], and the Table of Food Composition of the United States Department of Agriculture (USDA) [17]. The composition of some industrialized products was obtained from the manufacturers.

The reference standards for energy intake, according to age and gender, were from Food and Agriculture Organization/World Health Organization [18]. The macronutrient intake taken under consideration was 15-20% for protein, 40-50% for carbohydrates, and 35-40% for lipids. The energy adequacy percentage was >150% of the recommendations, according to the Nutrition Consensus [2]. The consumption of essential fatty acids (linoleic acid-n-6PUFA and alpha-linolenic acid-n3 PUFA) was assessed according to the Dietary Reference Intakes, DRI’s proposed by the Institute of Medicine (IOM) [19].

The evaluation of the level of physical activity was performed by applying a questionnaire to charge and or patients and followed the recommendations from the Centers for Disease Control and Prevention (CDC2008) which determine how suitable the accomplishment of physical activity 300 min/week [20]. To the calculation of time spent in different with the physical activity, there was the product of the duration (min/day) and frequency (days/week) activity reported. Were classified as insufficiently active those who have not accumulated a minimum of 300 weekly minutes and active, those with longer than 300 min of any physical activity.

The blood samples done by venipuncture were taken after an overnight fast of 12 h. The Blood tests were carried out by technicians from the Department of Pathology of the IFF/Fiocruz, by venipuncture, after overnight fasting for 12 h. Blood samples were scheduled preferably on the same days of consultations and/or other procedures and routine tests of CF patients in the IFF, directly from the legal guardian and/or adolescent himself. The C-reactive protein (CRP) was dosed by nephelometry and the interleukins (IL-1 β, IL-6 and IL-8) and the TNF-α by eBioscience® ELISA kits. This analysis was performed in duplicate for some samples.

The study considered normal CRP when the value was equal to less than 0.5 mg/dL [21].

All data mentioned above were available in the patients’ record and nutritional statuses were obtained close to date of laboratory dosages.

This project was approved by the Ethics Committee in Research of the IFF/Fiocruz (Document No.: 0052/07). The Consent form was signed in duplicate by the legal representative of all patients participating in the study and/or adolescent himself.

**Statistical Analysis**

In the descriptive analysis, for continuous variables with Normal distribution, the mean and standard deviation values were
presented. Otherwise, median, minimum and maximum values were presented. The normality of the variables was assessed using the Kolmogorov-Smirnov test. The categorical variables were described through absolute frequencies and percentages. The univariate analysis were performed to identify possible associations between the explanatory variables and the outcomes, and those with significance levels lower than 0.20 were considered as possible predictors in the linear regression and Poisson models with robust variance, for the outcomes fat percentage and nutritional status, according to the AMA, respectively. The stepwise method was used to select the variables that best explained the variations in such outcomes. The level of statistical significance considered in the models was of 5%. The analyses were conducted using software R version 3.0.1

Results

Data from 46 patients were analyzed of which 60.9% were female, and mean age of 11.9 ± 2.83 years old. Most at least one mutant allele for Delta F508 (60.8%), had pancreatic insufficiency (80.4%) and were diagnosed with CF aged older than two years (60.8%).

The prevalence of malnutrition by arm muscle circumference and arm muscle area was of 37.8% and 52.2%, respectively. The body fat content was reduced to only 17.8% and 26.1% of patients, according to the values of the TSF and to Slaughter’s equation, respectively. 22.9% of the patients were considered active. The subscapular/triceps skinfolds ratio was ≥1 in 17.8% of the patients. 95.6 % of patients had height for age greater than the 5th percentile.

The standard CRP value has been found in 66.7% of patients (Table 1). The recommended intake of energy, fat and PUFAs (n3-n6) was achieved in 76.1%, 45.7% and, 17.4% of patients respectively (Table 2).

Table 3 shows the results of the multiple linear regression models for the body fat percentage. Insufficiently active, diets with total energy intake (TEI) below RDA’s 150% recommendation of FAO/WHO, increasing age and the concentrations of IL-8 series contributed significantly to the increase in body fat percentage. Conversely, increasing the percentage of PUFA n-6 in relation to TEI is associated with a decrease in the fat percentage. It was calculated in the study of power for the AMA, the largest power was assigned to the variable "PCR" (79.3%) and lower assigned to variables "Genetics" and "Lipids" (3.24% and 3.86%, respectively).

The result of the body fat percentage was statistically significant on linear regression model for female patients shows that they exhibit an average increase of 3.7 percentage points of fat compared to males, children and adolescents insufficiently active have, on the study of power for the AMA, the largest power was assigned compared to those with normal CRP values. It was calculated in the study of power for the AMA, the largest power was assigned to the variable "PCR" (79.3%) and lower assigned to variables "Genetics" and "Lipids" (3.24% and 3.86%, respectively).

Table 1: Inflammatory markers in children and adolescents with cystic fibrosis treated at Health of the National Women’s Institute of Child and Adolescent Fernandes Figueira/Fiocruz-Rio de Janeiro from 2010 to 2011.

| Variable     | Median (Min-Max) |
|--------------|------------------|
| IL-1 β (pg/ml) | 13.85 [0-182.1]  |
| IL-6 (pg/ml)   | 10.65 [1.1-51.4] |
| IL-8 (pg/ml)   | 2.35 [0-219.7]   |
| TNFα (pg/ml)   | 12.30 [337.8]    |
| CRP (mg/dL)    | N (%)            |
| <0.5           | 30 (66.7)        |
| ≥0.5           | 15 (33.3)        |

IL: Interleukine; CRP: C-reactive protein; TNFα: Tumor necrosis factor

Table 2: Characteristic of food intake of children and adolescents with cystic fibrosis at Health of the National Women’s Institute of Child and Adolescent Fernandes Figueira/Fiocruz-Rio de Janeiro from 2010 to 2011.

| Variables (TEI) (%) recommended | Results N (%) |
|---------------------------------|--------------|
| <15                            | 11 (23.9)    |
| ≥15                            | 35 (76.1)    |
| Carbohydrates (TEI%)            | 48.1 ± 6.1   |
| <40                            | 4 (8.7)      |
| 40–50                          | 27 (58.7)    |
| >50                            | 15 (32.6)    |
| Lipids (TEI%)                  | 35.0 ± 4.6   |
| <35                            | 25 (54.3)    |
| 35–40                          | 16 (34.8)    |
| >40                            | 5 (10.9)     |
| Proteins (TEI%)                | 16.9 ± 2.9   |
| <15                            | 10 (21.7)    |
| 15–20                          | 28 (60.9)    |
| >20                            | 8 (17.4)     |
| PUFA (TEI%)                    | 7.1 ± 3.1    |
| ≤10                            | 36 (78.2)    |
| >10                            | 10 (21.7)    |
| ω6:ω3                          | 8.4 ± 2.4    |

Pufa: Polyunsaturated fatty acids; TEI: Total energy intake

Table 3: Multiple linear regression model for the body fat percentage in children and adolescents with cystic fibrosis, Health of the National Women’s Institute of Child and Adolescent Fernandes Figueira/Fiocruz-Rio de Janeiro from 2010 to 2011.

| Variable     | Coefficient Estimate (% body fat) | 95% CI | p-value |
|--------------|----------------------------------|-------|---------|
| Female       | 3.767                            | -0.109 - 7.643 | 0.056 |
| Age          | 0.831                            | 0.131 - 1.532 | 0.021* |
| Insufficient activity | 6.029                         | 1.602 - 10.456 | 0.009* |
| TEI (<150%)  | 7.52                             | 2.927 - 12.113 | 0.002* |
| ω6 (TEI%)    | -0.7                             | -1.368 - -0.032 | 0.040* |
| IL-8         | 0.064                            | 0.010 - 0.118 | 0.023* |

*p ≥ 0.05; TEI: Total energy intake; IL: Interleukin

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This study found a prevalence of 52.8% of malnutrition assessed by arm muscle area of children and adolescents with cystic fibrosis at Health of the National Women’s Institute of Child and Adolescent Fernandes Figueira/Fiocruz-Rio de Janeiro from 2010 to 2011.

| Variable                | Prevalence ratio | 95% CI  | p-value |
|-------------------------|------------------|---------|---------|
| CPR ≥ 0.5 MG/DL         | 1.902            | 1.131-3.197 | 0.015* |
| TEI (% recommended)    | 2.711            | 0.792-9.273 | 0.112  |

*P ≥ 0.05; CPR: C-reactive protein; TEI: Total energy intake; AMA: Arm muscular area; PS: 5th percentile

average, an increase of approximately 6 points in fat percentage compared to those who active. Patients who consumed diets with less than the FAO/WHO 150% recommendation showed, on average, an increase of 7.5 points in fat percentage, compared to those with diet’s TEI equal or superior than the recommendation. The increase of each 1 year in age, resulted in an average increase of 0.83 percentage points in the fat percentage and the increase of 1 pg/mL in the concentration of IL-8 series, causes an average increase of 0.064 points in the body fat percentage. The patients on diets with TEI within the energy recommendations presented, on average, a 2.7 times prevalence for the outcome, compared to those on diets with less than the 150% recommended TEI. However, the difference among the groups was not significant.

It was calculated in the study of power for each of the outcomes (For the % fat, the major powers were obtained for the variables "calorie intake" (81.3%) and "physical activity" (69.55%) and the lowest for "Lipids" (3.62%), "Carbohydrates" (5.80 %) and "Genetics" (6.58%).

**Discussion**

This study found a prevalence of 52.8% of malnutrition assessed by arm muscle area despite not corrected for bone area, which may have overestimated the musculature [16]. This, suggest that the lean body mass (LBM) was the initially more affected component. The body fat content was less committed co-reduction of only 17.8% and 26.1% of patients in accordance with the TSF values and Slaughter’s equation, respectively. Other studies detected similar results [22-23].

The LBM reduction is the best marker of nutritional status and is considered a predictor of morbidity and mortality. This is an important finding because in cystic fibrosis, it is independent of lung function [24].

The LBM depletion can be explained by use of protein is more used as an energy source (gluconeogenesis) in response to the negative energy balance [24]. According to this study, there is an increased percentage of body fat in those with inadequate energy intake, possibly by the reduced LBM. Another possibility would be the pro-catabolic intermediary metabolism inducing the muscle proteolysis [25].

Patients who consumed diets with total energy intake within the recommendations had a 2.7 times higher prevalence of malnutrition compared those who consumed below it, although the difference was not statistically significant. This demonstrates the complexity of the CF malnutrition pathogenesis, and makes it difficult to conclude on the effect of energy imbalance in the muscle depletion process, explaining the failure of the nutritional intervention in the muscle mass in the wasting syndrome (cachexia) [26].

One possible explanation would be that some systemic factors, not assessed in this study, interfere in the protein turnover, such as increased oxidative stress due to the low level of systemic inflammatory activity, chronic or intermittent hypoxia, low concentrations of anabolic hormones (testosterone, IGF1), and intramuscular factors such as muscle load and acidosis, concentration of cytokines and local free radicals. Perhaps, therefore, the increase in energy intake has contributed only to increase body fat mass and in the adequacy to the percentage of body fat observed in most patients.

The intake, of energy observed by most patient meet the CF Nutrition Consensus recommendation suggests that many of them did not develop anorexia. Other authors also found no anorexia in CF patients, and no association with weight loss in the period free of exacerbation of the moderate disease [2,26]. Although small percentage can have it developed for several reasons such as depression, action of cytokines produced by inflammatory and infectious process and excess pulmonary secretions.

Moreover, the inappropriate intake of fat, by the majority of patients, can be one of the causes for the high prevalence of malnutrition in this population, confirming the finding of the classic study on the difference in average survival in two reference centers (Boston and Toronto), which was explained by the improvement in nutritional status due to increased intake of lipids [27].

The ratio n6/n3 (8:1) consumed by patients observed is important, once these PUFAs compete among themselves for the same metabolic pathways of stretching and desaturation [28], and the imbalance of these reduction of linoleic acid and of the docosahexaenoic acid and increase of the arachidonic acid) in the plasma and tissues, may be responsible for inflammation and early development of lung disease [29]. So the amount PUFA of n3 and n6 may possibly also have been inadequate although the model have indicated that an increase of n6 result a decrease in the body fat percentage.

However, the total fat intake was unsatisfactory, so the amount of PUFA n3 and n6 can possibly also have been inadequate the amount of PUFAs n3 and n6 was likely to be inadequate as well, even though the model (Table 3) have pointed out that an increase in consumption of omega-6 fatty acids would imply a reduction in the body fat percentage. Possibly by the reduction of saturated and trans-fats intake that are related to increased adiposity. Thus the recommendation of the higher amount of lipids in the diet of patients with cystic fibrosis must contain lipids good quality as with n3 polyunsaturated mainly DHA and EPA.

The low prevalence of sufficient active patients is a concern once aerobic and strength exercise improve the bronchial tree clearance, reduces the progressive decline of the lung function, increases muscle mass and the physical strength, promotes bone development and raises self-esteem and quality of life.
[4]. Although it has been recently suggested that the CF gene presence in the skeletal muscle sarcoplasmic reticulum may contribute to exercise intolerance and muscle atrophy [30]. The results showed an association between poor level of physical activity and an increase of 6 points in the percentage of body fat (p<0.01).

The concentration of cytokines in the serum was undetectable in some patients. This finding complies with studies that demonstrated that in some situations the cytokines may get compartmentalized, for example, in the lungs, or because most of patients were clinically stable (CRP <0.5 mg), or by the inclusion of the study on those using ibuprofen and azithromycin [31,32].

Two results stand out in this study. The first was that the only cytokine that in the multiple linear regression models showed a positive association with the percentage of body fat was the IL-8. Once most patients showed proper amount of CRP, suggesting systemic inflammation of absence, this study may suggest that the concentrations of IL-8 are more associated to the percentage of adipose tissue than the inflammatory response. Other studies support this hypothesis as they found higher concentrations of IL-8 in patients with higher BMI [33]. A finding that may support this hypothesis is that the skinfolds ratio average (SSF/TSF) found showed that the majority presented obesity or risk of central obesity despite the high prevalence of malnutrition in the sample.

The accumulation of abdominal fat also has been observed in malnourished patients with CF and attributed to chronic inflammation, corticosteroid therapy, physical inactivity, and relative reduction of growth or anabolic hormone [33].

The second noteworthy finding was the higher CRP value in children and adolescents with a higher prevalence of malnutrition, measured by the AMA, compared to those with proper amounts of this protein, suggesting that it may be considered a prognostic indicator of malnutrition.

A limitation of the current study lies on the fact that, since it is a cross-sectional analysis, it points only to associations, without establishing a cause-effect relationship. In addition, the disease severity varies in these patients, thus making the population more heterogeneous. Other limitation was the lack of cut-off point for the interleukins that the dosages of the cytokines are made in the blood in a single moment. The ideal marker would be the one that would reflect the inflammation level to which the patient was exposed along the disease [32].

**Conclusion**

This study concluded that the C-reactive protein may be considered a prognostic indicator of malnutrition. Although the fat intake it is important for the nutritional status and these patients are assisted in a reference center, the total lipid intake was still lower than what recommended, this shows the difficulty to follow the prescribed diet.

The total energy intake and the practice of exercises are important factors to preserve the lean body mass. The positive association of interleukine-8 with the body fat percentage of seems to be more associated with obesity, and in most patients the subscapular/triceps skinfolds ratio average suggests a greater distribution of fat in the abdominal region that may be the cause for the increased production of interleukin-8.
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