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Original

Association of nutritional status, plasma, albumin levels and pulmonary function in cystic fibrosis

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Abstract

Background & aims: **Malnutrition is related with pulmonary disease. The aim was to analyze the association of lung function respectively to nutritional status, identified pulmonary pathogens and socioeconomic condition of patients attending a pediatric CF reference center.**

Methods: **Cross-sectional study performed with CF patients aged 6 to 18 years attending a CF-Center in southern Brazil. Nutritional status, plasma albumin level and pulmonary bacterial colonization were assessed. The outcome studied was forced expiratory volume in 1 second (FEV_1).**

Results: Eighty-five patients were included in this study. FEV_1 was significantly associated with body mass index (BMI) percentiles, plasma albumin level and methicillin resistant Staphylococcus aureus (MRSA) pulmonary colonization. Regression analysis showed that BMI below the 10th percentile was associated with a 25.58% drop in FEV_1 and plasma albumin levels equal to or lower than 4.1 mg/dL was associated with 18.6% FEV_1 reduction. FEV_1 was 14.4% lower in the MRSA infected patients. Plasma albumin of 4.25 mg/dL predicted FEV_1 of 60% with 76.9% sensitivity and 72.2% specificity, and 85.7% accuracy. The socioeconomic status was not association with pulmonary function.

Conclusion: **BMI below the 10th percentile and albumin below 4.1 mg/dL were predictors of low FEV_1. Chronic MRSA infection was associated with lower FEV_1. Longitudinal studies may better complement these results.**

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Key words: *Cystic fibrosis. Nutritional status. Pulmonary function.*

ASOCIACIÓN ENTRE EL ESTADO NUTRICIONAL, NIVELES DE ALBÚMINA PLASMÁTICA Y FUNCIÓN PULMONAR EN PACIENTES CON FIBROSIS QUÍSTICA

Resumen

Objetivos: **Analizar la asociación entre la función pulmonar y tres factores: el estado nutricional, el estado de patógenos pulmonares y el estado socio-económico de pacientes en un centro de referencia en atención a pacientes pediátricos con fibrosis quística.**

Métodos: **Se realizó un estudio longitudinal en pacientes con fibrosis quística, de 6 a 18 años atendidos en un centro de fibrosis quística del Sur del Brasil. Fueron evaluados: estado nutricional, niveles de albúmina plasmática y colonización bacteriana pulmonar. El principal resultado estudiado fue el volumen espiratorio forzado en el 1 segundo (FEV_1).**

Resultados: **Fueron incluidos en este estudio 85 pacientes. El FEV_1 se mostró significativamente correlacionado con percentiles del Índice de Masa Corporal (IMC), albúmina plasmática y colonización pulmonar por Staphylococcus aureus resistente a meticilina (SARM). El análisis de regresión mostró que el IMC abajo del percentil 10 estuvo asociado con una disminución del 25,58% en el FEV_1, y que niveles de albúmina plasmática iguales o menores a 4,1 mg/dL se correlacionaron on una reducción de 18,6% del FEV_1. El FEV_1 fue 14,4% menos en los pacientes infectados por SARM. La albúmina plasmática de 4,25 mg/dL predijo un FEV_1 de 60% con una sensibilidad de 76,9% una especificidad de 72,2% y presición de 85,7%. El estado socioeconómico no tuvo asociación con la función pulmonar.**

Conclusiones: **El IMC debajo del percentil 10 y albúmina plasmática menor que 4,1 mg/dL fueron predictivos de un bajo FEV_1. La infección crónica de SARM mostró asociación con un menor FEV_1.**

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Palabras clave: *Fibrosis quística. Estado nutricional. Función pulmonar.*

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Introduction

Nutrition plays an essential role in the survival and quality of life of cystic fibrosis (CF) patients. Several factors, including pancreatic insufficiency, chronic suppurative pulmonary disease and anorexia may affect the energy balance, contributing to malnutrition.[1,2,3,4] Malnutrition may affect lung growth and reduce lean body mass, leading to diminished force in the contraction of the diaphragm and other respiratory muscles[5,6]. It may also be associated with reduced exercise tolerance, impaired immune response and antioxidant deficit, easing the way for the onset of infection and inflammation.[1,5,7]

Pulmonary disease increases energy demands, diminishes appetite and increases respiratory work due to progressive air flow obstruction. Pulmonary inflammation and anorexia triggered by the inflammatory mediators, as well as recurrent infections, create a negative energy balance that leads to malnutrition.[1,6,8] Furthermore low socioeconomic status is associoated with significantly poorer outcomes in children with CF.[9]

Several studies performed in developed countries have shown a relationship between malnutrition and progression of pulmonary disease.[1,3,6,10,11,12] In Brazil, however, there are no published data about this subject. The purpose of the present study was to analyze the association of lung function respectively to nutritional status, identified pulmonary pathogens and socioeconomic condition of patients attending a pediatric CF reference center in southern Brazil**.**

Materials and methods

A cross-sectional study was performed with CF patients, aged 6 to 18 years, recruited at a center of excellence of a tertiary care university hospital, Hospital de Clínicas de Porto Alegre/RS (HCPA), in southern Brazil. All patients were diagnosed by means of clinical history and by at least two sweat tests with chloride values equal to or higher than 60 mEq/l, or by the identification of two mutations in the CF gene who not displaying pulmonary exacerbation (requiring intravenous antibiotics).

The study was performed from July 2004 to December 2005, after approval by the Ethics and Research Committee at HCPA, and after obtaining the Free and Informed Consent of parents or guardians.

Nutritional evaluation

Weight and height were always determined by the same examiner using standardized techniques. Weight was assessed on a Filizola® electronic scale (maximum capacity of 150 kg and 50 g variation), the patients wearing a standard gown. Height was measured on a wall-mounted stadiometer, with the patients barefoot and not wearing any hair ornaments. The patients had their heels joined together, their back to the anthropometer, and their arms relaxed along the body. They held their head in a vertical position and looked straight ahead. The horizontal cursor was lowered to the top of the patient's head during inspiration.

Mid arm circumference (MAC) was determined at the midpoint of the non-dominant arm, with a flexible, non-extensible Barlow® measuring tape. Triceps skin fold (TSF) was measured at the midpoint of the non-dominant arm, with a Harpenden skinfold caliper. Mid arm muscle area (MAMA) was calculated with the equation MAMA (cm) = MAC- (TSF mm x 0.314). All the values were compared to the criteria established by Frisancho (1981).[13]

The body mass index percentiles (BMIp) were calculated in the SAS (SAS Institute Inc., Cary, NC) software, using the reference values of the Center for Disease Control (Internet: http://www/cdc.gov/growthcharts). The nutritional parameters used were BMIp as recommended by the CF Pediatric Nutrition Consensus Report.[14]

Plasma albumin levels was measured same period of the nutritional evaluation and spirometry using the bromocresol green colorimetric method, were obtained from the patient's charts.

Assessment of pulmonary function

A flow-volume curve was performed in the Master Screen Jaeger® spirometer (Wuerzburg, Germany), using the Zapletal table for the expected values.[15] Spirometry was always performed by the same examiner and its quality was checked by the attending physician by analyzing the curves. Spirometry was done according to the guidelines for Pulmonary Function testing 2002.[16] Forced expiratory volume at the first second (FEV_1) was chosen for analysis, since it is the most widely used parameter in the literature to quantify the obstructive ventilatory damage characteristic of CF.[1,10,11]

Other data

Bacterial examination of sputum specimens was done by primary seeding in the selective media chosen: mannitol Agar for *Staphylococcus aureus* detection, chocolate Agar for *Haemophilus sp* detection, McConkey Agar for detecting gram-negative rods, cetrimide Agar for detecting *Pseudomonas aeruginosa*, and the coagulase assay for *Staphylococcus aureus*. In vitro antibiotic sensitivity was tested according to Clinical and Laboratory Standards Institute, 2006.

The protocol used was based on data obtained from the charts, such as date of birth, sex, age, date of diagnosis, bacterial colonization, sweat electrolytes, genetic test and use of pancreatic enzymes. The Shwachmann Score (SS) was obtained by the physician and the nutritionist.[17] The parents/guardians informed the monthly family income and years of schooling of its members.

At each clinic (every two months) visit patients provided a sputum sample for culture. The bacterial colonization was considered when patients were infected in the last year. Co-infection could be present. There was no stratification by infective agent due to the small sample size at this CF center.

Statistical analysis

Sample size was calculated considering r = 0.40[16] in the association between FEV_1 and BMI percentiles. Eighty-six cases were estimated based on a 1% level of significance, 95% confidence interval, and a statistical power of 90%.

The FEV_1 values were compared among the different dichotomic categorical variables using the Student t test and by analysis of variance when there were more than 2 groups. The relationship between FEV_1 and the quantitative variables was assessed by the Pearson correlation coefficient. A bivariate linear regression analysis was performed. The variables that showed P value up to 0.15 with the dependent variable (FEV_1) were included in the subsequent multivariate analysis. Multiple regression analysis was used to verify the independent association of the factors studied.

A Receiver Operating Characteristics (ROC) curve was used to determine the sensitivity and specificity levels to predict a FEV_1 of 60%.

The level of significance adopted was 0.05 and the analyses were performed with the Statistical Package for Social Sciences packet (version 12.0 SPSS Inc., Chicago, IL).

Results

Among eighty-six CF patients selected, one was excluded due to poor cooperation during spirometry performance. In the sample studied, 55.3% were male; the mean age was 11.2 years (± 3.2 years), and the age at diagnosis was 2.5 years (± 3.2 years). The nutritional, demographic, clinical and genetic characteristics, as well as the pulmonary pathogen status of the studied population, are shown in table I.

Regarding nutritional status, 77.7% of the patients were considered normal when the BMI cutoff point was above the 25th percentile, according to the CF Consensus.[13] Mid Arm muscle area, an estimate of lean body mass, was below the 5th percentile in 16.5% of the patients and above the 25th percentile in 47% of them. By measuring the triceps skinfold, fat tissue depletion was found in 10.6%.

Regarding the socioeconomic situation of the families, 38.5% of the fathers and 34% of the mothers had not completed elementary school. The median monthly family income was U$ 454.54, i.e., 3.3 national minimum wages.

The DF508 homozygous and heterozygous patients presented FEV_1 of 79.11% and 78.48%, respectively; these values were significantly lower than those of patients with other mutations (96.15%) (P = 0.002). The mean values of % FEV_1 according to the pulmonary pathogen status of the studied CF population are shown in table II.

FEV_1 was significantly correlated with BMIp (r = 0.312, p = 0.004) (fig. 1), plasma albumin (r = 0.427, p = 0.000) (fig. 2) and mother's years of schooling (r =

Table I
Characteristics of patients with CF

	Mean (±SD)	*n%*
Nutritional characteristics		
Percentile Weight	40.93 ± 28.81	
Percentile Height	42.56 ± 29.83	
Percentile BMI	45.13 ± 26.55	
Albumin (mg/dL)	4.38 ± 0.44	
Demographic characteristics		
Mother's years of schooling	9.06 ± 3.71	
Father's years of schooling	8.31 ± 3.95	
Clinical characteristics		
Lung function (FEV_1)	84.1% ± 24.37	
Shwachmann score	80.4 ± 12.2	
Diabetes mellitus		5 (5.9%)
Exocrine pancreatic insufficiency		74 (87.1%)
Genetic mutations		
DF-508 homozygous		17 (20%)
DF-508 heterozygous		29 (34.1%)
Other mutations		26 (30.6%)
Not identification		13 (15.3%)
Pulmonary pathogen status		
Staphylococcus aureus		63 (74.1%)
Methicilin-resistant *Staphylococcus aureus*		16 (18.8%)
Pseudomonas aeruginosa		45 (52.9%)
Mucoid *Pseudomonas aeruginosa*		21 (24.7%)
Normal flora		3 (3.5%)

BMI: Body mass index.

Table II
Mean values of % FEV_1 according the pulmonary pathogen status of patients with CF

	MRSA		*P value*
	Yes	*No*	
Mean % FEV_1	60.53%	89.57%	< 0.001
	Pseudomona aeruginosa		*P value*
	Yes	*No*	
Mean % FEV_1	77.87%	91.12%	0.011

MRSA: methicilin-resistant *Staphylococcus aureus.*

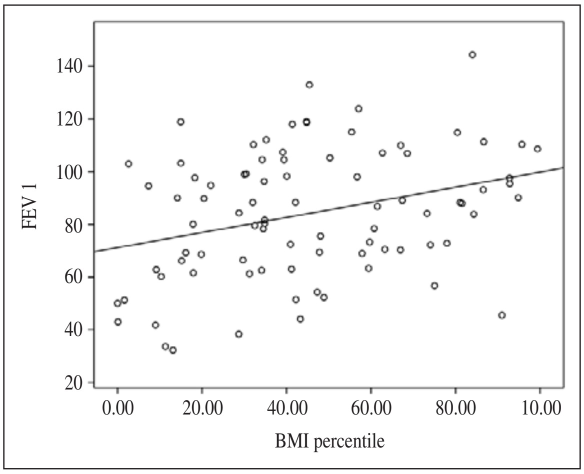

Fig. 1.—Scatterplot of % predicted forced expiratory volume at the first second (FEV_1) versus body mass index (BMI) percentile.

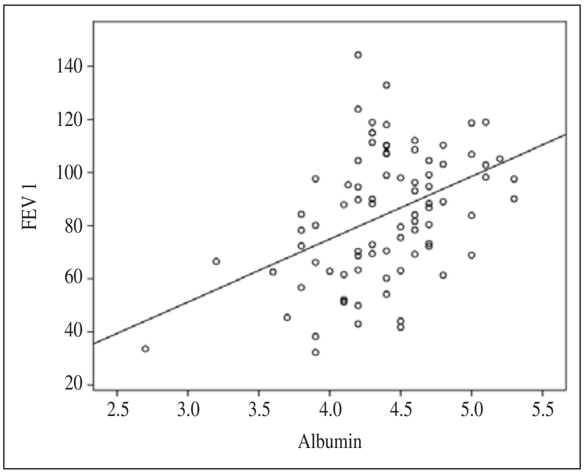

Fig. 2.—Scatterplot of % predicted forced expiratory volume at the first second (FEV_1) versus albumin.

0.229, p = 0.035). There was no correlation with father's years of schooling, age, time since diagnosis and age at diagnosis and body composition.

The variables showing an association with the dependent variable (FEV_1) $P \leq 0.15$ in the bivariate regression analysis and that were thought to be clinically meaningful were included in the subsequent multivariate analysis. Plasma albumin levels were classified in quartiles for easier definition of which albumin levels were associated with FEV_1 reduction. The BMI was also classified in percentile for the same purpose.

The significant predictors for FEV_1 are depicted in table III, and 37.9% (R^2 adjusted) of the variability observed in FEV_1 is statistically explained by this model. Regression analysis showed that BMI lower than the 10th percentile was associated with a 25.58% drop in FEV_1, and plasma albumin lower than or equal to 4.1 mg/dL corresponded to a 18.6% reduction in FEV_1. MRSA chronic pulmonary infection was associated with 14.4% reduction in FEV_1. *Pseudomonas aeruginosa* colonization, gender, pancreatic insufficiency and mother's years of schooling were not statistically significant. Family income was not included in the model analysis, because it was associated with the parent´s years of schooling. The graph of residues and the normality test did not show any trend that would indicate that the analysis was inadequate.

Table III
Multiple linear regression predictive of FEV_1

Variables	β	*Linear Regression Model* 95% CI	*P*
BMI < P10	-25.58	-4.93 - -46.23	0.016
Albumin up to 4.1 mg/dL	-18.60	-4.51 - -32.69	0.010
MRSA	-14.39	-1.02 - -27.76	0.035

F = 4.951 P < 0.001 df1 13 df2 71).
CI: Confidence Interval.
BMI: Body mass index.
MRSA: Methicillin-resistant *Staphylococcus aureus.*
Model adjusted for *Pseudomonas aeruginosa* colonization, gender, pancreatic insufficiency and mother's years of schooling.

The ROC curve for albumin to predict a FEV_1 of 60% showed an area of 0.79, 95% CI: 0.67-0.91, P = 0.001. The sensitivity for a cutoff point of 4.25 mg/dL was 76.9%, the specificity was 72.2% and the accuracy was 85.7%.

Discussion

In CF patients, nutritional status has a significant prognostic influence on the outcome of the disease[1,8]. In the present cross-sectional study we associated nutritional status and pulmonary function of CF children, and studied the relationship with pulmonary pathogen status and socioeconomic conditions.

The association between nutritional status and pulmonary function found in this study has already been demonstrated in the literature. Based on the CF Foundation Patient Registry data set, a better FEV_1 status at about 80% predicted or above was associated with BMI percentiles at 50th percentile and higher[2]. Pedreira et al. (2005) found a significant association between BMI Z score and FEV_1 (r = 0.59, P = 0.0001) and between muscle mass and FEV_1 (r = 0.30, P = 0.03).[11] Hart et al. (2004) demonstrated the correlation between nutritional status and diaphragm strength.[6] It has been reported that malnutrition causes loss of muscle mass, reduction in diaphragm performance, in strength and resistance of respiratory muscles, as well as the impairment of immune function. In addition, increased respiratory work and the interaction of the inflammatory and infectious processes increase energy demands, impairing pulmonary function even further.[1,5,7,8]

The association of BMI in the 10th percentile with FEV_1 enforced the use of this as the cut-off point for malnutrition, as stated by the CFF Pediatric Nutrition Consensus Report,[14] providing a foundation to establish stricter cutoff points for CF. Stricter classification standard requires early detection of nutritional risk, enabling effective nutritional intervention which could diminish the prevalence of malnutrition and nutritional risk, improving survival and the quality of life of these patients.

Since the present study is a cross-sectional analysis, it only indicates associations, not allowing the establishment of cause-effect relationship between nutritional status and pulmonary function.

In the present study, plasma albumin was reasonably correlated to FEV_1. Other studies have shown the relationship between plasma albumin and the severity of pulmonary disease, considering it as a prognostic factor in patients with CF.[19,20] Albumin is a potent antioxidant, present in high concentrations in the extracellular fluid, and can prevent the deactivation of the a1-proteinase inhibitor.[21] Albumin may be essential to maintain pulmonary gluthatione levels.[22] Oxidatively modified albumin has been found in the sputum of patients with CF, and this may cause loss of its antioxidant function.[23]

In a study that evaluated a model to predict CF patients life expectancy, plasma albumin levels were predictive of survival. The authors suggest that albumin is a more sensitive marker of survival than percentage of ideal body weight.[21] Low plasma albumin was associated with higher morbidity and mortality in CF patients.[23]

In this study, ROC curves showed that plasma albumin levels of 4.25 mg/dL were predictive of FEV_1 of 60% with good sensitivity, specificity and accuracy, possibly because it is a sensitive indicator of nutritional status and because of its interaction in the inflammatory reaction. Likewise, regression analysis showed that plasma albumin level lower than or equal to 4.1 mg/dL predicted a 18.6% fall in FEV_1. The albumin value of 4.1 mg/dL is the upper limit of the first quartile associated with a FEV_1 fall. These results show that only higher plasma albumin values are associated with better FEV_1 values.

The relationship between *Pseudomonas aeruginosa* colonization and pulmonary function deterioration is clearly established in the literature. Steinkamp and Wiedemann (2002) demonstrated that pulmonary function diminished in 56% of the adolescents with *Pseudomonas aeruginosa* and that pulmonary function of infected undernourished patients was worse than that of the non-infected ones[3]. In the present study, the presence of *Pseudomonas aeruginosa* was associated with lower FEV_1, however in the regression model this difference was non-significant, in contrast to what was found regarding MRSA colonization. The latter infection was associated with significantly reduced pulmonary function, and is one of the predictors of FEV_1. Co-infection by MRSA may possibly have an important impact in lung function, but studies that evaluate the effect of this bacteria separately are necessary to better understand its action.

A study with ten CF patients with MRSA concluded that MRSA infection did not significantly affect their pulmonary function, yet it affected their growth.[24] In the present study, infection was not correlated with BMIp, but only with FEV_1.

The socioeconomic situation of the families was consistent with the living conditions observed in a developing country, with low family income and low level of schooling. The variable years of maternal schooling was significantly correlated with FEV_1. Shechter et al. found that poorer patients with CF had a 3.65 fold higher risk of dying, and also presented deteriorated pulmonary function and nutritional status values.[9] Another recent study demonstrated that the mortality risk of patients of a better socioeconomic level was 40% lower than that of patients of lower socioeconomic level.[25]

A limitation of this study was that the patients' stages of pubertal development were not assessed. Delayed pubertal development is reported in CF and may affect the nutritional status. The reduced number of patients over 14 years of age (20% of population) also limited the conclusions concerning this age group. In addition, the patient's liver function tests, likely to interact with other variables, were not assessed.

This study contributes to a better understanding of the association of nutritional and lung function status of a CF population in a developing country. Based on these findings, the authors concluded that plasma albumin level lower than 4.1 mg/dl and BMI below the 10th percentile are predictive factors for low FEV_1. Longitudinal studies may better complement these results, seeking to understand the association between plasma albumin, nutritional status and FEV_1 in similar populations.

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