ORIGINAL ARTICLE

http://dx.doi.org/10.1590/1984-0462/;2019;37;4;00016

BODY MASS INDEX AND ALBUMIN LEVELS ARE ASSOCIATED WITH PULMONARY FUNCTION PARAMETERS IN PEDIATRIC SUBJECTS WITH CYSTIC FIBROSIS

Índice de massa corporal e níveis de albumina estão associados a parâmetros de função pulmonar em pacientes pediátricos com fibrose cística

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ABSTRACT

Objective: To evaluate the association of body mass index (BMI) and albumin with pulmonary function in cystic fibrosis (CF) pediatric subjects.

Methods: This is a cross-sectional study with clinically stable CF's subjects. Clinical (pulmonary function) and nutritional evaluation (body mass index and albumin) were performed. Univariate analysis was performed using simple linear correlations. Regression analysis was performed using an exit level of p<0.05.

Results: Seventy-eight CF's subjects (mean age 12.8±3.8 years) with mean albumin 4.2±0.4 mg/dL, predicted forced expiratory volume in 1 second (FEV1%) 80.8±22.6 and BMI median percentile 51.2 (1.3–97.7). In the multiple regression models, albumin, age and BMI percentile were associated with pulmonary function. Subjects with lower than 25 BMI percentile had 12.2% lower FEV_1%. An albumin increase of 0.1 mg was associated with 2.7% increase in predicted FEV1%, and one year increase in age was associated with reduction in 1.2% of predicted FEV1%.

Conclusions: BMI percentile, albumin and age were independently associated with predicted FEV1% in a tertiary referral hospital.

Keywords: Cystic fibrosis; Pediatrics; Nutritional assessment; Albumins; Body mass index.

RESUMO

Objetivo: Avaliar a associação do Índice de Massa Corporal (IMC) e da albumina com a função pulmonar em pacientes pediátricos com fibrose cística (FC).

Métodos: Estudo transversal com pacientes pediátricos com FC clinicamente estáveis. Foram realizadas avaliação clínica (função pulmonar) e nutricional (IMC e albumina). Análise univariada foi realizada usando correlação linear simples. Análise de regressão foi realizada usando o nível de significância de p<0,05.

Resultados: Foram incluídos 78 pacientes com FC (média de idade 12,8±3,8 anos) com média de albumina de 4,2±0,4 mg/dL, volume expiratório forçado em um segundo (VEF_1%) predito de 80,8±22,6 e mediana do percentual de IMC de 51,2 (1,3–97,7). No modelo de regressão múltipla, albumina, idade e percentual de IMC apresentaram associação com a função pulmonar. Indivíduos com IMC abaixo de 25% apresentaram VEF_1% predito 12,2% menor. Um aumento de 0,1 mg de albumina teve associação com aumento de 2,7% no VEF_1% predito, e um ano a mais de idade mostrou relação com a redução de 1,2% de VEF_1% predito.

Conclusão: O percentual de IMC, albumina e idade apresentaram associação independente com o VEF_1% predito em um hospital terciário de referência.

Palavras-chave: Fibrose cística; Pediatria; Avaliação nutricional; Albuminas; Índice de massa corporal.

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Received on April 16, 2018; approved on July 13, 2018; available online on May 07, 2019.

INTRODUCTION

Cystic fibrosis (CF) lung disease is associated with morbidity, and pulmonary function is the most important predictor of survival. Forced expiratory volume in 1 second (FEV_1%) is regarded as the best generally available measure for assessing CF lung disease.[1] Various factors are potentially associated with FEV_1%, such as nutritional status, chronic airway infection and oxidative stress.[2]

Association of lung function with nutritional status has long been recognized. Several studies have shown that weight gain leads to an improved pulmonary function, whereas weight loss can accelerate pulmonary function decline.[2-5] Stallings et al.[6] showed that better FEV_1% status at about 80% predicted or above was associated with body mass index (BMI) percentiles at the 50th percentile and higher. A previous study demonstrated that weigh-for-age ≥10th percentile at age were associated with higher survival at 18 years.[7]

Presence of chronic *Pseudomonas aeruginosa* in respiratory tract has been previously reported to be associated with faster decline in lung function in CF subjects. Studies showed a significantly association of chronic *Pseudomonas aeruginosa* infection with lower FEV_1%.[3,8,9] In addition, such infection is well recognized as a predictor of morbidity and mortality in young children with CF.[10,11]

The pathophysiology of CF is one of increased inflammation-related oxidative stress, particularly during exacerbations.[12] Lungs have multiple layers of defense against persistent oxidant stress, and albumin is an important non-enzymatic antioxidant of interest in this disease. In addition, it is the most abundant multifunctional plasma protein and it has been noted to be a substantial contributor to systemic antioxidant capability, as well as having anti-inflammatory functions.[13]

In a previous study, Khatri et al.[13] observed that albumin was significantly correlated with lung function and asthma quality of life scores. There is only one study that demonstrated albumin as a predictor of lung function in CF subjects.[14]

The objective of this study was to evaluate the association of BMI and albumin with pulmonary function in CF pediatric subjects.

METHOD

This was a cross-sectional study. Subjects were consecutively recruited from the pediatric CF outpatient clinic at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil. Subjects were eligible if they had a confirmed CF diagnosis by at least two abnormal sweat chloride test results. Subjects experiencing a pulmonary exacerbation in the last two weeks were excluded. The study was approved by the Human Research Ethics Committee (Protocol no. 09-429). Demographic, clinical, nutritional and biochemical data were obtained from patient medical records.

All participants underwent a clinical and nutritional evaluation. Clinical and demographic data such as age, age at diagnosis, pancreatic insufficiency (denoted by use of enzyme replacement therapy), genetic mutation analysis, presence or absence of bacterial colonization (*Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* — MRSA, *Pseudomonas aeruginosa*, mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia complex*), plasma albumin levels, and FEV_1% predicted were obtained from subject charts, and all the variables were acquired at the moment of the patient check-ups.

A flow-volume curve was performed in the Master Screen Jaeger® spirometer (Würzburg, Germany), using the Zapletal table for the expected values. 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.[15] 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.

Nutrition data (weight and height measurement) were analyzed as percentiles according to the World Health Organization (WHO) equations (weight/age; height/age; BMI/age). The cut-off point established to assess the relationship between nutritional status and lung function was the 25th percentile, according to the study of Konstan et al.[16]

Sample size was calculated considering r=0.42 in the association between FEV_1% and albumin, according to previous data from Simon et al.[14] Seventy-five cases were estimated based on the 5% level of significance, 95% confidence interval, and statistical power of 95%.

Descriptive statistics were used to describe subject characteristics. We first constructed regression models for FEV_1% as the main outcome, using anthropometric, biochemical and clinical data as independent variables. Univariate analysis was performed using simple linear correlations. Where a significant relationship was identified ($p<0.10$), a stepwise multiple linear regression was done using FEV_1% as the dependent variable and significantly associated anthropometric and biochemical data as the independent variables, controlling for age and sex. Regression analysis was performed using the exit level of $p<0.05$. All analyses were done using Statistical Package for the Social Sciences (SPSS) for Windows version 18.0 (IBM, Armonk, NY, United States).

RESULTS

Seventy-eight CF pediatric subjects participated in the study; 50% were female. The mean age of participants was 12.8±3.8 years old, the median of age at diagnosis was 2.1 years old. Mean albumin was 4.2±0.4 mg/dL, and FEV_1% predicted was 80.8±22.6, the BMI median percentile was 51.2 (1.3–97.7). Additional clinical data and other characteristics are provided in Table 1. The results of the multiple linear regression analyses for FEV_1% as the main outcome are shown in Table 2.

In the multiple regression models, albumin, age and BMI percentile were associated with pulmonary function. Subjects with lower than 25 BMI percentile had 12.2% lower FEV_1%. An albumin increase of 0.1 mg was associated with 2.7% increase in FEV_1% predicted, and one year increase in age was associated with reduction in 1.2% of FEV_1% predicted.

Table 1 Demographic and clinical characteristics of the children and adolescents patients with cystic fibrosis.

	n=78
Gender, n (%)	
Females	39 (50)
Age (years), mean±SD	12.8±3.8
Age at diagnosis (years), median (IR)	1.3 (0.4–6.0)
Mutation, n (%)	
Δ508 Homozygosis	29 (37.2)
Δ508 Heterozygosis	19 (24.4)
Others	8 (10.3)
Pancreatic insufficiency, n (%)	69 (88.5)
Albumin, mean±SD	4.2±0.4
Bacterial colonization, n (%)	
Staphylococcus aureus	60 (76.9)
Methicillin resistant *Staphylococcus aureus*	9 (11.5)
Pseudomonas aeruginosa	42 (53.8)
Pseudomonas aeruginosa mucoid	15 (19.2)
Burkholderia cepacia	19 (24.4)
Pulmonary function, mean±SD	
FEV_1% predicted	81.9±22.6
Nutritional markers, mean±SD	
Weight, percentile	52.6±.26.3
Height, percentile	43.3±26.9
BMI, percentile	49.9±27

n: number of cases; SD: standard deviation; IR: interquartile range; FEV_1%: forced expiratory volume in one second; BMI: body mass index.

DISCUSSION

This study demonstrates that FEV_1% has a direct association with BMI lower than 25th percentile, with age, and with albumin levels, underscoring the hypothesis that good nutritional status and albumin levels are important in CF. The regression model was able to explain approximately 40% of FEV1% variability.

Association of FEV_1% with BMI percentile is well recognized.[4,6,17,18] Our data demonstrated that being below the BMI 25th percentile was associated with 12% lower FEV_1%. Stallings et al.[6] showed that BMI percentiles at 25th was associated with FEV_1% status below 90% predicted in subjects aged 6 to 12 years old, and below 80% in subjects aged 13 to 20. In our previous study, we observed that subjects with a BMI below the 10th percentile had 25.58% lower FEV_1%.[14] Our data show that, even in subjects who were not malnourished, reduction in pulmonary function parameters was found.

In CF, lung function decreases with time, and it is thought that even a small decline of 1–2% per year is deleterious in the life expectancy of the subjects.[19] We observed similar results in this sample, in which one year increase in age was associated with reduction of approximately 1% of FEV_1% predicted.

The present study data demonstrate that an albumin increase of 0.1 mg was associated with 2.72% increase in FEV_1% predicted, even having most of the subjects a normal albumin level. In our previous study, we found that plasma albumin levels lower than or equal to 4.1 mg/dL predicted 18.6% fall in FEV_1%.[14] Besides that, we observed that plasma albumin levels of 4.2 mg/dL were predictive of FEV_1% of 60%

Table 2 Multiple linear regression analysis for pulmonary function in cystic fibrosis patients.

Pulmonary function	Multiple regression	β (95%CI)	Adjusted R^2
FEV_1% predicted	BMI<25 percentile	-12.2 (-21.9 to -2.6)*	0.368
	Age (years)	-1.2 (-2.3 to -0,1)*	
	Albumin	2.7 (1.6 to 3.8)**	

*p-value<0.01; **p-value<0.001; 95%CI: 95% confidence interval; FEV_1%: forced expiratory volume in one second; BMI: body mass index.

with good sensitivity, specificity and accuracy. Therefore, we hypothesized that albumin is an indicator of inflammatory process, and for this reason it is related with poor pulmonary function.[20] Khatri et al.[13] showed that plasma albumin levels directly correlated with FEV_1% predicted among asthmatic subjects (R=0.378; p=0.010).

In the current study, chronic *Pseudomonas aeruginosa* infection was not significantly associated with decreased lung function. These results could be explained by chronic *Pseudomonas aeruginosa* infection and age being covariates and, for this reason, loosing statistical power. However, other studies[3,21] showed significant association of *Pseudomonas aeruginosa* and lower lung function.

One of the limitations of our study was the cross-sectional design, so findings do not necessary reflect causality.

In conclusion, in pediatric CF's subjects BMI percentile, albumin and age were independently associated with FEV_1% predicted in a tertiary referral hospital. The results emphasize the relevance of evaluate the association between albumin levels and lung function in CF.

Funding

This study did not receive funding.

Conflict of interests

The authors declare no conflict of interests.

REFERENCES

1. Van Devanter DR, O'Riordan MA, Blumer JL, Konstan MW. Assessing time to pulmonary function benefit following antibiotic treatment of acute cystic fibrosis exacerbations. Respir Res. 2010;11:137.
2. Stephenson AL, Mannik LA, Walsh S, Brotherwood M, Robert R, Darling PB, et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. Am J Clin Nutr. 2013;97:872-7.
3. Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J. 2014;43:125-33.
4. Woestenenk JW, Stellato RK, Terheggen-Lagro SW, van der Ent CK, Houwen RH. The relationship between body growth and pulmonary function in children with cystic fibrosis. Acta Paediatr. 2014;103:162-7.
5. Lai HJ, Shoff SM, Farrell PM, Wisconsin Cystic Fibrosis Neonatal Screening Group. Recovery of birth weight z score within 2 years of diagnosis is positively associated with pulmonary status at 6 years of age in children with cystic fibrosis. Pediatrics. 2009;123:714-22.
6. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, Clinical Practice Guidelines on Growth and Nutrition Subcommittee, Ad Hoc Working Group. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008;108:832-9.
7. Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr. 2013;162:530-35.
8. Vandenbranden SL, McMullen A, Schechter MS, Pasta DJ, Michaelis RL, Konstan MW, et al. Lung function decline from adolescence to young adulthood in cystic fibrosis. Pediatr Pulmonol. 2012;47:135-43.
9. Que C, Cullinan P, Geddes D. Improving rate of decline of FEV1 in young adults with cystic fibrosis. Thorax. 2006;61:155-7.
10. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol. 2002;34:91-100.
11. Stern M, Wiedemann B, Wenzlaff P, German Cystic Fibrosis Quality Assessment Group. From registry to quality management: the German Cystic Fibrosis Quality Assessment project 1995 2006. Eur Respir J. 2008;31:29-35.
12. Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. Pediatr Pulmonol. 2015;50:S39-56.
13. Khatri SB, Peabody J, Burwell L, Harris F, Brown LS. Systemic antioxidants and lung function in asthmatics during high ozone season: a closer look at albumin, glutathione, and associations with lung function. Clin Transl Sci. 2014;7:314-8.
14. Simon MI, Drehmer M, Silva FA, Hoffmann A, Ricachinewsky C, Procianoy E, et al. Association of nutritional status, plasma, albumin levels and pulmonary function in cystic fibrosis. Nutr Hosp. 2011;26:1322-7.
15. Pereira CA, Neder JÁ, editors. Diretrizes para testes de função pulmonar. J Bras Pneumol. 2002;28:S1-82.
16. Konstan MW, Pasta DJ, Wagener JS, Van Devanter DR, Morgan WJ. BMI fails to identify poor nutritional status in stunted children with CF. J Cyst Fibros. 2017;16:158-60.
17. Kerem E, Webb AK. European Cystic Fibrosis Society Standards of Care: a road map to improve CF outcome. J Cyst Fibros. 2014;13:357-8.
18. Barni GC, Forte GC, Forgiarini LF, Abrahão CL, Dalcin PT. Factors associated with malnutrition in adolescent and adult patients with cystic fibrosis. J Bras Pneumol. 2017:43:337-43.

19. Döring G, Hoiby N, Consensus Study Group. Early intervention and prevention of lung disease in cystic fibrosis: a European consensus. J Cyst Fibros. 2004;3:67-91.

20. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, et al. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (Oxf). 2016;4:272-80.

21. Van Devanter DR. Antibiotic-resistant Pseudomonas aeruginosa in cystic fibrosis. Respiration. 2007;74:356.

ERRATUM

http://dx.doi.org/10.1590/1984-0462/;2019;37;4;00016erratum

In the manuscript "Body mass index and albumin levels are associated with pulmonary function parameters in pediatric subjects with cystic fibrosis", DOI: 10.1590/1984-0462/;2019;37;4;00016, published in the Rev. Paul. pediatr. 2019;37(4):414-418. Epub May 09, 2019, on page 414.

Where it reads:

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It should read:

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