Clinical, nutritional and spirometric evaluation of patients with cystic fibrosis after the implementation of multidisciplinary treatment*

Avaliação clínica, nutricional e espirométrica de pacientes com fibrose cística após implantação de atendimento multidisciplinar

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Abstract

Objective: Cystic fibrosis (CF) is a chronic multisystemic hereditary disease for which a multidisciplinary approach must be taken. The objective of this study was to show the evolution of a group of patients with CF after the implementation of multidisciplinary treatment. **Methods:** A retrospective study involving 19 patients (6-29 years of age) under clinical follow-up treatment at the University of São Paulo at Ribeirão Preto School of Medicine *Hospital das Clínicas*, located in the city of Ribeirão Preto, Brazil. The patients were divided into two groups: 6-12 (6-12 years of age) and 13+ (> 12 years of age). We collected data regarding body mass index (BMI), Z score, Shwachman score (SS), number of exacerbations/year, chronic colonization by *Pseudomonas aeruginosa*, and spirometric measurements (FVC, FEV_1, FEV_1%, and $FEF_{25-75\%}$). Data were collected at two different time points (before and after the implementation of the multidisciplinary treatment) and were analyzed with the Wilcoxon signed rank test. **Results:** The median age at the onset of symptoms was 10 months. In the 6-12 group, only BMI and FVC increased significantly. Although the other spirometric values increased, the differences were not significant. In the 13+ group, there were no significant differences between the two time points. There was a borderline significant decrease in SS and less than significant decreases in the spirometric measurements. However, the number of patients with alterations in volumes and flows decreased in both groups. **Conclusions:** Although our patient sample was small, the lack of changes in the spirometric parameters might reflect clinical and functional stability. In all of the patients evaluated, clinical, functional, and nutritional parameters remained stable throughout the study period. The implementation of a multidisciplinary approach might have contributed to this result.

Keywords: Cystic fibrosis; Spirometry; Body mass index; Physical therapy modalities.

Resumo

Objetivo: A fibrose cística (FC) é uma doença hereditária, multissistêmica e crônica, para a qual é importante uma abordagem multidisciplinar. O objetivo deste estudo foi mostrar a evolução de um grupo de pacientes com FC após a implantação desse tipo de atendimento. **Métodos:** Foram analisados retrospectivamente 19 pacientes (idades entre 6 e 29 anos) em acompanhamento clínico no Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, na cidade de Ribeirão Preto (SP). Os pacientes foram divididos em dois grupos: grupo 6-12 (6-12 anos) e grupo 13+ (> 12 anos). Dados referentes a índice de massa corporal (IMC), escore Z, escore de Shwachman (ES), número de exacerbações/ano, colonização crônica por *Pseudomonas aeruginosa* e medidas espirométricas (CVF, VEF_1, VEF_1% e $FEF_{25-75\%}$) foram obtidos. Os dados foram coletados em dois momentos (antes e após a implantação de atendimento multidisciplinar) e foram analisados com o teste dos postos sinalizados de Wilcoxon. **Resultados:** A mediana de idade de início de sintomas foi de 10 meses. No grupo 6-12, houve somente um aumento significativo do IMC e da CVF. As outras medidas espirométricas aumentaram, mas não significativamente. No grupo 13+, não houve diferenças significativas entre os dois momentos, sendo que o ES apresentou uma diminuição com significância limítrofe. Houve diminuição não significativa das medidas espirométricas. Entretanto, o número de pacientes com volumes e fluxos alterados diminuiu nos dois grupos. **Conclusões:** Apesar do grupo pequeno, a manutenção dos parâmetros espirométricos pode significar estabilidade clínica e funcional. Os pacientes estudados mantiveram estabilidade clínica, funcional e nutricional durante o período, e a implantação de abordagem multidisciplinar pode ter contribuído nesse sentido.

Descritores: Fibrose cística; Espirometria; Índice de massa corporal; Modalidades de fisioterapia.

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Introduction

Cystic fibrosis (CF) is a fatal disease and is the most common autosomal recessive hereditary disease in White individuals. Over 1,500 CF-related mutations have been identified.[1,2] The first such mutation was identified on the long arm of chromosome 7 and encodes cystic fibrosis transmembrane conductance regulator, a 1,480-amino acid protein that functions as a chloride channel in the apical membrane of epithelial cells. When there is a defect in this protein, the viscosity of secretions changes, which leads principally to malabsorption, sweat electrolyte loss, and changes in pulmonary secretions, leading to decreased mucociliary clearance.[3]

The phenotypic presentations (respiratory and gastrointestinal) differ from patient to patient. However, progressive pulmonary impairment is the most common cause of death. Increased secretion viscosity and the consequent difficulty in drainage lead to inflammation and infection that become chronic, with gradual loss of pulmonary function and progression to respiratory failure.[4-6] Therefore, control of pulmonary infections, improvement in the clearance of bronchial secretions, enzyme replacement therapy, and nutrition therapy contribute to reducing CF-related morbidity and mortality.[7-9]

Specialized, multidisciplinary treatment of patients with CF has been shown to have a strong relationship with decreased severity of profiles and increased survival. The World Health Organization (WHO) and the International Cystic Fibrosis (Mucoviscidosis) Association recommend the implementation of specialized centers, even in developing countries, since the treatment given at such centers can improve clinical outcomes and survival, principally when the treatment targets nutrition and lung disease control.[8-10]

The objective of the present study was to describe the clinical and pulmonary functional evolution of a group of patients with CF after the implementation of a multidisciplinary outpatient clinic.

Methods

We conducted a descriptive study—with retrospective data collection and cross-sectional analysis—in which we included patients who had been diagnosed with CF based on two positive pilocarpine iontophoresis sweat test results and whose clinical profiles were consistent with the diagnosis.[11] We included only patients who were under regular clinical follow-up treatment at the University of São Paulo at Ribeirão Preto School of Medicine *Hospital das Clínicas*, located in the city of Ribeirão Preto, Brazil, and were able to perform the spirometry maneuvers. The variables were analyzed at two different time points: before and four years after the opening of the Multidisciplinary Cystic Fibrosis Outpatient Clinic at the institution (in 2003 and 2007, respectively). At this outpatient clinic, patients were simultaneously evaluated by pulmonologists, gastroenterologists, nurses, physical therapists, nutritionists, psychologists, and social workers. All of the patients included in the present study were submitted to systematic collection of respiratory secretion for microbiological study, every one or two months. The collection was performed by a nurse or a physical therapist on the multidisciplinary team. Samples were collected by oropharynx swab, spontaneous expectoration, sputum induction, or oropharyngeal aspiration.

All patients were instructed to perform the same respiratory therapy techniques for airway clearance, including postural drainage, percussion, flow maneuvers, mechanical vibration, and manual vibration with compression for young children. Older children and adults were taught respiratory exercises (with the use of the shaker or flutter technique), assisted cough or cough stimulation techniques (such as huffing), diaphragmatic and pursed-lip breathing (in order to facilitate the deflation of the peripheral airways), and analysis of posture (with an emphasis on stretching). The importance of adhering to physical therapy and of the correct performance of the exercises (performed by the patients themselves or their mothers) were emphasized at every evaluation.

Patient nutritional status was evaluated once every one or two months and consisted of measuring weight and height, in order to calculate the body mass index (BMI), as well as analyzing the dietary report. The importance of adhering to the diet prescribed was emphasized.

For the analysis of most of the data collected, the 19 patients included in the present study

were divided into two groups, according to the initial age bracket: the 6-12 group (n = 8), which included children aged 6-12 years; and the 13+ group (n = 11), which included patients aged > 12 years. The results obtained for the two groups were analyzed at two different time points: in 2003 (before the implementation of the outpatient clinic) and in 2007 (four years after the implementation of the outpatient clinic).

All of the patients were wearing light clothes and no shoes when they were weighed. Patient height (in cm) was measured with a stadiometer (Harpenden; British Indicators, Burgess Hill, United Kingdom), with the patients standing straight and looking ahead, heels pressed against the wall. The data obtained were used to calculate the BMI. For the two groups, the analysis of the BMI was based on the median, as well as on the calculation of the Z score. The evaluation of the BMI was used for the clinical definition of the nutritional status and followed the recommendations put forward in international consensuses. The data obtained were compared with those of the specific BMI distribution curve proposed by the WHO for patients aged 2-19 years. Patients who were below the 10th percentile were considered to be undernourished, and those who were between the 10th and 25th percentiles were considered to be at nutritional risk. For patients over 19 years of age, we also used the specific WHO classification: BMI < 20 kg/cm^2 = underweight; BMI 20-25 kg/cm^2 = normal weight; and BMI > 25 kg/cm^2 = overweight.[12-14]

The Shwachman score (SS), the number of exacerbations per year, and the presence of chronic colonization by *Pseudomonas aeruginosa* were also analyzed.

Pulmonary function measurements, all of which were expressed as the percentage of predicted, were as follows: FVC; FEV_1; FEV_1/FVC ratio; and $FEF_{25-75\%}$. Spirometry was performed with a Vitatrace VT 130 spirometer (Pró Médico Ltda., Rio de Janeiro, Brazil), and the curves were registered on paper. We traced a volume-time curve, on which the measurements of FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$, corrected for body temperature and blood pressure standards, were based. The values of the best of five forced exhalations were registered as percentages of predicted, in accordance with the reference values proposed by Knudson et al., and compared with data from other studies conducted in Brazil.[15,16] The spirometric tests performed and the characteristics of the spirometer used were in accordance with the standards established by the American Thoracic Society.[17]

Chronic pulmonary colonization by *P. aeruginosa* was defined as the presenting with evidence of the bacterium in the bronchial tree for at least six months (three successive positive cultures for *P. aeruginosa*, with an interval of at least one month between each) and having no detectable, direct signs of infection or tissue damage, such as inflammation and fever.[18]

Acute pulmonary exacerbation was defined as the occurrence of one or more of the following signs and symptoms: increased cough; increased expectoration; fever; anorexia; weight loss; school absenteeism; work absenteeism; decreased exercise tolerance; decreased oxygen saturation; new pulmonary auscultation findings; new radiological findings; or an abrupt reduction (> 10%) in FEV_1.[19]

The statistical analysis of the data collected at the two time points was performed with the statistical program GraphPad Prism (GraphPad Software, San Diego, CA, USA), and the Wilcoxon signed rank test for paired samples was used, with an alpha error of 5%, since most of the data presented non-normal distribution and the number of individuals in each group was quite small. For all of the other data described, statistical analysis of the medians was performed.

The present study was approved by the Research Ethics Committee of the University of São Paulo at Ribeirão Preto School of Medicine (protocol no. 2094/2009).

Results

We studied the data of 19 patients who were able to perform spirometry, with the exception of the final data of 2 male patients who died during the follow-up period: 1 due to respiratory failure and 1 due to dilated cardiomyopathy. Of the 19 patients, 7 were female (5 in the 6-12 group and 2 in the 13+ group), and 12 were male. The 19 patients accounted for 30% of all patients who were under follow-up treatment at our facility in 2003. In addition, 1 patient moved to a different address. Of the 19 CF patients, 12 (63%) had been diagnosed before the age of 2 years, 6 (31%) had been diagnosed with CF by

Table 1 - Body mass index, Shwachman score, and number of exacerbations per year in the two groups under study at the two evaluation time points.[a]

Variable	6-12 group, 2003	6-12 group, 2007	p*	13+ group, 2003	13+ group, 2007	p*
BMI, kg/m^2	15.3 (13.6-18.5)	17.2 (14.8-20.5)	0.04	20.0 (13.5-21.5)	18.8 (16.9-28.8)	0.84
Exacerbations/year, n	3.12 (2.00-5.00)	2.12 (0.00-4.00)	0.48	2.5 (0.0-5.0)	2.5 (0.0-4.0)	0.62
Shwachman score	77.5 (55.0-90.0)	75.0 (65.0-85.0)	0.46	90.0 (55.0-90.0)	70 (50.0-85.0)	0.09

BMI: body mass index. [a]Values expressed as median (range). *Wilcoxon signed rank test for paired samples.

the age of 6 years, and 1 had been diagnosed with CF at the age of 12 years. The median age at diagnosis was 10.5 months.

We observed a significant increase in the BMI in the 6-12 group during the study period. However, all of the patients presented with a similar nutritional risk at the two evaluation time points, as did all of the patients aged 13-19 years in 2003. In 2007, 3 of the 4 patients over 19 years of age presented with normal BMI, and 1 migrated to the overweight group. However, this patient was a weightlifter, and the weight gain observed was due to an increase in muscle mass. The BMI Z score for the group formed by patients younger than 19 years of age was analyzed, and there was no significant difference between the medians (–0.4 in 2003 vs. –0.39 in 2007; p = 0.51). Although the SS was lower at the second evaluation time point than it was at the first evaluation time point, in both groups, the difference was not statistically significant. In the 13+ group, however, there was a borderline significant decrease in the SS. There were no significant differences between the two time points in terms of the number of exacerbations, and the patients who presented with colonization by *P. aeruginosa* in 2003 also did so in 2007: 1 patient in the 6-12 group and 6 in the 13+ group. These data are summarized in Table 1.

The median FVC, FEV_1, and $FEF_{25-75\%}$ (in percentage of predicted) increased in the 6-12 group during the study period. However, this increase was statistically significant for FVC only, being borderline significant for FEV_1. In the 6-12 group, the number of patients with changes in volumes and flows decreased. However, the number of patients with changes in the FEV_1/FVC ratio remained the same. In the 13+ group, all medians decreased. However, the difference was not statistically significant. The number of patients with changes in FVC and FEV_1 remained the same. However, the number of patients with changes in $FEF_{25-75\%}$ and in the FEV_1/FVC ratio decreased when the following cut-off points were considered: 80% of the predicted values for FVC and FEV_1; 70% of the predicted value for $FEF_{25-75\%}$; and 75% of the predicted value for the FEV_1/FVC ratio. These data can be seen in Tables 2 and 3.

Discussion

There are various norms stating that specialized CF treatment centers should have multidisciplinary teams in order to facilitate the overall evaluation of patients. However, this results in an increase in the complexity and costs of such centers, principally in developing countries. Nevertheless, in recent years, the implementation of a multidisciplinary approach at such centers has effectively slowed the decline in pulmonary function and the worsening of CT findings.[8-10,20]

Although all of the patients under study presented with early symptom onset and were diagnosed in a timely manner, they were divided into two groups by current age bracket and

Table 2 - Pulmonary function values for FVC, FEV_1, FEV_1/FVC ratio, and $FEF_{25-75\%}$ in the two groups under study at the two evaluation time points.[a]

Variable	6-12 group, 2003	6-12 group, 2007	p*	13+ group, 2003	13+ group, 2007	p*
FVC, % of predicted	78.0 (45.0-101.0)	86.0 (70-91)	0.01	82.5 (29.0-104.0)	63.0 (42.0-104.0)	0.54
FEV_1, % of predicted	70.0 (61.0-104.0)	80.0 (66.0-81.0)	0.07	70.5 (30.0-96.0)	45.0 (20.0-104.0)	0.46
FEV_1/FVC, % of predicted	82.5 (73.0-91.0)	83.0 (68.0-88.0)	0.62	72.0 (41.0-84.0)	64.0 (38.0-84.0)	0.46
$FEF_{25-75\%}$, % of predicted	55.0 (38.0-115.0)	64.0 (29.0-96.0)	0.68	38.5 (5.0-100.0)	19.5 (6.0-80.0)	0.54

[a]Values expressed as median (range). *Wilcoxon signed rank test for paired samples.

Table 3 - Distribution of the patients with altered pulmonary function in the two groups under study at the two evaluation time points.[a]

Variable	6-12 group, 2003	6-12 group, 2007	13+ group, 2003	13+ group, 2007
	(n = 8/19)	(n = 8/17)	(n = 11/19)	(n = 9/17)
FVC < 80% of predicted	4 (50.0)	1 (12.5)	4 (36.4)	4 (44.4)
FEV_1 < 80% of predicted	5 (62.5)	3 (37.5)	6 (54.5)	6 (66.6)
FEV_1/FVC < 75% of predicted	1 (12.5)	1 (12.5)	7 (87.5)	6 (66.6)
$FEF_{25-75\%}$ < 70% of predicted	6 (75.0)	5 (62.5)	10 (90.9)	8 (88.8)

[a]Values expressed as n (%).

were analyzed at two different time points. Despite the small sample size, we chose to divide the patients as described above because the evolution of CF varies by age bracket. In addition, it is known that the health status of patients is less affected early in life, when lung damage is not extensive. However, for the analysis of the BMI Z score in relation to the standard, we chose to analyze the sample as a whole, since the reference curve for BMI does not vary between birth and 19 years of age. The data for the comparison between the two time points, as well as those for patients over 18 years of age, were analyzed on the basis of the median. Although there was a significant increase in the BMI in the 6-12 group, the patients remained in the same percentile during the follow-up period. In the 13+ group, the BMI decreased, although not significantly. In the two groups, Z scores also decreased, although not significantly. Although skinfold measurements are highly recommended by international consensuses, they were not used in the present study, because these data were not available for all patients in 2003. The nutritional status of the patients in our study sample remained stable throughout the follow-up period. Preservation of nutritional status is one of the principal objectives of CF treatment, since malnutrition has a negative effect on ventilatory capacity, exercise tolerance, lung size, and pulmonary function, as well as predisposing to infection.[21-23]

In the 6-12 group, the number of patients with changes in lung volumes decreased. In addition, there was a significant increase in FVC and a borderline significant increase in FEV_1. The medians of other flows also increased, although not significantly. This suggests that the pulmonary function of younger patients was preserved throughout the four-year study period. The maintenance of pulmonary function values coincided with an improvement in BMI, as would be expected, because there is a strong correlation between BMI and FVC, which reflects lung size and appropriate developmental conditions. These incidental findings of improved pulmonary function in children are similar to those of other studies involving similarly aged patients and are due to the fact that pulmonary function and lung growth can improve by the age of 12 years.[24] In the 13+ group, the medians decreased, although not significantly. This was also observed in similarly aged CF patients in a study conducted in southern Brazil,[25] as well as in international studies.[26] In the present study, the median volumes and flows were similar to the median FVC and FEV_1 reported in the aforementioned study conducted in southern Brazil.[25] However, the $FEF_{25-75\%}$ values observed in the present study were slightly higher than were those reported in the aforementioned study (median of 46.0% vs. 35.0% at the age of 10 years and of 12.5% at the age of 18 years). The values found in the present study were also higher than were those found in another study conducted in Brazil,[27] which investigated adult patients with later-onset CF and, therefore, milder disease (FVC = 77% vs. 59%; and FEV_1 = 63% vs. 44%).

In the present study, FEV_1 values were below the mean for height, even in the younger patients, and we underscore the importance of FEV_1 as an analytical factor for prognosis and follow-up, as described by other authors.[8,9,26] In the present study, airway obstruction was more severe in the small airways, as evidenced by the $FEF_{25-75\%}$ values obtained. Although this measurement is not routinely used, $FEF_{25-75\%}$ has been shown to be important for the analysis of pulmonary function in patients with CF, since early and intense small airway impairment can occur in young children, as a result of early-

onset inflammation.[28] In the present study, $FEF_{25-75\%}$ was found to be the measurement that was most commonly altered in all of the patients, including those who were older. The older patients presented with decreased small airway function as early as in the first year of follow-up. As lung disease progressed, small airway function impairment peaked. In contrast, the FVC was affected later, reflecting the progression of the disease.

The number of exacerbations did not change in either group but was lower in the 13+ group, which might be due to the characteristics of the group, since some patients presented with milder manifestations, as previously described in another study conducted in Brazil.[27]

The SS is used in order to evaluate well-being and disease severity in CF patients, and, although there is no consensus regarding the best evaluation score, the SS has been reported to be an accessible instrument that is commonly used in the clinical follow-up of patients with CF.[29,30] The SS values decreased, and the decrease was borderline significant in the 13+ group. This was expected, since, in those patients, CF had been present for longer and tended to progress more rapidly. However, the SS remained in the same classification, which again indicates that the patients remained clinically stable during the follow-up period.

The present study has three major limitations. First, there was no control group, since none of the patients under follow-up treatment were excluded from the new outpatient clinic. Second, the data were collected retrospectively. However, these limitations could motivate other researchers to evaluate the data from their own facilities, thereby contributing to a more comprehensive evaluation. Third, the sample size was small. Despite these limitations, we believe that it was important to present the data regarding the functional stability of patients during the follow-up period, demonstrating the maintenance of pulmonary function and the decrease in the number of individuals with changes in lung volumes, findings that underscore the importance of the functional and multidisciplinary follow-up of CF patients for periodic control and for the evaluation of the therapeutic response. The changes brought about by the implementation of the multidisciplinary treatment did not show significant beneficial effects in the study sample. However, the multidisciplinary treatment might have contributed to a slight functional improvement in the younger patients. In the older patients, the multidisciplinary treatment might have contributed to the maintenance of clinical stability, nutritional status, and number of patients colonized by *P. aeruginosa*, as well as to the stability of the SS. In addition, the decrease in the number of individuals with changes in lung volumes and flows, as well as the improvement in FVC, observed in the children aged 6-12 years suggests that not every change detected was definitive, which is an additional stimulus for taking a multidisciplinary approach to such patients.

In order to determine which measures can effectively improve the quality of life of such patients, as well as the long-term effects of such measures, multicenter studies involving larger patient samples are needed, since therapeutic objectives that are more effective can only be established after an understanding of the evolution of CF has been gained.

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