

# Original Article

## Adherence to treatment in patients with cystic fibrosis\*

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### Abstract

**Objectives:** To evaluate the self-reported degree of adherence to treatment in patients with cystic fibrosis (CF), investigating associations with characteristics of the disease and with the degree of adherence perceived by health professionals. **Methods:** This was a prospective, cross-sectional study involving patients with CF monitored at a Program for Adults with CF. The degree of adherence was evaluated using a questionnaire. Patients were divided into two groups: greater degree of adherence and moderate/poor degree of adherence. Clinical data, Shwachman-Kulczycki clinical score, Brasfield radiographic score and spirometry data were obtained for all patients. **Results:** Out of 38 patients studied, 31 (81.6%) were classified as presenting a greater degree of adherence and 7 (18.4%) as presenting a moderate/poor degree of adherence. The self-reported patient adherence score correlated with the clinical score ( $r = -0.36$ ,  $p = 0.028$ ). The self-reported patient adherence score (median = 0.79) was higher than that perceived by health professionals (median = 0.71,  $p = 0.003$ ). A greater degree of adherence was self-reported for respiratory therapy (by 84.2%), exercise (by 21.1%), prescribed diet (by 65.8%), pancreatic enzymes (by 96.3%), vitamins (by 79.4%), inhaled antibiotic therapy (by 76.7%) and inhaled DNase (by 79.4%). **Conclusions:** Self-reported adherence of patients attending a Program for Adults with CF was good. The self-reported patient adherence score correlated inversely with the clinical score. Self-reported patient adherence was greater than the adherence perceived by health professionals.

**Keywords:** Cystic fibrosis; Patient compliance; Therapeutics.

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## Introduction

Cystic fibrosis (CF) is a genetic disease with an autosomal recessive inheritance pattern.<sup>(1)</sup> Its incidence ranges from 1/2500 to 1/3200 live births.<sup>(2)</sup> It is an irreversible disease, and, until recently, its evolution did not allow patients to survive until adolescence.<sup>(1)</sup>

In the past two decades, studies on CF have made significant headway, resulting in the institution of better treatment regimens and increasing mean survival of these patients to up to 35 years.<sup>(3,4)</sup> However, the treatment requires patient adherence to a complex self-care program that takes up a considerable portion of their time.<sup>(5,6)</sup>

Although treatment adherence is a relevant aspect in the daily practice of the management of these patients,<sup>(7)</sup> there have been no systematic evaluations of patients with CF monitored through programs for adults in Brazil. The quantification of patient-reported nonadherence to the principal therapeutic recommendations would be useful in subsequent attempts to search for the causes of this attitude in order to develop strategies to improve adherence to treatment.

The objective of this study was to analyze the self-reported adherence of patients treated through a program for adults with CF, establishing associations with clinical characteristics of the disease and with the degree of patient adherence as perceived by the multidisciplinary team.

## Methods

This was a prospective, cross-sectional study, carried out in a single center. The study was approved by the Ethics and Research Committee of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre Hospital de Clínicas). All patients aged 18 or older, or legal guardians in the case of patients under 18 years, gave written informed consent.

### *Study population*

The study population comprised patients monitored via a program for adults with CF in the HCPA Pulmonology Department.

We included patients diagnosed with CF in accordance with the consensus criteria,<sup>(8-10)</sup> aged 16 or older. In addition, we included only patients who were clinically stable for the preceding 30 days.

Clinical stability was defined as no clinical evidence of exacerbation, no modifications in the therapeutic regimen and no hospitalizations.

Exclusion criteria were failure to complete any of the questionnaires used in the study and refusal to give written informed consent.

### *Measurements and instruments*

Specific questionnaires were used in order to record clinical variables. The Shwachman-Kulczycki clinical evaluation score was used.<sup>(11)</sup> In the present study, the score was determined by the most qualified member of the team.

Spirometry was performed using a Jaeger spirometer, v 4.31a (Jaeger, Wuertzburg, Germany), in accordance with the Pulmonary Function Test Guidelines established by the Brazilian Thoracic Society.<sup>(12)</sup> Forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>) and the FEV<sub>1</sub>/FVC ratio were determined. Pulmonary function variables in percentage of predicted for gender, age and height were expressed using specific nomograms.<sup>(13)</sup>

Evaluation of peripheral oxygen saturation (SpO<sub>2</sub>) was performed with the patient at rest and using a model NPB-40 pulse oximeter (Nellcor Puritan Bennett, Pleasanton, CA, USA).

A conventional chest X-ray was performed in all individuals included in the study. The radiological score was determined by a senior pulmonologist using the Brasfield radiological scoring system.<sup>(14)</sup> The pulmonologist was blinded as to patient clinical status, patient identity and the study outcome measures.

Evaluation of adherence was performed using a questionnaire adapted from another study.<sup>(15)</sup> Two types of questionnaires were developed: one for the professionals of the multidisciplinary team and one for patients. Both questionnaire types addressed the following therapeutic aspects: question 1) respiratory therapy; question 2) physical activity; question 3) hypercaloric diet; question 4) pancreatic enzymes; question 5) vitamins A, D, E and K; question 6) antibiotic nebulization; and question 7) DNase nebulization. For each question, the weekly frequency of use of the therapeutic modality should be indicated: option a) every day or almost every day; option b) 3 to 5 days per week; or option c) less than 3 days per week. Questions 3

through 7 also included a fourth option (option d): 'no indication'.

The questionnaire for professionals of the multidisciplinary team was filled out during the outpatient medical visit. Questions 1 and 2 were answered by the physical therapist, questions 3 to 5 were answered by the nutritionist, and questions 6 to 7 were answered by the physician.

Each question was scored as follows: option a = 2 points; option b = 1 point; option c = 0 points. An adherence score was calculated based on the quotient between the total score obtained and the number of points possible. For questions 3 through 7, the responses were excluded from the calculation of the overall score if option d was checked.

Two scores were determined: patient adherence as perceived by the health professional and patient-reported adherence.

The application of the questionnaires for patient-reported adherence was carried out by a member of the research team who was not involved in the treatment of the patient and outside the clinical treatment environment. The patient was instructed as to the objective, confidentiality and completion of the questionnaires by the researcher.

### **Statistical analysis**

Data were entered into a Microsoft Excel 2000 database, after which they were processed and analyzed using the Statistical Package for the Social Sciences program, version 13.0.

Quantitative data were expressed as mean  $\pm$  standard deviation or as median (interquartile range - II). Qualitative data were expressed in numbers (% of all cases).

Patients were divided into two groups, according to the patient-reported adherence score: high degree of adherence (score  $> 0.70$ ); and moderate/poor degree of adherence (score  $\leq 0.70$ ). The analysis of quantitative data with normal distribution was performed using the t-test for independent samples. Analysis of continuous data with non-normal distribution was performed using Mann-Whitney U test. Qualitative data were analyzed using the chi-square test and, when necessary, Yates's correction or Fisher's exact test.

Correlations of the adherence score with continuous variables were analyzed using Pearson

linear correlation test or Spearman's correlation coefficient.

Kappa analysis was used to evaluate concordance between the adherence assessed by the team and the patient-reported adherence in each of the seven treatment aspects evaluated.

All statistical tests used were two-tailed. The level of significance was set at 5%.

Sample size was calculated considering proportional differences between the high adherence group and that with moderate/poor adherence.<sup>(16)</sup> For an expected 30% proportion of patients with moderate/poor adherence, using a total amplitude of 0.30 and a 95% confidence interval, the minimum sample size would be 36 patients.

### **Results**

In the period from August of 2005 to February of 2006, 38 of the 41 patients treated via the program for adults with CF were included in the study. There were 2 patients who did not agree to participate in the study, and 1 patient did not submit to clinical evaluation during the study period (patient was studying abroad).

Of the 38 patients evaluated, 20 were female and 18 were male. Mean age was  $23.8 \pm 6.5$  years. All but one of the patients were Caucasian.

Table 1 shows the general characteristics of the patients according to the classification of patient-reported adherence. Thirty-one (81.6%) patients were classified as presenting high adherence and 7 (18.5%) as presenting moderate/poor adherence. None of the variables studied were associated with the classification of adherence ( $p > 0.05$ ).

Table 2 presents clinical score, body mass index, pulmonary function and radiological score, according to the classification of patient-reported adherence. There was no statistically significant difference between groups for the variables studied ( $p > 0.05$ ).

Patient-reported adherence score (median = 0.79) was significantly greater than the adherence score perceived by the team (median = 0.71,  $p = 0.003$ ).

Analysis of correlations demonstrated inverse association between the patient-reported adherence score and Shwachman-Kulczycki clinical score ( $r = -0.36$ ,  $p = 0.028$ ). Correlations of the adherence score with remaining variables were not statistically significant: age ( $r = 0.03$ ,  $p = 0.88$ ), age at diagnosis

**Table 1** – General characteristics according to the classification of patient-reported adherence.

Characteristic	High adherence n = 31	Moderate/poor adherence n = 7	p
Gender, n (male/female)	15/16	3/4	1.000
Marital status, n (% cases)			
Single	26 (83.9)	5 (16.1)	0.348
Married	3 (60.0)	2 (40.0)	
Separated/divorced	2 (100.0)	0 (0)	
Age, years (mean ± standard deviation)	24.0 ± 7.0	23.1 ± 4.0	0.806
Age at diagnosis, years (median - II)	9.0 (15.0)	11.0 (13.0)	0.600
Schooling, n (% cases)			
Elementary	3 (100.0)	0 (0)	0.542
High school	16 (84.2)	3 (15.8)	
College	12 (75.0)	4 (25.0)	
Family income, n (% cases)			
<5 times the MW	6 (85.7)	1 (14.3)	0.738
5-10 times the MW	20 (83.3)	4 (14.7)	
>10 times the MW	5 (71.4)	2 (28.6)	
Study, n (% yes)	11 (78.6)	3 (21.4)	1.000
Work, n (% yes)			
No	13 (76.5)	4 (23.5)	0.634
Part-time	3 (75.0)	1 (25.0)	
Full-time	15 (88.2)	2 (12.8)	

II: interquartile range; and MW: minimum wage.

( $r = -0.03$ ,  $p = 0.847$ ), body mass index ( $r = -0.15$ ,  $p = 0.375$ ), radiological score ( $r = -0.17$ ,  $p = 0.333$ ), FVC in % of predicted ( $r = -0.22$ ,  $p = 0.187$ ), FEV<sub>1</sub> in % of predicted ( $r = -0.09$ ,  $p = 0.602$ ) and SpO<sub>2</sub> ( $r = -0.11$ ,  $p = 0.508$ ). Figure 1 presents the principal correlations studied.

Table 3 demonstrates the weekly frequency of use of therapeutic regimens. The aspect for which the degree of patient-reported adherence was the greatest was the use of pancreatic enzymes (96.3% of the patients), followed by respiratory therapy (84.2% of the patients), use of vitamins A, D, E and K (79.4% of the patients), DNase nebulization (79.4% of the patients), use of an inhaled antibiotic (76.7% of the patients), following dietary orientation (65.8% of the patients) and physical activity (21.1% of the patients).

Table 4 shows the concordance analysis between adherence assessed by the health team and patient-reported adherence. We observed moderate concordance as to performance of physical activity ( $\kappa = 0.44$ ,  $p < 0.001$ ). Regarding the remaining treatment forms, there was no concordance or concordance was weak ( $p > 0.05$ ).

## Discussion

In this study, we evaluated patients monitored via a program for adults with CF regarding adherence to seven of the principal therapeutic recommendations in the management of this disease. We demonstrated high patient-reported adherence to most therapeutic recommendations. However, two recommendations presented very low adherence: physical activity and diet. Among the variables studied, the only one that correlated inversely, albeit weakly, with the patient-reported adherence score was the Shwachman-Kulczycki clinical score, which suggests that the most severe patients are more compliant with treatment. Concordance between the adherence assessed by the health team and patient-reported adherence was poor for most therapeutic recommendations, except for physical activity, for which the concordance was moderate. In general, patient-reported adherence was greater than that perceived by the health care team.

It is important to point out that the medication included as therapeutic recommendation in the study is distributed by the State Department of

**Table 2** – Clinical score, body mass index, pulmonary function and radiological score according to the classification of patient-reported adherence.

	High adherence n = 31	Moderate/poor adherence n = 7	p
S-K clinical score, points	70.0 (25.0)	85.0 (30.0)	0.115
BMI, kg/m <sup>2</sup>	20.8 ± 2.7	21.6 ± 3.5	0.521
FVC, % of predicted	63.0 ± 23.5	76.2 ± 26.7	0.281
FEV <sub>1</sub> , % of predicted	51.8 ± 27.0	63.5 ± 32.1	0.464
FEV <sub>1</sub> /FVC, % of predicted	78.5 ± 16.7	83.8 ± 14.4	0.475
SpO <sub>2</sub> , %	96.2 ± 2.2	97.3 ± 0.8	0.190
Brasfield score, points	15.0 (6.0)	18.9 (4.0)	0.065

S-K: Shwachman-Kulczycki; BMI: body mass index; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in one second; and SpO<sub>2</sub>: peripheral oxygen saturation; and Data expressed in median (interquartile range) or mean ± standard deviation.

Health at no charge, thereby excluding the issue of income as limiting factor of adherence.

An important aspect that might have contributed to the high adherence found in our study is the fact that the population of patients with CF, until then, was relatively small, and was regularly monitored at a referral center for the disease, with scheduled medical visits every 60 days, at most. At each medical visit, patients were sequentially evaluated by the pulmonologist, the nutritionist, the physical therapist and the psychologist. Patients were referred to other specialists when necessary.

Even though we found high adherence to respiratory therapy, it is of concern that 10.5% of the patients reported having less than 3 sessions per week, and that 5.3% reported having sessions 3 to 5 days a week, since this therapeutic measure constitutes a fundamental point in the management of the disease.

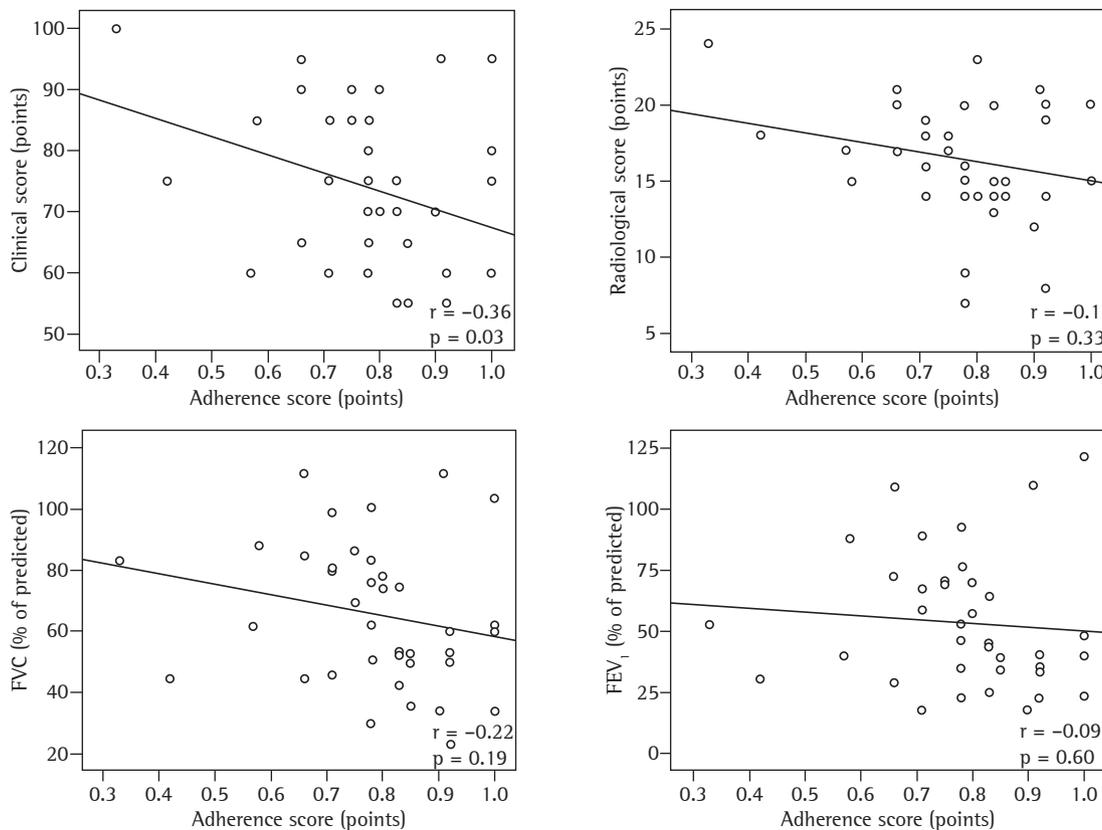
Studies that addressed the issue of adherence in CF are mentioned herein in order to compare their results with ours.

One group of authors<sup>(17)</sup> assessed adherence to treatment in 58 patients with CF. Each treatment form was scored with 0, 1 or 2, and identified, respectively, as poor, partial or complete adherence. Complete adherence was reported as follows: 93% to antibiotic prescriptions, 90% to vitamin prescriptions, 40% to prescriptions of respiratory therapy and 20% to diet prescriptions. In the present study, we also found high adherence to the use of vitamins. However, we did not study the use of oral antibiotic therapy and found much higher adherence to respiratory therapy.

Other authors<sup>(18)</sup> studied 65 patients with CF, aged 6 months to 17 years, with the objective of evaluating factors related to adherence to treatment in CF. They used an adherence scale filled out by the physician, by a family member or, depending on the case, by the patient. They observed that the principal therapeutic forms (medications, postural drainage, inhalation, exercises and diet) presented high adherence. Poor adherence was not associated with any psychopathological patterns or adjustment problems. In contrast, we studied a population monitored via a program for adults and also found high adherence to the use of respiratory therapy, oral medication (vitamins) and inhaled therapy (DNase and antibiotics). However, adherence to diet and physical activity was lower in our study.

One study<sup>(19)</sup> analyzed adherence to treatment in 60 patients with CF, aged 16 to 44 years. Fifty-three percent of the patients reported good adherence to respiratory therapy, 75% of the patients performed adequate physical activity, 97% presented good adherence to the use of pancreatic enzymes at main meals, 53% presented good adherence to the use of pancreatic enzymes with snacks, and 83% presented good adherence to the use of vitamins. Demographic characteristics and variables of severity of the disease were not associated with adherence. In comparison with this study, we also studied a population of adults. However, we found lower adherence to physical activity.

Another study<sup>(15)</sup> analyzed 91 patients with CF aged 14 to 40 years. Patients were evaluated using a questionnaire. An adherence score was calculated. The professionals on the health team also assessed adherence. Eighty-five percent of the patients



**Figure 1** – Correlations among adherence score and Shwachman-Kulczycki clinical score, Brasfield radiological score, forced vital capacity (FVC) and forced expiratory volume in one second ( $FEV_1$ ).

reported good adherence to the use of pancreatic enzymes at large meals, 84% to the use of vitamin supplements, 65% to the use of inhaled antibiotics, 50% to the use of vitamin supplements, 41% to the performance of respiratory therapy and 38% to the use of pancreatic enzymes with snacks. No correlation was observed between adherence and sociodemographic characteristics of the patients or between adherence and knowledge of the disease. Correlations between patient adherence score and that of health professionals were weak. That study evaluated patients of an age bracket similar to that of our study sample. However, they found lower adherence to respiratory therapy. The relationship between the patient-reported adherence score and adherence assessed by the health professionals was weak, as it was in our study.

Another group of authors<sup>(20)</sup> compared patient-reported adherence to the prescription of DNase with the record of medication dispensed by the pharmacy in 42 patients with CF treated at an

adult program. According to the criteria of medication dispensed, 24% of the patients presented good adherence, 48% presented moderate adherence, and 28% presented poor adherence. However, 82% of the patients classified their adherence as good, although only 24% requested and obtained a quantity of medication sufficient for adequate use. The attending physician and nurse more frequently overestimated than underestimated adherence to this aspect of the treatment (in 30% vs. 13% of cases). In our study, we used only the patient-reported approach and found high adherence to DNase. In addition, we identified poor concordance between the patient-reported evaluation and that of the health professionals.

The principal difficulty in studies on adherence to treatment refers is in how to measure this variable.<sup>(5,7,21,22)</sup> Evaluation of adherence can be subjective or objective. Subjective evaluation includes patient self-reporting, as well as reporting by parents and health professionals, using interviews

**Table 3** - Weekly frequency of use of therapeutic regimens.

Treatment form, % of yes	>5 days a week	3-5 days a week	<3 days a week
Respiratory therapy	84.2	5.3	10.5
Physical activity	21.1	42.1	36.8
Diet	65.8	23.7	10.5
Pancreatic enzymes	96.3	3.7	0.0
Vitamins A, D, E and K	79.4	14.7	5.9
Inhaled antibiotics	76.7	20.0	3.3
Dnase	79.4	17.6	2.9

**Table 4** - Analysis of the concordance between adherence as assessed by the health care team and that reported by patients.

Treatment form	kappa	P
Respiratory therapy	0.20	0.077
Physical activity	0.44	<0.001
Diet	-0.07	0.516
Pancreatic enzymes	-0.06	0.719
Vitamins A, D, E and K	-0.03	0.810
Inhaled antibiotics	0.18	0.209
DNase	0.14	0.278

or questionnaires. Self-reporting by patients can even include the use of a diary. Objective measures of adherence can be direct or indirect. Direct measures include serum or urine levels of medications or their metabolites. Indirect measures include comparison between pulmonary function at home treatment and at hospital treatment, counting capsules, record of medications by the pharmacy in charge or record of doses administered by mechanical devices that blindly measure the release of medication.<sup>(7,21,22)</sup> Although objective measures are more efficient, they are not always feasible to be used for evaluation of adherence. However, subjective measures that are based on patient self-reporting overestimate adherence. Nevertheless, subjective self-report techniques are easy to use and seem to allow, albeit with less sensitivity, the identification of a group of patients presenting nonadherence to treatment. This can be useful for identifying reasons for this attitude and for developing strategies designed to improve adherence to treatment.<sup>(5,7)</sup>

Another difficulty in the study of patient-reported adherence is the fact that there are no validated questionnaires for that purpose. In our study, we opted for the strategy of adapting a questionnaire used in another study.<sup>(15)</sup> We believe that the weekly use of therapeutic orientations as an objective reference for the questions has reduced the possible interference of this limiting factor.

The initial estimate of the sample size required in order to identify the group of patients with moderate/poor adherence was satisfactory in terms of the number of patients studied. However, one potential limitation is the fact that the study did not present sufficient power for the associations between patient-reported adherence and the clinical characteristics studied, especially due to the small

number of patients in the group with moderate/poor adherence.

In addition, the fact that 2 patients refused to participate in the study might have contributed to the overestimation of adherence, on the hypothesis that this occurred precisely because these patients had adherence problems.

In recent years, CF has also become a disease in adults.<sup>(23)</sup> However, the condition of chronic disease and the complexity of therapeutic regimens demand time and dedication on the part of the patient for adequate performance of the treatment.<sup>(21)</sup> The present study, carried out at a referral center for CF, quantified adherence of the patients included in the adult program, identifying two recommendations with a low degree of adherence. Therefore, our data add to the existing body of knowledge on the behavior of this group of patients in Brazil, informing decisions regarding the allocation of efforts in order to increase adherence. We have systematized the use of a simple instrument for this evaluation. The disproportionality between the patient-reported degree of adherence and the degree of adherence perceived by the professionals of the team suggests that objective measures for adherence be developed and added to the systematic evaluation of this group for an even better approach to this problem.

In conclusion, the present study showed that, in patients with CF treated at an adult program, patient-reported adherence to treatment was high for most therapeutic recommendations. However, lower adherence to dietary orientation and principally to the recommendation of physical activity demands efforts in order to find the causes for this attitude as well as strategies to improve adherence. The only characteristic that inversely correlated with the patient-reported adherence

score was Shwachman-Kulczycki clinical score. Patient-reported adherence was greater than that perceived by the health team.

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