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Research Article

Retrospective Study Pre and Post Gastrostomy in Pediatric Patients with Cystic Fibrosis: Brazilian Multicenter Study

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What is known?

There is a strong association between nutritional status and clinical outcomes in patients with cystic fibrosis, where malnutrition and poor lung function are the main sources of morbidity.

Studies have shown that the placement of percutaneous endoscopic gastrostomy (PEG) tube may improves BMI in patients with CF.

What is the new?

The placement of PEG in patients with progressive deterioration of nutritional status and lung function proved to be effective after 6-12 and 24 months, in improving z-score for weight and BMI.

There was a stabilization of pulmonary function after placement of PEg as well as a reduction in the length of hospital stay due to pulmonary exacerbations when comparing before and after the intervention.

Abstract

Background: In patients with cystic fibrosis (CF) there is a direct relationship between nutritional status and lung function. Gastrostomy (GT) allows larger and continuous caloric intake and is an option in cases where the oral route is not sufficient **Methods**: A multicenter retrospective study of pediatric CF patients who underwent gastrostomy between 2007 and 2021 in 7 referral centers for CF in Brazil. Some variables were collected in a chart review to characterize the sample. Anthropometric data: Z score for weight, height, Body Mass Index (BMI) and lung function (FEV1) were evaluated and compared at 5 different time points: pre-placement of GT (12 and 6 months before), at the time of placement and after procedure (6 and 12 months). **Results:** 42 patients were included in the study. BMI Z score decreased significantly 6 months before GT from -2.04 ± 1.6 to -2.2 ± 1.4 ($p< 0.05$), however, after 6 and 12 months of GT there was an increase in this parameter, -1.5 ± 1.4 and -1.5 ±1.6 ($p<0.05$) respectively. FEV1 showed a sharp drop from 12 months to 6 months before GT from 63% ± 18 to 48% ±19 ($P< 0.05$). From the time of GT placement there was a stabilization in FEV1 at 6, 12 and 24 months after (50 ±18%, 47 ±19%, 40 ±23% 43 ± 27%).

Conclusions: GT placement was a significant improvement in BMI Z score. We observed a marked decline in lung function prior to GT placement with a stabilization at 6 and 12 months after.

Key words: Cystic fibrosis; Gastrostomy; Malnutrition; Pediatrics

Abbreviations: GT: Gastrostomy; FEV1: Forced Expiratory Volume in 1 Second; GEE: Generalized Estimating Equations; LSD: Least Significant Difference; PEG: Endoscopic Gastrostomy; BMI: Body Mass Index

Introduction

Maintaining an adequate nutritional status is associated with preserving lung function in children with cystic fibrosis (CF) [1]. However, various international registries monitoring these patients have shown nutritional compromise with progressive decline in BMI over the years [2,3]. Maintaining weight, height, and BMI has become a central component of care for CF patients [4,5].

The estimated energy needs of these patients are approximately 110% to 200% of the recommended caloric value for the healthy population, taking into account age and sex [6,7]. In order for patients to meet these energy and nutrient recommendations, it is suggested to follow high-calorie diets, rich in proteins and fats, and often supplemented with oral nutritional supplements [7]. Despite these guidelines, some patients with CF do not meet these needs due to factors such as inadequate nutritional intake, high energy requirements, and nutrient losses in stools due to steatorrhea [8]. CF children with BMI above the 50th percentile show less decline in lung function and lower morbidity compared to patients with lower percentiles [9,10].

Studies have shown that the placement of Percutaneous Endoscopic Gastrostomy (PEG) tube improves BMI in patients with CF. However, it is still unclear whether this results in a significant improvement in lung function [11-13].

The objective of this study is to evaluate the evolution of nutritional status and lung function in patients who had undergone PEG at 7 CF treatment centers in Brazil. Clinical data, anthropometric variables, and pulmonary function were collected to assess the effectiveness of PEG in these patients.

Methods

A multicenter retrospective study with a convenience sample of pediatric patients aged 0 to 18 years, diagnosed with CF, who underwent PEG between 2007 and 2021 at 7 CF reference centers in Brazil. The study was approved by the ethics committee of the Hospital da Criança Santo Antônio under the number 1.0000.5683.

The patients were diagnosed with CF based on the measurement of chloride levels in sweat using quantitative methods ≥ 60 mmol/L in two samples or the identification of two pathogenic mutations related to CF [7]. Transplanted patients (liver or lung) prior to PEG placement with other diagnostic causes of malabsorption (e.g., short bowel syndrome, celiac disease) were excluded.

The following variables were collected through medical record review: gender, age, history of meconium ileus, age at diagnosis, presence of CF-related diabetes, presence of CF-related liver disease, use of pancreatic enzymes, class of genetic mutation, presence of bacterial colonization, days of antibiotic use prior to and after PEG, average time between indication and placement of PEG, and days of previous and post-PEG hospitalization.

Anthropometric data including Z scores for weight, height, BMI, and pulmonary function measured by Forced Expiratory Volume in the First Second (FEV1) were evaluated and compared at six different time points: 12 and 6 months before PEG placement, at the time of placement, and at 6, 12, and 24 months after placement. For each patient, the BMI Z score was calculated for each of the six time periods: 6 and 12 months before PEG, at the time of PEG, and 6, 12, and 24 months after PEG.

The null hypothesis that the median BMI variation for all patients, from the baseline period to each of the 6 follow-up periods, was equal to zero was tested using a non-parametric sign test. If the BMI variation for all patients was found to be significant, a non-parametric Kruskal-Wallis test was used to determine if the changes differed by gender and age group.

We examined the slope of lung function decline by comparing FEV1before and after PEG placement. A longitudinal mixed model analysis was used to evaluate the effect of PEG placement on lung function, measured as predicted percent of FEV1. In this approach, the measurements for each patient were modeled as a linear function of time, with a step change in the intercept (the difference between the estimated FEV1 immediately before and immediately after PEG placement) and a change in slope (the difference between the rate of change of FEV1 before and after placement).

Statistical Analysis

Quantitative variables were described using either mean and standard deviation (for symmetric distribution) or median and interquartile range (for asymmetric distribution), depending on the variable's distribution. Categorical variables were described using absolute and relative frequencies. Comparison between moments was performed using the Generalized Estimating Equations (GEE) model complemented by the Least Significant Difference (LSD) test. The linear model was used for numerical variables with a normal distribution, and the gamma or tweedie model with a logarithmic link function was used for variables with an asymmetric distribution. The significance level adopted was 5% ($p \leq 0.05$), and the analyses were conducted using SPSS version 27.0 software.

Results

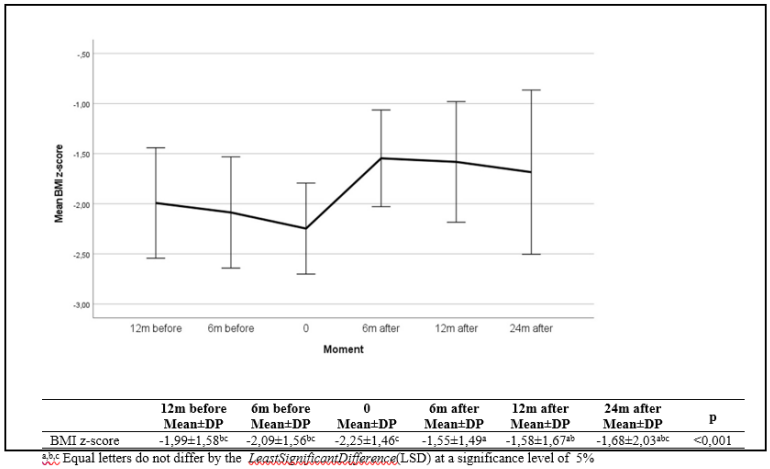
A total of 42 patients were included, with 55% being female. The median age at diagnosis was 5 months (1-32), the median age at PEG placement was 12.3 years (5-14), and the mean time between indication and PEG placement was 7 months (3-28). Among the analyzed patients, 5% were less than 2 years old at the time of GT placement, 35.7% were between 2 and 10 years old, and 59.5% were above 10 years old. Among the patients, 19% were colonized by Pseudomonas aeruginosa as the sole strain, and 35.7% of patients had this colonization associated with other strains. Meconium ileus was present at birth in 16.7% of the patients, diabetes related to CF in 16.7%, and CF-related liver disease in 16.7%. Among the patients included in the study, 97.2% were using pancreatic enzymes. Class 2 mutations on both alleles were found in 65% of the patients, 31% had the delta F508 mutation in homozygosity, and 85% had this mutation on one of the alleles. The characteristics of the patients included in the sample can be observed in Table 1.

Variables*	**n=42**
Age at PEG placement (months)	148 (59 – 172)
< 23 months	2 (4,8)
≥ 24 months and <120 months	15 (35,7)
≥ 120 months	25 (59,5)
Sex	
Male	19 (45,2)
Female	23 (54,8)
Age at diagnosis (months)	5 (1 – 32)
Meconium ileus	7 (16,7)
Diabetes	7 (16,7)
Cystic Fibrosis associated liver disease	7 (16,7)
Colonization	
Pseudomonas	8 (26,7)
Pseudomonas + Other bacteria	15 (36)
Mutation	
Class 2 in both alleles	27 (65,0)
Delta F508 in homozygosis	13 (31,0)
Delta F508 in heterozygous	35 (85,0)
Use of pancreatic enzymes	40 (95,2)
Tome between indication and PEG placement (months)	7 (3 – 28)

*described as mean ± standard deviation, median (25 th-75th percentiles) or n(%); PEG: gastrostomy

Table 1: Sample characteristics.

The Z-score of BMI was significantly higher at 6 months after PEG, where the Z-score of BMI ranged from -2.25 ± 1.46 at the time of PEG to -1.55 ± 1.49, representing a statistically significant increase ($p<0.001$). We also found a statistically significant increase at 12 months post PEG compared to the time of PEG placement, with a variation in the Z-score of BMI from -2.25 ± 1.46 to -1.58 ± 1.67 ($p=0.006$) (Figure 1). At the time of PEG, 50% of patients had a Z-score of BMI for age below -2 standard deviations, but when evaluated at 24 months after the procedure, only 21.5% of them remained with a Z-score of BMI for age below -2 standard deviations, which is considered malnutrition [24].

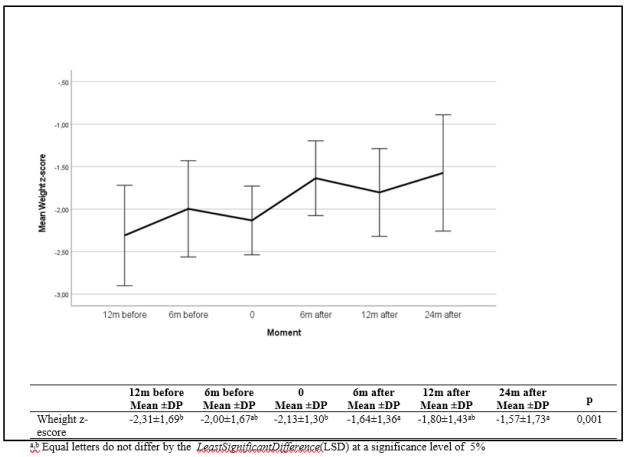


	12m before Mean±DP	6m before Mean±DP	0 Mean±DP	6m after Mean±DP	12m after Mean±DP	24m after Mean±DP	p
BMI z-score	-1,99±1,58^{bc}	-2,09±1,56^{bc}	-2,25±1,46^{c}	-1,55±1,49^{a}	-1,58±1,67^{ab}	-1,68±2,03^{abc}	<0,001

a,b,c Equal letters do not differ by the *LeastSignificantDifference*(LSD) at a significance level of 5%

Figure 1: Graph of Z-score of BMI before and after PEG placement.

The z-score for weight was significantly higher at 6 and 24 months post-PEG compared to the z-score at the time of PEG placement ($p<0.001$). At the time of PEG, the z-score for weight was -2.13 ± 1.30, while at 6 months and 24 months post-PEG, it changed to -1.64 ± 1.36 and -1.57 ± 1.73, respectively, as shown in Figure 2. There was no statistically significant difference in the z-score for height throughout the assessments ($p=0.173$).

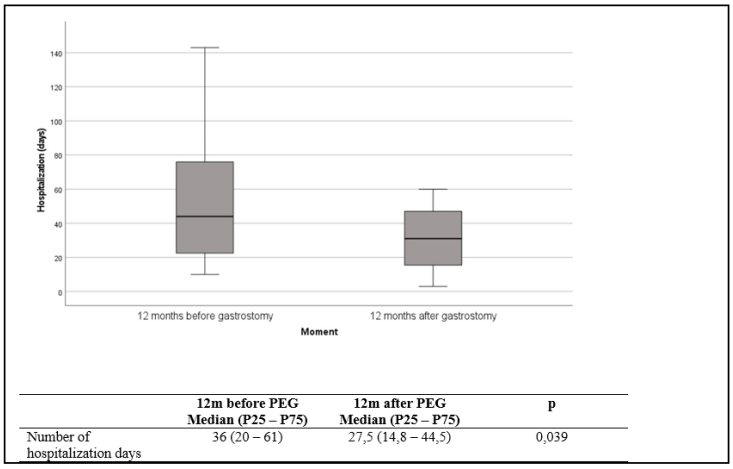


	12m before Mean ±DP	6m before Mean ±DP	0 Mean ±DP	6m after Mean ±DP	12m after Mean ±DP	24m after Mean ±DP	p
Wheight z-escore	-2,31±1,69^{b}	-2,00±1,67^{ab}	-2,13±1,30^{b}	-1,64±1,36^{a}	-1,80±1,43^{ab}	-1,57±1,73^{a}	0,001

a,b Equal letters do not differ by the *LeastSignificantDifference*(LSD) at a significance level of 5%

Figure 2: Graph of the z-score for weight before and after PEG placement.

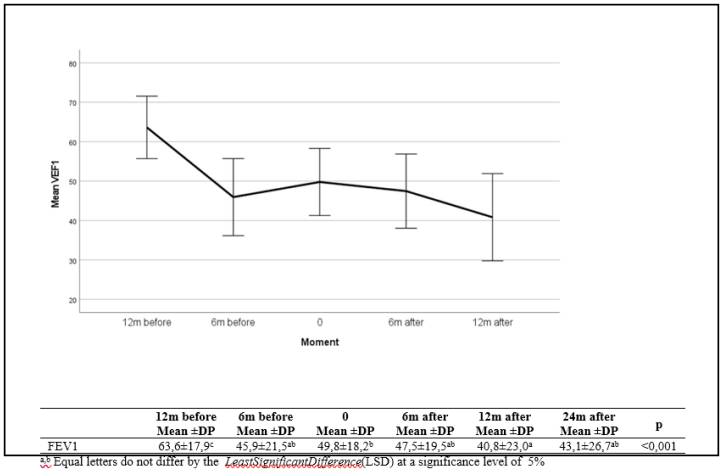
The average length of hospital stay 12 months pre-GT and 12 months post-PEG significantly decreased from 48 ± 7 days (95% CI: 35.96 to 64.91) to 30 ± 4 days (95% CI: 23.76 to 39.61; $p<0.05$), as observed in Figure 3. The average duration of antibiotic use 12 months before PEG was 61 ± 9 days in 19 patients (95% CI: 48.59 to 88.07), and 46 ± 6 days (95% CI: 36.28 to 59.44) in 18 patients 12 months post-PEG ($p=0.070$). For this analysis, a generalized estimation equation model with a Tweedie distribution and log link function was used.



	12m before PEG Median (P25 – P75)	12m after PEG Median (P25 – P75)	p
Number of hospitalization days	36 (20 – 61)	27,5 (14,8 – 44,5)	0,039

Figure 3: Graph showing the number of hospitalization days 12 months before and 12 months after PEG placement.

The values of FEV1 were significantly lower 12 months after GT (40.8 ± 23.0) compared to 12 months pre-GT (40.8 ± 23.0; $p < 0.001$) and GT (49.8 ± 18.2; $p = 0.023$). Additionally, the values of FEV1 at 12 months pre-GT were significantly higher than all other time points (63.6 ± 17.9; $p \leq 0.001$). There was no statistically significant difference in FEV1 between the time of GT and 24 months post-GT, as shown in Figure 4.



	12m before Mean ±DP	6m before Mean ±DP	0 Mean ±DP	6m after Mean ±DP	12m after Mean ±DP	24m after Mean ±DP	p
FEV1	63,6±17,9^{c}	45,9±21,5^{ab}	49,8±18,2^{b}	47,5±19,5^{ab}	40,8±23,0^{a}	43,1±26,7^{ab}	<0,001

^{a,b} Equal letters do not differ by the *LeastSignificantDifference*(LSD) at a significance level of 5%

Figure 4: variation of the Z-score of FEV1 across the 6 analyzed time points.

Discussion

Improving the nutritional status and, consequently, slowing down the progression of pulmonary disease in CF patients is of utmost importance. Previous studies have shown that nutritional rehabilitation improves [14-15], stabilizes, or delays the rate of pulmonary deterioration [16-19]. When oral diet and supplements fail to achieve adequate nutritional status, many CF centers use PEG feeding to improve the nutritional and respiratory status of these patients [20].

According to the Brazilian Guidelines for Nutrition in Cystic Fibrosis [7], criteria for implementing enteral nutrition therapy include: continuous weight loss or inadequate weight gain for a period of 3 to 6 months, even with the use of oral nutritional supplements; optimization of enzyme replacement therapy and strict dietary guidance with regular monitoring; for children and adolescents having difficulty reaching the 10th-25th percentile for the BMI/age or weight/age or height/age indicator, or having a BMI persistently below

the 10th percentile; for adults with a persistent BMI below 18.5 kg/m^2; in cases of anorexia with reduced food intake of at least 120% of the energy recommendation, and without medical contraindications. Enteral nutrition should be individualized and provide 40% to 60% of the daily energy requirements.

We observed in this study that the z-score of BMI and weight was significantly higher 6 and 12 months after PEG placement compared to previous time points, indicating an improvement in the nutritional status of these patients after the procedure. Additionally, we observed that the proportion of patients with BMI z-score below -2 standard deviations for age significantly decreased after 24 months of the procedure, suggesting an improvement in the nutritional status of these patients during this assessment period. This finding is consistent with other published studies, such as a study involving 54 CF patients with PEG where Williams et al. [5] demonstrated a significant improvement in BMI after GT placement. A study by Efrati et al. [21] involving 21 CF patients with GT confirmed improvement in BMI and found a trend towards stabilization of lung function.

Regarding the clinical characteristics of the patients, we observed that the median age at the time of diagnosis was 23 months, highlighting the importance of early diagnosis for proper disease management. It is important to note that some of these patients were born before full implementation of neonatal screening, which may explain the high median age. The median age at PEG placement was 10.1 years, suggesting that patients with more severe mutations may already exhibit significant manifestation of their nutritional condition at this age. The average time between indication and PEG placement was 7 months, indicating a prolonged period between recommendation and procedure execution, often due to the fears and uncertainties of the family. It is worth noting that there is still lack of knowledge and prejudices regarding the implementation of PEG among family members and patients.

A significant proportion of patients had colonization with Pseudomonas aeruginosa, which is consistent with common infection in these patients. We also identified cases of meconium ileus at birth, CF-related diabetes, and CF-related liver disease, indicating the presence of additional complications associated with CF in this sample, justified by the fact that these patients have more severe mutations.

Regarding pulmonary function parameters, we observed that the values of FEV1 progressively decreased in the 12 months prior to GT placement, which may be attributed to natural disease progression. However, there was no significant difference in FEV1 value between the time of PEG placement and 24 months after the procedure, indicating that PEG placement did not result in further deterioration of lung function during this period. Overall, we found that lung function stabilizes during the 2 years following PEG placement, indicating an improvement in the natural history of pulmonary disease in our patients [22,23]. A similar trend was observed in the Belgian CF Registry study, where FEV1 stabilization was found during a 5-year period after GT placement [24]. In Khalaf et al.'s study [25] involving 20 patients who underwent PEG, the decrease in FEV1 over 2 years was shown to be smaller in the PEG group (-0.04; 95% CI: -0.30 to 0.22; p=0.74) compared to the non-PEG group (-0.22; 95% CI: -0.45 to 0.01; p=0.06). These findings may suggest that PEG, in combination with improved energy and nutrient supply, can slow down the decline in lung function.

An important finding of this study was a significant reduction in the average length of hospital stay after 12 months of PEG placement. This suggests that the intervention may have a positive impact on reducing the need for hospitalization in these patients, which could be related to the improvement in nutritional status and better management of home therapies. We did not observe a statistically significant difference in the average duration of antibiotic use before and after PEG placement, although we did observe a trend towards reduction in this parameter after the intervention (p=0.07).

It is important to highlight that this study is the first Brazilian multicenter study to evaluate the impact of PEG placement on nutritional and pulmonary parameters in pediatric patients with CF over a period of 2 years. This study has some limitations, including its retrospective design, a limited sample size, and non-uniform data due to its multicenter nature. There are inherent differences among each center.

In our study, PEG placement resulted in a significant improvement in nutritional parameters, stabilization of the decline in lung function, and a reduction in hospitalization time for pediatric patients with CF, which may be associated with improved quality of life and increased survival. Further prospective studies need to be conducted to address some questions, including identifying the optimal timing for performing PEG in these patients.

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