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Original Article

The effect of enteral tube feeding in cystic fibrosis: A registry based study

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Abstract

Background: Long-term effect of enteral tube feeding (ETF) in cystic fibrosis (CF) remains equivocal.
Methods: A Belgian CF registry based, retrospective, longitudinal study, evaluated the pre- and post- ETF (n = 113) clinical evolution and compared each patient with 2 age, gender, pancreatic status and genotype class-matched controls.
Results: At baseline ETF had a worse BMI z-score ($p < 0.0001$) and FEV1% ($p < 0.0001$) compared to controls. Patients eventually receiving ETF, had already a significant worse nutritional status and pulmonary function at first entry in the registry. Both parameters displayed a significant decline before ETF-introduction. ETF had more hospitalization and intravenous antibiotic (IVAB) treatment days ($p < 0.0001$). After ETF introduction hospitalizations and IVAB decreased significantly. After ETF-introduction BMI z-score recuperated towards the original curve before the decline, but remained below the controls. Starting ETF had no effect on rate of height gain in children. The pre-index FEV1 decline (−1.52%/year ($p = 0.002$)) stabilized to +0.39%/year afterwards. Controls displayed decline of −0.48%/year ($p < 0.0001$).
Conclusion: ETF introduction improved BMI z-score and stabilized FEV1, associated with less hospitalizations and IVAB treatments. Higher mortality and transplantation in the ETF cases, leading to drop-outs, made determination of the effect size difficult.

Keywords: Cystic fibrosis; Tube feeding; Gastrostomy; Malnutrition; Pulmonary function

1. Introduction

Despite advances in nutritional support, malnutrition remains an important issue in CF patients. The vicious circle of increased energy needs due to recurrent or chronic pulmonary infections and inflammation, increased work of breathing as well as malabsorption, in spite of pancreatic enzyme replacement therapy (PERT) leads to an energy imbalance [1–3]. Compromised energy intake as a result of poor appetite, vomiting and nausea caused by respiratory infections, treatment side effects and psychological factors will further induce weight loss [4]. Finally, associated diseases such as CF related diabetes (CFRD), or gastro-oesophageal reflux or coinciding diseases as celiac disease can impede weight gain [5].

The close association between nutritional status and pulmonary function has repeatedly been demonstrated [6–9]. Body wasting and stunting are independent predictors of mortality in the CF population [10,11]. Despite the superiority

Abbreviations: ETF, enteral tube feeding; CF, Cystic Fibrosis; FEV1, Forced expiratory volume in one second; BMI, body mass index; FVC, Forced vital capacity; IV, Intravenous; AB, Antibiotics; BCFR, Belgian CF Registry; CFRD, CF related diabetes; BCC, *Burkholderia cepacia* complex; MRSA, Meticilline-resistent *Staphylococcus aureus*.

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of lean body mass in predicting respiratory muscle strength, pulmonary function and quality of life, body mass index (BMI) is frequently used in clinical practice due to its availability [12,13]. The European CF Society advises to endeavor for a BMI above the 50th percentile in children, above 22 kg/m^2 for adult female and above 23 kg/m^2 for adult men [14]. To improve nutritional status, multiple interventions are often tried consecutively or simultaneously. Even without any evidence from randomized trials, enteral tube feeding (ETF) is widely accepted as a treatment option for malnutrition [4]. Several pre- and post-interventional studies of different design have reported on outcomes on short- and medium-term [15–22]. They indicate a possible positive effect on nutritional status if the intervention is not started too late in the course of the disease. However, if this ETF effect translates into an improved health status remains unclear, since the results on pulmonary function remain equivocal [4]. The objective of this study was to evaluate whether tube feeding had an impact on nutritional and pulmonary outcomes on the long-term using the data of the Belgian CF Registry (BCFR).

2. Methods

2.1. Belgian CF registry

The BCFR was established in 1998. Since 2006, it is hosted, administered and analyzed by the Scientific Institute of Public Health (Brussels, Belgium). The BCFR contains data of >90% of the Belgian CF patients diagnosed by 2 positive sweat tests and/or two mutations in the CFTR gene. It uses input from the 7 Belgian CF reference centers and is an annual one-point registration of changes made during the preceding year.

2.2. Evaluated data

The electronic case reports of the BCFR were retrospectively analyzed, identifying all patients, children as well as adults, receiving enteral tube feeding (ETF) by means of gastrostomy or nasogastric tube between 2000 and 2013. The year in which tube feeding was first mentioned was considered as the index year (year T_0). All cases receiving ETF were matched on index year for age, gender, pancreatic status and mutation class with 2 not ETF-treated CF control patients. The mutations were classified in 5 mutations classes according to the classification described by De Boeck et al. (supplement 1) [23].

In both cases and controls, age at CF diagnosis (years) was noted. At yearly intervals, weight (kg), height (m), BMI (kg/m^2) and forced expiratory volume in 1 s (FEV1) were recorded at the last consultation of the calendar year. The % predicted FEV1 values were based on the "Global Lung function Initiative" equations. Z-scores for weight and height were determined with CDC references until 21 years [24]. BMI z-scores were determined with the Roland-Cachera reference [25] as it comprises a wider age range than the CDC reference. During the same timeframe, the number of hospitalization days and duration of intravenous antibiotic (IVAB) treatment were recorded on an annual basis. Furthermore, the presence of CF related complications such as CF related diabetes (CFRD), infections and colonization status (Leeds criteria) [26] at inclusion and at every evaluation interval were documented. Data for transplanted or deceased patients were included until the last entry before transplantation or death.

2.3. Exclusion criteria

Patients transplanted before T_0 and patients with <3 observations in addition to the data of T_0 were excluded.

2.4. Statistical methodology

The analysis was performed using the SAS software version 9.3 (SAS Institute, Cary NC, USA). Descriptive data of the study population were presented as median (Interquartile range). Normality of the data was determined by using the Kolmogorov–Smirnov test. Differences in BMI z-score, height z-score, FEV1, hospitalization days and days of IV AB between cases and controls were analyzed at year T_0, one year prior to T_0 (year T_{-1}) and 3 years post- T_0 (year T_{+3}). The independent two-sample t-test or Wilcoxon rank sum test was used to compare differences. Categorical variables were analyzed using the Pearson Chi-square or Fisher's exact test. Only two-sided tests were used with a threshold of $p < 0.05$. The Bonferroni correction method was used to address the problem of subgroup analyses [27].

Mixed-effects models were used to obtain population estimates for inference for the response while adjusting for confounders. Intermittent missing values were replaced using the Last Observation Carried Forward (LOCF) method. To have sufficient data for meaningful inference due to drop-out, the period of study was limited to 5 years pre- and 6 years post-T_0.

3. Results

3.1. Patient selection

All 1482 CF patients ever reported in the BCFR were considered. Before matching, 235 patients (3 ETF patients) did not meet the inclusion criteria due to the number of observations between 2000 and 2013; due to transplantation or death before 2000. Finally, 113 cases receiving ETF were identified and 226 age, sex, pancreatic status and genotype class matched controls were selected. 3 controls were excluded due to transplantation before T_0.

The median age at start of ETF was 10.3 (1.3 to 18.4) years and the median ETF duration was 2 (1to 5) years. At year T_0, the patients receiving ETF differed significantly from their matched controls (Table 1). Cases were diagnosed with CF earlier and had a worse nutritional and respiratory status.

3.2. Nutritional status

Cases did not only have a worse BMI z-score compared to controls at year T_0, but also at the first registration in the BCFR (BMI z-score − 1.3 (−2.1 to −0.5) vs. −0.5 (−1.3 to −0.2)