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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)

Table 1
Demographic and clinical data of cases receiving enteral tube feeding (ETF) and their controls at index. The grey area consists of the matched data. Abbreviations: n: number of patients; ETF: enteral tube feeding; BMI: body mass index; FEV1: forced expiratory volume in one second.

	Controls (n = 223)		Cases (n = 113)		p-Value
	n	Median (IQR)/%	n	Median (IQR)	
Gender (male)	104	46.4%	53	46.9%	0.963
Age (years) at start ETF or matching	223	9.9 (2.1–18.6)	113	10.3 (1.3–18.4)	0.584
Adult (≥18yr)	61	27.4%	32	28.3%	0.852
Pancreatic sufficient	10	4.5%	5	4.4%	0.980
Age diagnosis (years)	223	0.3 (0.1–2)	113	0.2 (0–1.2)	**0.018**
ETF duration (years)			113	2 (1–5)	

(p < 0.0001)). A summary of the differences at the different evaluation points (year T_{-1}, T_0, T_3) is given in Table 2.

Cases displayed an annual pre-T_0 decline in BMI z-score of −0.02 SD and a post- T_0 annual increase of +0.08 SD leading to a significant slope difference after introduction of ETF (p = 0.019). A non-significant trend towards recuperation of BMI z-score was already observed from T_{-1} towards T_0 in cases (p = 0.180). Afterwards, the BMI returned to its original curve without further correction towards the 50th percentile (Fig. 1). The BMI z-score was significantly better by T_3 compared to T_{-1}, however, there was no effect on growth rate in children.

In controls, the nutritional status determined by BMI z-score and height z-score was better than the cases at every evaluation point. They also displayed a slight increase in BMI z-score over time. The annual adjusted increase in BMI z-score was +0.04 SD throughout the observation period.

3.3. Pulmonary function

Similar to the BMI, the first entry of pulmonary function in the registry was significantly worse in cases (FEV1% controls: 83.2 (65.6 to 95.4) vs cases: 67.6 (43.1 to 81.0) (p < 0.0001)). There was also a significant difference in FEV1 between both groups at every evaluation point (Table 2).

To evaluate the pre- and post-intervention evolution a mixed model analysis was done adjusted for BCC infection, age, baseline FEV1, age at diagnosis, PI status, days IV antibiotics and days of hospitalization. When looking at the evolution over time, cases displayed a steep annual decline of −1.52% pre-T_0 whereas the FEV1 stabilized at a lower level during the first five years after introduction of ETF (slope difference p = 0.046) (Fig. 2). In the controls, the mixed-effects model adjusted for BCC infection, age, baseline FEV1, age at diagnosis, PI status, days IV antibiotics and days of hospitalization showed an annual deterioration in FEV1 of −0.48% (p < 0.0001).

The model showed that a better FEV1 at baseline, a higher BMI z-score, a late diagnosis and the absence of BCC among the cases receiving ETF were independently associated with a better change in FEV1. A higher number of hospitalization days were associated with a decline in FEV1.

3.4. Infections, intravenous antibiotic treatment and hospitalizations

At T_0 there were no differences in the prevalence of chronic *methicilline resistant Staphylococcus aureus* (MRSA) or *Aspergillus* infections. Despite having a higher prevalence of *Pseudomonas aeruginosa* infections in cases (p = 0.045) at T_0, there was no difference in chronic *Pseudomonas aeruginosa* colonization (p = 0.173) [25]. In contrast, chronic colonization by *Burkholderia cepacia* complex (BCC) at T_0 was only found in ETF cases (3.5% (n = 4)) (p = 0.012). During follow-up, no significant differences between both groups were found except for a higher *Aspergillus* colonization rate in controls.

Cases had significantly more hospitalization days and IVAB treatment days per year compared to controls at T_0 (Table 2).

Table 2
Evolution of clinical parameters of patient receiving enteral tube feeding (ETF) and controls (Co), one year before the index year, at the index year and 3 years after the index year. Significance of the observed differences is mentioned. Significance threshold for p is α < 0.05 for two sided tests between cases and controls. The Bonferroni correction sets the significance at α < 0.017 for multiple testing at the 3 time points within the same group. Abbreviations: H: height in children; BMI: body mass index; FEV1: forced expiratory volume in one second; hosp: hospitalizations; IV AB: intravenous antibiotics; n: number; IQR: interquartile range; y: year.

		Year -1		p-Value	Index year		p-value	Year +3		p-Value
		n	Median (IQR)	−1/0 y	n	Median (IQR)	0/+3 y	n	Median (IQR)	−1/+3 y
H z-score	ETF	53	−0.7 (−1.9 to −0.4)	0.253	84	−1.1 (−1.9 to −0.5)	0.658	65	−1 (−2.0 to −0.4)	0.523
	Co	107	−0.4 (−1.3–0.2)	0.918	178	−0.5 (−1.2–0.2)	0.428	137	−0.3 (−1 to −0.3)	0.456
P- value Co/ETF			**0.005**			**<0.0001**			**<0.0001**	
BMI z-score	ETF	67	−1.8 (−2.5 to −1)	0.180	105	−1.5 (−2.4 to −0.7)	0.040	87	−1.1 (−2 to −0.3)	**0.001**
	Co	137	−0.5 (−1.1–0.2)	0.447	220	−0.4 (−1.1–0.2)	0.121	186	−0.2 (−1–0.5)	0.042
P- value Co/ETF			**<0.0001**			**<0.0001**			**<0.0001**	
FEV1 (%)	ETF	61	49.1 (33.2–73.2)	0.885	73	51.4 (32.7–73.1)	0.062	64	63.7 (42.3–85.3)	0.045
	Co	111	73.3 (59.9–93)	0.194	150	82.7 (65.6–94.3)	0.377	177	83.7 (69–96)	0.019
P- value Co/ETF			**<0.0001**			**<0.0001**			**<0.0001**	
Hosp. days	ETF	63	14 (3–33)	**0.003**	107	30 (10–61)	**<0.0001**	82	6 (0–24)	**0.016**
	Co	133	0 (0–9)	0.421	207	1 (0–12)	0.146	173	0 (0–9)	0.620
P- value Co/ETF			**<0.0001**			**<0.0001**			**<0.0001**	
IV AB days	ETF	70	13 (0–46)	0.800	113	15 (0–45)	**0.006**	91	0 (0–28)	0.022
	Co	141	0 (0–12)	0.867	223	0 (0–14)	0.968	192	0 (0–14)	0.954
P- value Co/ETF			**<0.0001**			**<0.0001**			**0.023**	

Significant p-Values are indicated in bold.

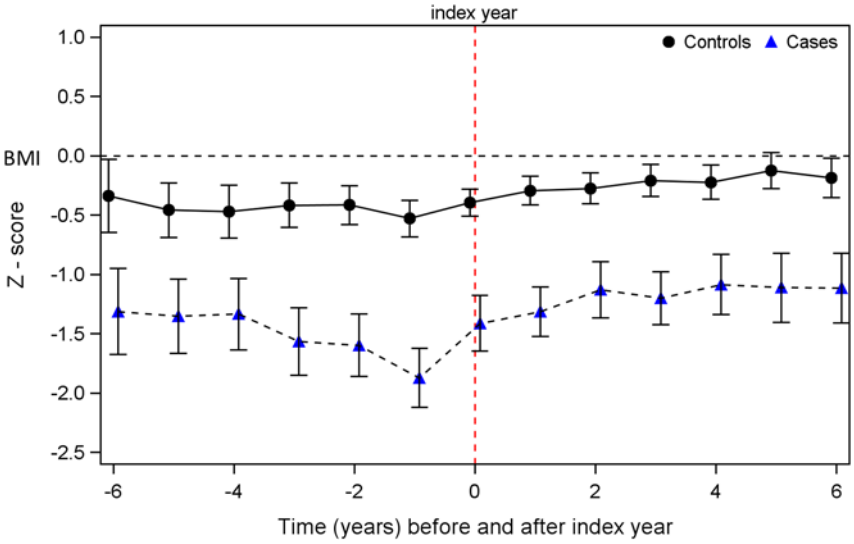

Fig. 1. Trend in BMI z-score (mean (95% CI)) in cases receiving ETF versus matched controls. ETF has been introduced in cases between year −1 and year 0 (index year). Abbreviations: BMI: body mass index; ETF: enteral tube feeding.

They had an increase in hospitalization days (Fig. 3) as well as IVAB days per year prior to T_0. Both decreased significantly in the 3-year period after initiation of ETF. Not only, did the median duration of hospitalization and IVAB treatment decrease, but the proportion of patients that were hospitalized also decreased significantly after introduction of ETF ($p < 0.001$)(T_{-1}: 81.0%; T_0: 88.8%; T_{+3}: 69.5%). Similar findings were observed when evaluating the proportion of cases receiving IVAB ($p = 0.009$ T_{-1}: 88.2%; T_0: 83.7%; T_{+3}: 67.2%). There were no comparable changes over time in the control population.

3.5. Mortality, transplantations, comorbidities

As expected, based on the pulmonary function at T_0, fatalities (cases: 8.9% (n = 10) vs controls: 1.8% (n = 4) ($p = 0.006$)) as well as transplantations (cases: 16.8% (n = 19) vs control: 2.7% (n = 6) ($p < 0.0001$)) occurred more frequently in EFT cases during the 3-year follow-up period after T_0. Cases exiting the cohort due to transplantation (28/113 ever) had a significantly worse FEV1 ($p < 0.0001$), BMI z-score ($p = 0.011$) and had a higher rate of IV AB days ($p < 0.0001$) and hospitalization days ($p < 0.0001$) at the last registration compared to the remaining ETF cases. In analogy, deceased cases (17/113 ever) also suffered from a worse FEV1 ($p = 0.011$) and had more hospitalization days ($p = 0.006$) at the last registration than the remaining cases. None of the fatalities were attributed to the ETF (causes of death listed in supplement 2).

Although there was no difference in CFRD between the groups before T_0 ($p = 0.605$), significantly more new CFRD diagnoses were reported in cases during the first 3 years post-T_0 compared to controls (cases: 11.5% (n = 13) vs controls 4.9% (n = 11) ($p = 0.027$)). However, during further follow-up,

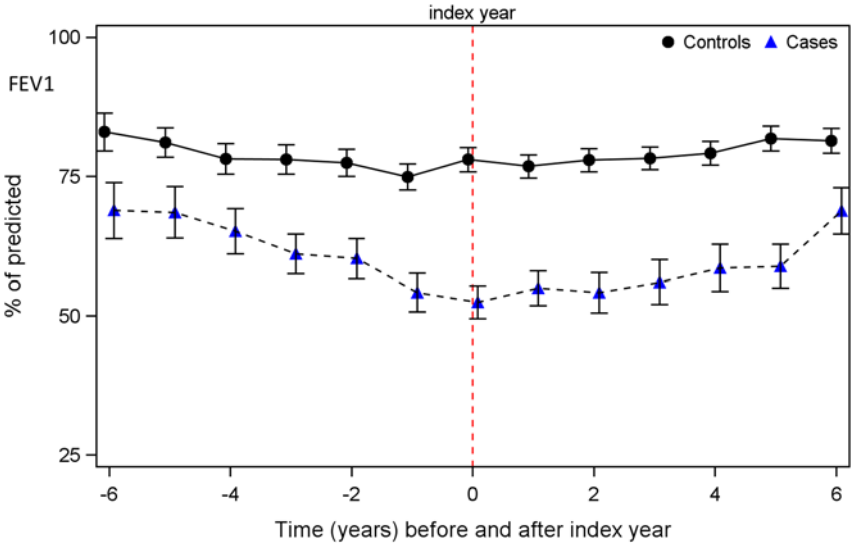

Fig. 2. Trend in FEV1% (mean (95% CI)) in cases receiving ETF versus matched controls. ETF has been introduced in cases between year −1 and year 0 (index year). Abbreviations: FEV1%: forced expiratory volume in one second as % of predicted; ETF: enteral tube feeding.

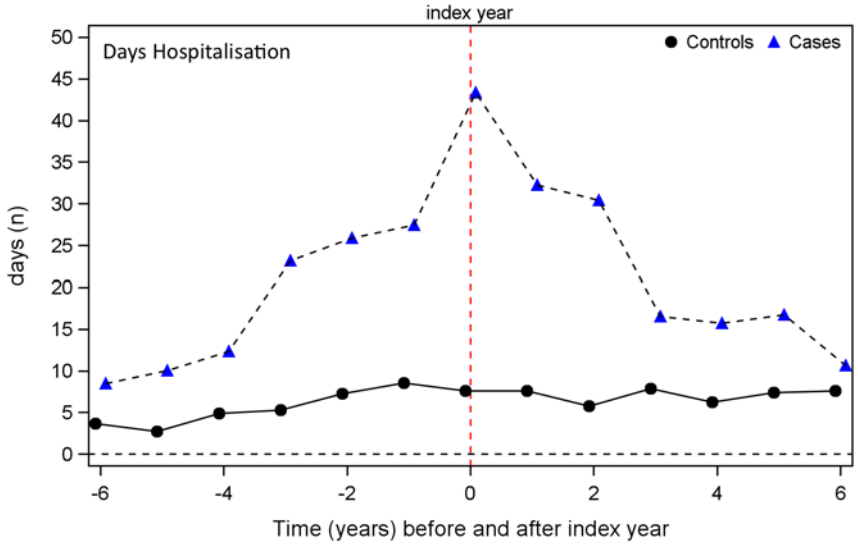

Fig. 3. Trend in days of hospitalization (mean (95% CI)) in cases receiving ETF versus matched controls. ETF has been introduced in cases between year −1 and year 0 (index year). Abbreviation: ETF: enteral tube feeding.

there was no significant difference in CFRD prevalence between the ETF groups and the control population (cases: 28.3% vs controls: 20.6% (p = 0.115)).

4. Discussion

According to the recent guidelines tube feeding is recommended when CF patients are unable to consume adequate amounts of macronutrients to achieve age appropriate weight and height, despite intensive follow-up [28]. However, the goals for nutritional status in the guidelines [14] appear difficult to achieve since even the control population had a median BMI of −0.4SD (−1.1 to 0.2SD) at T_0. Despite the low median BMI among patients in the BCFR, only 1.8 to 5.3% of them were yearly recorded as receiving tube feeding between 2000 and 2013 [29]. The hesitancy and the difficulty of initiating tube feeding are reflected by several observations in this study. The ETF cases had a significantly worse nutritional and pulmonary status at first entry in the registry as well as an important decline in pulmonary function and nutritional status towards T_0. Further on, this group had a significantly higher transplantation rate as well as mortality. White et al. described a delay of at least 5 months between the first suggestion of ETF and the actual tube insertion in adult CF patients [30]. The delay was explained by the patients' attitudes towards ETF, studied by Gunnel et al. [31]. They describe an apathy towards this treatment and incorrect assumptions concerning the gastric tube in patients without ETF [31]. Furthermore, the reported delay does not take into account hesitations in the team itself before suggesting ETF. Future studies are needed to evaluate whether the anticipatory planning and patient education, as suggested by the authors, will influence this delay.

In this registry-based study, it was impossible to determine the exact timing of ETF initiation during year T_0. However, it most likely accounts for the rapid, though non-significant improvement in BMI z-score noted when comparing year T_0 to year T_{-1}. There was a further correction of the BMI towards the original curve, which was maintained on the long-term. As has been described previously in other studies, cases returned to their own BMI curve but did not further improve towards the 50th percentile [17,19,21,22]. Patients with ETF have, however, a 10 times higher likelihood to obtain a BMI above the 50th percentile when compared to a BMI, sex, age, pancreatic and pulmonary function matched control group [32]. Why the 50th BMI percentile was not reached, remains unexplained. Compliance, insufficient caloric supplementation and the relatively short treatment duration (median 2 years (1.0–5.0)) might be contributing factors. Some reports warn for inferior results of ETF on weight gain and overall survival once FEV1 has dropped below 40–65% [17,21]. However, a poor pulmonary function does not exclude achievement of a satisfactory nutritional status [30,33].

In contrast to previous reports [18,19,21], we did not observe a significant improvement in the height z-score of children receiving ETF despite their significantly smaller stature at T_0. The impact of age at start, duration of tube feeding and amount of calories supplied on catch-up growth needs to be studied.

As described in most case series, the observed rate of pulmonary decline decreased after initiation of ETF (FEV1 slope before T_0 −1.52%/year and after T_0 + 0.39%/year) [16,17,19,21–23]. The control CF patients, on the contrary, showed a steady pulmonary function decline over the years (FEV1−0.48%/year). This positive effect seems to be slower than the nutritional status improvement, since stabilization was only detected one year after the start, whereas the BMI was already improving by T_0. The start of ETF coincided with a significant decrease in hospitalizations and IVAB courses. This was, however, not observed by White et al. [30]. Even so, more deaths and transplantations were observed during follow-up among our cases compared to controls, reflecting their worse general condition at T_0.

White et al. demonstrated a 4 times higher likelihood of CFRD diagnosis among CF patients receiving ETF [33]. These results are similar to our findings, since we found twice as many new CFRD diagnoses in the 3 years post-T_0 in ETF cases compared to controls. It suggests that some CF patients experience a persistent nutritional decline necessitating

nutritional interventions due to an impaired glucose metabolism. Increasing the carbohydrate load by introducing ETF might have precipitated the diagnosis of CFRD [33]. This observation argues for a strict glycemic control in all patients starting with ETF. On long-term, however, we did not find any difference in the prevalence of CFRD between both groups.

Any registry study presents a number of limitations and weaknesses. Missing data are an important issue. The data were collected over a number of years where treatment changes affecting both BMI and pulmonary function may have occurred, so confounding variables might be overlooked. The registry does not contain data on motivation for starting ETF (e.g. weight gain, improving nutritional status before transplant, palliative care…), amount of calories given and exact timing of the start of ETF. Furthermore, there is no information on adherence nor on the reason and exact timing of ETF discontinuation, so this can influence the results. The benefits of ETF on pulmonary function and nutritional status should be looked at with some reserve because of the high mortality rate (8.9% vs 1.8%) and transplantation rate (16.8% vs 2.7%) rate within the first 3 years following introduction of ETF among cases compared to controls. This makes the interpretation of the results complex, since the loss from the cohort leads to an overestimation of the positive effect of ETF because these patients had a worse nutritional and/or pulmonary status at the last registration compared to the remaining cases. Nevertheless, a beneficial effect of ETF is obvious since we already notice a rapid increase in BMI between year T_{-1} and T_0, even before any mortality occurs. The mixed model analysis shows that a higher BMI z-score was independently associated with a better FEV1. Furthermore, after introduction of ETF in cases, not only an absolute reduction of overall hospitalization days and treatment days with IVAB was noticed, also a proportional reduction of cases being treated with IVAB or being hospitalized was documented.

In conclusion, this registry study demonstrated an improved BMI z-score and a decrease in the pulmonary function decline after introduction of ETF. This resulted in a lower hospitalization rate and less need for IV AB treatment. However, results should be interpreted with care due to the high transplant and mortality rate shortly after introduction of ETF. Patients starting with tube feeding, had a risk of precipitating CFRD diagnosis during the years following the introduction of ETF, so careful glycemic control is important. Future research should focus on prospectively studying whether there is a difference in growth results according to the age at start, whether following the guidelines more strictly will lead to better BMI z-scores and eventually prevent the observed pulmonary function decline and whether different feeding formulae or enzyme administration methods might influence the results. Finally, influences of overnight feeding on circadian rhythm and sleep quality have never been studied.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcf.2018.01.004.

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