Original research

The Changing Landscape of Treatment for Cystic Fibrosis Related Diabetes

Mehdia Amini, Kevin Yu, Jessica Liebich, Vaishaliben Ahir, Emily Wood, Stewart Albert, Sandeep Dhindsa[*]

Division of Endocrinology, Diabetes and Metabolism, Saint Louis University School of Medicine, St. Louis, MO 63110, USA

ABSTRACT

Objective: Patients with Cystic Fibrosis related diabetes [CFRD] are treated with insulin and high calorie diets to maintain body mass. The combined CFTR modulator elexacaftor/tezacaftor/ivacaftor [ETI] decreases pulmonary exacerbations and improves nutritional status. We reviewed the effects of ETI on BMI, HbA1c and diabetes regimen in patients with CFRD over a period of three years.
Methods: Data of previously CFTR-modulator-naïve patients with CFRD and pancreatic insufficiency on ETI therapy were retrieved from an electronic health record database. Patients were followed for a mean duration of 2.7 ± 0.8 years after ETI initiation. Data pertaining to weight, BMI, HbA1c and diabetes regimen were collected at 6 months, 12 months, 2 years and at 3 years post-ETI initiation. Patients were then dichotomized based on their baseline BMI into a low BMI group and an "at target" BMI group. The effects of ETI on changes in weight, BMI, A1c and diabetes regimen were compared in both groups over a period of three years.
Results: Twenty-seven patients with CFRD (15 men/12 women), age 30.6 ± 11.5 (SD) years, BMI 22.4 ± 4.0 kg/m^2, were included. Fifteen patients had low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men) and 12 patients had at target BMI (≥ 22 kg/m^2 for women, $\geq$ BMI 23 kg/m^2 for men). Patients with low BMI had an increase in their BMI from 19.5 ± 1.7 to 21.4 ± 2.2 kg/m^2 at one year (p = 0.002), and 21.8 ± 1.8 kg/m^2 at three years (p = 0.004) after ETI initiation. Four patients (out of 15) in the low BMI group had achieved normal BMI by the end of study follow up. There was no change in weight in the at target BMI group. HbA1c and basal insulin requirements did not change in either group. Five patients started non-insulin therapies.
Conclusion: BMI increased after ETI therapy in CFRD patients with low BMI, but not in those with at target BMI. The use of non-insulin therapies is increasing in CFRD and should be evaluated in future studies.

Introduction

Cystic fibrosis-related diabetes [CFRD] is a frequent extra-pulmonary complication affecting approximately 50% of adults with cystic fibrosis [1]. The pathophysiology of CFRD is complex, multifactorial and incompletely described. Dysfunctional cystic fibrosis transmembrane conductance regulator [CFTR] protein results in viscous pancreatic ductal secretions, pancreatic exocrine obstruction, and damage to pancreatic beta islet cells [2]. There is also dysregulation of the incretin hormonal axis and direct beta cell destruction from intra-islet inflammation [1,3,4]. The insulin insufficiency promotes a catabolic state, with breakdown of protein and muscle, all of which has been linked to pulmonary function decline [1,5]. CFRD is a unique form of diabetes, with clinical features overlapping with both type 1 and type 2 diabetes. Patients with CFRD are at risk for microvascular complications, however the complication rate is lower as compared to type 1 or type 2 diabetes mellitus (DM) [6]. While the main cause of death in patients with type 1 and type 2 DM is cardiovascular disease, mortality in patients with CF (including those with CFRD) is primarily driven by lung disease [7]. The goal of therapy does not just focus on reducing the hemoglobin A1c (HbA1c); rather it is to limit post prandial hyperglycemia, glycosuria, calorie loss, and protein and muscle wasting [5]. The Cystic Fibrosis Foundation recommends that adult women and men should be encouraged to consume high calorie diets to maintain a BMI ≥ 22 kg/m^2 and BMI ≥ 23 kg/m^2 respectively [5], which correlates with improved pulmonary function and survival [8]. Insulin is the only recommend treatment of CFRD [5].

CFTR modulators have revolutionized the treatment of CF by directly improving the stability and function of the CFTR protein at the plasma cell membrane [1]. Therapy with CFTR modulators results in improved

lung function and nutritional status [9]. They may also have specific effects on insulin sensitivity, intra-islet cell inflammation, insulin exocytosis and glucagon secretion [2]. The most effective CFTR modulator (elexacaftor/tezacaftor/ivacaftor (ETI) was approved by the FDA in 2019 for people with CF who have at least one copy of the most common F508del mutation or at least one copy of 177 other specified mutations [9]. It is indicated for approximately 95% of the CF population [1]. Prior studies have suggested a positive correlation between ETI therapy and BMI in patients with CF [10,11], however the existing literature on the effects of ETI therapy in patients with CFRD is limited and lacks long-term follow up data. We reviewed our experience of previously CFTR modulator naïve patients with CFRD on ETI therapy over a total time span of three years. The primary outcome was the effect of ETI treatment on weight and BMI. Additionally, we analyzed the change in BMI in relation to the baseline BMI of patients. The secondary outcomes were changes in HbA1c and diabetes regimen.

Methods

This is a retrospective chart review study. Data were retrieved from the electronic medical records of Saint Louis University hospital clinic database using the program Epic and the sub-program Slicer/ Dicer. The search algorithm inclusion criteria were: "Patients", "Cystic Fibrosis", "August 1, 2018, through June 30, 2023", "Diabetes", and "medicine: ETI", "age 18 to 90 years."

We included patients with CFRD on ETI, after excluding patients who had used ETI for less than one year, had been on other CFTR modulators, had concurrent type 1 diabetes, or who were pregnant. All patients were on standard doses of ETI (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) during our three years follow up period. We collected information on weight, HbA1c and anti-hyperglycemic medications at baseline (defined as the date of initiation of ETI). All patients met with a dietician on planned and as-needed basis. CFRD patients who were not on any anti-hyperglycemic drugs were considered "managed with diet modifications". Duration of CFRD, presence of exocrine insufficiency, and class of CFTR variant were recorded. Follow-up data were collected at 6 months, 1 year, 2 years and 3 years (if available). Patients were then dichotomized based on their baseline BMI into a low BMI group and "at target" BMI group. The effects of ETI on changes in weight, BMI, HbA1c and diabetes regimen were compared in both groups over a period of three years.

Data were not collected beyond one year in one patient because of discontinuation of ETI due to side effects. Three-year data were not available in eight patients due to these reasons: patient moved away (n = 3), patient has not followed up (n = 4), or duration of ETI treatment was less than 3 years (n = 1). The mean duration of follow up was 2.7 ± 0.8 years. HbA1c was conducted at clinic visits by point-of-care Affinion AS100 analyzer (Abbott, Princeton, NJ).

Statistical analysis was performed by the program Statistica (https ://www.Statsoft.com). Data were distributed normally; hence results are presented as means ± standard deviation. Numerical data were analyzed by analysis of variance of repeated measures (RMANOVA). If the analysis of variance was significant, then post hoc comparisons were performed by the test of Fishers Least Significant Differences. Group comparisons were made by independent *t*-test. Categorical data were analyzed by the chi square test. Pearson correlation was used to test for regression between continuous variables. The study was approved, and a waiver of informed consent was granted by the St Louis University Institutional Review Board. The data set was de-identified after data collection, as per Health Insurance Portability and Accountability Act Authorization per section 164.512(i) of the Privacy Rule.

Results

There were 27 patients with CFRD (15 men/12 women). All patients had pancreatic insufficiency. The mean age was 30.6 ± 11.5 (mean ±

SD) years (Table 1). The predominant race in our cohort was non-Hispanic Caucasian (n = 25). One patient was non-Hispanic Black and one American Indian. All patients had known F508 del mutations in the CFTR gene (homozygous 24/ heterozygous 3). The mean duration of the CFRD was 11.6 ± 7.1 years. Most patients were treated with insulin (n = 18) for CFRD, but 9 patients were on diet modifications alone.

At the start of ETI therapy, the mean weight was 62.8 ± 15.5 kg, BMI was 22.4 ± 4.0 kg/m^2, and HbA1c was 7.7 ± 2.0%. Fifteen patients had low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men) and 12 patients had at target BMI (≥22 kg/m^2 for women, ≥BMI 23 kg/m^2 for men). The mean follow up duration in the low and at target BMI groups was 2.9 ± 0.7 and 2.5 ± 0.9 years, respectively. There was a trend towards an increase in weight and BMI (p = 0.052 for both by RMANOVA). The mean weight gain was 2.1 ± 3.7 kg at 6 months, 3.1 ± 5.4 kg at one year, 1.5 ± 6.6 kg at two years and 2.4 ± 6.5 kg at three years. However, we noted an inverse relationship of change in weight during follow up compared with the starting BMI (Fig. 1). Those with low BMI gained weight, whereas those with at target BMI either stayed at the same weight or lost weight. To further characterize this relationship, we compared the change in weight of patients with low BMI to those with at target BMI. The baseline characteristics of patients with low or at target BMI are shown in Table 1.

In the low BMI group (mean BMI 19.5 ± 1.7), ETI treatment was associated with a significant increase in weight (p by RMANOVA = 0.0002), as compared to baseline weight of 53.9 ± 10.4 kg, the weight at 6 months tended to increase (56.1 ± 9.4, p = 0.06), and was significantly increased at one year (58.9 ± 10.6 kg, p < 0.001). The increase in weight was maintained at two years (58.0 ± 11.1 kg, p = 0.001 from baseline) and three years (60.7 ± 10.2 kg, p = 0.001 from baseline), Fig. 2. Similarly, there were improvements in BMI in the low BMI group (p by RMANOVA < 0.001) from 19.5 ± 1.7 to 21.4 ± 2.1 kg/m^2 at one year (p < 0.0001). The increase in BMI was maintained at two years (21.1 ± 2.3 kg/m^2, p = 0.0006 from baseline) and three years (21.8 ± 1.8 kg/m^2, p = 0.01 from baseline), Fig. 3. Four patients (out of 15) in the low BMI group had reached the ideal goal of normal BMI by the end of study follow up. Two patients in the low BMI group did not gain weight. One patient had weight loss due to stage IV metastatic colon cancer while the other patient struggled with adherence to pancreatic enzyme replacement therapy and nutritional supplements.

In comparison, in the at target BMI group (mean BMI 26 ± 2.6 kg/m^2) there was no change in weight (p = 0.21 by RMANOVA) or BMI (p = 0.26 by RMANOVA) over our three year follow up. There was a trend towards an increase in weight at month 6 (p = 0.07), but not at one year

Table 1
Baseline demographics of patients with CFRD on ETI. Data are shown as means ± SD. Patients were divided into low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men) and at target BMI group (≥22 kg/m^2 for women, ≥23 kg/m^2 for men). Types of anti-hyperglycemic medications at both baseline and 3 years are mentioned at the end of table.

|	All	Low BMI	At target BMI	p
M/F	15/12	7/8	8/4	0.30
F508 mutation homozygous/ heterozygous	24/3	13/2	11/1	0.68
Age, years	30.6 ± 11.5	30.3 ± 12.7	31.0 ± 10.5	0.87
Duration of CFRD, years	11.6 ± 7.1	12.1 ± 7.5	10.8 ± 6.8	0.86
Weight, baseline, kg	62.8 ± 15.5	53.9 ± 10.4	73.9 ± 13.8	<0.001
BMI baseline, kg/m^2	22.4 ± 4.0	19.5 ± 1.7	26.0 ± 2.6	<0.001
HbA1c baseline, %	7.7 ± 2.0	7.6 ± 2.1	7.7 ± 2.1	0.90
Baseline medication, insulin/ diet/other	18/9/0	9/7/0	10/2/0	0.22
Medications at 3 years insulin/ diet/other	15/7/5	6/6/3	9/1/2	0.14
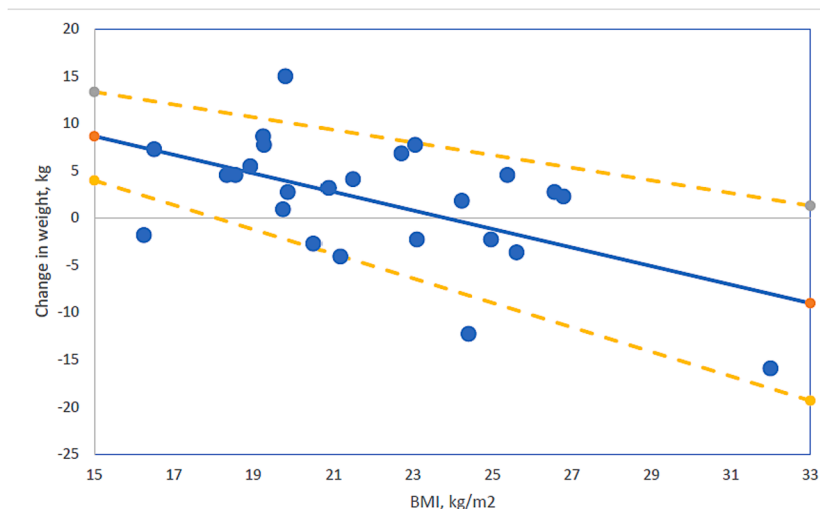
Fig. 1. Relationship of change in weight after 2 years on ETI with respect to baseline BMI. Regression shown as mean $\pm$ 95 % CI (r = -0.55, p = 0.005). Results were similar at 3 years (r = -0.53, p = 0.02).
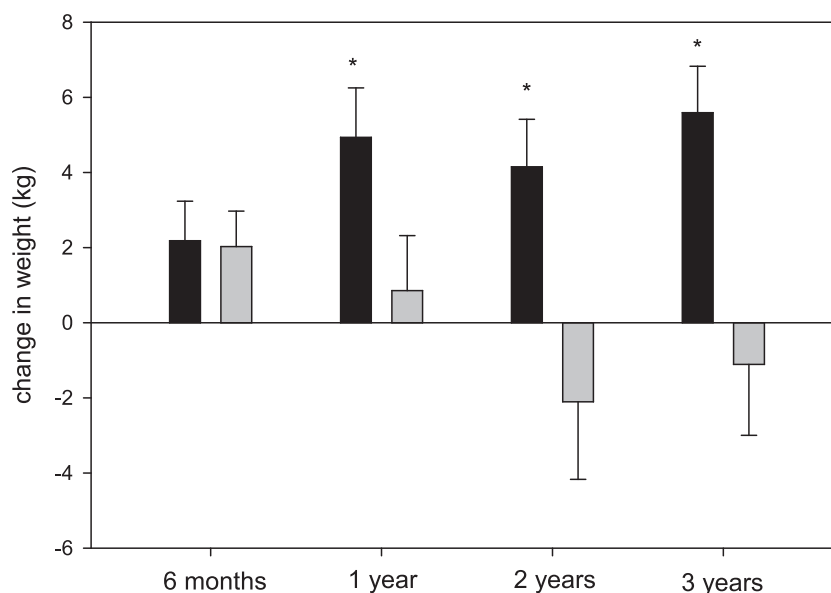

Fig. 2. Change in weight of patients with CFRD over three years since starting ETI. Black bars: Low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men). Grey bars: At target BMI (≥22 kg/m^2 for women, ≥23 kg/m^2 for men). Data are shown as mean $\pm$ standard error. * p $<$ 0.05 by *t*-test as compared to at target group.

or thereafter (Fig. 2).

The relative proportions of anti-glycemic regimens after 2 years of ETI were similar in the two BMI groups with regard to the use of insulin or diet alone, Table 1. There were 5 patients who were managed with the addition of non-insulin therapies at the discretion of the treating physician. In the low BMI group, two patients were started on glucagon like peptide-1 receptor agonists (GLP-1 RA), and one patient started a dipeptidyl peptidase (DPP)-4 inhibitor. In the at target BMI group, one patient was started on a GLP-1 RA and one patient started metformin along with a DPP-4 inhibitor. There were no incidents of pancreatitis over the three-year follow-up.

The trajectory of weight gain after ETI treatment remained unchanged even after exclusion of the three patients on GLP-1 RA. The weight in subjects in the low BMI group increased from baseline weight of 52.3 $\pm$ 10.2 kg to 57.2 $\pm$ 10.7 kg at one year (p $<$ 0.01), 56.3 $\pm$ 11 kg (p = 0.02) at two years and 59.4 $\pm$ 11 kg at three years (p $<$ 0.01). Similarly, there was an increase in BMI in the low BMI group from 19.1 $\pm$ 1.6 kg/m^2 to 21.1 $\pm$ 2.1 kg/m^2 at one year (p = 0.05). The increase in

BMI persisted at 2 years (20.6 $\pm$ 2.2 kg/m^2, p = 0.01) and at 3 years (21.7 $\pm$ 1.9 kg/m^2, p $<$ 0.01). There were no changes in weight or BMI in the at target BMI group, even after exclusion of the patient on GLP-1 RA (p = 0.51 and 0.44 respectively by RMANOVA).

During the three-year observation period on ETI, overall, there was no change in HbA1c (p = 0.97 by RMANOVA). HbA1c also did not change in either BMI groups (Fig. 4). The mean basal insulin dose at start of ETI was 10.6 $\pm$ 14 units/day and there were no changes in the mean basal insulin dose over our three-year study period. Due to heterogeneity in reporting, we were not able to accurately estimate prandial insulin requirements.

Discussion

The primary goal in the management of CFRD has been to maintain weight and BMI [1,5]. Patients with CF are at risk for malnutrition due to inadequate calorie intake, increased energy expenditure and malabsorption. The known association between malnutrition and worsening
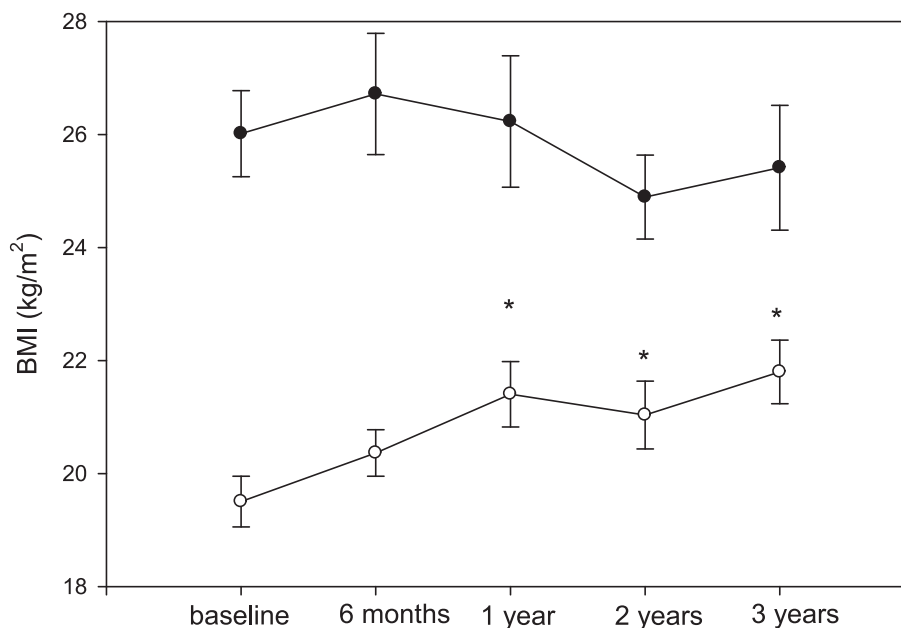
Fig. 3. BMI of patients with CFRD over three years since starting ETI. White circles: Low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men). Black circles: At target BMI (≥22 kg/m^2 for women, ≥23 kg/m^2 for men). Data are shown as mean $\pm$ standard error. * $p < 0.05$ by *t*-test as compared to at target group.
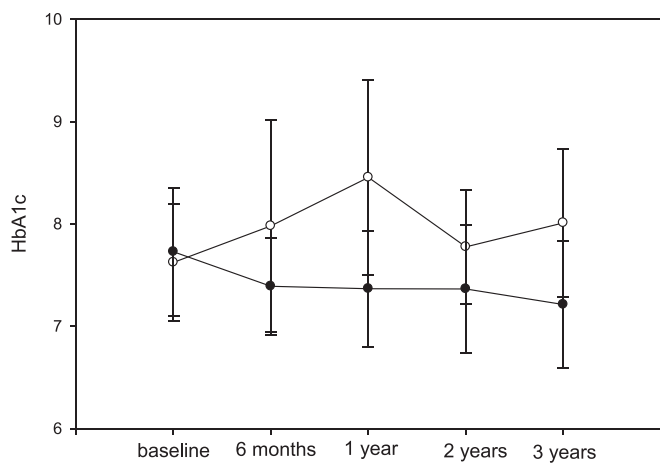

Fig. 4. Glycated hemoglobin in the low BMI (<22 kg/m^2 for women, <23 kg/m^2 for men, white circles) and at target BMI group (≥22 kg/m^2 for women, ≥23 kg/m^2 for men, black circles) after ETI initiation.

survival rates in CF has resulted in aggressive nutritional interventions over the past few decades, which has reduced the prevalence of malnutrition. At the same time, overweight/obesity has been emerging in the CF population as a new problem. We are the first group to report three year data on the effects of ETI therapy on changes in weight, BMI and HbA1c in previously CFTR modulator naïve patients with CFRD and pancreatic insufficiency. Our findings demonstrate that despite increases in weight after the first 6 months of therapy, patients with at target baseline BMI returned to their baseline weight while those with initially low BMI continued to gain weight.

Initiation of CFTR modulators has been associated with an increase in body weight in previous studies [12]. Stallings *et al* found that Ivacaftor treatment increased body weight by 2.5 kg in CF patients [13]. A 5-year observational study of the United States and United Kingdom CF registries demonstrated BMI increases in Ivacaftor treated patients with CF by 0.8 kg/m^2 [14]. One-year treatment with combination therapy lumacaftor–ivacaftor increased BMI by 0.9 kg/m^2 in 40 CF patients [15]. Since these studies, the more effective triple modulator ETI has been introduced. Middleton *et al* conducted a phase 3, randomized, double-blind, placebo-controlled trial in 403 subjects, 12 years and older, with F508Del CFTR mutations and showed an increase of 2.9 kg in body weight following ETI treatment for 24 weeks relative to placebo [10]. Another study revealed increases in BMI Z-scores from 0.3 to 0.8 in 20 youths and adults with CF within the first year after ETI initiation [16]. While these studies mostly found a positive impact of CFTR modulators on weight, they did not stratify for the presence of absence of CFRD.

Lurquin *et al* investigated the effects of ETI on weight, BMI, HbA1c and total insulin dose in a retrospective single center study in 17 patients with CFRD and pancreatic insufficiency who were treated with ETI (n = 4), tezacaftor + ivacaftor (TI) (n = 4) and TI with later switch to ETI (n = 9) [11]. The study suggested an increase in weight from baseline 60 kg to 64 kg (p = 0.001) after the initiation of combination CFTR modulator therapy (ETI and TI) over a median duration of 16 months; however, the magnitude of weight change of ETI monotherapy is unclear as the median duration of ETI use was only 1.75 months as compared to a median duration of 14.5 months of TI therapy. The data on insulin requirements was available in 8 patients on ETI (either from the start or after switch from TI) and suggested a slight reduction in insulin requirements from 0.75 to 0.67 U/kg. There was no significant change in HbA1c. Another observational study on 24 patients with CFRD and pancreatic insufficiency showed an increase in the percent of fat mass by a median value of 3 % (p = 0.029) over a 6 month period [17].

Peterson *et al* reported the findings from an observational study of 134 CF patients who had received ETI for one year [18]. The study included 46 patients with CFRD. ETI treatment was associated with a 4.6 kg increase in body weight and 1.5 kg/m^2 increase in BMI over one year. The increase in weight was similar in patients with and without diabetes. Decreases were observed in the rates of underweight (7.5% to 2.2%) and increases were observed in rates of overweight (19.4% to 31%) and obesity (7.5% to 9.7%). The effect of ETI on the rate of BMI increase was not modified by baseline weight (p = 0.53). In our study, we also found an initial increase in weight in patients with low as well as normal BMI. However, at one year and beyond, the body weight returned to baseline in the normal BMI group. It is possible that a longer duration of follow up after ETI initiation in the study by Peterson *et al* may have shown similar findings.

Furthermore, our patients with CFRD meet with a dietician regularly

and discuss their dietary choices. It is possible that our patients with low BMI perceived the weight gain after ETI therapy as beneficial, while those with at target BMI tried to modify their diet to limit weight gain. While we did not collect data on caloric intake of the study participants, it is likely that these discussions led to a decline in calorie intake in those with at target BMI.

There were also differences in the baseline patient characteristics among the two studies. Our study had a higher rate of homozygous F508del mutations (88% versus 58%), which is associated with more pronounced clinical manifestations, an earlier diagnosis of disease, higher sweat chloride levels and a higher prevalence of pancreatic insufficiency, as compared to compound heterozygotes and genotypes without F508del. While none of our patients had pancreatic sufficiency, 11 patients in the cohort of Peterson *et al* had pancreatic sufficiency. Interestingly, those 11 patients did not have a change in their BMI following ETI treatment. Possibly, those 11 patients were not malnourished and thus similar to the normal BMI group in our study. There were no changes in A1c or random blood glucose levels in CFRD patients after one year of treatment with ETI, which is consistent with our findings.

It is known that HbA1c has limited utility as an index of glycemia in CFRD because hyperglycemia is predominantly post-prandial and transient. We did not have access to other glycemic parameters such as oral glucose tolerance tests or systematic home glucose monitoring data. One retrospective single-center study in 11 adults with CFRD who used continuous glucose monitors (CGM) as part of their routine clinical care showed no changes in HbA1c, median glucose, percentage time spent in hyperglycemia or hypoglycemia at 3 months and at 6 months after ETI use as compared to baseline [19].

Other studies showed inconsistent effects on glycemia after ETI therapy. In a prospective, single center observational study, 34 adults with CF (17 with CFRD) and with at least one F508 del mutation were followed for 3–12 months after ETI initiation [20]. Blinded 14-day CGM sensors were applied within 3 months prior to starting ETI and again within 3–12 months after start of ETI. Although ETI initiation in adults with CFRD was associated with significant improvements in CGM derived measures of average glucose, percent time in range (70–180 mg/dL) and decrease in glycemic variability, 8 out of 17 subjects with CFRD were using non-blinded CGMs for their day to day diabetes management which may have affected the end results.

In our study, there was no significant change in basal insulin requirements over the three-year observation period. Five patients in our study started non-insulin therapies for CFRD. The use of non-insulin therapies in the management of CFRD has been limited in the past due to concerns over efficacy and safety. Instead, insulin has been preferred for its anabolic action. While there have been case reports of utilization of non-insulin therapies in CFRD, clinical trials have found mixed results [21]. Repaglinide was found to be similar to insulin therapy for glycemic control in a two-year long trial [22]. In contrast, sitagliptin did not show an effect on glycemia over 6 months in adults with CFRD [23]. More recently, addition of semaglutide was reported to improve glycemia and eliminate the need of prandial insulin in a patient with CFRD [24]. In our study, three patients started a GLP-1 analogue. Two of those patients were able to stop insulin therapy, while one patient is being managed with combined insulin and GLP-1 analogue.

Insulin is currently the only recommended treatment of CFRD [5]. However, clinical care guidelines are from 2010, which is prior to the arrival of the CFTR modulators in 2012. The characteristics of CF patients have changed since then, and obesity is emerging as a new phenomenon. In current times, one third of patients with CF are overweight or obese [25]. Obesity in patients with CFRD would increase insulin resistance [25–27] as is seen in type 2 DM [28]. Correspondingly, patients with CFRD may also benefit from weight reducing non-insulin therapies as an alternative, or in addition to insulin. Patients struggle with adherence to multiple daily insulin injections, cost of insulin therapy, access to a refrigerator for insulin storage outside of the house

and side effects of hypoglycemia with insulin therapy [29]. A holistic and individualized patient-centered approach is crucial in facilitating adherence to medical therapy and optimizing treatment of CFRD.

Our study is limited by its retrospective, non-blinded nature and small sample size, potentially limiting power to detect weight changes in the at target BMI group. There is a lack of non-CFRD comparator group. We did not have any Hispanic patients, and only two non-white patients. Hence, our results may not apply to minority populations with CF. In our clinic, it is the standard of care to put all eligible patients with CFRD on ETI, and there were very few ineligible patients to make up a comparator group. Therefore, a control group of patients with CFRD not on ETI therapy was not available.

In conclusion, we found that CFTR modulator therapy with ETI led to an increase in weight in adult CFRD patients with low BMI, but not in those whose BMI was already at target. ETI therapy did not result in changes in HbA1c or basal insulin dose, irrespective of baseline weight. There has also been a concern that with improved pulmonary therapy, along with the use of CTFR modulators, the rates of obesity may increase in patients with CF [25]. We did not see an increase in obesity in our study. Until now, insulin has been the only recommended treatment of CFRD [5]. In our three-year study, physicians were able to use alternate, non-insulin anti-glycemic therapies without any significant side effects. This suggests a paradigm shift in the treatment of CFRD in patients who are also treated with CFTR modulators. Therapy for CFRD may change to be more in line with that of type 2 diabetes. Further research is needed to explore the cardiovascular and renal effects of non-insulin therapies, such as GLP-1 RA and SGLT-2 inhibitors, in the management of CFRD.

CRediT authorship contribution statement

Mehdia Amini: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Kevin Yu:** Data curation. **Jessica Liebich:** Data curation. **Vaishaliben Ahir:** Data curation. **Emily Wood:** Writing – review & editing. **Stewart Albert:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Sandeep Dhindsa:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SD has received speaker honoraria from Marius Pharmaceutical and Acerus Pharmaceuticals and has received research support from Clarus Therapeutics. These interests are not related to and did not influence the current study. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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