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Glycemia and β-cell function before and after elexacaftor/tezacaftor/ivacaftor in youth and adults with cystic fibrosis

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ABSTRACT

Background: Diabetes is prevalent among people with CF (PwCF) and associated with worse clinical outcomes. CFTR modulators are highly effective in improving the disease course of CF. However, the effects of elexacaftor/tezacaftor/ivacaftor (ETI) on glucose metabolism in PwCF are unclear.
Methods: Twenty youth and adults with CF underwent frequently sampled oral glucose tolerance tests (fsOGTT) before and after ETI initiation. Glucose, insulin, and C-peptide were collected at 0, 10, 30, 60, 90, and 120 min after 1.75 g/kg (max 75 g) of dextrose. HbA1c and continuous glucose monitoring (CGM) were collected in a subset. Estimates of insulin secretion (C-peptide index), insulin resistance (HOMA2 IR and IS(OGTT Cpep)), and β-cell function (C-peptide oral disposition index, oDI_{coeo}), were compared before and after ETI.
Results: Participants were a median (IQR) of 20.4 (14.1, 28.6) years old, 75 % male. Follow-up occurred 10.5 (10.0, 12.3) months after ETI initiation. BMI z-score increased from 0.3 (-0.3, 0.8) to 0.8 (0.4, 1.5), $p = 0.013$ between visits. No significant differences were observed in glucose tolerance, glucose area under the curve, nor fsOGTT glucose concentrations before and after ETI. Median (IQR) C-peptide index increased from 5.7 (4.1, 8.3) to 8.8 (5.5, 10.8) $p = 0.013$ and HOMA2 IR increased ($p < 0.001$), while oDI_{coeo} was unchanged ($p = 0.67$). HbA1c decreased from 5.5 % (5.5, 5.8) to 5.4 % (5.2, 5.6) ($p = 0.003$) while CGM variables did not change.
Conclusions: BMI z-score and measures of both insulin resistance and insulin secretion increased within the first year of ETI initiation. β-cell function adjusted for insulin sensitivity (oDI_{coeo}) did not change.

Introduction

Cystic fibrosis related diabetes (CFRD) results from progressive insulin insufficiency and intermittent insulin resistance. From a young age, insulin insufficiency is present in most individuals with cystic fibrosis (CF) [1–3] placing this population at high risk for developing diabetes over time. CFRD is diagnosed in 15–20 % of adolescents and 30–50 % of adults [4] and associated with poorer nutrition, lower lung function, and increased mortality [5–7].

The pathophysiology of CFRD is multifactorial. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene lead to pancreatic exocrine and endocrine dysfunction at a young age [2,3]. In addition, pancreatic fibrosis and chronic inflammation contribute to progressive insulin insufficiency [8,9] with loss of β-cell mass and islet abnormalities. Conflicting information exists regarding the role of the CFTR in the β-cells [10,11]. The latest evidence suggests that CFTR does not directly regulate insulin secretion, but rather that CFRD results from a combination of reduced islet mass, pancreatic exocrine abnormalities that may indirectly impair β-cell function via paracrine effects, and fluctuating insulin resistance in the setting of a progressive chronic

Abbreviations: AUC, Area under the curve; BMI, Body mass index; CFRD, Cystic fibrosis related diabetes; FEV1, Forced expiratory volume in 1 *sec*; FVC, Forced vital capacity; HbA1c, Hemoglobin A1c; oDI, Oral disposition index; OGTT, Oral glucose tolerance testing; fsOGTT, Frequently sampled OGTT.

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disease [8].

With the advent of CFTR modulators, there has been intense interest surrounding the potential effects of these therapies on glucose homeostasis. With the earliest CFTR modulator ivacaftor, US FDA approved in 2012, small studies showed improvements in insulin secretion [12,13]. National registry data from the US and UK have also demonstrated a decreased incidence of CFRD in individuals treated with ivacaftor compared to the rest of the CF population [14]. In contrast, subsequent studies with the modestly effective modulator lumacaftor/ivacaftor have not shown improvements in insulin secretion nor glycemia [15–17]. The latest CFTR modulator approved by the FDA, elexacaftor/tezacaftor/ivacaftor (ETI), is highly effective for decreasing sweat chloride, decreasing pulmonary exacerbations, increasing body weight, and improving pulmonary function. However, its effects on insulin secretion and β-cell function in individuals with CF are unknown.

The objectives of this study were to perform secondary analysis of an existing data set to compare OGTT-derived estimates of insulin secretion, insulin resistance, and β-cell function before and after clinical initiation of ETI.

Research design and methods

Participants

Participants were selected from a larger group of individuals recruited into the EnVision CF Multicenter Study of Glucose Tolerance (NCT03650712). This prospective study includes 4 CF centers (University of Iowa, Children's Hospital Colorado, University of Minnesota, and Washington University in St Louis), and individuals are recruited to undergo annual frequently sampled OGTTs. Inclusion criteria were as follows: individuals had to be ≥6 years of age with a confirmed diagnosis of CF by sweat chloride and/or genetic testing. Participants on CFTR modulators were required to be on a stable dose for at least 8 weeks prior to study visit. Exclusion criteria included known diagnoses of type 1 or type 2 diabetes, organ transplantation, pregnancy, treatment with insulin or other medications affecting glucose homeostasis, initiation of antibiotics within 4 weeks, or hospitalization or use of systemic steroids within 8 weeks prior to study visits. Enrollment began July 2019.

For this analysis, data from individuals with OGTTs performed both within a year prior to (visit one, V1) and after initiation of ETI (visit two, V2) were included. The study was approved at all participating centers through a centralized IRB at the University of Iowa, and informed consent and assent, as appropriate, were obtained.

Procedures

Study visits

Study visits were conducted at each institution's outpatient clinical research center. Participants arrived the morning after a minimum 8 h fast. Weight and height were collected. Body mass index (BMI) was calculated, and in individuals under 20 years old, BMI z-score was determined based on CDC growth charts. In individuals ≥20 years of age, age 20 was used as a reference to calculate the BMI z-score in order to compare BMI between youth and adults, as done by others [18,19]. Chart review was performed to determine CF genotype, medications, pancreatic sufficiency status, and lung function from the most recent pulmonary clinic visit within 3 months.

Frequently sampled OGTTs. Following confirmation of fasting, an intravenous line was placed for blood draws, and participants consumed 1.75 g/kg (max 75 g) of dextrose. Blood samples for glucose, insulin, and C-peptide were drawn at 0, 10, 30, 60, 90, and 120 min post dextrose. OGTT results were used to define degree of glucose impairment – normal glucose tolerance (NGT, fasting glucose <126 mg/dL, 1 h glucose <200 mg/dL, and 2hr glucose ≤140 mg/dL), abnormal glucose tolerance (AGT, 1 h glucose ≥200 mg/dL and/or 2 h glucose 140–199 mg/dL), and CFRD (fasting glucose ≥126 and/or 2hr glucose ≥200 mg/dL).

Samples were drawn into lithium heparin tubes, processed, aliquoted and frozen at −80 °C. Glucose, insulin, and C-peptide were analyzed centrally at the University of Iowa. Glucose was measured by YSI analyzer (Yellow Springs, OH) and reported in mg/dL. Insulin and C-peptide were measured using a magnetic bead kit (#HMHEMAG-34 K, Millipore Sigma, Burlington, MA, USA). Insulin units were reported as mcU/mL and C-peptide units as pmol/L. When performing planned insulin calculations, some samples were noted to demonstrate unexpectedly high insulin concentrations. Although independent confirmation of a subset of samples with an alternate assay demonstrated generally accurate and precise performance of the Millipore assay, there appeared to be a relative deviance of the Millipore assay at lower insulin values on the comparator assay. Therefore, authors made the decision to utilize C-peptide, rather than insulin, to evaluate study outcomes.

Other studies. Hemoglobin A1c (HbA1c) and continuous glucose monitoring (CGM) were performed in a subset of individuals. HbA1c was measured locally (except UMN) on a Diabetes Control and Complications Trial-aligned instrument. Blinded CGM was collected in a subset of participants, as an optional procedure. In these individuals, a CGM (FreeStyle Libre Pro, Abbott, Alameda, CA) was inserted at each study visit, worn up to 14 days, then returned to the study team by mail.

OGTT derived measures of insulin secretion, insulin resistance, and β-cell function

OGTT-derived estimates of insulin secretion were determined with the following equations:

- Integrated AUC (iAUC) for glucose and C-peptide were calculated as the AUC above the fasting value over the 2-h sampling period using the trapezoidal method,
- C-peptide index = (C-peptide30–C-peptide0)/(glucose30–glucose0) was calculated as a measure of early insulin secretion over the first 30 min of the OGTT, and
- C-peptide iAUC/Glucose iAUC was calculated as a measure of insulin secretion over the entirety of the OGTT curve.

OGTT derived indices of insulin resistance were determined with the following equations:

- A C-peptide derived index of insulin resistance was calculated as HOMA2 IR [20] and insulin sensitivity as IS(OGTT C-pep) [21].

Oral disposition index (oDI), a measure of β-cell function accounting for insulin sensitivity, was calculated as oDI_{cpep} = C-peptide index*IS (OGTT C-pep).

To determine CGM variables, raw sensor glucoses were downloaded from the software and variables of interest were generated including average, maximum, and minimum sensor glucose, time in range (70–180 mg/dL), and additional measures of hyperglycemia and glucose variability.

Statistical analysis

Descriptive statistics were calculated. Paired t-tests were used to compare mean values between V1 (pre ETI) and V2 (post ETI) for all variables where the normality assumption was met. The Wilcoxon signed rank test was used for non-normally distributed variables and median (interquartile ranges) reported. Pearson correlation coefficients were used to exam the relationships between change in weight and changes in insulin secretion and sensitivity. Analyses were performed in R version 4.1.3. A p-value <0.05 was considered significant.

Results

Participant characteristics

Twenty individuals were included who completed fsOGTTs both before and after ETI initiation. The median (IQR) age of participants was 20.4 (14.1, 28.6) years, ranging from 11.3 to 58.9 years at baseline, 75 % were male, and 90 % pancreatic insufficient. Eleven participants (55 %) had been on another CFTR modulator prior to ETI. Baseline clinical characteristics are summarized in Table 1.

Participants were on ETI a median of 10.5 months (range 3–19, IQR 10.0, 12.3) at the time of V2. From V1 to V2, 5 individuals demonstrated improvement in glucose tolerance (i.e. CFRD changing to AGT, or AGT changing to NGT), 6 individuals demonstrated worsening of glucose tolerance (i.e. NGT to AGT, or AGT to CFRD), and 9 individuals had no change in glucose tolerance categories (Fig. 1). Additional glycemic outcomes as well as weight, BMI z-score, FEV1% predicted, and FVC% predicted before (V1) and after ETI initiation (V2) are presented in Table 2. Absolute weight ($p < 0.001$) and BMI z-score ($p = 0.013$) of the overall group increased significantly between visits. FEV1% predicted and FVC% predicted both increased ($p < 0.01$).

OGTT derived measures of insulin secretion and insulin sensitivity

Fasting, 1 h, and 2 h glucose, as well as glucose AUC (Table 2, Fig. 2**a**) did not change between visits. OGTT-derived estimates of insulin secretion, including C-peptide index and Cpep iAUC:Glucose iAUC, increased from V1 to V2 (Table 2). Fig. 2**b** illustrates the increase in OGTT C-peptide concentrations between visits. Fasting C-peptide increased and HOMA2 IR also increased from V1 to V2 while IS(OGTT C-pep) decreased ($p < 0.001$). Net β-cell function accounting for insulin sensitivity, as estimated by oDI_{cpep}, did not change from visit one to visit two.

Because youth are subject to transient decreases in insulin sensitivity during puberty, we separately examined changes in insulin secretion, sensitivity, and oral disposition index between visits in youth ≤18 years ($n = 8$) and adults ($n = 12$) (Supplemental Table 1). Weight increased in both youth (47 kg (41, 59) to 59 kg (50, 68), $p = 0.01$) and adults (66 kg (57, 77) to 73 kg (59, 80), $p = 0.003$) from V1 to V2, but the increase in BMI z-score was only significant in adults. In youth, insulin secretion as measured by C-peptide index did not change (7.9 (5.8, 13.4) to 10.6 (0.3, 17.2), $p = 0.11$), however insulin sensitivity as measured by IS

Table 1
Patient characteristics at baseline.

Population Demographics, n = 20	
Age, years	20.4 (14.1, 28.6)
Male, n (%)	15 (75)
Weight (kg)	58.8 (47.8, 68.3)
BMI z-score*	0.28 (−0.30, 0.78)
FEV_1% predicted	96.0 (66.0, 101.8)
FVC % predicted	96.5 (79.8, 105.8)
Glucose Tolerance Category	
Normal Glucose Tolerance, n (%)	11 (55)
Abnormal Glucose Tolerance, n (%)	7 (35)
Cystic Fibrosis Related Diabetes, n (%)	2 (10)
Genotype	
Homozygous F508del	8 (40)
Heterozygous F508del	12 (60)
Pancreatic Insufficient, n (%)	18 (90)
Prior CFTR modulator use, n (%)	
-ivacaftor	3 (15)
-ivacaftor/lumacaftor	1 (5)
-ivacaftor/tezacaftor	7 (35)

Data presented as median (Q1, Q3) or N (%); Abbreviations: BMI = body mass index, FEV1 = forced expiratory volume in 1 *sec*, FVC = forced vital capacity, CFTR = cystic fibrosis transmembrane conductance regulator.
*all BMIs combined as BMI z-scores. For adults >20, applied CDC references for 20 yr olds.

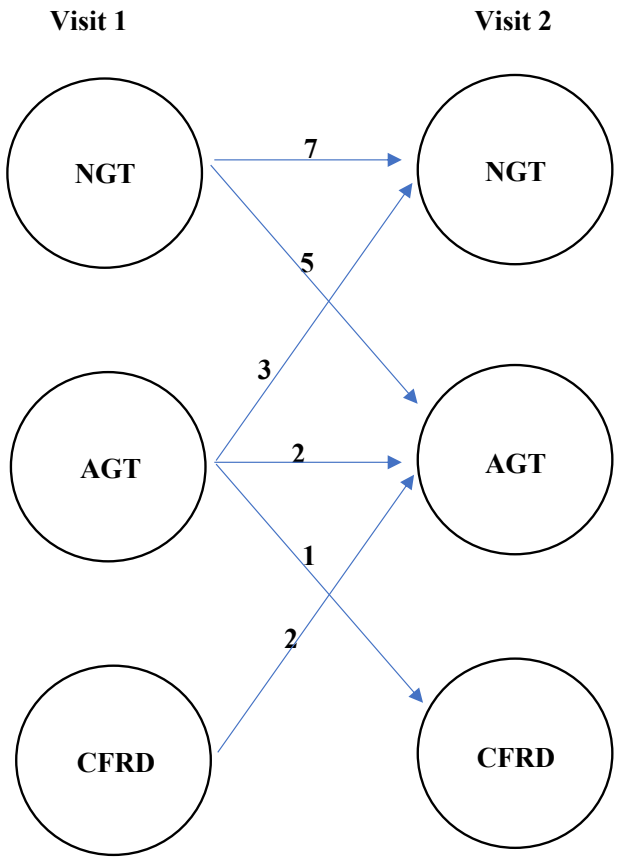

Fig. 1. Glucose Tolerance Categories before and after ETI.

Table 2
Outcomes pre/post elexacaftor/tezacaftor/ivacaftor.

Outcome (n = 20)	Visit 1	Visit 2	p-value[#]
Weight (kg)	58.8 (47.8, 68.3)	68.3 (55.7, 79.3)	**<0.001**
BMI z-score (combined)	0.28 (−0.30, 0.78)	0.76 (0.40, 1.46)	**0.013**
FEV_1 % predicted	96.0 (66.0, 101.8)	101.0 (75.0, 106.0)	**<0.001**
FVC % predicted	96.5 (79.8, 105.8)	100.5 (85.5, 106.3)	**0.005**
Fasting glucose (mg/dL)	92 (89, 96)	91 (88, 96)	0.70
1hr glucose (mg/dL)	161 (146, 190)	183 (158, 198)	0.34
2hr glucose (mg/dL)	128 (102, 167)	104 (92, 149)	0.38
Fasting C-peptide (pmol/L)	302 (181, 341)	435 (308, 600)	**<0.001**
Glucose Total iAUC mg/dL	6317 (4311, 7727)	6599 (4579, 9153)	0.87
C Peptide Total iAUC (pmol/L)	5.9×10^4 (4.8×10^4, 8.5×10^4)	9.2×10^4 (7.4×10^4, 1.2×10^5)	**<0.001**
C-peptide index	5.7 (4.1, 8.3)	8.7 (5.5, 10.8)	**0.013**
C pep iAUC:Glucose iAUC	10.7 (7.4, 15.6)	14.2 (10.7, 19.1)	**0.012**
HOMA2 IR	0.69 (0.40, 0.77)	0.96 (0.68, 1.28)	**<0.001**
IS(OGTT C-pep)	9.70 (7.96, 14.02)	6.50 (4.90, 8.03)	**<0.001**
Oral disposition $index_{cpep}$	47.9 (42.4, 90.0)	48.4 (36.7, 93.3)	0.67

Data presented as Median (Q1, Q3) or N (%); Abbreviations as follows BMI = body mass index, FEV1 = forced expiratory volume in 1 *sec*, FVC = forced vital capacity, AUC = area under the curve. P-values <0.05 presented in Bold.

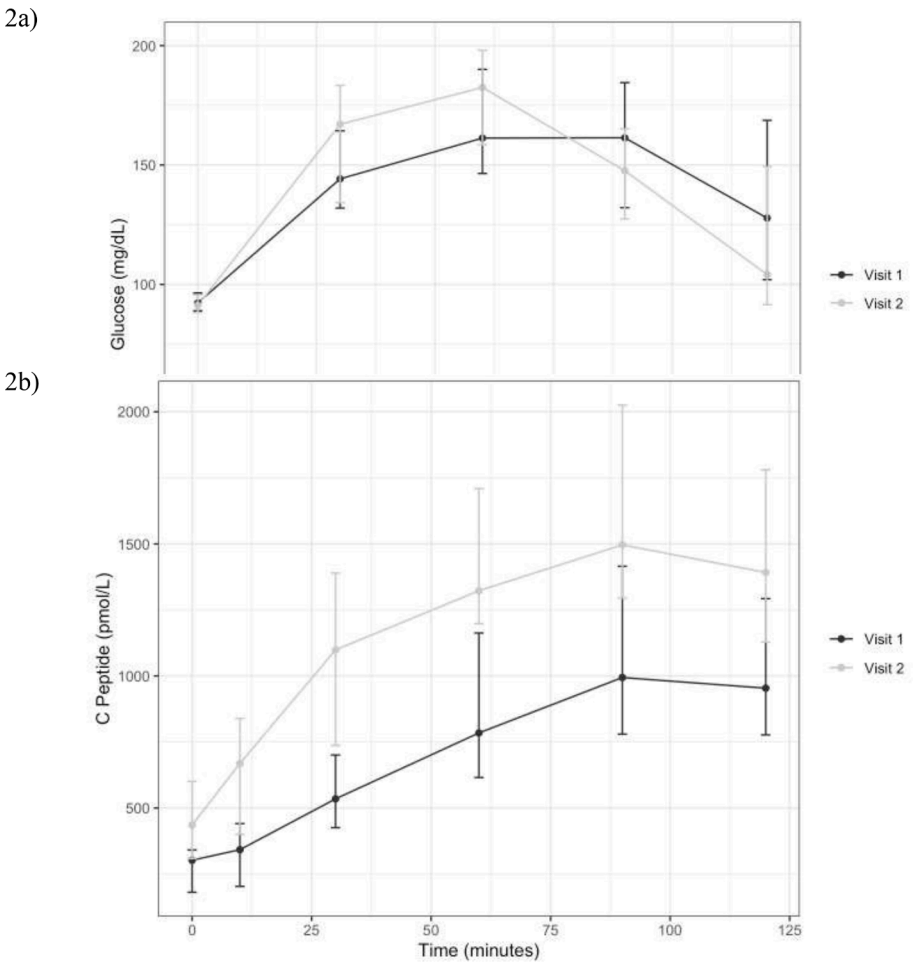

Fig. 2. OGTT curves for glucose (2a) and C-peptide (2b) before ETI (Visit 1) and after ETI (Visit 2). Data represent Median (IQR) concentrations at each time point.

(OGTT C-pep) decreased (8.8 (8.0, 10.0) to 6.2 (4.5, 8.1), p = 0.04). In the adults, C-peptide index increased (4.7 (3.0, 6.0) to 5.8 (4.6, 8.9), p = 0.04) and IS(OGTT C-pep) decreased (11.6 (8.6, 14.3) to 6.5 (5.4, 7.9), p = 0.003). Oral disposition index$_{c\text{-}pep}$ in both youth and adult groups did not change from V1 to V2.

Eleven participants were previously on modulator therapy, which may have placed them in a better clinical position at baseline and reduced changes on ETI compared to the modulator naïve group. When data from this subgroup of 11 participants were compared before and after ETI, we found significant increases in absolute weight, weight z-score, FEV1% predicted, FVC% predicted, fasting C-peptide, C-peptide iAUC, and HOMA IR2. There were decreases in IS(OGTT C-pep) and no change in C-peptide oDI, as described in the overall group (Supplemental Table 2).

Next, we examined whether or not there was a relationship between absolute weight gain between visits and changes in insulin secretion and sensitivity. The change in absolute weight (kg) correlated significantly with change in C-peptide index (r = 0.52, p < 0.05) but did not correlate with change in fasting C-peptide, HOMA2 IR, nor other measures of insulin secretion or insulin sensitivity (data not shown).

HbA1c and CGM

There was a significant decrease in median HbA1c (n = 15) from 5.5 % (5.5, 5.8) to 5.4 % (5.2, 5.6), p = 0.003 (Fig. 3) from V1 to V2. CGM data were available in a subset of participants, n = 9. At V1, CGM was worn for a median (IQR) of 7.8 (4.3, 9.0) days, and at V2 CGM was worn 11.3 (8.4, 13.50) days, p = 0.08. No statistically significant differences

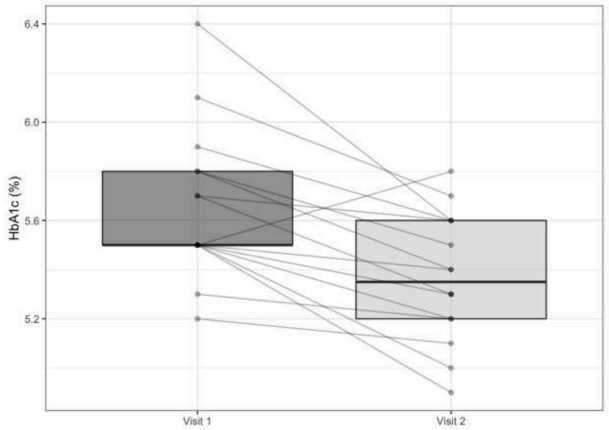

Fig. 3. HbA1c values at Visit 1 and Visit 2, with individual data points, darker horizontal line representing median, and box representing interquartile range.

were detected in any CGM measures (Table 3). There were trends suggesting glucose concentrations at V2 were lower as captured by mean sensor glucose, time in range of 70–180 mg/dL, and %time < 70 mg/dL. Percent time spent < 54 mg/dL was no different between visits (0.3 % vs 1.3 %, p = 0.80).

Table 3
CGM variables before and after elexacaftor/tezacaftor/ivacaftor.

CGM variables, n = 9	Visit 1	Visit 2	p-value
Average sensor glucose (mg/dL)	109 (101, 110)	87 (87, 102)	0.10
Maximum sensor glucose (mg/dL)	203 (188, 218)	200 (162, 220)	0.41
Minimum sensor glucose (mg/dL)	40 (40, 60)	42 (40, 54)	1.00
Time in range (70–180 mg/dL)	95 (91, 98)	85 (65, 90)	0.08
% time >140 mg/dL	10.2 (4.2, 16.3)	4.7 (1.2, 8.8)	0.34
% time >180 mg/dL	1.0 (0.1, 3.4)	0.2 (0.0, 1.1)	0.44
% time >250 mg/dL	0.0 (0,0)	0.0 (0,0)	1.00
% time <70 mg/dL	2.2 (1.8, 9.2)	14.9 (3.6, 36.3)	0.06
% time <54 mg/dL	0.3 (0.0, 1.3)	1.3 (0.1, 8.1)	0.80
Standard deviation (mg/dL)	23 (20, 28)	24 (19, 28)	0.55
Coefficient of variation	0.24 (0.19, 0.26)	0.23 (0.21, 0.33)	0.64
Mean amplitude of glycemic excursions	51 (43, 65)	59 (39, 70)	0.64

Data presented as Median (Q1, Q3).

Discussion

This is the first report, to our knowledge, examining measures of insulin secretion and resistance in pediatric and adult patients, before and after initiation of the highly effective CFTR modulator elexacaftor/tezacaftor/ivacaftor. Despite an increase in BMI z-score, there were no changes in fasting, 1 h, nor 2 h glucose measures on OGTT, nor glucose AUCs after ETI initiation. Measures of insulin secretion increased, however, measures of insulin resistance also increased, and there was no net change in β-cell function as estimated by oDI_{cpep}. Median HbA1c decreased slightly although no significant changes in glycemia were captured by CGM. The findings from this study provide novel insights on the early effects of the highly-effective modulator ETI on glucose homeostasis in people with CF.

To our knowledge, three published studies have assessed glycemic outcomes before and after initiation of ETI. The first by Scully and colleagues is a prospective, single-center, observational study in CF adults who wore CGM before and a median of 7.1 (range 3–11) months after ETI initiation. Among the 23 participants who completed the study, improvements were found in several CGM-derived measures of hyperglycemia and glycemic variability, with greater improvements described in participants with pre-existing CFRD [22]. Our cohort only included patients without pre-existing CFRD, and CGM findings reported by Scully and colleagues similarly showed minimal changes in glycemia captured by CGM in the non-CFRD group. In a second report, a single-center retrospective chart review by Petersen and colleagues, authors examined HbA1c, as well as weight, BMI, blood pressure, and lipids in adults with CF before and after initiation of ETI [23]. Here the authors described improvements in HbA1c in the subgroup without CFRD (−0.16 %, $p < 0.005$), but no improvements in HbA1c in the subgroup with CFRD, thus coming to different conclusions about the potential glycemic lowering effects of ETI in individuals with and without pre-existing CFRD. Lastly, a recent publication by Korten and colleagues described short-term OGTT changes in 16 adolescents with CF before and 4–6 weeks after ETI initiation [24]. In contrast to our findings, these authors described improvements in glucose tolerance, no changes in fasting insulin nor C-peptide, and decreases in insulin and C-peptide AUC. Notably, participants in the study by Korten had a lower BMI z-score at baseline and no changes in weight nor BMI were noted in their short window of follow up. For context, our study participants demonstrated an increase in overall BMI z-score and absolute BMI in the adult subgroup consistent with findings described in placebo controlled phase 3 trials [25] and real world studies of weight gain adjusting for pre-treatment weight trajectories [23] after ETI initiation.

Studies investigating the clinical effects of CFTR modulator therapies on insulin secretion have been few. Small case series assessing insulin secretion in individuals treated with ivacaftor have demonstrated increases in insulin response during OGTT and increases in acute insulin secretion in response to intravenous (IV) glucose (in 4 out of 5 individuals) within one month of ivacaftor initiation [12]. In another study of glucose metabolism 4 months after ivacaftor initiation, 12 participants with normal to mild glucose intolerance underwent detailed β-cell function testing, including OGTT, mixed-meal tolerance testing (MMTT), as well as IV glucose-potentiated arginine stimulation testing [13]. Investigators demonstrated increases in insulin secretion and disposition index after initiation of ivacaftor, while insulin sensitivity did not change. Notably, no changes in fasting glucose nor glucose excursions during MMTT were observed, which was attributed to the relatively normal glucose tolerance of the overall group at baseline.

Change in glycemic outcomes after initiation of the modestly-effective CFTR therapy lumacaftor-ivacaftor (lum-iva) have been underwhelming. As part of the PROSPECT trial, a multicenter prospective observational study in individuals homozygous for F508del treated with lum-iva, a subset of 39 individuals underwent OGTTs at baseline, 3, 6, and 12 months after modulator initiation. No changes were found in glucose, insulin AUC, nor time to peak insulin [15]. Another small study in 9 youth found no changes in HbA1c nor CGM parameters before and after treatment with lum-iva [16]. A study from France, in contrast, reported improvements in glucose tolerance in 40 individuals treated with lum-iva [26]. However, participants with NGT were not included, and the variability in glucose tolerance fell within range of that previously described in the CF population [27] such that conclusions of improvement in glucose tolerance should be interpreted with caution.

Taken together, results from studies to date, including the findings from this report, suggest heterogeneity in glycemic response to CFTR modulators, with modest improvements at best in short term β-cell function in response to highly-effective modulator therapies. No consistent improvements in glycemic measures have been seen across studies. The variability in outcomes reported may relate to differences in age groups studied. For example, despite the lack of statistically significant change in insulin secretion in our small group of youth, C-peptide index in this group was greater than that described in the adults at baseline and may reflect generally better β-cell reserve seen in younger individuals with CF and/or the normal insulin resistance associated with adolescence. Furthermore, varying study outcomes may relate to differences in the timing of assessment post-modulator initiation as well as different methods of glycemic assessment, i.e. HbA1c, CGM, OGTT, MMTT, versus IV clamp studies. Additionally, many of these studies included a small number of participants, making it difficult to draw definitive conclusions.

It is nevertheless tempting to speculate that the increased insulin secretion after ETI observed in our study may be an indicator of relative improvements in β-cell function. In a retrospective analysis of 46 adults with CF, mean age of 43 years at follow up, conducted prior to the widespread introduction of highly effective CFTR modulators, increased weight and decreased insulin sensitivity were observed in the absence of compensatory increases in insulin secretion, leading to increased rates of abnormal glucose tolerance over time [28]. In a prospective study of young children 3 months to 5 years of age with and without CF, children with CF exhibited higher glucose concentrations by 3–6 years of age, without the increase in insulin secretion seen in age-matched controls without CF [2]. In contrast, our findings demonstrate compensatory increases in endogenous insulin secretion in the setting of weight gain and increased insulin resistance, resulting in maintenance of glucose tolerance. These findings were demonstrated in the overall group as well as the subgroup of adult participants in this study, implicating underlying mechanisms beyond the transient increases in insulin resistance seen in puberty.

The effects of ETI on the natural history and progression to CFRD remain to be seen. Registry studies have described relative declines in incidence of CFRD 5 years after introduction of ivacaftor [14], suggesting longer term benefits on glucose homeostasis and progression to

diabetes, although the exact mechanisms for these improvements remain unclear. Impaired CFTR expression in pancreatic ducts impairs paracrine signaling and contributes to islet dysfunction [11,29]. Additional mechanisms contribute to islet inflammation and the impairment of β-cell function, including IL-1β immunoreactivity [9] and infiltration with CD8+ and CD4 + *T*-cells [3,8]. These accumulating effects are postulated to contribute to progression of CFRD. Therefore, intervention with CFTR modulators at a young age may lead to greater preservation of β-cell function over time. Impaired α-cell function and glucagon hypersecretion have also been implicated in the development of CFRD, and reductions in glucagon secretion have been described after initiation of ivacaftor, suggesting additional mechanisms for improving glycemia through CFTR modulation [13].

Notably, despite no improvements in OGTT glucose concentrations, oDI, nor CGM measures, we did find a decrease in HbA1c, a finding reported in at least two other studies after CFTR modulator initiation [23,30]. Although no statistically significant changes in free-living glucose outcomes were detected by CGM, several CGM measures trended lower, including %time <70 mg/dL. The small number of participants in this subgroup may have limited the power to detect significant changes. No participants were on insulin and given the lack of change in β-cell function observed, one hypothesis is that decreased glucagon hypersecretion may have contributed to observed trends in glucose and HbA1c decline, however studies including measurement of glucagon to assess for potential α-cell modulation before and after ETI are needed. Another hypothesis to explain the decrease in HbA1c is that ETI may be altering hemoglobin and red blood cell kinetics, such that higher hemoglobin levels [31] are resulting in lower HbA1c rather than direct lowering of average glucoses. This hypothesis warrants testing in larger studies including both direct measures of glycemia as well as indices of red blood cell turnover.

This study has several strengths and limitations. Published studies to date reporting glycemic outcomes post-ETI have been single-center, and this study enrolled participants from multiple centers including youth and adults. Furthermore, in addition to CGM and HbA1c data, this is the first study to report effects of ETI on OGTT derived estimates of insulin secretion, insulin sensitivity, and oDI. Notably, the participants with available data included in this analysis were predominantly male therefore, caution should be applied in generalizing these findings to females. Another limitation is the lack of reported insulin concentrations. However, C-peptide is a valid and widely used method of assessing pancreatic β-cell function and arguably preferable to insulin due to its slower half-life and more stable testing window, as well as more predictable peripheral clearance [32]. The findings reported here are exploratory, and larger prospective studies, including evaluation of additional nutritional and lifestyle measures such as body composition and physical activity, are needed to provide greater insights into the long-term effects of ETI on glucose homeostasis.

In conclusion, although highly-effective CFTR modulator therapies hold promise for improving insulin secretion, an alternate narrative is that rising BMIs may lead to insulin resistance and increased secretory demand on β-cells that eventually leads to β-cell dysfunction, diabetes, and increased cardiometabolic risks. Our findings highlight the need for future studies to better understand the effects of CFTR modulator-related weight gain, and anticipated changes in insulin sensitivity and secretion over time, to inform treatment and management strategies in the CFTR modulator era.

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CRediT authorship contribution statement

Christine L. Chan: Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Andrea Granados:** Conceptualization, Investigation, Writing – review & editing. **Amir Moheet:** Conceptualization, Investigation, Writing – review & editing. **Sachinkumar Singh:** . **Timothy Vigers:** . **Ana Maria Arbeláez:** Writing – review & editing. **Yaling Yi:** Investigation, Data curation. **Shanming Hu:** Investigation, Data curation. **Andrew W. Norris:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review & editing, Supervision, Funding acquisition. **Katie Larson Ode:** Conceptualization, Formal analysis, Resources, Data curation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christine L. Chan reports a relationship with Vertex Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. Amir Moheet reports a relationship with Vertex Pharmaceuticals Inc that includes: speaking and lecture fees. CLC serves as an Associate Editor for JCTE.

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Appendix A. Supplementary data

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