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Continuous glucose monitoring in youth with cystic fibrosis treated with lumacaftor-ivacaftor

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Abstract

Background—The effects of lumacaftor-ivacaftor therapy on glycemia have not been thoroughly investigated. Continuous glucose monitoring (CGM) provides detailed information about glycemic patterns and detects glucose abnormalities earlier than traditional screening tools for diabetes.

Methods—CGM measures, HbA1c, and oral glucose tolerance test (OGTT) results were collected and within-subject results compared in F508del homozygous youth with CF before and after initiation of lumacaftor-ivacaftor using the Wilcoxon signed-rank test.

Results—Nine youth with CF (6 males, median age 12.7 years) were enrolled. CGM was performed in all participants before (median 26 weeks) and after lumacaftor-ivacaftor (median 29 weeks). HbA1c and fasting plasma glucose increased (p=0.02) after lumacaftor-ivacaftor initiation. No changes in OGTT 1 hour or 2 hour glucose nor CGM measures were observed overall. When analyzed by sex, males showed lower glycemic variability, as reflected by the mean amplitude of glycemic excursions, on the post-treatment CGM.

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Conclusions—Glycemic abnormalities persisted in CF patients treated with lumacaftor-ivacaftor, although sex-dependent differences in glycemic response to treatment may exist.

Keywords

cystic fibrosis transmembrane conductance regulator protein modulator; cystic fibrosis related diabetes; continuous glucose monitoring

Introduction

Due to advances in treatment of cystic fibrosis (CF), individuals are surviving into adulthood, but with longer lifespans they are also facing an increase of CF-related comorbidities. Cystic fibrosis-related diabetes (CFRD) is one of the most common co-morbidities and affects up to 20% of the adolescent population and 40–50% of the adult CF population (1). CFRD is a significant burden to patients with CF and is associated with increased morbidity and mortality (2–4). Although not approved as a diagnostic tool for diabetes, continuous glucose monitoring (CGM) is one of the most sensitive tools for detecting early glucose abnormalities and CGM abnormalities have been well described even in those with normal oral glucose tolerance tests (OGTT) (5, 6).

Although the pathophysiology of CFRD has traditionally been attributed to exocrine pancreatic dysfunction leading to ‘collateral damage’ to β-cells, there is now evidence of cystic fibrosis transmembrane conductance regulator protein (CFTR) channel presence in pancreatic islet β-cells, and CFTR defects have been found to contribute to abnormalities in insulin secretion (7, 8). The question of whether newer targeted therapies aimed at correcting CFTR channel function might improve glucose metabolism is gaining attention. Three small publications assessing glucose metabolism in individuals with G551D mutations – including one case report (9), a report of two siblings (10), and a larger study of five individuals with CF (11) – demonstrated improvements in insulin secretion with ivacaftor treatment. However, the G551D mutations only account for 4–5% of CF cases worldwide. Lumacaftor-ivacaftor (Orkambi®), a combination CFTR modulator therapy approved for individuals with CF homozygous for F508del mutations, includes a medication correcting intracellular processing of CFTR (lumacaftor) with one that corrects the CFTR gating abnormality (ivacaftor). While this CFTR modulator treatment targets the basic defect in CF, it only modestly improves CFTR channel activity. A recent study in five patients with homozogous F508del CF treated with lumacaftor-ivacaftor did not detect differences in glucose metabolism nor acute insulin secretion measured by oral glucose tolerance testing (OGTT) nor intravenous glucose tolerance testing (12). Whether or not CGM may detect subtle changes in glucose metabolism after CFTR modulator treatment, specifically lumacaftor-ivacaftor, has not previously been studied.

Our group has been collecting CGM data in youth with CF across the glycemic spectrum. As an increasing number of CF youth are started on CFTR modulator therapy, we designed a study to compare CGM tracings before and after lumacaftor-ivacaftor, to determine whether or not this CFTR modulator leads to detectable changes in glycemia. The primary objective

of this sub-study was to determine whether short-term CGM changes can be detected in homozygous F508del CF youth treated with lumacaftor-ivacaftor.

Methods

Participants

Participants were enrolled from our pulmonary and diabetes clinics and had a known diagnosis of CF. For this study, we included those who were homozygous for F508del, had worn CGM within 12 months prior to lumacaftor-ivacaftor initiation, or were anticipating treatment with lumacaftor-ivacaftor. Participants were either clinically prescribed lumacaftor-ivacaftor and met prescribing criteria at the time of drug initiation (age >12 years) or receiving this medication open-label . Exclusion criteria included changes in dose of medications affecting glucose metabolism (e.g. insulin, atypical antipsychotics etc.), and hospitalization or systemic steroid requirement within 6 weeks prior to visit for CGM. This study was approved by the Colorado Multiple Institutional Review Board (Aurora, Colorado) and parents and participants provided appropriate consent/assent.

Study visits

CGM data were obtained twice in all participants, within 12 months prior to starting lumacaftor-ivacaftor, and within 12 months after initiating this therapy. All participants were on lumacaftor-ivacaftor for at least 3 months by the time of the second CGM. Body mass index z-score was calculated from height and weight collected at the time of each CGM placement. Lung function data (FEV1 and FVC) were obtained from pulmonary office visits surrounding the time of each CGM placement.

CGM Measures

All participants wore a blinded iPro®2 continuous glucose monitor (Medtronic, Minimed, Inc Northridge, CA) for a minimum of 3 and up to 7 days. CGM summary variables were calculated with R software, version 3.1.1 (13) after manual review of raw glucose values downloaded from CGM software. Analysis of CGM data has been previously described (14). Briefly, CGM measures were calculated in each participant in contiguous 24-hour intervals to include an equal percentage of daytime versus nighttime sensor glucoses (288 sensor glucose values per day). Sensor data dependent on total duration of CGM wear, including time spent above/under a glucose cut-point, area under the curve (AUC), and number of excursions were averaged over the total days of CGM wear. Mean amplitude of glycemic excursions (MAGE) was calculated using EasyGV version 9.0.R2 (© University of Oxford).

Laboratory measures

HbA1c was collected in all participants at both CGM time points. HbA1c was measured on a DCA Vantage Analyzer (Siemens, Deerfield, Illinios), a DCCT aligned instrument, with an inter-day coefficient of variation (CV) of 2.8%.

OGTTs were available in a subset of participants at the time of initial CGM. Only HbA1c and fasting plasma glucose, but not a complete OGTT, were obtained in participants with a

diagnosis of CFRD (whether by OGTT or hospitalization) already taking insulin at the time of the initial CGM. A complete OGTT was obtained in all participants at the time of the second CGM. All participants on insulin held long acting insulin 24 hrs before the OGTT and short acting insulin for 4 hours before the OGTT. The OGTT was performed with collection of fasting glucose, followed by administration of oral dextrose at a dose of 1.75g/kg (maximum dose of 75g) with 1h and 2hr glucose measurements post dextrose consumption. OGTT results were used to characterize patients as having normal glycemia (NGT, defined as FG <100 mg/dl, 1hr ≤200 mg/dl, and 2hr ≤140 mg/dl), abnormal glycemia (AGT, defined as impaired fasting glucose of 100–125 mg/dl, impaired glucose tolerance with 2 hour OGTT glucose of 140–199 mg/dl, or indeterminate glucose with 1hr ≥200 mg/dl), or CFRD (defined as FG ≥126 mg/dl or 2hr OGTT ≥200 mg/dl). If an OGTT was not obtained within 3 months of initial CGM wear, classification of that participant's glycemic status was based on the most recent clinically obtained OGTT.

Statistical Analysis

Descriptive statistics calculated included median and range for continuous variables, frequencies and percentages for categorical variables. The Wilcoxon signed-rank test was used to compare variables before and after lumacaftor-ivacaftor initiation. A p-value of <0.05 was considered significant. Analysis was done in R software, version 3.4.4 (13).

Results

Participant Characteristics

Recruitment began in August 2015 and continued through July 2017. A total of nine participants were studied. Baseline characteristics, obtained at the time of the first CGM, are shown in Table 1. Three participants had NGT, 5 had AGT, and 1 had CFRD based on their latest OGTT results. Pulmonary function data were obtained a mean±SD of 1.6±2.7 days from time of CGM wear. All were pancreatic insufficient and 1 was on G-tube feedings at the time of CGM wear #1 and #2. All were on standard doses of lumacaftor 200 mg/ivacaftor 125 mg (two tablets orally twice daily) with the exception of the youngest participant who was on a lower dose of lumacaftor 100mg/ivacaftor 125mg (two tablets orally twice daily) through an open-label study.

Glycemia and CGM Data

The initial CGM data were collected a median of 26 (range 4 −30) weeks before lumacaftor-ivacaftor. The follow up CGM data were collected a median of 29 (range 12–44) weeks after lumacaftor-ivacaftor. Glycemic data and clinical measures at these two time points were compared (Table 2). There were no changes in clinical metrics (weight, BMI, FEV1, FVC). No statistically significant changes were noted in CGM measures after lumacaftor-ivacaftor. HbA1c and FPG increased at the second visit (p=0.02), although, these changes were not clinically significant. The 1 and 2 hr OGTT glucose values were not statistically different after lumacaftor-ivacaftor compared to before lumacaftor-ivacaftor. However, some individuals did change glycemic category based on OGTT – NGT>CFRD (female), AGT>NGT (male), NGT>AGT (male), CFRD>NGT (male) (Supplemental Figure). Four participants were treated with the same doses of insulin during both CGM #1 and CGM #2,

and the type and dose of insulin did not change between CGM #1 and CGM #2. Although only 1 out of the 4 had a diagnosis of CFRD confirmed by OGTT at the time of the first visit, the other 3 historically had diagnoses of CFRD based on episodes of persistent hyperglycemia during hospitalizations requiring insulin, remained on insulin after hospitalization, and did not undergo another OGTT within 3 months of CGM #1.

Glycemic Data in Males vs Females

We next compared glycemic outcomes by sex (Table 3). In males (n=6), HbA1c increased from 5.2% to 5.4% (p=0.04) and fasting glucose increased from 84 mg/dL to 98 mg/dL (p=0.06) after lumacaftor-ivacaftor. Sensor glucose standard deviation, peak glucose, and % time >200 mg/dl showed trends towards improvement in males with less hyperglycemia and glucose variability (p=0.06). MAGE was lower post-lumacaftor-ivacaftor in males (p=0.03). The female subset (n=3) showed no significant differences in any glycemic parameters.

Discussion / Conclusion

In this study, we evaluated the effect of lumacaftor-ivacaftor on glycemic profiles as captured by pre-/post-lumacaftor-ivacaftor CGMs in 9 homozygous F508del CF pediatric participants. No significant changes in CGM variables were detected overall, although HbA1c and fasting glucose levels increased between the two time points. However, HbA1c and fasting glucose remained clinically within the normal range. When analyzed separately by sex, males appeared to show some improvement in CGM glycemic variability as measured by MAGE. No improvements to the glycemic profiles were noted in the females, but this group was quite small. These findings do not support significant improvements in glycemic outcomes in CF youth with early glucose abnormalities after the start of lumacaftor-ivacaftor.

A previously published small pilot study in five G551D participants receiving ivacaftor demonstrated impressive improvements in insulin secretion as measured by insulin area under the curve from an OGTT and improvements in acute insulin response to intravenous glucose in four out of five patients after only 1 month of ivacaftor therapy (11). Complete resolution of CFRD in a 25 year-old male (dF508/G551D) on 20 units/day of insulin glargine, who ultimately required no insulin after 13 months of ivacaftor, was also reported (9). Although we did not directly measure insulin secretion in our participants, we assessed glycemia with CGM, a robust measure of day-to-day glucose readings and did not find significant improvement.

Interestingly, potential sex differences were noted with males appearing to demonstrate improvements in glycemic variability, while no CGM improvements were noted in females. OGTT-based changes were seen in several of our participants. Although high intraindividual variability has been reported in OGTT categorization of individuals over time (15), historically CFRD prevalence and outcomes have been based on OGTT, and CFRD prevalence and outcomes have been reported to be worse in females (16, 17). One study found increased insulin clearance in females to be associated with increased glucose intolerance relative to males (18), although the exact mechanisms to explain these observed sex discrepancies are unknown.

The pathophysiology of CFRD is multifactorial and has traditionally been associated with pancreatic exocrine insufficiency, ductal obstruction, pancreatic fibrosis, and eventual islet destruction leading to loss of beta-cell mass (19). Abnormalities in incretin secretion, delayed gastric emptying (20), and intermittent decreases in insulin sensitivity secondary to inflammation, pulmonary exacerbations, and systemic steroids further exacerbate glucose tolerance (19, 21). However, studies have also highlighted the lack of correlation between beta-cell mass and insulin secretion abnormalities in animal models (22, 23) and more recent studies in ferret CF models (22) as well as infants and toddlers with CF have demonstrated the presence of early abnormalities in insulin secretion (24), implying a direct role of CFTR dysfunction.

As lumacaftor-ivacaftor has less CFTR activating effects in F508del patients than ivacaftor alone in patients with G551D and other gating mutations (25), our study's findings, along with the recent report from Thomassen et al (12), demonstrate that abnormalities in glucose homeostasis are harder to correct in the F508del population.

Limitations

The study was limited by the relatively small number of participants recruited. Despite our attempts to recruit more patients into this study, eligible youth at our CF center were started on lumacaftor-ivacaftor so rapidly that it quickly became difficult to find individuals who had not yet started treatment, to obtain pre-treatment glycemic data. There were multiple CGM measures assessed but no corrections for multiple comparisons and these findings should be considered hypothesis generating. We had robust measures of glycemic patterns with CGM, but no direct measures of insulin secretion. Whether or not early changes in insulin secretion might be detected are unknown but currently under investigation in larger studies (PROSPECT: NCT02477319). Furthermore, participants consumed their free-living diets while wearing CGM, and notably, after lumacaftor-ivacaftor initiation, dietary recommendations are modified to include increased fat intake for CFTR modulator absorption. Because dietary records with detailed macronutrient content were not collected, nor were fixed diets prescribed during the weeks of CGM wear, whether or not post-modulator diet changes may have affected comparison of CGM are unclear; however one might speculate that increased dietary fat would potentially reduce acute post-prandial glycemic excursions and glycemic variability due to lower carbohydrate:fat ratios. This hypothesis requires further study. Although no changes were noted in clinical metrics, sweat chloride, a biomarker of CFTR activity, was not obtained. Lastly, as the timing of CGM collection was not specifically pre-defined, the range when CGM was obtained before and after lumacaftor-ivacaftor was wide. Glycemic data from CGM #2 were collected a median of 29 weeks after lumacaftor-ivacaftor and it is possible that a longer period of observation is required to detect glucose changes with these modulator compared to ivacaftor alone.

In conclusion, minimal impacts of lumacaftor-ivacaftor on glycemic control were detected as measured by CGM in youth with early glucose abnormalities. Future studies in young children on CFTR modulators are required to determine whether intervention at an earlier age, or more highly effective combination CFTR modulator, may have greater impacts on β-

cell function and glucose metabolism. Whether or not these CFTR modulators will impact the natural history and progression of CFRD remains to be seen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CGM	Continuous glucose monitoring
CFRD	Cystic fibrosis related diabetes
CFNG	Cystic fibrosis normal glycemia
CFAG	Cystic fibrosis abnormal glycemia
CFTR	Cystic fibrosis transmembrane conductance regulator protein
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HbA1c	Hemoglobin A1c
MAGE	Mean amplitude of glycemic excursions
OGTT	Oral glucose tolerance testing

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Highlights

- The impact of CFTR modulators on CGM patterns has not previously been studied Nine youth wore CGM before and after lumacaftor-ivacaftor treatment
- No differences in glucose patterns were detected pre/post lumacaftor-ivacaftor

Table 1 :

Demographic and clinical characteristics *

	All participants (n=9)	
Age, years	12.7 (11−15.6)	
Male, n (%)	6 (67)	
Weight z-score	−0.38 (−1.53, 0.84)	
BMI z-score	−0.44 (−1.79, 0.58)	
HbA1c, %	5.2 (5.0,5.6)	
OGTT status at baseline		
NGT, n (%)	3 (33)	
AGT, n (%)	5 (56)	
CFRD, n (%)	1 (11)	
# on insulin, n (%)	4 (44)	
Interval from CGM#1 to Lumacaftor-Ivacaftor start, weeks	26 (4 − 30)	
Days of CGM #1 wear	6 (5,6)	
Interval from Lumacaftor-Ivacaftor to CGM#2, weeks	29 (12 − 44)	
Days of CGM #2 wear	6 (3,6)	
Tanner Stage, n (%)	Visit #1	Visit #2
I	1 (11)	1 (11)
II	1 (11)	−
III	−	1 (11)
IV	3 (33)	3 (33)
V	2 (22)	3 (33)
Unknown	2 (22)	1 (11)
G-tube feedings, n(%)	1 (11)	
Pancreatic insufficient, n (%)	9 (100)	
FEV1%	96 (93, 117)	
FVC%	104 (92, 124)	

* Data from initial visit, unless otherwise indicated. Individual classification may have changed from pre-CFTR modulator treatment to post-CFTR modulator treatment. This value is calculated using the pre-treatment classification.

Data presented as median (range) unless otherwise indicated

Table 2:

Glycemic measures before and after lumacaftor-ivacaftor

Glycemic measures	Before lumacaftor-ivacaftor (n=9)	After lumacaftor-ivacaftor (n=9)	Wilcoxon P-value
HbA1c, %	5.2 (5.1,5.5)	5.5 (5.3,5.6)	**0.02**
OGTT, fasting, mg/dl	89 (79,98)	94 (93,111)	**0.02**
OGTT, 1 hour, mg/dl	176 (157,197)	246 (174,251)	0.08
OGTT, 2 hour, mg/dl	141 (109,152)	137 (127,152)	0.68
OGTT status, n (%)			1
NGT	3 (33)	3 (33)	
AGT	5 (56)	5 (56)	
CFRD	1 (11)	1 (11)	
CGM variables			
Average sensor glucose, mg/dl	116 (105, 121)	115 (109, 119)	0.82
Minimum sensor reading, mg/dl	67 (58,68)	67 (59,72)	0.5
Maximum sensor reading, mg/dl	241 (179,267)	206 (193,216)	0.25
% time over 120 mg/dl	35 (10, 38)	32 (29, 40)	0.82
% time over 140 mg/dl	13 (3,20)	12 (5,15)	0.91
% time over 200 mg/dl	1.0 (0, 2.0)	0.1 (0, 0.5)	0.27
Average # excursions >140 mg/dl per day	3 (2, 4)	4 (2, 4)	0.67
Average # excursions >200 mg/dl per day	0.3 (0, 0.8)	0.2 (0, 0.3)	0.67
% time under 60 mg/dl	0 (0,0)	0 (0,0)	1
% time under 70 mg/dl	0.1 (0, 0.8)	0 (0, 1.4)	0.93
Average area under curve per day	1.7×10^5 (1.5×10^5,1.7×10^5)	1.7×10^5 (1.6×10^5,1.7×10^5)	0.82
Sensor reading standard deviation	28 (16,32)	22 (18,26)	0.43
Mean amplitude of glycemic excursion	65 (37, 73)	50 (40, 63)	0.30
Clinical measures			
Forced vital capacity (%)	104 (97,118)	99 (95,121)	0.09
Forced expiratory volume in 1 sec (%)	96 (95,110)	103 (88,108)	0.81
Weight z-score	−0.38 (−0.86, 0.04)	−0.16 (−0.84,0.24)	0.36
BMI z-score	−0.44 (−0.8,−0.1)	−0.1 (−0.94,0.39)	0.57

Data presented as Median (25^{th}%ile, 75^{th}%ile) unless otherwise specified

Abbreviations: OGTT=oral glucose tolerance test; NGT= normal glycemic tolerance; AGT= abnormal glycemic tolerance; CFRD=cystic fibrosis related diabetes; CGM=continuous glucose monitoring; BMI=body mass index

Table 3:

Glycemic data before and after lumacaftor-ivacaftor in Males vs Females

	Males Pre-lumacaftor-ivacaftor, n=6	Males Post-lumacaftor-ivacaftor, n=6	Wilcoxon P-value	Females Pre-lumacaftor-ivacaftor, n=3
HbA1c, %	5.2 (5.0,5.2)	5.4 (5.2,5.5)	**0.04**	5.5 (5.5,5.6)
OGTT status, n (%)				
NGT	2 (17)	3 (50)		1 (33)
AGT	3 (33)	3 (50)		2 (33)
CFRD	1 (50)	0 (0)		0 (33)
OGTT, fasting, mg/dl	84 (77, 93)	94 (92,108)	0.06	99 (94, 100)
OGTT, 1 hour, mg/dl	163 (161,189)	188 (171,239)	0.31	198 (172, 200)
OGTT, 2 hour, mg/dl	152 (125,165)	128 (117, 135)	0.56	109 (106,125)
CGM variables				
Average sensor glucose, mg/dl	113 (106, 120)	110 (104, 117)	0.69	116 (111, 124)
Minimum sensor glucose, mg/dl	61 (45, 66)	68 (61, 72)	0.22	73 (71, 74)
Maximum sensor glucose, mg/dl	249 (192, 265)	203 (172, 214)	0.06	186 (183, 238)
% time over 120 mg/dl	29 (21, 38)	29 (17, 33)	0.56	38 (26, 42)
% time over 140 mg/dl	14 (6, 18)	8 (4, 14)	0.44	8 (5, 19)
% time over 200 mg/dl	1.33 (0.25,1.93)	0.06 (0,0.29)	0.10	0 (0,3.96)
Average # excursions over 140 mg/dl per day	3 (2, 4)	3 (2, 4)	1	2 (2,3)
Average # excursions over 200 mg/dl per day	0.5 (0.1, 0.8)	0.2 (0.0, 0.2)	0.36	0 (0,1)
% time under 60 mg/dl	0 (0,1.4)	0 (0,0)	0.42	0 (0,0)
% time under 70 mg/dl	0.7 (0.2,2.0)	0.1 (0, 1.1)	0.44	0 (0,0)
Average area under curve/day	1.6×10^5 (1.5×10^5 1.7×10^5)	1.6×10^5 (1.5×10^5, 1.7×10^5)	0.69	1.7×10^5 (1.6×10^5, 1.8×10^5)
Standard deviation	29 (19,31)	21(17,26)	0.06	16(16, 28)
Mean amplitude of glycemic excursion	67 (47,72)	52 (36, 62)	**0.03**	37 (34,61)
Clinical measures				
Forced vital capacity (%)	100.5 (95.5,105.5)	97 (89.75,101.25)	0.25	122 (113,123)
Forced expiratory volume in 1 sec (%)	95.5 (93.5,96)	95.5 (86.5,105.25)	1	110 (110,110.5)
Weight z-score	−0.62 (−1.22,−0.07)	−0.5 (−1.12,0.14)	0.22	−0.25 (−0.32,0.3)
BMI z-score	−0.62 (−1.23,−0.18)	−0.37 (−1.24,0.24)	0.44	−0.29 (−0.48,0.14)

Data presented as Median (25^{th}%ile, 75^{th}%ile) unless otherwise specified

Abbreviations: OGTT=oral glucose tolerance test; NGT= normal glycemic tolerance; AGT= abnormal glycemic tolerance; CFRD=cystic fibrosis related diabetes; CGM=continuous glucose monitoring; BMI=body mass index