Can continuous glucose monitoring predict cystic fibrosis-related diabetes and worse clinical outcome?

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ABSTRACT

Objective: To determine whether abnormal continuous glucose monitoring (CGM) readings (hypoglycemia/hyperglycemia) can predict the onset of cystic fibrosis-related diabetes (CFRD) and/or clinical impairment (decline in BMI and/or FEV_1) in pediatric patients with cystic fibrosis (CF). **Methods:** This was a longitudinal prospective cohort study involving CF patients without diabetes at baseline. The mean follow-up period was 3.1 years. The patients underwent 3-day CGM, performed oral glucose tolerance test (OGTT), and had FEV_1 and BMI determined at baseline. OGTT, FEV_1, and BMI were reassessed at the end of the follow-up period. **Results:** Thirty-nine CF patients (10-19 years of age) had valid CGM readings at baseline, and 34 completed the follow-up period (mean = 3.1 ± 0.5 years). None of the study variables predicted progression to CFRD or were associated with hypoglycemic events. CGM could detect glucose abnormalities not revealed by OGTT. Patients with glucose levels ≥ 140 mg/dL, as compared with those with lower levels, on CGM showed lower BMI values and z-scores at baseline—17.30 ± 3.91 kg/m² vs. 19.42 ± 2.07 kg/m²; p = 0.043; and −1.55 ± 1.68 vs. −0.17 ± 0.88; p = 0.02, respectively—and at the end of follow-up—17.88 ± 3.63 kg/m² vs. 19.95 ± 2.56 kg/m²; p = 0.039; and −1.65 ± 1.55 vs. −0.42 ± 1.08; p = 0.039. When comparing patients with and without CFRD, the former were found to have worse FEV_1 (in % of predicted)—22.67 ± 5.03 vs. 59.58 ± 28.92; p = 0.041—and a greater decline in FEV_1 (−36.00 ± 23.52 vs. −8.13 ± 17.18; p = 0.041) at the end of follow-up. **Conclusions:** CGM was able to identify glucose abnormalities not detected by OGTT that were related to early-stage decreases in BMI. CGM was ineffective in predicting the onset of diabetes in this CF population. Different diagnostic criteria for diabetes may be required for individuals with CF.

Keywords: Cystic fibrosis; Glucose intolerance; Glucose tolerance test; Diabetes mellitus.

INTRODUCTION

Cystic fibrosis-related diabetes (CFRD) is the commonest comorbidity in cystic fibrosis (CF). The pathophysiology of CFRD is theorized to involve insulin insufficiency, but unlike diabetes mellitus type 1, β-cell damage in CF is not caused by autoimmunity, and it is associated with some degree of insulin resistance due to inflammation and medications.[1]

CFRD is correlated with a progressive decline in pulmonary function and nutritional status, and, therefore, lower survival.[2,3] In accordance with recommendations from a consensus guideline publication,[4] the gold standard for CFRD screening is the oral glucose tolerance test (OGTT). The OGTT is a burdensome examination, as samples are collected over a long period, fasting is required before the test, and low gastrointestinal tolerability poses challenges to adherence.[5] OGTTs can induce hypoglycemic episodes following the glucose load.[6-8] Continuous glucose monitoring (CGM) could be a sensitive method to detect spontaneous hypoglycemia/hyperglycemia in CF patients, and this exam has been validated for use in children and adolescents with CF.[9,10]

Hypoglycemia in CF could be associated with a delayed first phase of insulin secretion paired with a diminished glucagon response, liver disease, undernourishment, gastrointestinal disorders, and other incretin dysfunctions. CFRD and hypoglycemia in CF share a similar pathophysiological basis.[11] For CGM, the cutoff values for hypoglycemia are classified into two levels applicable to type 1 and type 2 diabetes (in mg/dL): < 70 (level 1) and < 54 (level 2).[12]

Although the risk of microvascular complications exists, the main goal of CFRD management is to control lung bacterial growth, avoid a decline in pulmonary function and nutritional status, and ensure glycemic control.[13]

The present study aimed to determine whether abnormal CGM readings (hypoglycemia/hyperglycemia), when compared with the gold standard OGTT, could

predict the onset of CFRD and/or clinical impairment (decline in BMI or FEV_1 in percentage of predicted values) in pediatric CF patients.

METHODS

Patients and study design

A prospective, single-center study was conducted between August of 2014 and January of 2019. All of the patients—from 10.0 to 19.9 years of age and with two pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and/or with two sweat chloride test results ≥ 60 mEq/L— treated at an outpatient clinic of a CF referral center were invited to participate (N = 63).

The sweat test was conducted with a quantitative ionic analysis of sweat (iontophoresis) after pilocarpine stimulation of the skin.[14] Genetic testing was performed using genetic sequencing; the genotype was classified as homozygous or heterozygous for the p.Phe508del variant and by its severity based on *CFTR* mutation classes.

Data collection, data analysis, and outcome measures

The CF patients were followed up during their routine clinical quarterly visits. Two-time points were evaluated in this study: T0 (baseline), the time when participants underwent CGM and OGTT, and T1 (end of the follow-up period), the time of the routine visit closest to the first newly diagnosed cases of CFRD by OGTT in the cohort. For those who did not develop CFRD, T1 was determined as the last visit before study termination.

No participants were experiencing pulmonary exacerbations, were receiving systemic corticosteroid therapy, or were pregnant at the time of data collection. Individuals with improper CGM calibration, CGM readings performed in < 36 h, who did not complete OGTT, or who were diagnosed with diabetes based on the American Diabetes Association criteria[15] were excluded. No patient received enteral nutrition or therapy with CFTR modulators, or underwent lung transplantation during the follow-up period.

All study participants wore the CGMS Gold® (Medtronic MiniMed, Fridley, MN, USA) for a minimum of 36 h and up to 3 days at the start of the follow-up period. The number of peaks (≥ 140 mg/dL and ≥ 200 mg/dL) and valleys (< 54 mg/dL) was adjusted for CGM duration. CGM data were provided by MiniMed Solutions Software, version 1.7a (Medtronic Minimed). The numbers of peaks ≥ 140 mg/dL and ≥ 200 mg/dL (total and per day); number of valleys < 54 mg/dL (total and per day); proportion of time during which interstitial glucose values remained at < 54 mg/dL, ≥ 140 mg/dL, and ≥ 200 mg/dL; AUC for interstitial glucose values < 54 mg/dL, ≥ 140 mg/dL, and ≥ 200 mg/dL; and association of peaks (mg/dL) ≥ 200 mg/dL with valleys < 54 mg/dL were evaluated.

The patients were continuously instructed about the clinical signs of hypoglycemia (weakness, tremors, hunger, irritability, and others) during the appointments. For the study, they were instructed once again when the CGM device was placed. After removing the device, they answered a questionnaire about complications during CGM device use, in which they were actively asked about hypoglycemia (values < 70 mg/dL detected through capillary blood glucose measurements and/or clinical signs of hypoglycemia).

CGM classification was based on OGTT cutoff values for normal glucose tolerance (NGT; interstitial glucose < 140 mg/dL), impaired glucose tolerance (IGT; interstitial glucose between 140 and 199 mg/dL), and CFRD (interstitial glucose ≥ 200 mg/dL at least twice). Moreover, two subgroup analyses were performed by analyzing glucose abnormalities (CFRD+IGT) vs. NGT for both CGM and OGTTs.

An OGTT was requested annually as per guideline recommendations[4]; however, we only tracked the study variables at the two study time points (T0 and T1), because adherence was inadequate during follow-up. Based on the results of OGTT, performed according to the WHO protocol[16] and using the enzymatic colorimetric method, we classified participants according to the American Diabetes Association criteria[15]—NGT: fasting blood glucose (BG) < 126 mg/dL or BG < 140 mg/dL at 120 min; IGT: fasting BG < 126 mg/dL or BG of 140-199 mg/dL at 120 min; and diabetes: fasting BG ≥ 126 mg/dL or BG ≥ 200 mg/dL at 120 min (at least twice).

Spirometry was conducted in compliance with the standards of the American Thoracic Society and the European Respiratory Society.[17] FEV_1 in percentage of the predicted values was evaluated at T0 and T1.[18]

Two pediatric endocrinologists evaluated the weight, height, BMI, and pubertal stage of the participants at T0 and T1. BMI was presented as absolute values and z-scores based on the 2006 WHO child growth standards.[19] Pubertal stage was evaluated using Marshall & Tanner staging criteria.[20,21]

Exocrine pancreatic function (exocrine pancreatic insufficiency [PI] < 200 μg/g) was evaluated based on fecal elastase-1 levels at T0 using the Pancreatic Elastase 1 Stool Test (ScheBo, Giessen, Germany).[22]

The study protocol was approved by the Research Ethics Committee of the *Faculdade de Ciências Médicas, Universidade Estadual de Campinas* (Protocol no. 3.328.215). All participants or their legal guardians provided written informed consent for study participation. Minors provided written assent as well.

Statistical analysis

All analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corp., Armonk, NY, USA). Differences were considered statistically significant at two-tailed $p < 0.05$. Qualitative variables were expressed as absolute and relative frequencies, and quantitative variables

were expressed as medians and minimum-maximum values. Mann-Whitney and Kruskal-Wallis tests were used in order to compare two and three or more independent groups, respectively. A nonparametric multiple comparison test was used to identify intergroup differences.

Associations with qualitative variables were analyzed by the Fisher's exact test or the Fisher-Freeman-Halton test, as appropriate. For paired evaluations, we used the McNemar-Bowker test and the Wilcoxon test.

A univariate logistic regression analysis was performed to identify CFRD predictors. Predictors with a $p < 0.2$ in the univariate analysis were included in the multivariate analysis by generalized estimating equation models.

RESULTS

Of the 63 patients recruited, 13 declined to participate, 1 had several pulmonary exacerbations, 2 provided CGM readings for < 36 h, and 8 were diagnosed with CFRD. Therefore, 39 nondiabetic patients with CF underwent a 3-day blinded CGM and were followed for a mean period of 3.1 ± 0.5 years. Among those, 34 participants completed the study follow-up (Figure 1). At T0, we were unable to know who would become diabetic, we only had the classification as having IGT or NGT according to OGTT results. In addition, all patients in the cohort had comparable lung function and nutritional status at T0. Three patients were classified as having CFRD by OGTT at T1.

Demographic data are shown in Table 1. During the follow-up period, the patients with PI showed no changes in clinical parameters, fecal fat balance, and steatocrit. Patients who remained with interstitial glucose levels < 140 mg/dL (n = 8) on CGM did not develop CFRD during the follow-up period, and only 1 experienced a single episode of asymptomatic hypoglycemia. All patients classified as having CFRD based on CGM had asymptomatic hypoglycemic episodes. None of the patients who progressed to CFRD had peaks ≥ 200 mg/dL during CGM evaluation. The relationship between OGTTs (at T0 and T1) and CGM is presented in Figure 2.

The peak/valley pattern (total and per day), AUC, and proportion of time during which the values (in mg/dL) were ≥ 140, ≥ 200, and < 54 on CGM showed no associations with the OGTT classification either at T0 or T1. Individual CGM variables are described in Table S1.

Eleven patients (32%)—7 were males, 7 were homozygous for p.Phe508del *CFTR* variant, and 7 presented with PI—had glucose levels < 54 mg/dL during CGM. There were no associations of BMI, FEV_1, OGTT results, sex, p.Phe508del genotype, and PI with hypoglycemia on CGM (at T0). None of the patients who experienced hypoglycemia needed intervention for recovery. None of analyzed clinical or laboratory variables were associated with hypoglycemic episodes or could predict the onset of CFRD (data not shown).

A secondary analysis was conducted by grouping hypoglycemic and hyperglycemic (≥ 200 mg/dL) episodes to determine whether this conjunction could be related to CFRD outcome; no significant association was found ($p = 0.664$).

Patients who developed CFRD, in comparison with those who did not, had worse FEV_1 (in % of predicted values)—22.67 ± 5.03 vs. 59.58 ± 28.92; $p = 0.041$—at T1 (Table 2).

BMI z-scores and crude BMI values are shown according to OGTT (at T1) and CGM (at T0) results in Table 2. Lower BMI values were noted in those who developed CFRD than in those who did not at T0 (14.37 ± 1.22 kg/m^2 vs. 18.13 ± 3.65 kg/m^2; $p = 0.049$) and at T1 (14.81 ± 0.67 kg/m^2 vs. 18.71 ± 3.46 kg/m^2; $p = 0.022$). The subgroup analysis regarding OGTT results at T1 between glucose abnormalities (CFRD+IGT) and NGT showed a significant difference in BMI values only at the end of the follow-up period. However, considering CGM-based classification at T0 (but not OGTT-based classification), the subgroup analysis showed significantly lower crude BMI values and BMI z-scores that were maintained from T0 to T1. Curiously, regarding the OGTT classification (IGT vs. NGT) at T0, no significant differences were noted in FEV_1 or BMI (Table S2).

A logistic regression analysis was conducted to ascertain the effect of time, adjusted for independent variables, on CFRD development. Participants classified as having IGT (on OGTT) had a higher chance of developing CFRD (OR = 21.67; 95% CI: 7.03-67.36; $p < 0.01$), whereas that chance was lower among the participants having NGT (OR = 1.84; 95% CI: 1.06-3.19; $p = 0.031$). According to the univariate logistic analysis, male sex, p.Phe508del homozygous
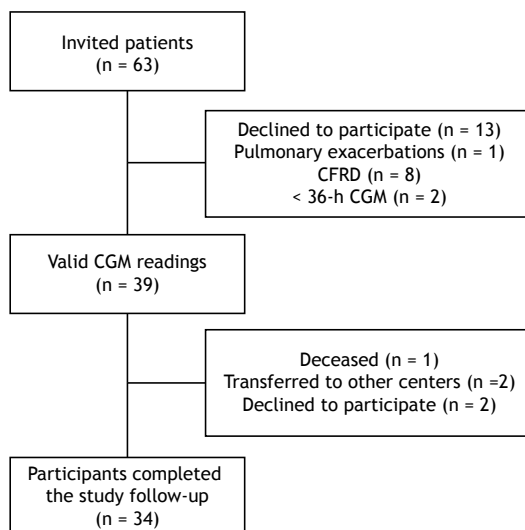

Figure 1. Flow chart of patient selection process. CFRD: cystic fibrosis-related diabetes; and CGM: continuous glucose monitoring.

Table 1. Clinical and demographic data of the patients with cystic fibrosis enrolled in the study.[a]

Variable	Time point		p*
	T0	T1	
Sex			
Male	16/34; 47.1		N/A
Female	18/34; 52.9		
Pubertal stage[20,21]			
Prepubertal	4/34; 11.8	None	N/A
Pubertal	30/34; 88.2	34/34; 100	
OGTT			
NGT	24/34; 70.6	20/34; 58.8	N/A
IGT	10/34; 29.4	11/34; 32.4	
CFRD	None	3/34; 8.8	
Pancreatic insufficiency	23/34; 70.6		N/A
BMI, kg/m^2	17.35 (12.39-30.18)	17.58 (14.04-31.04)	0.025
FEV$_1$, % of predicted	71 (18-113)	55 (16-112)	0.001
Age, years	16.10 (10.8-19.5)	18.80 (13.6-23.3)	N/A
CFTR pathogenic variants			
p.Phe508del/p.Phe508del	15/34; 44.12		N/A
p.Phe508del/p.Gly542Ter	5/34; 14.71		
p.Phe508del/Unknown	2/34; 5.88		
p.Phe508del/p.Gln890Ter	1/34; 2.94		
p.Phe508del/p.Arg553Ter	1/34; 2.94		
p.Phe508del/621+1G>T	1/34; 2.94		
p.Phe508del/1716+18672 A>G	1/34; 2.94		
p.Phe508del/p.Lys684SerfsX38	1/34; 2.94		
p.Phe508del/1717-1G>A	1/34; 2.94		
p.Phe508del/p.Arg1066Cys	1/34; 2.94		
p.Phe508del/p.Asn1303Lys	1/34; 2.94		
p.Gly542Ter/p.Arg1162Ter	1/34; 2.94		
p.Gly542Ter/Unknown	1/34; 2.94		

OGTT: oral glucose tolerance test; NGT: normal glucose tolerance; IGT: impaired glucose tolerance; CFRD: cystic fibrosis-related diabetes; *CFTR*: cystic fibrosis transmembrane regulator; T0: baseline; and T1: end of the follow-up period. [a]Values expressed as n/N; % or median (minimum-maximum values). *Wilcoxon test (α = 0.05).
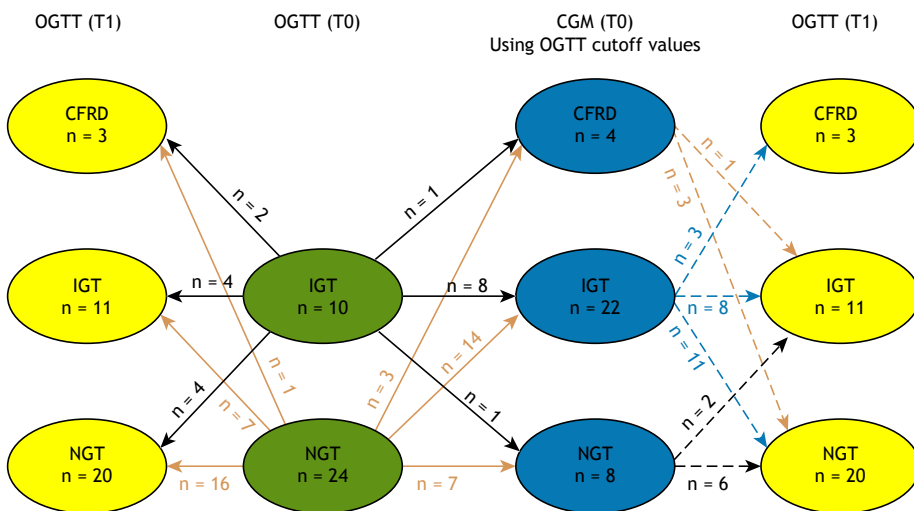
Figure 2. Relationship of oral glucose tolerance test (OGTT) at baseline (T0) and at the end of the follow-up period (T1) with continuous glucose monitoring (CGM) at T0 using OGTT cutoff values in accordance with the American Diabetes Association[15] criteria—normal glucose tolerance (NGT): interstitial glucose < 140 mg/dL; impaired glucose tolerance (IGT): interstitial glucose between 140 and 199 mg/dL; cystic fibrosis-related diabetes (CFRD): interstitial glucose ≥ 200 mg/dL at least twice.

Table 2. Correlation of FEV_1 (in % of the predicted values) and BMI (in kg/m² and z-score) with oral glucose tolerance test at the end of the follow-up period (T1) and continuous glucose monitoring at baseline (T0) results.[a]

Oral glucose tolerance test (at T1)

Variable	CFRD (n = 3)	IGT (n = 11)	NGT (n = 20)	p*	CFRD (n = 3)	IGT+NGT (n = 31)	p*	CFRD+IGT (n = 14)	NGT (n = 20)	p*
FEV_1 (T0)	70 (31-75)	63 (20-113)	76.5 (18-108)	0.399	70 (31-75)	72 (18-113)	0.524	65.50 (20-113)	76.5 (18-108)	0.180
FEV_1 (T1)	22 (18-28)	55 (17-104)	59.5 (16-112)	0.116	22 (18-28)	56 (16-112)	0.041	45.50 (17-104)	59.5 (16-112)	0.274
FEV_1 (T1 – T0)	-47 (-52 to -9)	-3 (-21 to 24)	-2.5 (-63 to 19)	0.146	-47 (-52 to -9)	-3 (-63 to 24)	0.041	-9 (-52 to 24)	-2.5 (-63 to 19)	0.522
BMI z-test (T0)	-3.08 (-3.46 to -2.12)	-2.01 (-5.03 to 0.69)	-0.53 (-3.30 to 2.21)	0.027+	-3.08 (-3.46 to -2.12)	-0.75 (-5.03 to 2.21)	0.041	-2.09 (-5.03 to 0.69)	-0.53 (-3.30 to -2.21)	0.017
BMI z-test (T1)	-3.42 (-3.87 to -3.03)	-2.03 (-3.76 to 0.15)	-0.67 (-3.09 to 2.24)	0.030+	-3.42 (-3.87 to -3.03)	-1.25 (-3.76 to 2.24)	0.014	-2.88 (-3.87 to 0.15)	-0.67 (-3.09 to 2.24)	0.010
BMI z-test (T1 – T0)	-0.41 (-0.91 to -0.34)	-0.03 (-2.22 to 1.58)	-0.01 (-1.37 to 1.59)	0.324	-0.41 (-0.91 to -0.34)	-0.03 (-2.22 to 1.59)	0.172	-0.15 (-2.22 to 1.58)	0.01 (-1.37 to 1.59)	0.341
BMI (T0)	14.53 (13.07-15.51)	17.31 (12.81-23.81)	18.96 (12.39-30.17)	0.072	14.53 (13.07-15.51)	17.72 (12.39-30.17)	0.049	16.20 (12.81-23.81)	18.96 (12.39-30.17)	0.083
BMI (T1)	15.13 (14.05-15.26)	17.49 (14.34-21.89)	19.39 (14.05-31.04)	0.013++	15.13 (14.05-15.26)	18.08 (14.05-31.04)	0.022	15.77 (14.05-21.89)	19.39 (14.05-31.04)	0.015
BMI (T1 – T0)	0.73 (-0.38 to 0.97)	0.21 (-3.53 to 2.16)	1.03 (-2.24 to 4.29)	0.307	0.73 (-0.38 to 0.97)	0.57 (-3.53 to 4.29)	0.909	0.25 (-3.53 to 2.16)	1.03 (-2.24 to 4.29)	0.478

Continuous glucose monitoring at T0 (using OGTT cutoff values)

Variable	CFRD (n = 4)	IGT (n = 22)	NGT (n = 8)	p	CFRD (n = 4)	IGT+NGT (n = 30)	p	CFRD+IGT (n = 26)	NGT (n = 8)	p
FEV_1 (T0)	69 (43-80)	68 (20-113)	79.50 (18-108)	0.441	69 (43-80)	71 (18-113)	0.817	68 (20-113)	79.50 (18-108)	0.205
FEV_1 (T1)	47 (33-67)	54 (16-112)	70 (16-105)	0.650	47 (33-67)	55 (16-112)	0.738	54 (16-112)	70 (16-105)	0.368
FEV_1 (T1 - T0)	-24.50 (-42 to 24)	-7 (-52 to 17)	-2.5 (-63 to 19)	0.969	-24.50 (-42 to 24)	-3 (-63 to 19)	0.310	-9 (-52 to 24)	-2.5 (-63 to 19)	0.858
BMI z-test (T0)	-1.44 (-5.03 to -0.44)	-1.38 (-4.19 to 2.21)	-0.04 (-1.48 to 1.12)	0.059	-1.44 (-5.03 to -0.44)	-0.78 (-4.19 to 2.21)	0.336	-1.38 (-5.03 to 2.21)	-0.04 (-1.48 to 1.12)	0.02
BMI z-test (T1)	-1.55 (-3.45 to -1.43)	-1.64 (-3.87 to 2.24)	-0.40 (-1.86 to 0.83)	0.103	-1.55 (-3.45 to 1.43)	-1.10 (-3.87 to 2.24)	0.392	-1.60 (-3.87 to 2.24)	-0.40 (-1.86 to 0.83)	0.039
BMI z-test (T1 - T0)	-0.09 (-1.04 to 1.58)	0.03 (-2.22 to 1.59)	-0.09 (-1.11 to 0.17)	0.841	-0.09 (-1.04 to 1.58)	0.01 (-2.22 to 1.59)	0.777	0.03 (-2.22 to 1.59)	-0.09 (-1.11 to 0.17)	0.591
BMI (T0)	15.39 (12.81-19.92)	16.86 (12.39-30.18)	19.05 (15.77-22.30)	0.090	15.39 (12.81-19.92)	17.54 (12.39-30.17)	0.239	16.32 (12.39-30.17)	19.05 (15.77-22.30)	0.043
BMI (T1)	16.60 (14.97-17.58)	17.53 (14.05-31.04)	20.33 (16.78-22.85)	0.083	16.60 (14.97-17.58)	18.14 (14.05-31.04)	0.239	17.42 (14.05-31.04)	20.33 (16.78-22.85)	0.039
BMI (T1 - T0)	01.21 (-2.34 to 2.16)	0.65 (-3.53 to 4.29)	0.34 (-2.11 to 2.88)	0.881	1.21 (-2.34 to 2.16)	00.56 (-3.53 to 4.29)	0.738	0.67 (-3.53 to 4.29)	0.34 (-2.11 to 2.88)	0.796

CFRD: cystic fibrosis-related diabetes; IGT: impaired glucose tolerance; and NGT: normal glucose tolerance. [a]Values expressed as median (minimum-maximum values). *Kruskal-Wallis and Mann–Whitney tests ($\alpha = 0.05$). +NGT (nonparametric multiple comparison test) showed a statistically significant value. ++CFRD ≠ NGT (nonparametric multiple comparison test) showed a statistically significant value.

Table 3. Univariate logistic analysis with variables to predict cystic fibrosis-related diabetes.

Variable	OR	95% CI	p*
Age	1.1	0.94 to 1.29	0.223
Male sex	4.99	1.63 to 15.18	0.005
p.Phe508del homozygous[a]	4.62	1.55 to 13.74	0.006
Pancreatic insufficiency	1.51	0.41 to 5.53	0.539
BMI, kg/m^2	0.78	0.63 to 0.97	0.028
FEV_1 (% of predicted values)	0.98	0.96 to 1.0	0.09
Peak ≥ 140 mg/dL/day (CGM-T0)	1.09	0.75 to 1.58	0.655
Valley < 54 mg/dL/day (CGM-T0)	0.93	0.29 to 3.03	0.906

CGM: continuous glucose monitoring; T0: baseline. [a]p.Phe508del classification was used because it is the only pathogenic variant routinely screened in our center. *Generalized estimating equation (α = 0.05).

status, and BMI were significantly related to CFRD development (Table 3). However, the multivariate logistic regression analysis showed no significant associations (data not shown).

DISCUSSION

This single-center study was conducted to compare the ability of OGTT with that of CGM in predicting the onset of CFRD and clinical impairment in CF patients. In the study population, abnormal CGM results based on the American Diabetes Association OGTT cutoff points[15] were not associated with an increased rate of CFRD or a decline in FEV_1 over a mean of 3.1 years of follow-up.

Although OGTT is the recommended gold standard for CFRD diagnosis, it is not an optimal tool, as the cutoff values are extrapolated from adult type 2 diabetes model based on the prevention of microvascular complications, which are not the leading causes of death in individuals with CF. Moreover, type 2 diabetes is not the same as CFRD.[23] A considerable lack of adherence to OGTTs has been reported.[5] Therefore, alternative screening methods are being investigated, especially those that could be related to the clinical outcomes of CF patients.

A study showed that CGM was useful for CFRD diagnosis and as an indication for early insulin therapy initiation, even though OGTT results were not confirmative.[24] Our study could not show this relationship, although dysglycemia detected by CGM readings was able to identify early BMI impairment in our patients. This difference may have occurred because of the shorter follow-up period in our study, as well as the shorter time of CGM use due to the model of the device used in our cohort.

In our study, when glucose abnormalities (CFRD and IGT) were grouped, lower BMI values and z-scores at baseline and at the end of the follow-up period were identified through CGM but not through baseline OGTT results. A study reported decreased pulmonary function and an increased rate of *Pseudomonas aeruginosa* infections among patients with CGM peaks of ≥ 200 mg/dL, although there was no detectable difference in BMI.[25]

Another study evaluated 25 children with CF and found that a proportion of time ≥ 4.5% with glucose levels > 140 mg/dL on CGM was associated with a decline in pulmonary function and weight gain in the previous 12 months.[26] Our study included a more robust case series with a longer follow-up period and detected lower BMI on patients with peaks ≥ 140 mg/dL during CGM; however, no associations were found of peaks, peaks per day, AUC, and proportion of time with glucose levels ≥ 140 mg/dL with FEV_1. The deterioration of FEV_1 and nutritional status occurs years before the diagnosis of CFRD.[2] In this context, we identified that patients who developed CFRD showed poorer FEV_1 at T1 but not at T0, as well as lower BMI at both T0 and T1 in our sample. Although the metric > 10% of the time with glucose levels ≥ 140 mg/dL on CGM is being used, it has yet to be incorporated into the guidelines, and thus it has not been considered for evaluation.

Despite the lack of significant differences, all patients who developed CFRD had a p.Phe508del homozygous status and PI and were classified as having "severe" disease (≤ 40% of predicted FEV_1) on spirometry and as being under weight (BMI) at T1. This is consistent with the literature available.[1] Furthermore, the decline in FEV_1 between T1 and T0 was greater in those classified as having CFRD according to the CGM classification than in those classified as having NGT and IGT. However, this decline was not significant in our study, which could be due to the small sample size.

Being female is considered a risk factor for CFRD, although the pathophysiology related to it is not well understood.[1] All patients who developed CFRD were male; thus, according to the univariate logistic regression analysis, being male seemed to be a potential predictor. However, in the multivariate analysis, the significance disappeared after adjustment.

Hypoglycemia during OGTT may indicate dysregulation of insulin secretion and could represent a stage preceding the onset of CFRD.[27] Our CGM study results showed that hypoglycemic events were unrelated to an increased risk of CFRD during the mean 3.1-year follow-up period. Radike et al. reported similar findings.[7] However, the prevalence of hypoglycemia was higher (32%) in our study.

The prevalence of hypoglycemia (< 50 mg/dL) in CF patients during an OGTT was reported to be 15%,[6] although this percentage could be attributed to the lower cutoff values used in that study. Furthermore, the age of the patients ranged from 8 to 31 years, whereas it ranged from 10.0 to 19.9 years in our study. Therefore, the discrepancies in cutoff values and methods could have contributed to the higher prevalence rates in our study.

Despite the higher sensitivity of CGM, its accuracy has been questioned regarding its precision in detecting consistent hypoglycemia and the lack of consensus guidelines, because no data are linking CGM to long-term outcomes in CF patients.[28] Although CGM was unable to predict the onset of CFRD based on the extrapolation of the criteria used for the OGTT,[15] 4 patients with glycemic values ≥ 200 mg/dL were identified by CGM but not by OGTT, and none of the participants who remained with interstitial glucose values < 140 mg/dL on CGM progressed to CFRD during the study period, leaving an open question of whether these patients might skip an OGTT. Gojsina et al.[24] showed that CGM could have higher sensitivity, since CFRD patients diagnosed by CGM had significantly lower hemoglobin A1c levels when compared with those diagnosed by OGTT.

Given its cost, CGM may not be available in all services for routine use and could be considered in individuals who are unable to undergo OGTT and in symptomatic NGT patients. CGM is a valid tool for the detection of dysglycemia in the CF population, and previous studies with a longer duration of CGM were able to demonstrate an association between dysglycemia detected by CGM and CF clinical outcomes.[24] CGM deals with the daily life and not with a controlled situation as does OGTT. CGM for the determination of glucose metabolism could be equated to 24-h ambulatory blood pressure monitoring for hypertension.

CGM can detect glucose abnormalities not detected by OGTT.[23,24] In our study, those abnormalities were associated with early BMI impairment, although they were not related to the current definition of the onset of CFRD based on the OGTT classification.[15] Perhaps, the reason why CGM could not predict the onset of CFRD was that the OGTT cutoff values[15] adopted might have been inadequate and/or the fact that CGM and OGTT are different tools from technical and interpretive standpoints. Moreover, according to the Endocrine Society, there is insufficient evidence for the establishment of an optimal postprandial blood glucose value.[24,29]

Only 3 of our participants developed CFRD; thus, it was not possible to make any statement about cutoff values, but we recommend that future multicenter studies evaluate CGM values between 140 and 200 mg/dL to determine appropriate cutoff values, since there are studies showing associations between values within this range and clinical outcomes.[30,31] It remains unclear whether a single CGM variable or a combination of these variables could predict clinically significant CF outcomes and potentially reformulate the CFRD concept. Additionally, CFRD patients are known to need insulin, but it is unknown if CF patients without overt diabetes but with CGM-detected glucose abnormalities could benefit from insulin use.[32] However, Gojsina et al.[24] showed that CFRD patients diagnosed by CGM benefit from insulin therapy with improvements in BMI z-score.

To clinical practice, the ideal tool would be able to predict a worse clinical evolution in short/medium terms, and, in our opinion, the adopted follow-up period fulfills this objective. Then, the same diagnostic criteria should not be used for CF individuals and those without CF, because the major cause of mortality in CF patients is not related to microvascular complications but rather to the worsening of the lung disease. The establishment of a tool that is correlated with clinical impairment in CF, mainly pulmonary function and BMI, could allow for early intervention and lead to savings related to public health care costs, as deteriorating clinical conditions lead to a greater number of hospitalizations, more aggressive therapies, and an increased need for oxygen therapy and lung transplants, in addition to the implications for quality of life and survival of CF patients.

The strengths of our study include the large sample size from a single CF referral center, the prospective design, the standardized data collection, and a pubertal pediatric cohort with high miscegenation. However, certain limitations must be recognized. Since CFRD is age related, a longer follow-up period would increase the number of patients diagnosed with this entity. The arbitrary use of OGTT cutoff values to classify CGM results is another limitation. Ideally, CGM should be performed during and at the end of the follow-up period, but, unfortunately, we were unable to do that. The CGM device available for the study was the CGMS Gold® (Medtronic Minimed), which allowed readings for a short period. Although the sample size is large for a single-center study, the small number of patients who developed CFRD during the follow-up period limited our ability to conduct multivariate regression analysis with the current dataset.

In conclusion, CGM can identify glucose abnormalities not detected by OGTT and may be more sensitive for the early detection of decreases in BMI. However, based on our data, we were unable to identify early predictors for the onset of CFRD among the variables studied. Individuals with interstitial glucose levels < 140 mg/dL on CGM might not need to perform OGTT in the short/medium term. Furthermore, we could have an alternative tool for those patients who are unable to perform OGTT and for those classified as having NGT on OGTT but with poor clinical evolution. Different diagnostic criteria for diabetes may be required for the CF population.

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AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Moran A, Becker D, Casella SJ, Gottlieb PA, Kirkman MS, Marshall BC, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: a technical review. Diabetes Care. 2010;33(12):2677-2683. https://doi.org/10.2337/dc10-1279

2. Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. Eur J Pediatr. 1992;151(9):684-687. https://doi.org/10.1007/BF01957574

3. Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med. 2000;162(3 Pt 1):891-895. https://doi.org/10.1164/ajrccm.162.3.9904075

4. Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2018;19 Suppl 27:64-74. https://doi.org/10.1111/pedi.12732

5. Cystic Fibrosis Foundation [homepage on the Internet]. Bethesda, Maryland: Cystic Fibrosis Foundation; c2019 [cited 2020 Jan 15]. Cystic Fibrosis Foundation Patient Registry 2018 Annual Data Report. Available from: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf

6. Battezzati A, Battezzati PM, Costantini D, Seia M, Zazzeron L, Russo MC, et al. Spontaneous hypoglycemia in patients with cystic fibrosis. Eur J Endocrinol. 2007;156(3):369-376. https://doi.org/10.1530/eje.1.02344

7. Radike K, Molz K, Holl RW, Poeter B, Hebestreit H, Ballmann M. Prognostic relevance of hypoglycemia following an oral glucose challenge for cystic fibrosis-related diabetes. Diabetes Care. 2011;34(4):e43. https://doi.org/10.2337/dc10-2286

8. Haliloglu B, Gokdemir Y, Atay Z, Abali S, Guran T, Karakoc F, et al. Hypoglycemia is common in children with cystic fibrosis and seen predominantly in females. Pediatr Diabetes. 2017;18(7):607-613. https://doi.org/10.1111/pedi.12470

9. Dobson L, Sheldon CD, Hattersley AT. Validation of interstitial fluid continuous glucose monitoring in cystic fibrosis. Diabetes Care. 2003;26(6):1940-1941. https://doi.org/10.2337/diacare.26.6.1940-a

10. O'Riordan SM, Hindmarsh P, Hill NR, Matthews DR, George S, Greally P, et al. Validation of continuous glucose monitoring in children and adolescents with cystic fibrosis: a prospective cohort study. Diabetes Care. 2009;32(6):1020-1022. https://doi.org/10.2337/dc08-1925

11. Armaghanian N, Brand-Miller JC, Markovic TP, Steinbeck KS. Hypoglycaemia in cystic fibrosis in the absence of diabetes: A systematic review. J Cyst Fibros. 2016;15(3):274-284. https://doi.org/10.1016/j.jcf.2016.02.012

12. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-1640. https://doi.org/10.2337/dc17-1600

13. Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr. 2008;152(4):540-545.e1.

https://doi.org/10.1016/j.jpeds.2007.09.025

14. GIBSON LE, COOKE RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics. 1959;23(3):545-549. https://doi.org/10.1542/peds.23.3.545

15. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26 Suppl 1:S5-S20. https://doi.org/10.2337/diacare.26.2007.s5

16. World Health Organization. International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation [monograph on the Internet]. Geneva: World Health Organization; 2006 [Cited 2018 Nov 12]. Available from: https://apps.who.int/iris/handle/10665/43588

17. Miller M, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338. https://doi.org/10.1183/09031936.05.00034805

18. Rodrigues JC, Cardieri JM, Bussamra MH, Nakaie CM, Almeida MB, Silva FL, et al. Provas de função pulmonar em crianças e adolescentes. J Pneumol. 2002;28(Suppl 3):207-221.

19. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 2006;450:76-85. https://doi.org/10.1111/j.1651-2227.2006.tb02378.x

20. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291-303. https://doi.org/10.1136/adc.44.235.291

21. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13-23. https://doi.org/10.1136/adc.45.239.13

22. Borowitz D, Baker SS, Duffy L, Baker RD, Fitzpatrick L, Gyamfi J, et al. Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis. J Pediatr. 2004;145(3):322-326. https://doi.org/10.1016/j.jpeds.2004.04.049

23. Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: Pathophysiology, screening and diagnosis. J Cyst Fibros. 2019;18 Suppl 2:S3-S9. https://doi.org/10.1016/j.jcf.2019.08.016

24. Gojsina B, Minic P, Todorovic S, Soldatovic I, Sovtic A. Continuous Glucose Monitoring as a Valuable Tool in the Early Detection of Diabetes Related to Cystic Fibrosis. Front Pediatr. 2021;9:659728. https://doi.org/10.3389/fped.2021.659728

25. Leclercq A, Gauthier B, Rosner V, Weiss L, Moreau F, Constantinescu AA, et al. Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. J Cyst Fibros. 2014;13(4):478-484. https://doi.org/10.1016/j.jcf.2013.11.005

26. Hameed S, Morton JR, Jaffé A, Field PI, Belessis Y, Yoong T, et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care. 2010;33(2):221-226. https://doi.org/10.2337/dc09-1492

27. Tofé S, Moreno JC, Máiz L, Alonso M, Escobar H, Barrio R. Insulin-secretion abnormalities and clinical deterioration related to impaired glucose tolerance in cystic fibrosis. Eur J Endocrinol.

2005;152(2):241-247. https://doi.org/10.1530/eje.1.01836

28. Ode KL, Moran A. New insights into cystic fibrosis-related diabetes in children. Lancet Diabetes Endocrinol. 2013;1(1):52-58. https://doi.org/10.1016/S2213-8587(13)70015-9

29. Leahy JJL, Aleppo G, Fonseca VA, Garg SK, Hirsch IB, McCall AL, et al. Optimizing Postprandial Glucose Management in Adults With Insulin-Requiring Diabetes: Report and Recommendations. J Endocr Soc. 2019;3(10):1942-1957. https://doi.org/10.1210/js.2019-00222

30. Taylor-Cousar JL, Janssen JS, Wilson A, Clair CG, Pickard KM, Jones MC, et al. Glucose >200 mg/dL during Continuous Glucose Monitoring Identifies Adult Patients at Risk for Development of Cystic Fibrosis Related Diabetes. J Diabetes Res. 2016;2016:1527932. https://doi.org/10.1155/2016/1527932

31. Chan CL, Vigers T, Pyle L, Zeitler PS, Sagel SD, Nadeau KJ. Continuous glucose monitoring abnormalities in cystic fibrosis youth correlate with pulmonary function decline. J Cyst Fibros. 2018 Nov;17(6):783-790. https://doi.org/10.1016/j.jcf.2018.03.008

32. Pu MZ, Christensen-Adad FC, Gonçalves AC, Minicucci WJ, Ribeiro JD, Ribeiro AF. Insulin therapy in patients with cystic fibrosis in the pre-diabetes stage: a systematic review. Rev Paul Pediatr. 2016;34(3):367-373. https://doi.org/10.1016/j.rppede.2016.03.006