Continuous glucose monitoring to evaluate glycaemic abnormalities in cystic fibrosis

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ABSTRACT

Objective This study aimed to determine the glycaemic profile of patients with cystic fibrosis using a continuous glucose monitoring system (CGMS), and to evaluate the associations of glycaemic abnormalities with sex, age, pubertal stage, *CFTR* gene mutations, nutritional status, lung function, oral glucose tolerance test, glycated haemoglobin concentrations, fasting insulin concentrations, C peptide concentrations and exocrine pancreatic function.

Study design This observational study evaluated CGMS data from 39 patients with cystic fibrosis who were treated at a referral centre. The patients were 10–19.9 years old, and were categorised according to whether they had normal results (27 patients) or glucose intolerance (12 patients) during the oral glucose tolerance test.

Results The maximum interstitial glucose concentration among individuals with normal oral glucose tolerance test results was 174.9±65.1 mg/dL (9.7–3.61 mmol/L), compared with 170.4±40.9 mg/dL (9.46–2.27 mmol/L) among individuals with glucose intolerance. The CGMS revealed that 18 of the 27 patients with normal oral glucose tolerance test results had peak interstitial glucose concentrations of >140 mg/dL (7.8 mmol/L), and that 4 of these individuals had peak levels of >200 mg/dL (11.1 mmol/L). None of the analysed clinical or laboratory characteristics predicted the occurrence of hyperglycaemic peaks on CGMS.

Conclusions The present study revealed that CGMS could detect hyperglycaemia among patients with cystic fibrosis and 'normal' oral glucose tolerance test results, and that their clinical and laboratory characteristics were not useful in discerning between patients who did and did not exhibit these excursions.

What is already known on this topic?

- Cystic fibrosis-related diabetes (CFRD) is associated with a reduced life expectancy, reduced lung function and poorer nutritional status.
- Early identification of CFRD and effective intervention can help prevent some of the deleterious effects.
- Oral glucose tolerance test (OGTT) fails to detect some glycaemic abnormalities in cystic fibrosis (CF).

What this study adds?

- Some patients with CF with normal OGTT results had peak interstitial glucose concentrations of >140 mg/dL (7.8 mmol/L) and >200 mg/dL (11.1 mmol/L) based on the continuous glucose monitoring system (CGMS).
- These missed hyperglycaemic peaks were not associated with any of the clinical or laboratory tests that we evaluated.
- To our knowledge this is the first Latin American study on the role of CGMS in children and young people with CF.

INTRODUCTION

Cystic fibrosis (CF) is a chronic and progressive autosomal recessive genetic disease that is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), which affects the function of the CFTR protein.[1] The absence or malfunction of this protein causes altered sodium transport and increased viscosity of mucous secretions, which leads to obstruction of the glandular ducts and canaliculi.[2] Approximately 20% of adolescent and 40%–50% of adult CF cases involve cystic fibrosis-related diabetes (CFRD).[3] These patients exhibit a delayed insulin response to a glucose load, although their basal secretion is relatively preserved. The delayed insulin response is associated with loss of the first phase of insulin secretion, which is observed in all patients with CF, including individuals with normal glucose tolerance (NGT).[4] CFRD is the last stage of a spectrum of progressive glucose tolerance abnormalities.[1–5]

Hyperglycaemia and insulin deficiency negatively affect lung function in patients with CF.[6 7] Furthermore, diabetes and glucose intolerance (IGT) are associated with a reduced life expectancy among these patients, who experience reduced lung function, nutritional status and survival, compared with individuals with NGT.[8 9] The oral standard (0 and 120 min) glucose tolerance test (OGTT) is currently used to diagnose CFRD,[1 10] although elevations at non-traditional times are common. Elevations of glucose concentrations at 60 min could be harmful, or be an early marker for worsening lung disease (forced expiratory volume in 1 s (FEV_1)).[11] Therefore, normal OGTT results do not exclude the possibility of transitional postprandial hyperglycaemia.[1 12] Continuous glucose monitoring system (CGMS) can be used to improve the diagnosis, management and tracking of CFRD.[13] The Food and Drug Administration has approved the

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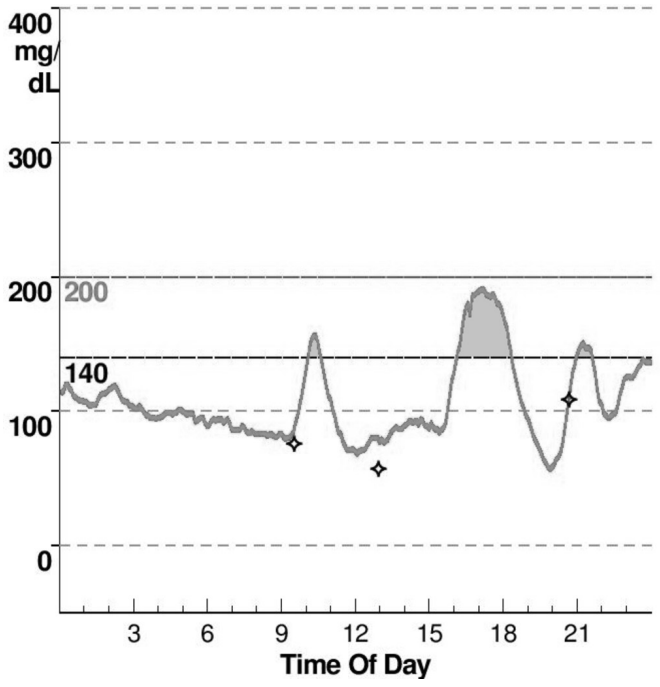

Figure 1 Area under the curve illustration (grey area) for peaks above 140 mg/dL (7.8 mmol/L).

use of CGMS for children and adolescents with CF, which may enhance diagnoses that are based on OGTT results.[1 14 15]

METHODS

Participants and tests

Between August 2014 and June 2015, all patients aged 10–19.9 years old who visited the outpatient clinic of our CF referral centre were invited to participate in the study. All individuals were diagnosed with CF based on the identification of two *CFTR* mutations or at least two sweat chloride test results of >60 mEq/L. All participants were clinically stable (based on evaluations by two paediatric pneumologists), were not receiving systemic corticosteroid therapy and were not pregnant at the time of the data collection. We excluded individuals who had a CGMS reading for <36 hours, individuals who did not complete the OGTT, individuals with improper CGMS calibration (two capillary blood glucose readings per day)[8] and individuals who were diagnosed with diabetes using the American Diabetes Association (ADA) criteria. Of the 63 invited patients, 12 did not agree to participate, 1 had several pulmonary exacerbations, 2 provided CGMS readings for <36 hours, 8 had diagnosed CFRD and 1 did not complete the OGTT.

The WHO protocol for OGTT[16] and the enzymatic colourimetric method were used to classify the participants as having NGT (fasting blood glucose concentrations of <126 mg/dL (7 mmol/L) and <140 mg/dL (7.8 mmol/L) at 120 min), IGT (fasting blood glucose concentrations of <126 mg/dL (7 mmol/L) and 140–199 mg/dL (7.8–11.0 mmol/L) at 120 min) or diabetes (fasting blood glucose concentrations of ≥126 mg/dL (7 mmol/L) or ≥200 mg/dL (11.1 mmol/L) at 120 min, in two tests). All participants also underwent CGMS monitoring (Medtronic MiniMed CGMS System Gold) using a probe that was inserted into the subcutaneous tissue of the abdominal wall through an introducer needle and spring device (Sen-Serter). The probe was protected externally using a clear and antiallergic dressing, and remained in the participant for up to three weekdays at home. All included patients were followed up by the referral centre's nutritionist and nutrologist.

The same paediatric endocrinologist evaluated each participant's weight, height, body mass index (BMI) and pubertal stage at the CF outpatient clinic. The WHO's 2006 curve was used to calculate the z scores for BMI,[17] and pubertal staging was evaluated using Tanner's morphometric criteria.[18 19] Genetic testing was performed using PCR or genetic sequencing. The sweat test was performed using a quantitative ionic analysis of sweat (iontophoresis) after stimulation of the skin using pilocarpine.[20] Laboratory tests (glycated haemoglobin (HbA1c), C peptide, fasting insulin, β-chorionic gonadotropin and OGTT) were performed at the centre's clinical laboratory. Normal HbA1c findings were defined as ≤6% after high-performance liquid chromatography, as we aimed to detect glucose abnormalities and not outright diabetes (ADA criteria >6.5%).

Exocrine pancreatic function was tested using faecal elastase-1 measurements with the ScheBo Pancreatic Elastase 1 Stool Test ELISA. Exocrine pancreatic insufficiency was considered present in cases with values of <200 µg/g.[21] Spirometry testing was performed based on the standards of the American Thoracic Society and the European Respiratory Society, and the predicted percentage of FEV_1 was evaluated.[22] MiniMed Solutions software (V.1.7a) was used to calculate the parameters for CGMS, including area under the curve (AUC), percentage of total time and hyperglycaemia peaks.

The software calculates the AUC at intervals of 5 min, as shown in figure 1 and the equation below:

$$\frac{\sum (SensorGlucoseValue - Limit) * 5min}{TotalNumberofSamplesinDay * 5min}$$

Statistics

All data were analysed using SPSS software (V.16.0) and MiniMed Solutions software (V.1.7a). Differences were considered statistically significant at two-tailed P values of <0.05. Qualitative variables were expressed as number and frequency. Quantitative variables were expressed as the mean value, SD, median value, and maximum and minimum values. Student's t-test and the Mann-Whitney test were used to compare two independent groups, and the Kruskal-Wallis test was used to compare three or more independent groups. The associations with qualitative variables were analysed using the X^2 test, Fisher's exact test or the Fisher-Freeman-Halton test, as indicated. The correlations of age with the CGMS parameters were analysed using Spearman's correlation coefficient.

RESULTS

All included participants (n=39) underwent OGTT and were assessed for sex, puberty, BMI, *CFTR* mutations, exocrine pancreatic function, FEV_1, fasting insulin concentrations, HbA1c concentrations and C peptide concentrations (table 1). All 39 participants had fasting insulin values that were within the reference range (2.0–28.4 µUI/mL). The NGT group had a mean age of 15±2.9 years (range: 10.8–19.5 years), while the IGT group had a mean age of 15.4±2.4 years (range: 10.8–19.2 years) (P=0.711, Student's t-test). Age was not correlated with CGMS peaks of >140 mg/dL (7.8 mmol/L) (P=0.364), CGMS peaks of >200 mg/dL (11.1 mmol/L) (P=0.51), the CGMS AUC (mg/dL*day) for peaks of >140 mg/dL (7.8 mmol/L) (P=0.36) or >200 mg/dL (11.1 mmol/L) (P=0.439), or with the percentage of total time for peaks of >140 mg/dL (7.8 mmol/L) (P=0.433) or >200 mg/dL (11.1 mmol/L) (P=0.381).

Table 1 Participant characteristics according to their oral glucose tolerance test results

	NGT	IGT	Total	P
Sex				
Male	13	8	21	0.470*
Female	14	4	18	
Puberty† (Tanner)				0.704‡
Prepubertal (B1/G1)	3	2	5	
Pubertal (B3/G2/G3/G4)	11	6	17	
Full puberty (B4/B5/G5)	13	4	17	
Body mass index§ (kg/m^2)				0.732‡
Obese (z score >+2)	1	0	1	
Overweight (z score +1 to +2)	2	0	2	
Underweight (z score <–2)	7	5	12	
Eutrophic (z score –2 to +1)	14	6	20	
Mutation¶				0.457††
Other**	19	6	25	
F508del/F508del	8	5	13	
Pancreatic insufficiency				1.000††
Yes	19	9	28	
No	8	3	11	
FEV_1‡‡				
Normal (≥80%)	9	3	12	0.922‡
Lightly impaired (60%–79%)	10	5	15	
Moderately impaired (41%–59%)	3	1	4	
Severely impaired (≤40%)	4	3	7	
Glycated haemoglobin				0.348††
Normal (≤6%)	24	9	33	
Elevated (>6%)	3	3	6	
C peptide§§ (ng/mL)				1.000††
Normal (≥ 0.8)	18	7	25	
Decreased (<0.8)	2	0	2	

*X^2 test with continuity correction.
†Tanner and Marshall pubertal staging.[18 19]
‡Probability based on the bilateral Fisher-Freeman-Halton test.
§4 individuals who were >18 years old (z score not calculated using the 2006 WHO curve[17]).
¶1 individual has a mutation that is currently being evaluated.
**Other: two alleles that were not homozygous F508del/F508del.
††Two-sided Fisher's exact test.
‡‡1 individual with NGT did not undergo spirometry.
§§12 individuals did not undergo C peptide testing.
FEV_1, forced expiratory volume in 1 s; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Twenty-eight participants (16 male, 12 female) exhibited one or more CGMS peaks of >140 mg/dL (7.8 mmol/L). Among these participants, 18 were initially classified as having NGT and 10 were initially classified as having IGT, based on OGTT results. Therefore, 18 of the 27 participants (67%) with 'normal' OGTT results exhibited CGMS peaks of >140 mg/dL (7.8 mmol/L). Furthermore, six participants (three male, three female) exhibited one or more CGMS peaks of >200 mg/dL (11.1 mmol/L), with four participants initially being classified as having NGT and two participants initially being classified as having IGT, based on OGTT results. Thus, 15% of participants with 'normal' OGTT results exhibited CGMS peaks of >200 mg/dL (11.1 mmol/L), as well as 17% of participants who were initially classified as having IGT.

There were six children with an HbA1c >6.0%, indicating already some impairment of glucose metabolism (table 1). Only 1 patient out of 39 had HbA1c >6.5%, but with normal OGTT results at standard times of 0 and 120 min.

There were no statistically significant associations between peak distributions (>140 mg/dL (7.8 mmol/L) or >200 mg/dL (11.1 mmol/L)) and sex, *CFTR* mutations, BMI, pubertal staging, exocrine pancreatic function, FEV_1, OGTT, HbA1c or C peptide concentrations. In addition, these variables were not significantly associated with the AUC values (mg/dL*day) or the percentage of total time spent at >200 mg/dL (11.1 mmol/L). The AUC values of >140 mg/dL (7.8 mmol/L) (mg/dL*day) were only significantly associated with HbA1c concentrations (P=0.026) and OGTT results (P=0.044) (table 2). The percentage of total time spent at values of >140 mg/dL (7.8 mmol/L) was only significantly associated with HbA1c concentrations (P=0.027) (table 3).

Table 4 shows the distributions of the CGMS values for total time, minimum, maximum, mean and median interstitial glucose values according to the OGTT results.

DISCUSSION

This study reveals that incidental hyperglycaemia in patients with CF was not significantly predicted by their clinical and laboratory characteristics (age, BMI, sex, pubertal stage, *CFTR* mutations, exocrine pancreatic function, lung function, OGTT results, HbA1c concentrations, fasting insulin concentrations or C peptide concentrations). Previous reports[23 24] have indicated that conventional laboratory tests (HbA1c, fasting insulin, C peptide and classic OGTT at 0 and 120 min) were not sensitive enough to detect early glucose metabolism dysfunction in CF cases. OGTT is not appropriate for testing patients with CF, mainly when it is done only at 0 and 120 min.[12] Furthermore, the OGTT cut-off values are based on a healthy population and do not account for the unique characteristics of patients with CF.[13]

Patients with CF have an elevated risk of CFRD if they have homozygous F508del mutations, female sex, older age or exocrine pancreatic insufficiency.[25] The fact that we did not observe these differences is likely related to the fact that

Table 2 Area under the curve values (mg/dL*day) for individuals with peak CGMS values of >140 mg/dL (7.8 mmol/L)

	n	Mean	SD	Minimum	Median	Maximum	P
OGTT							
NGT	18	1.72	2.49	0	1	10	0.044
IGT	10	0.6	1.26	0	0	4	
HbA1c							
Normal (≤6%)	22	1.64	2.36	0	1	10	0.026
Elevated (>6%)	6	0.17	0.41	0	0	1	

P values were calculated using the Mann-Whitney test.
CGMS, continuous glucose monitoring system; HbA1c, glycated haemoglobin; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

Table 3 Percentage of total time (%) for individuals with CGMS peak values of >140 mg/dL (7.8 mmol/L)

	n	Mean	SD	Minimum	Median	Maximum	P
OGTT							
NGT	18	5.56	4.48	0	4.5	14	0.357
IGT	10	3.8	4.13	1	2	14	
HbA1c							
Normal (≤6%)	22	5.82	4.46	0	4.5	14	0.027
Elevated (>6%)	6	1.67	1.75	0	1	5	

P values were calculated using the Mann-Whitney test.
CGMS, continuous glucose monitoring system; HbA1c, glycated haemoglobin; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

we excluded individuals with diabetes, as we wished to identify the glycaemic profile of patients with CF but not CFRD, and to potentially identify patients with hyperglycaemia despite 'normal' OGTT results. Interestingly, the absence of significant differences between the NGT and IGT groups may suggest that they are actually part of a mixed group that cannot be adequately distinguished by OGTT. It is not unusual to find different OGTT values for the same individual on different days. This is important as even an incidental hyperglycaemia can potentially cause a degree of clinical impairment in patients with CF.[26] Nevertheless, we did not evaluate treatment adherence in the present study, and poor adherence may at least partially explain the absence of significant differences between these two groups.

Similar to the findings of Moreau *et al*,[27] we observed that patients with normal OGTT results can exhibit CGMS peaks of >200 mg/dL (11.1 mmol/L), as 67% (18/27) of our patients with NGT results had at least one peak of >140 mg/dL (7.8 mmol/L) and 15% (4/27) had at least one peak of >200 mg/dL (11.1 mmol/L). These results support the use of CGMS as a complementary diagnostic tool in this population, as increases in blood glucose at unconventional times may not be reflected in the OGTT results, which might reduce its diagnostic ability.

The early detection of glucose abnormalities might benefit patients with CF, as some studies suggest that insulin treatment can provide clinical improvements in cases of IGT and indeterminate glycaemia.[10 26 28] Furthermore, early detection may be associated with lower treatment costs, as these patients would have better BMI and lung function, which would require fewer therapeutic interventions.[29]

We know that just as an insulin deficiency occurs because of the underlying disease, there is also a glucagon deficiency. This is why these patients have more hypoglycaemia (often asymptomatic) than the population without CF. In our series, 29 of 39 patients had glucose concentrations lower than 70 mg/dL (3.9 mmol/L). However we did not perform any statistical analysis, since our intention was to correlate clinical and laboratory characteristics with hyperglycaemia. Furthermore, it is known that CGMS has a range of 40–400 mg/dL (2.2–22 mmol/L), being better for detection of hyperglycaemia than hypoglycaemia.

Our results indicate that not all CGMS parameters should be used to detect glycaemic excursions. We found that analysis of the CGMS AUC values from our participants was unreliable, as the software performs the calculations at 5 min intervals and would not be able to identify individuals with peaks that last for <5 min. This fact is likely related to the significant difference in the associations of HbA1c concentrations and OGTT results with the AUC values for peaks of >140 mg/dL (7.8 mmol/L). When we discarded AUC values of 0 among individuals with peaks of >140 mg/dL (7.8 mmol/L), this difference disappeared (P=0.822 for OGTT, P=0.399 for HbA1c).

Among the individuals with peaks of >140 mg/dL (7.8 mmol/L), the association between the AUC values and the OGTT results was statistically significant. Furthermore, patients with NGT results exhibited relatively high mean and median CGMS values, which suggests that they experienced more glucose excursions (>140 mg/dL (7.8 mmol/L)), compared with individuals with IGT results. Therefore, these patients could be identified using CGMS, despite their apparently normal OGTT results.

There are several issues that must be considered when evaluating the association of AUC values for peaks of >140 mg/dL (7.8 mmol/L) with HbA1c concentrations. First, HbA1c is not a good parameter for screening patients with CF, and there are

Table 4 Interstitial glucose values and lengths of CGMS according to OGTT results

CGMS		n	Mean	SD	Minimum	Median	Maximum	P
Minimum value (mg/dL, mmol/L)	NGT	27	60.8 3.37	12.7 0.7	40 2.2	63 3.5	80 4.4	0.360
	IGT	12	56.7 3.15	10.3 0.57	40 2.2	58.5 3.25	73 4.0	
Mean value (mg/dL, mmol/L)	NGT	27	97 5.38	10 0.55	78 4.33	100 5.5	116 6.44	0.419
	IGT	12	95.3 5.29	7.2 0.4	79 4.38	96.5 5.35	103 5.7	
Maximum value (mg/dL, mmol/L)	NGT	27	174.9 9.7	65.1 3.61	98 5.44	164 9.1	400 22.2	0.773
	IGT	12	170.4 9.46	40.9 2.27	119 6.6	158 8.77	267 14.8	
Total time (min)	NGT	27	4193.5	496	2475.0	4255.0	5800.0	0.573
	IGT	12	4151.3	315.1	3520.0	4282.5	4475.0	

P values were calculated using the Mann-Whitney test.
CGMS, continuous glucose monitoring system; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

multiple explanations for its poor diagnostic ability in this population. For example, glycation can be altered by hypoxia, chronic inflammation and shorter red blood cell half-lives, which may provide apparently normal values, even in patients with blood sugar disorders that are identified during OGTT.[10 30] Nevertheless, we found six patients with HbA1c greater than 6%, demonstrating some glucose metabolism disturbance. The associations of HbA1c concentrations with AUC values and percentage of total time for individuals with CGMS peak values of >140 mg/dL (7.8 mmol/L) could be explained by hypoxia, chronic inflammation and shorter red blood cell half-life.

Therefore, we recommend retaining OGTT as a standard screening tool, based on its low cost and good accessibility, although CGMS may be performed for cases with normal OGTT results. In this setting, the CGMS provides a good indicator of interstitial and plasma glucose concentrations, and is accurate, repeatable and reproducible.[15] Several studies have also confirmed that OGTT is not the most appropriate method for assessing patients with CF, and that CGMS is superior in this setting.[13 27]

CONCLUSION

Although CGMS can detect hyperglycaemia before OGTT, it is unclear whether this undetected hyperglycaemia could affect patients with CF. Furthermore, the OGTT cut-off values are not ideal for these patients, as glucose concentrations of <200 mg/dL (11.1 mmol/L) may already have aggravated their underlying disease. The present study revealed that patients with apparently 'normal' OGTT results frequently had glycaemic excursions that were detected on CGMS, and that their clinical and laboratory characteristics were not useful in discriminating between patients who did and did not exhibit these excursions. Therefore, multicentre longitudinal studies are needed to determine if these excursions in patients with CF and normal OGTT results have any significant effects on patients' health.

Contributors MZMHP and AFR conceived the study, interpreted the data and drafted the manuscript. MZMHP sourced the data. MZMHP, AFR, ACG and WJM reviewed the medical details of each case. AMM conducted the statistical analysis. JDR and AFR reviewed the manuscript. MZMHP designed the study, interpreted the data and critically reviewed the manuscript, and is the corresponding author of this manuscript. All authors approved the final manuscript as submitted.

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