CASE REPORT

Continuous glucose monitoring and dysglycaemia in young children with cystic fibrosis: A case series

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Case Report

Cystic fibrosis-related diabetes (CFRD) was first described in 1955 and almost always occurrs in subjects with pancreatic insufficiency.[1] It was subsequently shown to affect lung function and growth.[2] The prevalence of CFRD increases with age. International guidelines recommend commencing screening for CFRD at 10 years of age, using the Oral Glucose Tolerance Test (OGTT).[3] Few studies have been performed on glucose tolerance in children younger than 10 years, and most of those have used OGTT (e.g. Yi *et al.*[4]). However, those studies have shown that dysglycaemia is frequently present in young patients with cystic fibrosis.

In our regional paediatric cystic fibrosis (CF) clinic, high blood glucose levels (BGLs) in young children noted on routine blood tests, or during testing for poor growth, prompted the consideration of whether they may have dysglycaemia.

Key points

1 Continuous glucose monitoring (CGM) screening is achievable and acceptable in young children.
2 We describe three children aged 4–10 years with cystic fibrosis who show evidence of dysglycaemia on CGM.
3 CGM enables real-life monitoring of the results of insulin treatment.
4 Large multicentre studies are needed to study CGM as a means of cystic fibrosis-related diabetes screening and diagnosis in young children.

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Continuous glucose monitoring systems (CGM) can accurately record glucose levels in free-living conditions. In older children and adults with CF, CGM has been shown to detect dysglycaemia despite normal OGTT, and treatment targeted to hyperglycaemia on CGM has led to improved lung function and weight followed by reduced decline in pulmonary function.[5] There are no published criteria for diagnosing CFRD on the basis of CGM data.

We used the Abbott Freestyle Libre CGM device, for which we have experience in older children with cystic fibrosis. This is a calibration-free, intermittently-scanned CGM system, which involves a minimally invasive placement of a sensor incorporating a small subcutaneous needle over the upper arm, and is worn typically for 2 weeks. The device measures a current signal generated by the glucose-oxidase reaction in interstitial fluid and calculates a glucose level. It can sample every 15 min, and 24-h profiles can be downloaded remotely. The user is not blinded to the result but 'scans' the device ≤8 hourly to ensure continuity of data collection.

We have selected for demonstration the results of monitoring using the Freestyle Libre system, in selected subjects under 10 years of age from our paediatric cystic fibrosis clinic. The selection arose from an audit of CGM in young children; at that time, our clinic had 14 children with CF between 6 and 10 years old. Of these, eight had had prior evidence of dysglycaemia on CGM, and two had still not been tested. We have selected three children who provide clear visual demonstration of dysglycaemia readily detected with CGM. Two had had their first CGM before 5 years of age, and one had compound CFTR heterozygosity. Management of dysglycaemia in these subjects was based on paediatric endocrinology advice.

We obtained informed consent from the children and their families to share these results.

Demographic and test data for the three subjects are shown in Table 1.

Diagnosis and management of these subjects are as follows:

Subject A (Fig. 1, A). This 4-year 7 -month old was screened due to growth failure and a respiratory exacerbation. Weight went from 55th to 30th percentile, height from 40th to 20th percentile, and BMI from 65th to 50th percentile during the 12 preceding months, despite attention to dietary input and adequate enzyme treatment. Following CGM analysis (Table 1), the subject was commenced on a combination of slow and rapid-acting insulin. Repeat CGM while taking glargine 3u plus aspart 2u before breakfast showed improvement in glycaemic control, with an average BGL of 5.5 mmol/L, excursions >7.8 mmol/L 14% of the time

Table 1 Baseline characteristics and test results for subjects A, B and C. All subjects were pancreatic insufficient and taking enzyme and vitamin replacement therapy

| Subject	A	B	C
Age (years and months)	4y7m	8y11m	4y2m
CFTR variants	Homozygous ΔF508	ΔF508/N1303K	Homozygous ΔF508
Reason for test	Poor growth, respiratory deterioration	Poor growth	High post-operative blood glucose level
BMI *Z*-score	0.05	−1.08	−0.72
FEV1% predicted	82	101	Not done
No. of hospital admissions from birth to baseline	8	10	5
HbA1C (mmol/mol)	38	37	34
Plasma C-peptide (pmol/L)	1150	Not done	137
Anti-GAD antibody level (U/mL)	0.3	0.5	0.2
IA2 antibody level (U/mL)	<0.1	1.0	<0.1
Islet cell autoantibodies	Not detected	Not detected	Not available
CGM average daily capture and days worn	86% over 14 days	74% over 14 days	100% over 17 days
Total number of readings	1166	1073	1588
Proportion of readings >7.8 mmol/L	41%	28%	19%
Average reading (mmol/L)	7.9	6.9	6.6
Highest reading (mmol/L)	19.5	16.0	15.8
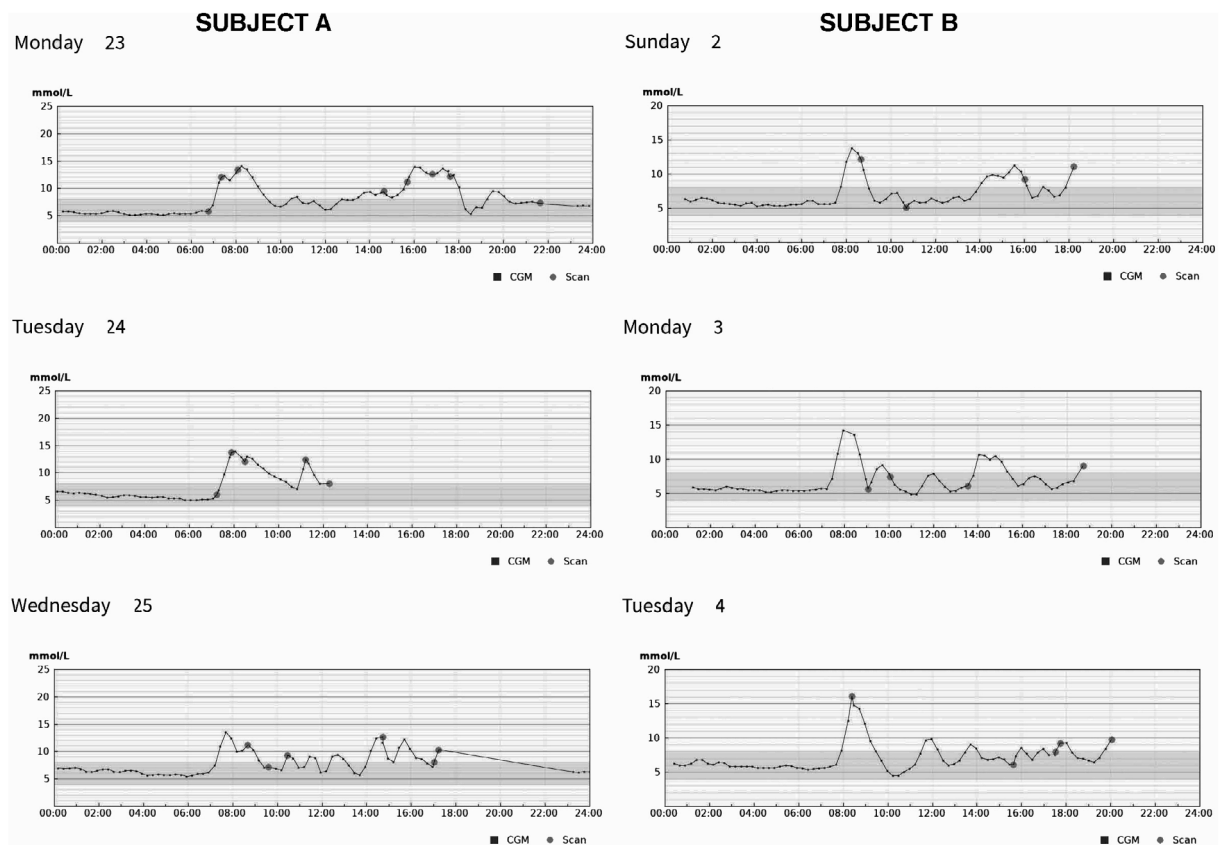
Fig. 1 CGM data for three consecutive days (day and date shown) in each case for subjects A and B at baseline. In each graph, the grey horizontal bar indicates the normal range of CGM glucose. Small dots represent automatic sampling at 15-min intervals (connecting lines have been drawn in to improve the visibility of the trend). Large dots represent times the device was scanned. Both subjects show peaks of high glucose after breakfast and in the afternoon. Note that the analysis of the data in the Table is based on all 14 days of data and not just this sample. CGM, continuous glucose monitoring.

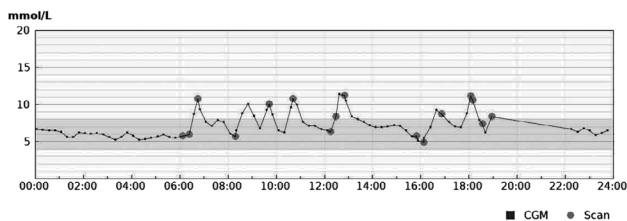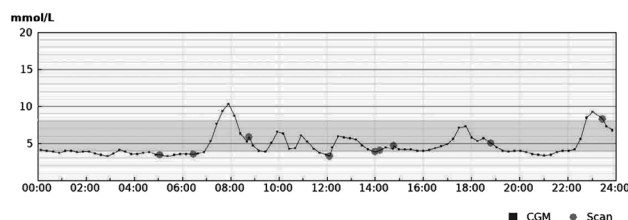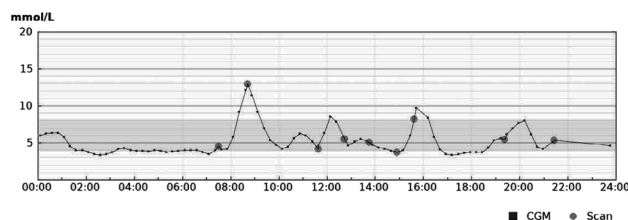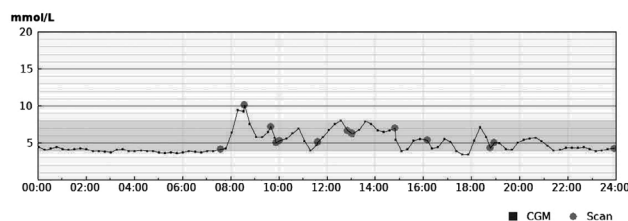## SUBJECT C: Baseline   On insulin
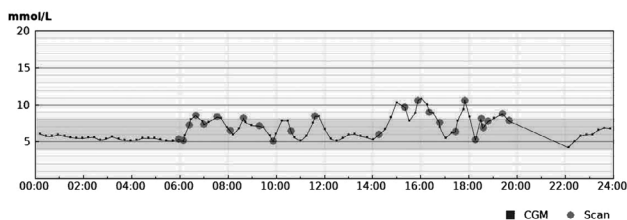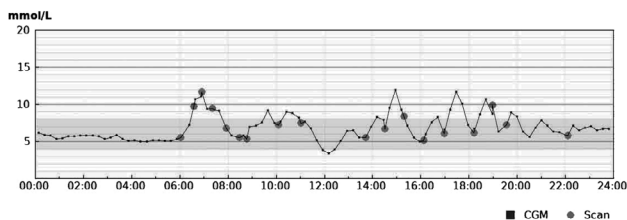
Fig. 2 CGM scans for 3 consecutive days each for subject C, at baseline and 15 months later while treated with insulin. The explanation of the depiction is as in Figure 1. At baseline, there are frequent high levels of glucose in the morning and afternoon. On insulin, a post-breakfast peak remains, but the levels otherwise are lower. CGM, continuous glucose monitoring.

and highest glucose reading of 14.7 mmol/L. Growth did not show significant improvement; however, FEV1% predicted steadily increased from 82% before treatment to 110% 2 years later.

Subject B (Fig. 1, B) had initial screening with CGM at the age of almost 9 years due to growth impairment, along with high random BGLs. Initial CGM showed dysglycaemia but treatment was deferred due to procedural and needle anxiety. Repeat CGM testing a year later showed glucose levels >7.8 mmol/L 20% of the time and multiple peaks above 11.1 mmol/L. Insulin treatment was commenced during a period of overnight feeding in hospital. Follow-up CGM 15 months later while taking glargine 5u daily showed average glucose reading of 5.9 mmol/L and 13% of readings above 7.8 mmol/L. The BMI had increased from 14.3 kg/m^2 (15th percentile) to 16.56 kg/m^2 (33rd percentile), whereas FEV1% predicted remained stable at around 100%.

Subject C (Fig. 2) was admitted for bronchoalveolar lavage and respiratory tune-up at the age of 4 years 2 months. Weight had fallen from 35th to 25th percentile and BMI from 50th to 20th percentile over the preceding 12 months, despite optimising dietary input and pancreatic enzymes. A routine post-procedure blood glucose of 16 mmol/L prompted investigation. Following

CGM (Fig. 2, Baseline), the subject was commenced on insulin. After 9 months (by now on 4.5u isophane mane), Subject C's weight had increased to the 40th percentile, and BMI to the 25th percentile. The subject was not able to perform spirometry at the time of initial testing. Subsequent spirometry has shown FEV1% predicted levels between 86% and 93%. Follow-up CGM at the age of 5 years 5 months (Fig. 2, on insulin) showed a reduction in average glucose level from 6.6% to 4.9% and a reduction in hyperglycaemic episodes from 18% to 8% of readings above 7.8 mmol/L. In the evenings, there are readings just below 3.9 mmol/l; these were not associated with symptoms or confirmed with finger-prick blood glucose at the time.

Discussion

Continuous glucose monitoring is acceptable and readily used in young children. In practice, CGM is more convenient than OGTT, as the sensor can be applied in clinic in a matter of minutes, without booking a separate appointment for an OGTT, which requires fasting, attendant risk of hypoglycaemia, repeated blood sampling, and staff monitoring over several hours. As a method

of demonstrating dysglycaemia, CGM has the advantages of displaying an extended time profile of glucose during normal daily activities, and meals, rather than response to a single glycaemic load. These cases, and the reports of other workers,[5,6] suggest that the guideline recommendations to screen children for CFRD from 10 years and older may miss many younger children with dysregulation of blood glucose, who could potentially benefit from treatment. We acknowledge the limitations of our small data set, and that non-blinded CGM may have influenced dietary behaviour. In this case series, we have not been able to demonstrate that treatment of dysglycaemia in young children consistently improves their growth or lung function. On the other hand, insulin given to young children who are known to show day-day variability in CGM readings[6] may risk hypoglycaemia.

We are treating these cases as CFRD, requiring insulin, but recognise that we are doing so without consensus diagnostic criteria of CFRD based on CGM. Some authors have listed criteria for reporting measurement[7] or practical management based on CGM,[8] but to our knowledge, there are no currently registered clinical trials of CGM as a screening or diagnostic tool for CFRD in young children. We believe larger multicentre studies should be undertaken to examine CGM for diagnosing CFRD and the safety and efficacy of early diagnosis and treatment of CFRD in young children.

Acknowledgements

References

1 Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. *Front. Endocrinol.* 2018; **9**: 20.

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**: 684–7.

3 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**: 64–74.

4 Yi Y, Norris AW, Wang K *et al*. Abnormal glucose tolerance in infants and young children with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 2016; **194**: 974–80.

5 Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. *J. Cyst. Fibros.* 2018; **17**: 798–803.

6 Prentice BJ, Ooi CY, Verge CF, Hameed S, Widger J. Glucose abnormalities detected by continuous glucose monitoring are common in young children with cystic fibrosis. *J. Cyst. Fibros.* 2020; **19**: 700–3.

7 Battelino T, Danne T, Bergenstal RM *et al*. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care* 2019; **42**: 1593–603.

8 Chan CL, Ode KL, Granados A, Moheet A, Moran A, Hameed S. Continuous glucose monitoring in cystic fibrosis – A practical guide. *J. Cyst. Fibros.* 2019; **18**: S25-S31.

Loving together by Evan Xu (aged 8) from "A Pop of Colour" art competition, Youth Arts, Children's Hospital at Westmead