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Continuous Glucose Monitoring As A Useful Decision-Making Tool For Adults With Cystic Fibrosis

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Abstract

To the Editor: In cystic fibrosis (CF) there are established links between poor glycemic control and poor respiratory function (1), as well as a decline in body mass index (BMI) (2). Development of CF-related diabetes (CFRD) increases with age and thus is becoming more frequent in adult clinics with increased longevity and the additional pancreatic stress with high dose glucocorticoid following successful lung transplant (3). Glycated hemoglobin (HbA1c) is not a reliable measure of diabetic status in CF, and oral glucose tolerance test (OGTT) may both over and underestimate daily hyperglycemia (4). We report the results of a clinic-based pilot study which aimed to determine if use of continuous glucose monitoring (CGM) (4) in adults with CF is tolerable and helpful to patients, useful to clinical practice decision-making and if it improves clinical status. No other studies have been conducted using CGM in adults with CF with the express purpose of improving clinical decision-making and clinical status, but this is the evidence that would assist services in allocating resources for this technology.

Patients were recruited between August and December 2011 from the CF Clinic at Royal Prince Alfred Hospital, Sydney, Australia. This clinic has 240 patients, of whom 25% have CFRD. The inclusion criterion was the immediate requirement of a management decision that might be enhanced by the additional glucose metabolic information provided by CGM as determined by the clinic endocrinologists (LS & KS). Exclusion criteria were a current acute exacerbation of respiratory disease and significant coagulopathy with CF-related liver disease. Approval for the study was obtained from the Hospital's Ethics Committee (X11-0106 & HREC/11/RPAH/146). Informed consent was obtained before enrolment to the study. The participants undertook CGM (iPro2®; Medtronic MiniMed, Northridge, CA, USA) for six days while continuing their normal diet, lifestyle and treatments. Fingerstick capillary blood glucose levels, before meals and bedtime, were used to retrospectively calibrate the monitors. After the CGM period, participants completed a qualitative questionnaire to assess their experience with the device. Using CGM output provided by CareLink™ Pro software (Medtronic MiniMed, Northridge, CA, USA) and standard clinical information, a management decision was made incorporating published clinical guidelines and patient input (5). At baseline an OGTT was conducted. At baseline and six months follow up, participants had a clinical examination including respiratory function (FEV1), HbA1c, and BMI assessment. Descriptive statistics were performed to examine clinical data at baseline and 6 months follow up. Pearson's correlation coefficient was used to determine associations between variables.

Fourteen participants (11 females; median age 25 years [range 21–58]) enrolled in the study and all successfully undertook CGM for the prescribed period. The Table reports individual participant clinical data (and group means) at baseline and follow up along with CGM informed therapy decisions/changes. Four participants (ID# 2, 9, 11 and 14) were excluded from longitudinal analyses with reasons provided in the Table. In the 10 valid cases at follow up, 7 participants had a reduction in HbA1c (mean change -0.8% (95% Confidence Interval: -1.7 to 0.1), 6 participants had a reduction in BMI (mean change 0.0kg/m2, 95% CI: -0.8 to 0.7) and 8 participants had a reduction in FEV1 (L) (mean change -0.12 L, 95% CI: -0.24 to 0.0) and its %-predicted value (mean change -4.7, 95% CI: -9.7 to 0.3). Interpretation of these pilot study results is limited by the small sample size, pre-post design and lack of CGM at follow up.

Table 1

Individual participant clinical data and CGM informed therapy decisions/changes

ID #	Baseline OGTT result[a]	HbA1c (%) Baseline	HbA1c (%) 6 mo FU	BMI (kg/m^2) Baseline	BMI (kg/m^2) 6 mo FU	Lung function Baseline FEV$_1$ (L)	Lung function %P	Lung function 6 mo FU FEV$_1$ (L)	Lung function %P	Mean CGM Glucose (mmol/L) [range]
1	CFRD[b]	6.2	5.8	24.6	23.8	2.7	87.9	2.67	87.5	7.5 (3.0-13.8)
CGM informed Tx change: History of GDM; continued insulin post-pregnancy with no follow up OGTT. Repeated hypoglycemia so insulin was ceased. CGM confirmed CFRD. Insulin dose was recommenced at a reduced level and injection times altered with a reduction in hypoglycemia. Lower GI diet suggested (6).										
2	CFRD	5.5	5.5	20.6	19.6	2.2	57.9	2.35	62.1	6.6 (2.2-21.4)
Excluded from longitudinal analysis due to CGM fingerprick calibration being inadequate.										
3	CFRD[b]	8.5	8.8	22.7	21	2.9	69	2.72	64.9	8.6 (2.3-22.2)
CGM informed Tx change: HBGM mostly in target range. CGM revealed daytime hyperglycemia and insulin was adjusted. Severe endogenous depression.										
4	CFRD[b]	13.6	10.1	21.2	23.1	1.79	53.7	1.58	47.7	13.8 (3.2-22.2)
CGM informed Tx change: Refusal to inject insulin when away from home. CGM allowed tailored, three insulin type regimen.										
5	CFRD[b]	7.1	6.5	23	22.6	0.88	33.8	0.89	34.3	7.0 (2.7-16.0)
CGM informed Tx change: CGM confirmed the need for consistent pre-prandial insulin dosing.										
6	CFRD[b]	9.0	6.5	17.3	17	0.44	14.5	0.38	12.5	10.3 (4.4-22.0)
CGM informed Tx change: Patient was on the active transplant list with 24 hour home oxygen. CGM confirmed need for more aggressive insulin therapy despite reduced oral intake										
7	CFRD[b]	8.0	7.3	22	22.4	3.28	120	3.12	98.8	9.2 (2.2-19.8)
CGM informed Tx change: Patient was > 10 years post-double lung transplant. CGM supported change to three insulin type regimen to manage prednisone induced hyperglycemia.										
8	IGT	5.6	5.7	24.7	25.4	2.85	91.1	2.72	87.5	6.9 (3.2-15.0)
CGM informed Tx change: Diabetic BGLs on HBGM and CGM. Patient elected to commence insulin before evening meal.										
9	IGT	6.7	6.6	20.5	20.3	0.56	19.6	0.52	18.3	6.7 (3.3-15.7)
CGM outcomes: Some post-prandial BGLs in diabetic range. Excluded from longitudinal analysis as patient received a double lung transplant soon after CGM study and required insulin.										
10	IGT	5.4	5.1	20.2	19.7	2.42	54	1.92	42.9	5.9 (2.2-12.2)
CGM informed Tx change: Severe liver disease with hypersplenism; reduced RBC half-life; osteoporosis. Symptoms suggestive of hypoglycemia but CGM showed BGLs in normal range. Advised on lower GI diet (6).										
11	IGT	5.6	NA	22	21.3	2.65	80.7	2.22	68.3	7.5 (3.3-21.8)
CGM informed Tx change: CGM showed weekend BGLs often in diabetic range. Patient elected to have insulin instituted for some meals. Excluded from longitudinal analysis due to insufficient HbA1c data.										
12	IGT	5.7	5.5	23.9	24.8	4.05	96.7	4.19	100.3	6.6 (4.3-13.4)
CGM informed Tx change: OGTT BGL diabetic at 1 hour, impaired at 2 hours. Started lower GI diet (6).										
13	IGT	5.4	5.4	19.8	19.3	1.38	50.3	1.29	47.2	6.2 (3.8-10.4)
CGM informed Tx change: History of GDM with insulin ceased post-pregnancy. IGT on OGTT. CGM confirmed non-diabetic status and evidence of hypoglycaemia (asymptomatic). Lower GI diet suggested (6).										
14	NGT	NA	5.7	19.7	20	1.23	35.2	1.58	45.4	6.2 (3.8-10.4)
CGM outcomes: Excluded from longitudinal analysis due to repeated exacerbations of respiratory disease with hospitalization which made it difficult to screen for CFRD. CGM allowed a rapid, opportunistic assessment showing NGT.										
Mean (SD)		**7.5 (2.4)**	**6.7 (1.5)**	**21.9 (2.2)**	**21.9 (2.5)**	**2.27 (1.13)**	**67.1 (30.3)**	**2.15 (1.15)**	**62.4 (28.5)**	

[a] World Health Organization criteria
[b] On insulin therapy at the time of CGM

Abbreviations: Blood Glucose Level (BGL), Continuous Glucose Monitoring (CGM), Cystic Fibrosis-Related Diabetes (CFRD), Follow Up (FU), Forced Expiratory Volume in One Second (FEV1), Gestational Diabetes Mellitus (GDM), Glycemic Index (GI), Home Blood Glucose Monitoring (HBGM), Impaired Glucose Tolerance (IGT), Normal Glucose Tolerance (NGT), Oral Glucose Tolerance Test (OGTT), Percent Predicted FEV1 (%P), Therapy (Tx).

Nonetheless, this study showed an apparent improvement in HbA1c, and provides preliminary evidence of the clinical utility of CGM in adults with CF. Despite the HbA1c improvement in the majority of participants, the traditional markers of improvement in CF, lung function and weight, did not reflect this. The typical inflammation related fluctuations that occur in lung function and BMI in patients with CF may explain why we failed to see an improvement in these measures. Positive correlations were found at baseline between HbA1c and i) maximum CGM glucose concentration ($R2=0.676$; $P<0.01$), ii) mean CGM glucose concentration ($R2=0.871$; $P<0.05$) and iii) area under the curve (AUC) above 7.8 mmol/L ($R2=0.954$; $P<0.001$). Baseline BMI positively correlated with FEV1 ($R2=0.436$, $P<0.05$) and percent-predicted FEV1 ($R2=0.464$, $P<0.05$). Similar associations were observed at six months. None of these correlations are unexpected. Neither BMI nor FEV1 were significantly correlated with HbA1c at baseline or follow-up, again consistent with the debatable clinical utility of HbA1c in CF.

A randomized controlled trial is warranted to examine the long-term clinical benefits of incorporating intermittent CGM into clinical practice as a tool to improve glucose metabolic status and as a result, weight status and lung function.

Overall, participants' indicated that CGM was well tolerated and that the visual presentation of the iPro2® CGM data made discussions about their physician's reasons for altering treatment easier to understand. CGM importantly allowed meaningful clinical decisions to be made with the participation of the patient. CF patients are used to being involved in complex management decisions and are wary about additional burdens to their intensive daily self-management regimens. CGM has been found to enhance management of Type 1 Diabetes in motivated individuals (7) so it is likely that the decisions based on our data may yield similar results.

In summary, this pilot study demonstrated that in adults with CF, CGM was well-tolerated, provided additional useful clinical data for physicians and appeared to be associated with improved glycemic control in a group of varying age and clinical status. However, improved glycemic control did not correspond with improved lung function which declined in this sample. In Australia, the cost of the glucose sensor is currently over three times the scheduled fee for an OGTT under the universal health insurance system (Medicare). This consideration plus the initial cost for iPro2® may limit CGM application in public hospital services. Future controlled studies are needed to examine if CGM use alters behavior, long term glycemic control and other clinical outcomes in adult patients with CF.

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