Validation of Continuous Glucose Monitoring in Children and Adolescents With Cystic Fibrosis

A prospective cohort study

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OBJECTIVE — To validate continuous glucose monitoring (CGM) in children and adolescents with cystic fibrosis.

RESEARCH DESIGN AND METHODS — Paired oral glucose tolerance tests (OGTTs) and CGM monitoring was undertaken in 102 children and adolescents with cystic fibrosis (age 9.5–19.0 years) at baseline (CGM1) and after 12 months (CGM2). CGM validity was assessed by reliability, reproducibility, and repeatability.

RESULTS — CGM was reliable with a Bland-Altman agreement between CGM and OGTT of 0.81 mmol/l (95% CI for bias ± 2.90 mmol/l) and good correlation between the two (r = 0.74–0.9; $P < 0.01$). CGM was reproducible with no significant differences in the coefficient of variation of the CGM assessment between visits and repeatable with a mean difference between CGM1 and CGM2 of 0.09 mmol/l (95% CI for difference ± 0.46 mmol/l) and a discriminant ratio of 13.0 and 15.1, respectively.

CONCLUSIONS — In this cohort of children and adolescents with cystic fibrosis, CGM performed on two occasions over a 12-month period was reliable, reproducible, and repeatable.

Diabetes Care **32:1020–1022, 2009**

Little is known about the evolution of diabetes and pancreatic disorders in adults with cystic fibrosis (CF) and less in children and adolescents with cystic fibrosis. Patients with CF-related diabetes have a sixfold increase in morbidity and mortality (1). The diagnosis of CF-related diabetes is usually asymptomatic, lying dormant for 2–6 years before diagnosis (1–3). Identification of disordered glucose metabolism before major β-cell loss may be beneficial, since early insulin therapy improves lung function and reduces the number of acute respiratory infections (4,5).

Standard methods of glycemic assessment, random or fasting glucose concentrations, and/or oral glucose tolerance tests (OGTTs) underdiagnose CF-related diabetes (6). Continuous glucose monitoring (CGM) in the normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) stages may allow earlier diagnosis of CF-related diabetes (7), but before this methodology can be applied to children and adolescents with CF, validation is required. Consequently, we have assessed CGM in terms of reliability, repeatability, and reproducibility in 102 children and adolescents with CF on two occasions over 24 months.

RESEARCH DESIGN AND METHODS

— A prospective multicenter cohort study of 102 genetically confirmed children and adolescents with CF (48 males, 54 females) aged 9.5–19.0 years was conducted over 24 months. All children underwent "paired testing," with OGTT and CGM and the initial OGTT used to classify children and adolescents with CF into three groups: NGT, IGT, or CF-related diabetes based on World Health Organization criteria (8). CGM (Medtronic Minimed CGM Gold; Medtronic Diabetes, Watford, U.K.) was recorded at the start of the study (CGM1 visit 1) and after a minimum of 12 months (CGM2 visit 2). Blood glucose concentration was measured using a YSI compatible CX7 Delta Analyzer. After the OGTT was complete, the CGM device remained in situ in the home environment for 72 h on all patients. Patients entered a minimum of four self-monitored blood glucose samples (One Touch Ultra meter; LifeScan, Milpitas, CA) for daily CGM calibration. Ethical approval was obtained from the ethics committees of the three participating hospitals. The study protocol was carried out in accordance with the Declaration of Helsinki.

Statistical analysis

All data were extracted from the Medtronic Mini Med Solutions CGM sensor, MMT-730 version 3.0c (3.0.128). Mean and SD of the interstitial glucose concentrations for all CGM recordings were derived. Analysis was performed in SPSS version 15.

Validity of CGM in children and adolescents with CF was assessed by determination of reliability, reproducibility, and repeatability. Reliability was assessed by

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Received 24 October 2008 and accepted 3 March 2009.
Published ahead of print at http://care.diabetesjournals.org on 11 March 2009. DOI: 10.2337/dc08-1925.

Table 1—*Validity of CGM at visit 1 (CGM1) and visit 2 (CGM2) in 102 children and adolescents with cystic fibrosis* (n = 102)

	NGT*		IGT*		CFRD*		Control subjects
	CGM1	CGM2	CGM1	CGM2	CGM1	CGM2	CGM
Interstitial glucose (mmol/l)†	6.25 ± 1.84	6.35 ± 1.85	6.97 ± 2.65	6.56 ± 2.60	7.97 ± 3.29	8.03 ± 3.43	5.10 ± 0.71
CV (%)†	23.2	25.5	25.0	28.5	37.6	32.3	15.3
DR	10.1	9.1	10.3	7.6	10.9	19.9	NA

Data are mean ± SD, percent, and DR. Validity is based on reliability, reproducibility, and repeatability measures. *The baseline glucose tolerance category is based on standard oral glucose tolerance testing 2-h glucose concentrations: NGT <7.8, IGT 7.8–11, and CFRD >11.1 (8). Normal healthy control subject data shown to be significantly different from all children and adolescents with CF; †$P < 0.001$.

Bland-Altman analysis of agreement (9,10) along with Pearson's correlation coefficient. Reproducibility tested the null hypothesis that the mean difference between the coefficients of variation (CVs) of observations was zero using a paired Student's t test. Repeatability was derived from Bland-Altman analysis and calculation of a discriminant ratio (DR) (11). Data are expressed as mean values with 95% CIs where appropriate. Significance was set at the 5% level.

RESULTS — A total of 104 out of 160 children and adolescents with CF (aged 9.5–19.0 years) were studied. A total of 102 valid CGM results were obtained at CGM1 and 92 at CGM2. The average number of valid CGM sensor readings used was 710 (range 499–1,410).

Mean interstitial CGM glucose for all children and adolescents with CF was 6.7 ± 2.3 mmol/l (means ± SD) on CGM1 and 7.0 ± 2.6 mmol/l CGM2. Mean interstitial CGM glucose for NGT, IGT, and CF-related diabetes is shown in Table 1. All values were significantly higher than in normal healthy nondiabetic subjects (mean 5.1 ± 0.7 mmol/l, $P < 0.0001$).

Validitation of CGM in CF

Reliability. Bland and Altman analysis revealed a mean difference between CGM glucose and OGTT glucose of 0.81 ± 1.47 mmol/l with a 95% CI of the bias ± 2.90 mmol/l. A significant correlation was found between glucose measured by CGM and the blood glucose at five time points in a standard OGTT (r = 0.74–0.91, $P < 0.01$).

Reproducibility. Reproducibility was assessed by comparing CVs at five different time points of OGTT and within the subgroups (Table 1). There were no significant differences in the CVs of the CGM assessment between visits, irrespective of glucose tolerance category.

Repeatability. The mean difference between CGM1 and CGM2 interstitial glucose concentrations was 0.09 ± 2.38 mmol/l with 95% CI for the difference of ± 0.46 mmol/l. The DRs (the variability of an individual to the variability of the group) for CGM1 and CGM2 were 13.0 and 15.1, respectively. Subgroup DRs are shown in Table 1 and indicate that CGM has the ability to identify subjects with high variability, such as CF-related diabetes, within this cohort of children and adolescents with CF.

CONCLUSIONS — This study demonstrates that CGM is a valid method for assessing glycemia in children and adolescents with CF, extending similar observations in adults with CF (7). The validation of CGM in children and adolescents with CF is essential before other prospective research can be undertaken with CGM in children and adolescents with cystic fibrosis and is warranted because of the higher glucose concentrations observed in these patients compared with the general population.

As expected, there was a linear correlation between five-point OGTT plasma blood glucose and the corresponding CGM glucose readings (r = 0.74–0.91). Rather than use correlation or Clarke error grid analysis, which both describe association, we used Bland-Altman analysis of agreement (9,10). The mean difference between the two methods was 0.81 mmol/l with a 95% CI ± 2.90 mmol/l, which is a reasonably acceptable bias for clinical practice.

CGM was reproducible in children with CF with varying degrees of glucose intolerance, since there were no significant differences in the CVs of the CGM assessment between visits, irrespective of diagnosis.

Finally, we have demonstrated that CGM was repeatable as the mean difference between CGM1, and CGM2 was 0.09 mmol/l. Further, all DRs were >1, indicating that CGM has the ability to discriminate between different subjects and allow comparison between subjects.

In conclusion, CGM is a valid measure of glycemia in children and adolescents with CF. These observations suggest that CGM is not influenced by the CF chloride channel defect and has become a useful tool for the assessment of glycemia in children and adolescents with CF.

Acknowledgments— Funding for this study was provided by the Cystic Fibrosis Association of Ireland.

S.O'R. was supported by an European Society for Pediatric Endocrinology Clinical Research Fellowship sponsored by Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Early parts of this study were presented as oral communications at the 66th Scientific Sessions of the American Diabetes Association, Washington, DC, 9–13 June 2006 and the 43rd Annual Meeting of the European Association for the Study of Diabetes 2007.

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