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 (CACF).

Research design and methods- Paired oral glucose tolerance testing (OGTT) and CGM monitoring was undertaken on 102 CACF (age 9.5-19.0 years) at baseline (CGM1) and after 12months (CGM2). CGM validity was assessed by: reliability, reproducibility and repeatability.

Results- CGM was reliable with 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 0.09mmol/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 CACF, CGM performed on 2 occasions over a 12 month period was reliable, reproducible and repeatable.
Little is known about the evolution of diabetes and pancreatic disorders in adults with Cystic Fibrosis (CF) and less in children and adolescents (CACF). Patients with CF Related Diabetes (CFRD) have a six-fold increase in morbidity and mortality (1). The diagnosis of CFRD is usually asymptomatic lying dormant for 2-6 years prior to diagnosis (1-3). Identification of disordered glucose metabolism before major beta cell loss may be beneficial as 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 Testing (OGTT), under-diagnose CFRD (6). Continuous Glucose Monitoring (CGM) in the Normal (NGT) and Impaired Glucose Tolerance (IGT) stages may allow earlier diagnosis of CFRD (7) but before this methodology can be applied to CACF validation is required. Consequently, we have assessed CGM in terms of reliability, repeatability and reproducibility in 102 CACF on 2 occasions over 24 months.

RESEARCH DESIGN AND METHODS

Patient population: A prospective multi-center cohort study of 102 genetically confirmed CACF (48M; 54F); aged 9.5-19.0 years conducted over 24 months. All children underwent ‘paired testing,’ with OGTT and CGM and the initial OGTT used to classify CACF into three groups: NGT, IGT or CFRD based on WHO criteria (8). CGM (Medtronic Minimed CGM Gold, (Medtronic Diabetes, Watford, United Kingdom) 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 an YSI compatible CX7 Delta Analyzer. After the OGTT was complete the CGM device remained in situ in the home environment for 72 hours 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 declarations 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 standard deviation (SD) of the interstitial glucose concentrations for all CGM recordings were derived. Analysis was performed in SPSS version 15.

Validity of CGM in CACF was assessed by determination of reliability, reproducibility, and repeatability. Reliability: was assessed by 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 (CV) of observations was zero using 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% Confidence Intervals (CI) where appropriate. Significance was set at the 5% level.

RESULTS

General: 104 out of a total of 160 CACF (aged 9.5-19.0 years old) were studied. 102 valid CGM results were obtained at CGM1 and 92 at CGM2. The average number of valid CGM sensor readings used was 710 (range 499-1410).

Mean interstitial CGM glucose for all children and adolescents with CF was 6.7mmol/l (SD 2.3) on CGM1 and 7.0mmol/l (SD 2.6) CGM2. Mean interstitial CGM glucose for NGT, IGT and CFRD is shown in Table 1. All values were significantly higher
Validation of CGM in Children with CF

Validation of CGM in CF

a). Reliability

Bland and Altman analysis revealed a mean difference between CGM glucose and OGTT glucose of 0.81mmol/l (SD 1.47) with a 95% CI of the bias +/- 2.90mmol/l. A significant correlation was found between glucose measured by CGM and the blood glucose at 5 time points in a standard OGTT (r = 0.74-0.91, p<0.01).

b). Reproducibility

Reproducibility was assessed by comparing CVs at 5 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.

c). Repeatability

The mean difference between CGM 1 and CGM 2 interstitial glucose concentrations was 0.09mmol/l (SD 2.38) with 95% CI for the difference of ± 0.46mmol/l. The DRs (the variability of an individual to the variability of the group) for CGM 1 and CGM 2 were 13.0 and 15.1 respectively. Subgroup DRs are shown in Table 1 and indicates that CGM has the ability to identify subjects with high variability such as CFRD within this cohort of CACF.

DISCUSSION

This study demonstrates that CGM is a valid method for assessing glycaemia in CACF extending similar observations in adults with CF (7). The validation of CGM in CACF is essential before other prospective research can be undertaken with CGM in CACF and is warranted because of the higher glucose concentrations observed in these patients compared to the general population. As expected there was a linear correlation between 5 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 0.81mmol/l with a 95% CI +/-2.90mmol/l, which is a reasonably acceptable bias for clinical practice.

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

Finally we confirmed that the CGM was repeatable as the mean difference between CGM 1 and CGM 2 was 0.09mmol/l. Further all DRs were >1 indicating that CGM has the ability to discriminate between different subjects and allow comparison between subjects.

CONCLUSIONS

CGM is a valid measure of glycemia in CACF. 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 CACF.

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Disclosures: all authors have no relevant conflict of interest to disclose.
REFERENCES:
**Table 1** Validity of CGM at visits 1 (CGM 1) and visit 2 (CGM 2) in 102 Children and Adolescents with Cystic Fibrosis (CACF). Validity based on reliability, reproducibility and repeatability measures.

<table>
<thead>
<tr>
<th></th>
<th>NGT*</th>
<th>IGT*</th>
<th>CFRD*</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CGM1</td>
<td>CGM2</td>
<td>CGM1</td>
<td>CGM2</td>
</tr>
<tr>
<td>Mean of interstitial glucose (mmol/l)</td>
<td>6.25**</td>
<td>6.35**</td>
<td>6.97**</td>
<td>6.56**</td>
</tr>
<tr>
<td>Standard deviation of interstitial glucose (+/- mmol/l)</td>
<td>1.84**</td>
<td>1.85**</td>
<td>2.65**</td>
<td>2.60**</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>23.2%**</td>
<td>25.5%**</td>
<td>25.0%**</td>
<td>28.5%**</td>
</tr>
<tr>
<td>Discriminent Ratio (DR)</td>
<td>10.1</td>
<td>9.1</td>
<td>10.3</td>
<td>7.6</td>
</tr>
</tbody>
</table>

*The baseline glucose tolerance category is based on standard oral glucose tolerance testing 2hour glucose concentrations: NGT <7.8, IGT: 7.8-11 and CFRD: >11.1(8). Normal healthy controls (Controls) data shown to be significantly different from all CACF, p<0.001**.