EARLY GLUCOSE ABNORMALITIES IN CYSTIC FIBROSIS ARE PRECEDED BY POOR WEIGHT GAIN

Running title: EARLY GLUCOSE ABNORMALITIES IN CYSTIC FIBROSIS

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Objective: Progressive Beta-cell loss causes catabolism in Cystic Fibrosis (CF). Existing diagnostic criteria for diabetes were based on microvascular complications rather than CF-specific outcomes. We aimed to relate glycemic status in CF to weight and lung-function changes.

Research Design and Methods: We determined peak blood glucose (BGmax) during Oral Glucose Tolerance Tests (OGTT) with samples every 30 minutes on 33 consecutive children (aged 10.2-18 years). Twenty-five also agreed to Continuous Glucose Monitoring (CGM, Medtronic). Outcome Measures were change in weight Standard Deviation Score (wtSDS), %Forced Expiratory Volume in 1 second (%FEV1), and %Forced Vital Capacity (%FVC) in the year preceding OGTT.

Results: Declining wtSDS and %FVC were associated with higher BGmax (both p=0.02) and with CGM-time above 7.8mmol/l (p=0.006 and p=0.02 respectively), but not with BG120mins. Decline in %FEV1 was related to CGM-time above 7.8mmol/l (p=0.02). Using Receiver Operating Characteristic (ROC) analysis to determine optimal glycemic cut-offs, CGM-time above 7.8mmol/l >4.5% detected declining wtSDS with 89% sensitivity and 86% specificity (AUC 0.89, p=0.003). BGmax >8.2 mmol/l gave 87% sensitivity and 70% specificity (AUC 0.76, p=0.02). BG120mins did not detect declining wtSDS (AUC 0.59, p=0.41). After excluding 2 patients with BG120mins >11.1 mmol/L, decline in wtSDS was worse if peak BG was >8.2mmol/l (-0.3±0.4 vs 0.0±0.4 for BG <8.2, p=0.04) or if CGM-time above 7.8mmol/l was >4.5% (-0.3±0.4 vs +0.1±0.2 for time <4.5%, p=0.01).

Conclusions: BGmax on OGTT ≥ 8.2 mmol/L and CGM-time above 7.8mmol/l ≥4.5% are associated with declining wtSDS and lung-function in the preceding 12 months.
Progressive Beta-cell loss causes catabolism and weight loss in Cystic Fibrosis(1, 2). Weight is a prognostic indicator(3), and prevention of weight decline is a major clinical objective in children and adolescents with CF. Median life expectancy of patients with CF has risen progressively over recent decades, but remains drastically shorter than that of the general population (approximately 36 years)(4). The presence of CF Related Diabetes (CFRD) is associated with an increase in early mortality of up to 6-fold(5). CFRD is usually diagnosed by the North American CF Foundation criteria(6) and elsewhere by the World Health Organization (WHO) criteria for diabetes mellitus(7). These criteria were designed to identify patients at risk of microvascular complications in Type 2 diabetes mellitus(8) and were not designed with CF-specific outcomes in mind. Microvascular complications occur in CF(9), however catabolic decline in weight and deteriorating lung function may be more relevant outcomes. Poor weight gain is associated with worsening lung function(10, 11) and both are associated with early mortality(12, 13). Weight and lung function decline have been shown to precede the diagnosis of CFRD by standard criteria(2), but the earliest glycemic abnormality associated with clinical decline has not been determined. Glycemic status can be assessed in detail using an Oral Glucose Tolerance Test (OGTT) with 30-minute samples and, more recently, Continuous Interstitial Fluid Glucose Monitoring (CGM). We aimed to determine the relationship between glycemic status and the change in weight standard deviation score (SDS) and the change in lung function over the preceding year.

**RESEARCH DESIGN AND METHODS**

In a prospective protocol, 33 consecutive children with CF (median age 13.1, range 10.2-18 yrs) underwent OGTT when clinically stable, as part of an annual screening program for all CF patients aged 10 years or older. All were under the care of a Paediatric Respiratory physician at the Sydney Children’s Hospital CF clinic. When clinically stable with respect to lung disease, patients fasted for at least 8 hours, and underwent an OGTT, consuming 1.75g/kg of carbonated dextrose solution (maximum 75g). No patient refused the OGTT. Venous or finger pricking samples were collected at 0, 30, 60, 90 and 120 minutes for measurement of glucose and insulin. Glucose levels were performed by the hospital laboratory, using a standard glucose oxidase method (Beckman Coulter, Fullerton, California). Insulin levels were performed on a standard chemiluminescence immunoassay (Immulite, Siemens Healthcare Diagnostics, Deerfield IL, limit of detection 2mU/L). Beta-cell function and insulin sensitivity were estimated using HOMA2(14).

Twenty-five patients (76%) also agreed to Continuous interstitial fluid Glucose Monitoring (CGM, Medtronic). Patients refusing CGM were not different from those undergoing CGM according to the clinical characteristics listed in Table 1. Local anaesthetic cream and play therapy were used to minimise distress of intravenous cannulation and CGM insertion. Mean duration of CGM was 60.2 hours (+ 14.6).

Patients entered capillary blood glucose values into the CGM device at 60 minutes after CGM insertion and subsequently before breakfast and dinner each day. These pre-meal calibration times were selected to avoid moments of rapid changes in interstitial and blood glucose levels (personal communication, J. Mastrotopato, Medtronic). Percentage time above 7.8mmol/L and area above 7.8mmol/L (mmol/L*day) were determined using MiniMed Solutions™ software [MMT-7310 Version 3.0C (3.0.128),
The 7.8mmol/L threshold corresponds to the WHO cut-off for impaired glucose tolerance at 120 minutes on OGTT. Patients were instructed to continue their high-energy, high-fat, CF-specific diet, and routine activities. No patients were treated with glucocorticoids at the time of OGTT or CGM.

Height, weight and lung function, were measured by respiratory laboratory staff at each visit, using a stadiometer, electronic weight scales and a Sensormedics Vmax system (Cardinal Health, Dublin, OH). Percentage predicted Forced Expiratory volume in 1 second (%FEV1) and Percentage predicted Forced Vital Capacity (%FVC) were calculated using the method reported by Knudson(15).

Weight standard deviation score (wtSDS) was calculated using CDC 2000 growth data, on Growth Analyser Software (version 3.5, www.growthanalyser.org). For each patient, the rate of change in %FEV1, %FVC and wtSDS over the 12 months prior to the OGTT was determined from the slope obtained by linear regression analysis. The mean number of data points during the 12 month period was 10 (±8).

The study was approved by the local Ethics committee. Statistical analysis was performed with SPSS software (Version 17).

RESULTS

According to the blood glucose at 0 and 120 minutes (BG120mins) on OGTT, 18 patients (55%) had normal glucose tolerance by WHO criteria (NGT), 13 (39%) had impaired glucose tolerance (IGT, BG120mins 7.8-11mmol/L), and 2 (6%) were diabetic (CFRD, BG120mins ≥11.1mmol/L). None had fasting hyperglycaemia (≥7mmol/L). In contrast to peak BG, peak insulin was delayed. The time of peak insulin occurred at 120 minutes in 14/27 (42%), at 90 minutes in 8/27 (24%), at 60 minutes in 5/27 (15%) and in no patients at 0 or 30 minutes (insulin values were incomplete or not performed in the remaining 6/33 patients). Mean time to insulin peak was 58 minutes (+19) for NGT vs 75 minutes (+16) for IGT (p=0.03). Median fasting insulin was only 4mU/L (range 0-21). Using HOMA2, mean beta-cell function for the whole group was only 29.5% (95% CI 24.6-34.5), and median insulin sensitivity was 90.1% (interquartile range 30-417).

Table 1 outlines the clinical characteristics of the 33 patients at the time of OGTT. Mean wtSDS for the 33 patients was −0.78 (95% confidence interval −1.2 to −0.4). Decline in wtSDS over the preceding year occurred in 23/33 patients (70%).

Decline in wtSDS over the preceding year was associated with higher BGmax (Figure 2, R²=0.17, p=0.02) and longer percentage of CGM time above 7.8mmol/l (Figure 2, R²=0.28, p=0.006), but not with BG120mins (R²=0.000025, p=0.98).

Decline in %FEV1 was associated with longer percentage of CGM-time above 7.8mmol/l (R²=0.16, p=0.05), but not with BGmax (R²=0.12, p=0.06) or BG120mins (R²=0.0036, p=0.75). Decline in %FVC was associated with higher BGmax (R²=0.16, p=0.02) and percentage CGM-time above 7.8mmol/l (R²=0.20, p=0.02), but not with BG120mins (R²=0.032, p=0.30).

We used Receiver Operating Characteristic (ROC) analysis(16) to determine optimal glycemic cut-offs for detecting CF-specific outcomes. Figure 3 shows the results of the ROC analyses.

- CGM-time above 7.8mmol/l ≥4.5% detected declining wtSDS with 89% sensitivity and 86% specificity (Area Under the ROC Curve, AUC 0.89, p=0.003).
EARLY GLUCOSE ABNORMALITIES IN CYSTIC FIBROSIS

- CGM time above 7.8 mmol/l was ≥4.5% in 17/25 patients (68%).
- BG_{max} ≥8.2 mmol/L gave 87% sensitivity and 70% specificity (AUC 0.76, p=0.02, see Figure 3).
- BG_{max} was ≥8.2 mmol/L in 23/33 patients (69.7%).
- In contrast to BG_{max}, BG_{120mins} did not detect declining wtSDS (AUC 0.59, 95% CI 0.38 to 0.80 p=0.41) and BG_{120mins} >11.1 mmol/L had only 10% sensitivity. CGM time above 7.8 mmol/L was not significantly better at detecting declining wtSDS than BG_{max} because the 95% confidence intervals around the AUCs in the ROC analyses overlapped (0.5 to 1 and 0.56 to 0.96 respectively). Longer percentage CGM time above 7.8 mmol/L correlated with higher BG_{max} on OGTT (p=0.006 and R^2 =0.28).

Using ROC analysis to examine lung function, percentage CGM-time above 7.8 mmol/L ≥4.5% detected a fall in %FVC of 3% or more over the preceding 12 months (a clinically significant decline) with 79% sensitivity and 46% specificity (AUC 0.79, p=0.01) but BG_{max} did not (AUC 0.69, p=0.07). Neither percentage CGM time above 7.8 mmol/L, nor OGTT BG_{max} detected a fall in %FEV1 over the preceding year of ≥3% (respectively AUC 0.65, p=0.20 and AUC 0.58, p=0.44). BG_{120mins} was unable to detect a fall ≥3% in either %FVC (AUC 0.69, p=0.06) or %FEV1 (AUC 0.55, p=0.64). ROC analyses for declining weight and lung function using CGM percentage time above 8.2 mmol/L and CGM area above 8.2 mmol/L and CGM area above 7.8 mmol/L did not improve the ROC AUC (data not shown).

Fasting insulin (but not beta-cell function or insulin sensitivity as measured by HOMA2) was higher in patients with BG_{max} <8.2 mmol/L (6.5 mU/L, range 3-9), compared to those with BG_{max} ≥8.2 mmol/L (3 mU/L, range 0-21, p=0.02). WHO groups of NGT or IGT had indistinguishable fasting insulin, B-cell function and insulin sensitivity (data not shown).

After excluding the 2 patients with CFRD by WHO criteria (because they had BG_{120mins} ≥11.1 mmol/L and would currently be eligible for insulin treatment), we compared groups defined with cut-points from the ROC analysis (Table 2). The decline in wtSDS was significantly worse in patients with BG_{max} ≥8.2 mmol/L (-0.3 ± 0.4) versus those with BG_{max} < 8.2 mmol/L (0.0 ± 0.4, p=0.04). The decline in wtSDS was also worse in those with ≥4.5 percentage CGM-time above 7.8 mmol/L (-0.3 ± 0.4 vs 0.1 ± 0.2 in those <4.5%, p=0.01). There was, however, no significant difference in wtSDS comparing normoglycemic (BG_{120mins} < 7.8 mmol/L) and impaired (BG_{120mins} 7.8 - 11 mmol/L) groups defined by WHO criteria (-0.2 ± 0.4 vs -0.2 ± 0.4, p=0.94).

Groups defined by glycemic thresholds (OGTT BG_{max} ≥ or < 8.2 mmol/L, Percentage CGM time ≥ or < 4.5%) and markers of catabolic decline (change in weight SDs ≥ 0 or < 0, change in %FEV1 or %FVC ≥ or < 3) were indistinguishable by gender, genotype category (F508del homozygous, F508del heterozygous, other, or unknown) or by the presence or absence of exocrine pancreatic sufficiency (data not shown).

CONCLUSIONS

We found that glucose abnormalities are related to the CF-specific outcomes of decline in lung function and weight over the preceding year. Current WHO glycemic categories of normal glucose tolerance and impaired glucose tolerance (based on 120 minute BG during OGTT), could not distinguish patients with declining weight standard deviation score from those with stable or increasing scores. In contrast, we found that peak BG greater than or equal to 8.2 mmol/l on 30 minute sampling-OGTT and CGM-time above 7.8 mmol/L ≥4.5% could do so reliably.
In a retrospective analysis of 38 diabetic children and adults with CF and non-diabetic CF controls, Lanng and colleagues reported a gradual decline in weight, BMI and lung function up to 4 years preceding the diagnosis of CFRD(2). Lanng diagnosed CFRD by 1985 WHO criteria (based on 120 minute BG during OGTT, but with higher thresholds than in current use). Our findings suggest that 120 minute BG elevation is a late event, whereas peak BG greater than or equal to 8.2mmol/l on 30 minutely sampling-OGTT and CGM-time above 7.8mmol/L ≥4.5% are early glucose abnormalities which are associated with decline in lung function and weight over the preceding year. Lanng’s patients had lung function decline of greater magnitude than our patients, probably reflecting improved outcomes over recent decades.

The central problem leading to CFRD is insulin deficiency(1, 18). Relative insulin resistance due to stress hormones may occur during exacerbations of lung disease, leading to temporary worsening of glycemic status(18, 19). We avoided this confounding effect by ensuring that the OGTT and CGM were performed when the patients were clinically stable. Furthermore, fasting insulin levels and HOMA2 calculations of beta-cell function and insulin sensitivity in our patients demonstrated insulin deficiency (rather than insulin resistance) as the underlying problem. This confirms the findings of Mohan and colleagues who found abnormalities of insulin secretion and not insulin resistance among 60 adult CF patients(20).

We found that glucose abnormalities (on OGTT and CGM) and markers of clinical decline (fall in weight SDS or lung function over the preceding year), were common, and were not limited to those with the more severe genotype with homozygous F508del, nor to those with exocrine insufficiency.

Screening practices vary, and many centres are yet to adopt the recommendations(21, 22) to perform yearly OGTTs on all patients over 10 years of age. Moran and colleagues do perform annual OGTTs, and have reported improvements in mortality, nutritional status and lung function in patients with CFRD, attributing these improvements to early diagnosis, and aggressive treatment(23). We found that peak blood glucose is missed in the vast majority of patients by 0 and 120 minute samples (32/33 or 97%), indicating the need for sampling every 30 minutes during the OGTT. This is supported by the findings of Dobson et al, who showed that non-diabetic patients with CF had substantial hyperglycemia at 30, 60, and 90 mins, but identical 0 and 120 minute BGs compared to healthy aged matched controls(24). Hyperglycemia promotes bacterial growth and it is possible that it may contribute to clinical decline even in those with relatively preserved beta cell function. Palerm(25) recently reported blood glucose values in normal subjects following meals, and found that they rarely exceeded 150mg/dL, or 8.3mmol/L. This is very similar to our CF-specific cut-off of 8.2mmol/L for BGmax on OGTT.

Lippe and Sperling(26) reported reduced and delayed insulin secretion in subjects with cystic fibrosis compared to healthy age matched controls. We also found delayed peak insulin secretion in our subjects. This is consistent with a model of progressive beta cell loss leading to progressive insulin deficiency and worsening glycemic status. We propose that stages of progressive Cystic Fibrosis Insulin Deficiency (CFID) can be usefully defined by BG on OGTT, as CFID1 (BGmax ≥8.2 and <11.1), CFID2 (BGmax ≥11.1 and BG120 <11.1), CFID3 (BG120 ≥11.1, corresponding to CFRD without Fasting Hyperglycemia [FH-]) and CFID4 (Fasting BG≥7, corresponding to CFRD FH+). Moran et al recently showed in a randomized controlled trial that insulin treatment in adults with CFRD without fasting hyperglycemia (corresponding to CFID3) resulted in
improved body mass index (27), although there was no significant change in lung function or number of hospitalizations. We found that CGM is a useful tool in detecting early glycemic abnormalities, which performed as well as OGTT on ROC analysis, and correlated with peak BG on OGTT. It has previously been used in CF (24, 28), but is not currently licensed for diagnostic use. Furthermore, 24% of our patients refused to undergo CGM, whereas all agreed to have the OGTT. It is possible that the acceptability of CGM may improve as the devices become smaller and more discreet. Our findings suggest that CFRD with and without fasting hyperglycemia are late events, which are preceded by more subtle glycemic abnormalities on CGM and 30 minutely sampled-OGTT. These early glucose abnormalities are associated with decline in lung function and weight over the preceding year. It is likely that progressive deficiency of insulin, a powerful anabolic hormone, may be responsible for this decline, suggesting that early insulin therapy may be beneficial in CF before the onset of CFRD as currently defined.

ACKNOWLEDGMENTS
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Disclosure: Nothing to disclose.
REFERENCES:
**Figure Legends:**

**Figure 1:** Glucose and insulin levels during the Oral Glucose Tolerance Test. Boxes show the median and interquartile range. Whiskers show the 5th and 95th percentiles.

**Figure 2:** Decline in wtSDS over the preceding year by BG_{max} on OGTT (**Panel A**), and by percentage CGM time above 7.8mmol/L (**Panel B**). The vertical lines at 8.2mmol/L and 4.5% CGM time above 7.8mmol/L represent optimal cut-offs determined by the ROC analysis in Figure 3.

**Figure 3:** Determination of optimal glycemic cut-points for detecting decline in weight SDS over the preceding 12 months by Receiver Operating Characteristic (ROC) analysis. **Panel A** plots sensitivity versus false positive rate (1-specificity) for all possible cut-points in BG_{max} by Oral Glucose Tolerance Test (OGTT). The point closest to the top left-hand corner (8.2mmol/L) maximizes sensitivity and specificity and is the optimal cut-point. **Panel B** shows percent time above 7.8 mmol/L on Continuous interstitial fluid Glucose Monitoring (CGM) with optimal cut-point 4.5%. **Panel C** shows the same data for BG_{120mins} on OGTT, which did not detect declining weight SDS. The cut-point of 11.1mmol/L used in the WHO diagnostic criteria is marked.

**Table 1:** Characteristics at the time of Oral Glucose Tolerance Test (OGTT).

Characteristics of the 33 patients with Cystic Fibrosis at the time of their Oral Glucose Tolerance Test (OGTT), and change over the preceding 12 months in weight, height and lung function.

<table>
<thead>
<tr>
<th>Characteristics at time of OGTT</th>
<th>Mean ± 1SD or Number and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>13.7 ± 2.8</td>
</tr>
<tr>
<td>Sex (Male, Female)</td>
<td>16 (49%), 17 (51%)</td>
</tr>
<tr>
<td>Exocrine Enzyme Replacement</td>
<td>30 (91%)</td>
</tr>
<tr>
<td>Genotype Category:</td>
<td></td>
</tr>
<tr>
<td>(Homozygous F508del)</td>
<td>20 (61%)</td>
</tr>
<tr>
<td>(Heterozygous F508del)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>(Other)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>(Unknown)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Age of diagnosis of CF (Years)</td>
<td>0.47 ± 2.0</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-0.78 ± 1.1</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-0.41 ± 0.92</td>
</tr>
<tr>
<td>Change in Weight SDS*</td>
<td>-0.16 ± 0.38</td>
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<tr>
<td>Change in Height SDS*</td>
<td>0.03 ± 0.24</td>
</tr>
<tr>
<td>%FEV1</td>
<td>85 ± 20</td>
</tr>
<tr>
<td>%FVC</td>
<td>94 ± 17</td>
</tr>
<tr>
<td>Change in %FEV1*</td>
<td>-5 ± 8</td>
</tr>
<tr>
<td>Change in %FVC*</td>
<td>-3 ± 8</td>
</tr>
</tbody>
</table>

*over the preceding year
Table 2: Change in weight SDS and lung function over the preceding year by glycemic groups. Change in weight and lung function in the preceding 12 months in 31 patients with Cystic Fibrosis, excluding the 2 patients with BG_{120mins} ≥ 11.1 mmol/L (diabetic by WHO criteria). Groups are compared according to 3 different glycemic cut-offs.

<table>
<thead>
<tr>
<th>CF-Specific OGTT Cut-Off</th>
<th>WHO Categories based on BG_{120}</th>
<th>CF-Specific CGM Based Cut-Off</th>
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<tr>
<td>BGmax (mmol/L)</td>
<td></td>
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</tr>
<tr>
<td>≥ 8.2</td>
<td>7.8-11mmol/L</td>
<td>≥ 4.5%</td>
</tr>
<tr>
<td>n= 21/31 (68%)</td>
<td>&lt; 7.8mmol/L</td>
<td>&lt; 4.5%</td>
</tr>
<tr>
<td>10/31 (32%)</td>
<td></td>
<td>n=15/23 (65%)</td>
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<table>
<thead>
<tr>
<th>Change in*</th>
<th>mean ± SD</th>
<th>p-value</th>
<th>mean ± SD</th>
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<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>WtSDs</td>
<td>-0.3 ± 0.4</td>
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<td>-0.2 ± 0.4</td>
<td>0.94</td>
<td>-0.3 ± 0.4</td>
<td>0.01</td>
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<tr>
<td>%FEV1</td>
<td>-6 ± 7</td>
<td>0.48</td>
<td>-6 ± 7</td>
<td>0.83</td>
<td>-6 ± 7</td>
<td>0.31</td>
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<tr>
<td>%FVC</td>
<td>-4 ± 7</td>
<td>0.21</td>
<td>-5 ± 6</td>
<td>0.21</td>
<td>-4 ± 7</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*over the preceding year

#Excluding 2 patients (BG_{120} ≥ 11.1mmol/L)
Figure 1

![Box plot showing glucose and insulin levels over time.](image-url)
Figure 2

Panel A

Panel B
Figure 3

Panel A

\[ \text{BG}_{\text{max}} \]

8.2 mmol/L

\[ \text{AUC} = 0.76 \]

\[ P = 0.02 \]

Panel B

\[ \text{Percent CGM Time} > 7.8 \text{ mmol/L} \]

4.5%

\[ \text{AUC} = 0.89 \]

\[ P = 0.003 \]

Panel C

\[ \text{BG}_{120} \]

\[ \text{AUC} = 0.59 \]

\[ P = 0.41 \]