Elevation of 1-Hour Plasma Glucose During Oral Glucose Tolerance Testing Is Associated With Worse Pulmonary Function in Cystic Fibrosis

JILL BRODSKY, MD1
SHAYNE DOUGHERTY, CRNP1
RAMKRISHNA MAKANI1
RONALD C. RUBENSTEIN, MD, PHD2
ANDREA KELLY, MD, MSCE1

OBJECTIVE—Cystic fibrosis (CF)-related diabetes (CFRD) is associated with declining pulmonary function and increased mortality. During oral glucose tolerance testing (OGTT), CFRD is defined by 2-h plasma glucose (PG2). We hypothesized PG elevations during OGTT resolving by 2 h, not meeting CFRD criteria, influence pulmonary function in CF. Thus we investigated the frequency of elevated 1-h OGTT PG (PG1) and its relationship with pulmonary function.

RESEARCH DESIGN AND METHODS—Retrospective review of OGTTs was performed between August 2005 (annual screening initiation) and June 2008 at Children’s Hospital of Philadelphia CF Center. First-time, well state OGTTs (PG0, PG1, PG2) were analyzed. Additional data collected were: percent predicted forced expiratory volume in 1 s (FEV1), BMI percentile, colonization with pathogens such as Pseudomonas aeruginosa and Burkholderia cepacia, and worsening nutritional status, among others (3). Further highlighting its clinical significance, CFRD is associated with increased morbidity and up to a sixfold greater mortality rate (2, 4).

CFRD is hypothesized to result primarily from insulin deficiency, although some element of insulin resistance is likely present as well. Before the development of frank diabetes, insulin secretion is delayed and blunted (5). The earliest changes in glucose tolerance involve variable postprandial hyperglycemia. Progressive decline in insulin secretion leads to impaired glucose tolerance (IGT) and, ultimately, CFRD.

The oral glucose tolerance test (OGTT) is recommended for screening purposes (6), and the diagnostic criteria for CFRD are similar to those for other forms of diabetes. However, the appropriateness of using conventional thresholds derived from epidemiologic studies in non-CF patients for the diagnosis of CFRD has been questioned (7). In type 2 diabetes, glycemic thresholds defining diabetes are based on glucose concentrations associated with microvascular complications, such as diabetic retinopathy and nephropathy (8). Although microvascular complications are relevant in CF (9), the paradigm for defining glucose abnormalities in CF is shifting to focus on outcomes more immediately relevant to CF, such as nutritional status and pulmonary function. This paradigm shift is underscored by a recent randomized control trial in which insulin treatment was associated with improved nutritional status in adults with CFRD without fasting hyperglycemia (10).

In 2009, the North American CFRD Consensus Committee restructured glucose tolerance categories in CF, based on the fasting and 1- and 2-h plasma glucose
One-hour plasma glucose and pulmonary function during an OGTT (6): normal glucose tolerance (NGT), IGT, CFRD, and indeterminate glycaemia (INDET). This new category of INDET occurs in individuals with normal fasting and 2-h plasma glucose but who have 1-h plasma glucose concentrations greater than 200 mg/dL. The clinical relevance of this INDET category with regard to clinical outcome in CF is not known.

The goals of this study were to investigate the frequency of abnormal 1-h plasma glucose during an OGTT and to explore the relationship between the 1-h plasma glucose (PG1), percent predicted forced expiratory volume in 1 s (FEV1), and BMI percentile in a pediatric CF population. We hypothesized that elevations in PG1 would be both common and negatively associated with percent predicted FEV1 and BMI percentile. Our data suggest that elevations of PG1 are in fact associated with worse clinical outcomes in CF and provide a foundation for further investigation regarding optimal management of CFRD.

**RESEARCH DESIGN AND METHODS**

**Subjects**

In August 2005, The Children’s Hospital of Philadelphia CF Center initiated annual CFRD screening in children over age 6–8 years using a standard OGTT (75 g/kg dextrose, maximum dose 75-g) after an overnight fast. This retrospective chart review is limited to OGTT performed for the first time in individual subjects between August 2005 and June 2008 in the well state, defined as no hospitalizations or oral or intravenous glucocorticoid exposure within 6 weeks before OGTT. Patients that had undergone lung transplant or had a previous diagnosis of CFRD were excluded. Patients who were unable to cooperate with pulmonary function testing because of young age or behavioral/developmental issues were excluded from the analyses examining associations between OGTT and pulmonary function.

**Data**

Data were collected from clinical records and CF care at the time of the OGTT. This retrospective chart review is limited to OGTT performed for the first time in individual subjects between August 2005 and June 2008 in the well state, defined as no hospitalizations or oral or intravenous glucocorticoid exposure within 6 weeks before OGTT. Patients that had undergone lung transplant or had a previous diagnosis of CFRD were excluded. Patients who were unable to cooperate with pulmonary function testing because of young age or behavioral/developmental issues were excluded from the analyses examining associations between OGTT and pulmonary function.

**RESULTS**

During 2005 through 2008, first-time OGTT were performed in 101 children with CF. Complete OGTT data (PG0, PG1, PG2) were available in 89 subjects. Clinical characteristics of the 101 children included OGTT plasma glucose concentrations, percent predicted FEV1 and percent predicted forced vital capacity (FVC) according to the Wang-Hankinson reference equations (REF), and BMI percentile. Sputum cultures to assess bacterial colonization were performed on spontaneously expectorated sputum (when available) or by cough swabs. All of these evaluations were performed as part of standard clinical care at the time of the OGTT. OGGT results were categorized according to PG2 as normal (PG2 <140 mg/dL), IGT (PG2 140–199 mg/dL), and CFRD (PG2 ≥200 mg/dL), as well as according to PG1 and INDET (PG1 ≥200 mg/dL but PG2 <140 mg/dL or PG1 ≥140 mg/dL but <200 mg/dL).

**Statistical methods**

Means and SD were calculated for continuous variables; proportions were used to characterize categorical data. Simple linear regression was used to test the associations between OGTT PG, as a continuous variable, and pulmonary function tests, BMI percentile, and other clinical factors such as age, sex, and sputum bacterial colonization. Multivariable linear regression was then used to test the associations between OGTT PG and percent predicted FEV1 after adjustment for BMI percentile. The regression models were assessed further through the Shapiro-Wilk test of normality of the residuals and the Cook-Weisberg test for heteroscedasticity.

Data analysis was performed using Stata 9 (Stata Corporation, College Station, TX). Two-sided tests of hypotheses were used, and a $P < 0.05$ was considered statistically significant.

**CONCLUSIONS**

In children with CF undergoing routine OGTT for CFRD screening, the 1-h PG is commonly elevated despite normal fasting and 2-h PG concentrations. In fact, until the recent introduction of the INDET category of glucose tolerance in CF, ~10% of our center’s pediatric CF population would have been labeled as having normal glucose tolerance despite an elevated PG1, or 1-h PG. More importantly and likely clinically relevant, our data suggest that the 1-h OGTT PG is negatively associated with percent predicted FEV1 even after adjustment for BMI percentile. In contrast, fasting and 2-h PG concentrations, parameters upon which we typically rely

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>42/59</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.5 ± 3.9</td>
</tr>
<tr>
<td>White</td>
<td>99 (98%)</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>52% ± 25</td>
</tr>
<tr>
<td>Percent predicted FEV1</td>
<td>94.5% ± 18.3</td>
</tr>
<tr>
<td>Percent predicted FVC</td>
<td>98.7% ± 16.8</td>
</tr>
<tr>
<td>MSSA or MRSA</td>
<td>23</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>24</td>
</tr>
</tbody>
</table>

Data are mean ± SD. MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus.
Table 2—Unadjusted associations between OGTT and pulmonary function and BMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dependent</th>
<th>Partial β-coefficient (95% CI)</th>
<th>P value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent predicted FEV₁</td>
<td>PG₁</td>
<td>−0.11 (−0.18 to −0.04)</td>
<td>&lt;0.0003</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>BMI percentile</td>
<td>0.19 (0.05–0.33)</td>
<td>0.007</td>
<td>0.07</td>
</tr>
<tr>
<td>Percent predicted FVC</td>
<td>PG₁</td>
<td>−0.06 (−0.13 to 0.005)</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>BMI percentile</td>
<td>0.19 (0.06–0.32)</td>
<td>0.004</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>PG₁</td>
<td>−0.11 (−0.21 to −0.005)</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjusted for BMI percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent predicted FEV₁</td>
<td>PG₁</td>
<td>−0.10 (−0.17 to −0.02)</td>
<td>0.009</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>BMI percentile</td>
<td>0.14 (−0.01 to 0.29)</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>Percent predicted FVC</td>
<td>PG₁</td>
<td>−0.05 (−0.11 to 0.02)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>BMI percentile</td>
<td>0.18 (0.04–0.32)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Elevations of PG₁ are also associated with abnormalities in inflammatory markers and metabolic characteristics in patients without a diagnosis of diabetes. Adults with PG₁ >155 mg/dL had significant increases in inflammatory markers and lipid ratios, higher white blood cell count and fibrinogen levels, and worse insulin sensitivity (14). Moreover, subjects with normal glucose tolerance as defined by fasting and 2-h PG, but who had PG₁ >155 mg/dL, had a fivefold greater risk of type 2 diabetes than those subjects with PG₁ <155 mg/dL (15). These findings further highlight the importance of understanding the role of hyperglycemia that occurs earlier than the 2-h mark.

Both CFRD and IGT are associated with greater declines in pulmonary function (16). Glucose abnormalities occurring earlier than 2 h during a OGTT have also been associated with declines in weight in the year preceding the OGTT (17). More concerning, CFRD is associated with increased mortality (2). Recent data from the University of Minnesota suggest, however, that early diagnosis and treatment of CFRD can improve survival (2). In a 1-year randomized control trial of CFRD without fasting hyperglycemia, insulin treatment improved BMI percentile, and, although not statistically significant, trends in reversing declines in pulmonary function were suggested.

Current recommendations for the treatment of blood glucose abnormalities in CF rely on the 2-h blood glucose concentration, which is defined as abnormal based upon its ability to predict development of microvascular complications. In the setting of CF, worsening pulmonary function and poor nutritional status are the more clinically relevant causes of significant morbidity and mortality. Given that current median predicted survival for people with CF is only ~37 years, pulmonary function and nutritional status eclipse microvascular disease as clinically significant causes of morbidity and mortality in CF. Thus our findings of worse percent FEV₁ in the setting of increasing PG₁ but not PG₂ suggest earlier and not typically assessed glucose abnormalities may have implications for pulmonary status and that reliance on PG₂ may miss an important impetus for intervention.

In this study, a negative association between PG₁ and baseline percent FEV₁ was identified; however, this association

Figure 1—Plasma glucose excursions during OGTT.
One-hour plasma glucose and pulmonary function

does not differentiate between 1) a causal effect and 2) glucose abnormalities and worsening percent FEV₁, both arising as manifestations of worsening CF disease. In fact, PG₁ may only be an early marker of pulmonary decline. It is important to also note that although the model is statistically significant, the R² was low; an association between glucose abnormalities is therefore suggested, but the clinical impact of this association has yet to be determined. The finding of increasing PG₁ predicting worse percent FEV₁ in subsequent years would provide support for this causal effect, while an intervention study targeting the 1-h OGTT blood glucose would provide important insights into the role of glucose/insulin in nutritional status and pulmonary function.

We have identified a significant association between elevated PG₁ and decreased percent predicted FEV₁ in children with CF. These findings support a new paradigm for the approach to PG abnormalities in CF by defining PG abnormalities by risk of pulmonary function decline and nutritional status compromise rather than microvascular complications, as well as support further investigation of glycemic control defined by PG₁ in CF.

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J.B. wrote the article, contributed to discussion, and researched data. S.D. researched data and contributed to discussion. R.M. researched data. R.C.R. researched data, contributed to discussion, and reviewed and edited the article. A.K. researched data, contributed to discussion, wrote the article, and reviewed and edited the article.

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