Blood Glucose and Serum Insulin Levels in Children with Cystic Fibrosis

A. D. MILNER
From The Hospital for Sick Children, London

Impaired glucose tolerance was shown to be present in a proportion of children with cystic fibrosis more than 30 years ago (Andersen, 1938), though symptomatic diabetes mellitus was not recognized as a complication until 1955 (Schwachman and Leubner, 1955).

This paper presents the results of blood glucose and serum insulin levels after oral and intravenous glucose, and after intravenous glucagon and tolbutamide, in a series of children with cystic fibrosis, including two with symptomatic diabetes mellitus. These investigations were done to discover which patients were at risk as regards diabetes mellitus. In addition, they provide further information on the mechanism of impaired glucose tolerance in cystic fibrosis.

Subjects and Methods

Of the 61 children investigated, 27 were in-patients at the time of the tests and 34 were out-patients. All had clinical features of cystic fibrosis and sweat sodium levels greater than 70 mEq/l. All were on normal diets, with good carbohydrate intake, apart from one who had a disaccharide-free diet. The fat intake in 2 of the children was mainly medium-chain triglycerides. Control values for insulin levels after oral glucose loads were obtained from investigations carried out earlier by this laboratory on 22 in-patient children who were subsequently found to have no features which might be expected to affect glucose or insulin response.

Oral glucose tolerance test with insulin levels. The children were fasted for 12 hours before the test with the exception of those under 1 year who were fasted for 6 hours.

Capillary blood samples obtained by finger-prick were collected after an oral 20% glucose load. Further samples were then collected at 30-minute intervals for 21 hours. Dosage was calculated from the formula of Poulton and Payne (Wilkinson, 1960).

Glucose and insulin levels after intravenous glucose load. After a 12-hour fast, venous samples were collected before, and at 3, 15, 30, 45, 60, and 75 minutes after an intravenous glucose load of 0·5 g./kg. body weight, given as a 50% solution over 45 seconds (Crawford, 1938).

A scalp vein needle was left inserted in an antecubital vein for the duration of the test, and between sampling the needle was connected to a slow normal saline drip to maintain patency. The blood glucose results were plotted on semi-logarithmic graph paper, with the glucose levels in logarithmic scale in ordinate and the time as abscissa, providing a straight line relation. From this, the time taken for the blood sugar to return to 100 mg./100 ml. blood was measured (Crawford, 1938). In addition, the coefficient of glucose assimilation, K, a measure of tissue avidity for glucose, was calculated from the formula of Conard (1955).

Glucose and insulin levels after intravenous glucagon. The procedure described above was followed except that glucagon, 20 μg./kg. (Chiumello, del Guercio, and Bidone, 1968), was given intravenously over a period of 15 seconds instead of the glucose load.

Glucose and insulin levels after intravenous tolbutamide. The same procedure was adopted for this investigation, tolbutamide 25 mg./kg. being given intravenously over 15 seconds (Chiumello et al., 1968).

Blood sugar estimations. Blood samples were collected into sodium fluoride and estimated by a modified method of Folin and Wu (Wilkinson, 1960). In addition, 77 samples were also estimated using a glucose oxidase method (Huggett and Nixon, 1957).

Serum insulin levels. Serum insulin levels were estimated by radioimmunoassay according to the method of Grant (1968), which is a modification of the double antibody method of Morgan and Lazarow (1963). All samples were in duplicate, and values over 40 μU/ml. were repeated after double dilution, as the accuracy of this method falls over that level. Insulin estimations carried out on 6 different occasions on a control plasma gave a mean result of 36 μU/ml. with a standard deviation of ± 2·5 μU/ml.

Results

Oral glucose tolerance test. According to
the results of the glucose tolerance tests, the patients were arranged into the following groups. (a) Symptomatic diabetes: Blood sugar rising above 190 mg./100 ml., with symptoms of diabetes, i.e. polyuria, polydipsia, etc. (b) Chemical diabetes: Blood sugar rising above 190 mg./100 ml., but no symptoms of diabetes. (c) Impaired tolerance: Blood glucose not rising above 190 mg./100 ml. but with blood glucose of over 120 mg./100 ml. at 2 hours. (d) Normal glucose tolerance: Blood glucose not rising above 190 mg./100 ml. and falling below 120 mg./100 ml.

Of the 61 children, 18 were found to have abnormal glucose tolerance tests, of which 2 had symptomatic diabetes mellitus, 5 had chemical diabetes, and 11 had impaired tolerance. These abnormalities were more common in the younger children, as shown in Table I. No correlation could be found between impaired glucose tolerance and height or weight centiles, family history of diabetes mellitus, or severity of chest x-ray changes.

**TABLE I**

*Incidence of Glucose Tolerance Test Groups in Children with Cystic Fibrosis at Different Age-groups*

<table>
<thead>
<tr>
<th>Age-group</th>
<th>0–1 yr.</th>
<th>1–5 yr.</th>
<th>5–10 yr.</th>
<th>10–15 yr.</th>
<th>15 yr. +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>7 mth.</td>
<td>3 yr.</td>
<td>6 mth.</td>
<td>11 yr.</td>
<td>16 yr.</td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td>Test Group</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>.</td>
<td>10</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

**TABLE II**

*Time taken for Blood Glucose to Fall to 100 mg./100 ml. blood after Intravenous Glucose Load*

<table>
<thead>
<tr>
<th>Age-group</th>
<th>Case No.</th>
<th>Time for Blood Glucose to Fall to 100 mg./100 ml. (min.)</th>
<th>K Value</th>
<th>Glucose Tolerance Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–10 yr.</td>
<td>1</td>
<td>160</td>
<td>0.66</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>1.61</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>1.5</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>1.73</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Average*</td>
<td>51</td>
<td>1.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–15 yr.</td>
<td>5</td>
<td>66</td>
<td>1.42</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>1.38</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>1.26</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>1.98</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>63</td>
<td>1.51</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Average excludes Case 1 who had symptomatic diabetes. The glucose assimilation constant K, and the glucose tolerance test group in the 8 children studied are shown. The average values do not include Case 1 who had symptomatic diabetes.

**Fig. 1.**—Serum insulin levels after oral glucose load in children aged 0–1 year. Mean values and ± SD are shown. • = children with cystic fibrosis; ○ = controls.

**Fig. 2.**—Serum insulin levels after a glucose load in children aged 1–5 years. Mean values and ± SD are shown. • = children with cystic fibrosis; ○ = controls.
efficiency of glucose assimilation K was low in all children studied. The results are shown in detail in Table II.

Insulin levels after intravenous glucose load. The mean maximum insulin response was higher to intravenous than to oral glucose loads in the 8 children with cystic fibrosis investigated. The results are shown in Fig. 6.

Glucose levels after intravenous tolbutamide. The blood glucose fell to 85%, 70%, and 66% of the fasting level in 3 children with cystic fibrosis. These children had a glucose tolerance test of (d), (c), and (b) types, respectively.

Insulin response to intravenous tolbutamide and intravenous glucagon. The insulin response to intravenous glucagon was measured in 4 patients, including the 3 children who were given intravenous tolbutamide. The maximum responses to glucagon and tolbutamide range from 17 to 30 μU/ml and are shown in Table III.

Estimation of blood glucose using glucose oxidase. Results were on average 15 mg./100 ml lower than those obtained by the Folin and Wu method.

Discussion

In 1938 Andersen reported on 3 children with cystic fibrosis who had abnormal glucose tolerance
Maximum Insulin Level After Intravenous Glucagon and Tolbutamide

<table>
<thead>
<tr>
<th>Case No. and Glucose Tolerance Test Group</th>
<th>Max. Insulin Level after Glucagon (µU/ml.)</th>
<th>Max. Insulin Level after Tolbutamide (µU/ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6D</td>
<td>26.5</td>
<td>30</td>
</tr>
<tr>
<td>2B</td>
<td>29.5</td>
<td>22.5</td>
</tr>
<tr>
<td>5C</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>8D</td>
<td>28.5</td>
<td>—</td>
</tr>
</tbody>
</table>
tests performed were within the normal range, as described by Crawford (1938), none returning to 100 mg./100 ml. within 45 minutes of the administration of the glucose. The average time (excluding the diabetic child, Case 1) was 61 minutes.

Values obtained for the glucose assimilation constant \( K \) were also probably abnormal, being 1·61 for those under 10 years and 1·51 for those over 10 years. Control figures obtained by Loeb (1966) of 2·7 and 2·3, respectively, are not strictly comparable, as he gave 0·66 g. glucose/kg., as against 0·5 g. glucose given in this series.

The intravenous toltbutamide tolerance test gave a poor response in 1 out of 3 children, i.e. a fall to 85% of the fasting level. Rosan et al. (1961) found a similar response in one-third of children with cystic fibrosis.

The insulin responses to intravenous glucose, glucagon, and toltbutamide were more rapid than to oral glucose, but no significant difference could be detected in the insulin levels produced by these three stimuli. Though there was considerable overlap, the average insulin response to intravenous glucose was higher than that to oral glucose. This requires further elucidation but is in contradiction to the findings in normal adults who have a greater insulin response to oral than to intravenous glucose; this is thought to be due to a glucagon-like substance released from the liver or intestines (McIntyre, Holdsworth, and Turner, 1965).

These findings, which agree with those of Handwerger et al. (1968), are also found in patients with hepatic cirrhosis (Megyesi, Samols, and Marks, 1967), and it is hoped that further work will be carried out to assess liver function in these children.

These findings suggest that in cystic fibrosis there is a dual defect in insulin secretion: (1) defective release of insulin from the islet cells of the pancreas in response to hyperglycaemia; (2) defective release of a glucagon-like substance from the alimentary system.

It is not at present known whether the children found to have abnormal glucose tolerance tests are more liable to progress to symptomatic diabetes mellitus, but it is hoped that careful follow-up of these children will provide this information in the future.

Summary

The results of glucose and insulin levels after oral glucose and intravenous glucose, glucagon, and toltbutamide in 61 children with cystic fibrosis are presented. The results suggest that the increased incidence of impaired glucose tolerance found in them is due to a defect in the release of a glucagon-like substance from the alimentary system, in addition to defective islet cell function.

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Correspondence to Dr. A. D. Milner, The Hospital for Sick Children, Great Ormond St., London W.C.1.
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A. D. Milner

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