Insulin secretory reserve in insulin dependent patients at time of diagnosis and the first 180 days of insulin treatment

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Abstract. Eleven newly diagnosed insulin dependent patients were studied before and during the first 16 h after start of insulin treatment. All the patients were found to have significant amounts of C-peptide in plasma indicating residual insulin secretion. The fall in blood glucose after start of insulin therapy was followed by a parallel decrease in C-peptide (R = 0.99, P < 0.01) suggesting that the beta-cells may respond to variation in blood glucose.

Eight of the patients were studied 1, 4, 7, 14, 90 and 180 days after start of insulin therapy. During the first 90 days of treatment an increasing maximal C-peptide concentration was found after a standard breakfast test meal. Two thirds of this improvement in beta-cell function was found after the initial 14 days with an average increase in maximal C-peptide of 260 per cent. The sensitivity to glucose improved.

The onset of ketosis prone diabetes mellitus is associated with severe beta-cell failure (Enk 1977; Ludvigsson & Heding 1978; Block et al. 1972; Heinze et al. 1979). In 12 children with IDDM Ludvigsson & Heding (1978) found C-peptide immunoreactivity in all on admission to hospital. Block et al. (1972) found no C-peptide immunoreactivity in 3 of 4 patients during initial ketoacidosis, but 2–20 weeks later beta-cell function was found in all. This is in accordance with the findings of Faber & Binder (1977a), who found residual beta-cell function in all of 17 patients one month after start of insulin treatment.

The purpose of the present study was to follow the beta-cell function from the time of diagnosis and during the first weeks of treatment as well as to study the interrelationship between blood glucose variations and insulin secretion.

Material and Methods

Eleven insulin dependent patients were studied before (0-day) and 1, 4, 7, 14, 90 and 180 days after diagnosis and start of insulin treatment. The patients were considered insulin dependent according to the following criteria at admission to hospital: glucosuria ≥ 5%, significant ketonuria (more than or equal to ++ with Ketestix), body weight below 110% of the ideal for sex and height (Natvig 1956) and age less than forty years. None of the patients were in coma at the time of diagnosis. All the patients gave informed consent to the investigation. Three of the 11 patients were not re-studied after the initial 16 h. Clinical data appear from Table 1.

Low-dose insulin therapy was started at once at admission to hospital (0-day) with 12 IU of Actrapid® im followed by 6 IU im hourly until ketonuria and glucosuria had disappeared. Blood samples were taken before and 1, 2, 3, 4, 5, 6, 7, 8, 12 and 16 h after start of insulin treatment. From the morning of day 1 all but two patients started treatment with intermediate acting insulin once or twice daily. Two patients were treated for the two first days only with fast acting insulin.

One, 4, 7, 14, 90 and 180 days after diagnosis the beta-cell function was evaluated using a test meal comprising 490 calories (60% carbohydrate, 26% fat and 14% protein). After an overnight fast the patients injected their morning insulin dose 10 min before start of
Table 1.
Individual clinical data and blood glucose, ketonuria and C-peptide before start of insulin treatment in 11 insulin-dependent patients. Subjects 1–8 were followed prospectively for 180 days.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age at onset</th>
<th>% of ideal weight</th>
<th>Total carbon dioxide (mmol/l)</th>
<th>Blood glucose (mmol/l)</th>
<th>Ketonuria (Ketostix®)</th>
<th>C-peptide (pmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>25</td>
<td>93</td>
<td>24.8</td>
<td>25.0</td>
<td>+++</td>
<td>0.24</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>35</td>
<td>86</td>
<td>17.5</td>
<td>16.4</td>
<td>+++</td>
<td>0.31</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>30</td>
<td>77</td>
<td>22.4</td>
<td>15.3</td>
<td>+++</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>15</td>
<td>92</td>
<td>26.7</td>
<td>17.5</td>
<td>+</td>
<td>0.30</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>24</td>
<td>88</td>
<td>26.1</td>
<td>19.7</td>
<td>+</td>
<td>0.10</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>29</td>
<td>94</td>
<td>15.8</td>
<td>10.8</td>
<td>+++</td>
<td>0.13</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>29</td>
<td>80</td>
<td>22.7</td>
<td>14.4</td>
<td>+++</td>
<td>0.20</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>35</td>
<td>103</td>
<td>28.0</td>
<td>18.6</td>
<td>+++</td>
<td>0.06</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>34</td>
<td>82</td>
<td>18.4</td>
<td>14.7</td>
<td>+++</td>
<td>0.19</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>20</td>
<td>90</td>
<td>29.6</td>
<td>21.1</td>
<td>+</td>
<td>0.34</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>37</td>
<td>80</td>
<td>24.3</td>
<td>12.8</td>
<td>+++</td>
<td>0.28</td>
</tr>
</tbody>
</table>

eating. Blood samples were taken −10, 0, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after start of eating, except for day 1 and 4, where blood samples only were taken before and at 60, 90 and 120 min after start of eating. The meal was completed within 10 min.

The average insulin secretory reserve was assessed using the individual maximum C-peptide value obtained 60, 90 and 120 min after start of eating. The sensitivity of the remaining beta-cell to changes in blood glucose was expressed as the slope of the individual regression lines between blood glucose and C-peptide using all the values from −10 to 180 min. The patients were discharged from hospital 14 days after start of insulin treatment.

Blood glucose control was assessed by calculating mean blood glucose (3 pre- and 3 post-prandial values) and glucosuria/24 h. Blood glucose was measured by a glucose oxidase method. C-peptide concentration was measured by the method of Heding (1975) employing the antiserum M1230 (Faber et al. 1976). The within and between assay coefficients of variation to C-peptide were 3.2% and 9.6% respectively (Faber et al. 1976). The cross-reactivity with human proinsulin is very low with antiserum M1230. Thus the proinsulin has to exceed normal fasting level with a factor of more than 200 before any proinsulin is measured as CPR (Faber et al. 1978). With this antiserum a C-peptide concentration of 0.06 pmol/ml or more implies residual insulin secretion (Faber et al. 1976). Plasma insulin concentration (IRI) was measured radioimmunologically using ethanol for the precipitation of the antigen-antibody complex (Heding 1972).

For statistical estimations Wilcoxon's test was used for comparison of mean concentrations and Spearman's rank correlation test for calculation of the coefficients of correlation. The level of type I error (2α) was set at 0.05.

Results

On admission to hospital all 11 patients had significant amounts of C-peptide in plasma, 0.21 pmol/ml, range: 0.06–0.34. Neither blood glucose nor total carbon dioxide was correlated to C-peptide at admission. The fall in blood glucose after start of insulin therapy (Fig. 1) was followed by a parallel decrease in C-peptide (R = 0.99, P < 0.01); when calculated from the average values. No correlation was found between C-peptide and IRI.

In the 8 patients, who were followed prospectively (Fig. 2), initial C-peptide was 0.19 pmol/ml (range 0.06–0.31). The maximal C-peptide values increased from 0.25 pmol/ml (range 0.10–0.58) at day 1 to 0.32 pmol/ml (range 0.16–0.68) at day 4. At day 7 all patients had higher maximal C-peptide values (mean 0.35 pmol/ml, range 0.19–0.78) compared with onset (P < 0.05). A further improvement in maximal C-peptide values was demonstrated at day 14 (mean 0.50 pmol/ml, range 0.20–0.92), and all patients, except one, had higher values than at day 7 (P < 0.05). Four patients
demonstrated highest C-peptide values after 90 days (mean 0.64 pmol/ml, range 0.21–1.11). Two patients had highest values after 180 days (mean 0.45 pmol/ml, range 0.11–1.12), whereas two patients had already obtained their highest values after 14 days of treatment.

The beta-cell sensitivity increased from day 7 (mean 22.2 pmol/mmol, range 8.0–51.3) to day 14 (mean 37.5 pmol/mmol, range 10.5–79.5) \( (P < 0.05) \). A further increase in beta-cell sensitivity was demonstrated at day 90 (mean 47.5 pmol/mmol, range 9.7–85.0) compared with day 7 \( (P < 0.05) \). Beta-cell sensitivity was reduced after 180 days (mean 27.5 pmol/mmol, range 7.4–94.2) compared with the results after 90 days of insulin treatment \( (P < 0.05) \), but the sensitivity after 180 days was not different from the results 14 days after onset.

As a group a significant gradual decrease in glucosuria/24 h and mean blood glucose was found during the first 14 days, in spite of no day-to-day variation in average insulin dose after the third day (Fig. 2). The glucosuria/24 h after 90 and 180 days was 6 ± 4 g/24 h and 14 ± 7 g/24 h, respectively. This was found in spite of and average reduction in insulin dose, of \( (0.27 ± 0.04 \text{ IU}/24 \text{ h}) \) and \( (0.28 ± 0.04 \text{ IU}/24 \text{ h}) \) \( (P < 0.05) \), respectively, when compared to the dose at discharge from the hospital.

Discussion

In this study we found measurable C-peptide in all of 11 patients before start of insulin therapy. None of the patients had severe ketoacidosis at onset, and on an average C-peptide values were about 20 per cent of the maximal levels found in normals during every day life (Faber & Binder 1977b). Presumably this represents the maximal secretory capacity at time of onset because of the high stimulating glucose level. We do, however, not know whether the C-peptide level would increase further after additional stimuli, ex. glucagon. The study also shows that the beta-cells can modulate insulin secretion in response to variations in blood glucose during the initial ketoacidosis. In this small material no correlation was found between residual beta-cell function and severity of ketosis at onset. During the first 3 months of treatment a constant and considerable improvement in insulin secretory reserve was found. On an average 62 per cent of this took place during the initial 14 days. Ludvigsson & Heding (1978) followed 10 children with IDDM at monthly intervals from time of admission to hospital and up to 10 months after. They found the same C-peptide values 1 month after onset as those noted at onset. During the following months there was a continuous steady decline in fasting C-peptide. These findings may
used stimulated CPR values, which seem to be less dependent of the prevailing blood glucose (Faber & Binder 1977b; Hendriksen et al. 1977). In accordance with the present study Faber & Binder (1976) found maximal average diurnal C-peptide values between 2 and 5 months after start of insulin treatment.

In the present study the beta-cell function was investigated four times during the initial 14 days of disease, and a significant improvement was found already after 7 days. After 14 days the beta-cell function had improved by an average factor of 2.6 as compared to the time of diagnosis. The results obtained by Mirouze et al. (1978), by means of the artificial pancreas, suggest that strict metabolic control may have led to a more pronounced and sustained functional beta-cell recovery. In accordance with the prospective study of Faber & Binder (1976) the beta-cell function was declining 180 days after diagnosis.

During the first 14 days of treatment an improvement in the degree of metabolic control was obtained. This could not be explained by an intensified insulin treatment because the dose and daily distribution of insulin were constant. It probably represents the combined effect of increased endogenous insulin release and gradual decreased insulin resistance accompanying metabolic control of the patient (Ginsberg 1977; Alford 1971). In keeping with previous studies (Faber & Binder 1976; Ludvigsson & Heding 1978) low glycosuria was found 90 and 180 days after onset of disease in spite of a less daily dose of insulin than at time of diagnosis.

**References**


represent an earlier maximal functional recovery in children, because we found that fasting C-peptide values 90 days after diagnosis were significantly higher than initial C-peptide values. The interpretation of their results is however difficult because they compared the C-peptide values at onset with fasting C-peptide values which to some extent are dependent on the concomitant fasting blood glucose (Faber & Binder 1977b). We have


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