Residual B Cell Function in Patients with Long-Standing NIDDM and its Relation to Metabolic Control and Diabetic Complications

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Abstract

We have evaluated the residual pancreatic B cell function by glucagon load test in 28 patients with non-insulin-dependent diabetes mellitus (NIDDM) of a duration of 20 years or more. The increase in serum C-peptide at 6 minutes after glucagon administration (JC-peptide) was used as an index of residual B cell function. There was much less JC-peptide in patients treated with insulin than in those treated with sulfonylurea (p<0.05), and it was significantly correlated with the body mass index (r=0.40, p<0.05). Long term metabolic control assessed by the average annual mean fasting blood glucose for the observation period (mean, 21 years) was not correlated with JC-peptide (r=-0.13). The prevalence of retinopathy which needed photocoagulation therapy and of neuropathy in patients with poor residual B cell function (JC-peptide<0.3 ng/ml) was the same as that in those with good residual B cell function (JC-peptide≥1.0 ng/ml). The present study shows that the residual B cell function is not correlated with long term glycemic control and the prevalence of diabetic complications in long-standing NIDDM patients.

Insulin secretion in patients with non-insulin-dependent diabetes mellitus (NIDDM) has been shown to be influenced by a number of factors such as adiposity, some genetic factors, aging, physical activity, type of treatment and so forth (DeFronzo and Ferrannini, 1982; Ward et al., 1984).

Although an inverse correlation has been shown between insulin secretion capacity and metabolic control in patients with insulin-dependent diabetes mellitus (IDDM) (Clarson et al., 1987; Sjöberg et al., 1987), there are few reports on the relationship between them in those with NIDDM (Lev-Ran et al., 1986). When hyperglycemic stress on pancreatic B cells has persisted for a long time, it may lead to the exhaustion of the B cells, resulting in more diminished B cell function in such patients.
The purpose of the present study is to evaluate the residual B cell function in long-standing NIDDM patients and to examine its relation to long-term metabolic control. Furthermore, since it was reported that the persisting residual B cell function would be associated with a decreased incidence of diabetic complications in long-standing IDDM (Eff et al., 1978; Sjoberg et al., 1987), we also examined the relationship between the residual B cell function and the chronic diabetic complications.

Subjects and Methods

Twenty-eight NIDDM patients (12 males and 16 females) who had attended the outpatient diabetic clinic at Kyushu University Hospital before 1965 participated in this study. None of the patients had a history of ketoacidosis and all were regarded as NIDDM according to the WHO criteria (WHO, 1985). Some of their clinical characteristics are shown in Table 1. Their mean age was 66±12 years. The onset of diabetes was considered to be marked by the development of hyperglycemic symptoms (thirst, polyuria, etc.) or the first detection of glycosuria (mean age of onset: 42±12 years). Almost all the patients had been referred to our hospital soon after the onset of the disease, and the mean observation period was 21±4 years. Three patients were treated with diet alone, 11 patients with sulfonylurea and 14 patients with insulin, of whom 10 patients had been changed from oral hypoglycemic agents to insulin and 4 patients had been continually treated with insulin.

Table 1. Clinical characteristics of patients

<table>
<thead>
<tr>
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<th>Male : Female</th>
<th>12 : 16</th>
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<tr>
<td>Age (years)</td>
<td>66±12(37-85)</td>
<td></td>
</tr>
<tr>
<td>Age at onset of diabetes (years)</td>
<td>42±12(18-61)</td>
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<tr>
<td>Observation period (years)</td>
<td>21± 4(13-28)</td>
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<tr>
<td>Treatment</td>
<td></td>
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<tr>
<td>Diet</td>
<td>3</td>
<td></td>
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<tr>
<td>Sulfonylurea</td>
<td>11</td>
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<td>Insulin</td>
<td>14</td>
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Values are the mean±SD.

Glycemic control was assessed by averaging the mean annual fasting blood glucose throughout the observation period (mean FBG). Whole capillary blood glucose was determined by the Hagedorn-Jensen method until 1976 and by the glucose oxidase method thereafter. The glucagon load test was performed, that is, venous blood was sampled before and 6 minutes after intravenous administration of glucagon (Novo, 1 mg). Serum C-peptide was measured by radioimmunoassay (Daiichi Radioisotope Laboratories, Tokyo, Japan). The increase in serum C-peptide at 6 minutes after glucagon injection (JC-peptide) was used as an index of residual B cell function. Diabetic retinopathy was regularly checked by an ophthalmologist and photocoagulation therapy was performed in patients with advanced retinopathy except one patient who had retinal detachment due to retinal tears. Diabetic neuropathy was considered to be present when two of three signs (decreased vibratory sensation, absence of knee or Achilles' tendon reflex) were present.

For a statistical analysis, student's t-test and Fisher's exact method were used. The result was considered to be significant when the p value was less than 0.05. The values are expressed as the mean±SEM.

Results

Figure 1 shows the changes in serum C-peptide levels in response to glucagon administration in patients treated with diet, sulfonylurea or insulin. Serum C-peptide at the basal level and 6 minutes after glucagon injection was 1.0±0.2 ng/ml and 1.8±0.5 ng/ml in patients treated with diet, 1.1±0.2 ng/ml and 2.1±0.3 ng/ml in those treated with sulfonylurea and 0.8±0.1 ng/ml and 1.3±0.2 ng/ml in those treated with insulin, respectively. JC-peptide was significantly lower in patients treated with insulin than in those treated with sulfonylurea (p<0.05).

As shown in Figure 2, a significant correlation was seen between JC-peptide and body mass index (BMI) (r=0.40, p<0.05).

Figure 3 shows the relationship of
B CELL FUNCTION IN LONG-STANDING NIDDM

Fig. 1. The changes in serum C-peptide levels (±SEM) in response to intravenous administration of glucagon (Novo, 1 mg)
*p<0.05 vs. patients treated with sulfonylurea

Fig. 2. The correlation between the increase in serum C-peptide after glucagon administration and body mass index (r=0.40, p<0.05)

ΔC-peptide to fasting blood glucose at the time of the first visit to our hospital (Fig. 3A, r=-0.28, ns), mean FBG through the observation period (Fig. 3B, r=-0.13, ns) and fasting blood glucose at glucagon load test (Fig. 3C, r=-0.23, ns).

As shown in Figure 4A, the prevalence of retinopathy which needed photocoagulation therapy and of neuropathy was significantly higher in poorly controlled patients (mean FBG≥141 mg/dl) than in well controlled ones (mean FBG≤140 mg/dl), respectively (p<0.05). On the other hand, as shown in Figure 4B, the prevalence of complications in patients with good residual B cell function (ΔC-peptide≥1.0 ng/ml) and those with poor residual B cell function (ΔC-peptide≤0.3 ng/ml) was similar. In the remaining patients (0.4 ng/ml≤ΔC-peptide≤0.9 ng/ml), the prevalence of photocoagulation and neuropathy was 18% (2/11) and 45% (5/11), respectively, and it was not significantly different from that in pa-
Fig. 3. The relationship of the increase in serum C-peptide after glucagon administration to fasting blood glucose at the first attendance (A, $r = -0.28$, ns), the average of the annual mean fasting blood glucose for the observation period (mean, 21 years) (B, $r = -0.13$, ns) or fasting blood glucose at the glucagon load test (C, $r = -0.23$, ns).

Discussion

The glucagon load test has been widely used to evaluate the residual pancreatic B cell function because of its simplicity and reproducibility. Although Faber et al., proposed that serum C-peptide at 6 minutes after glucagon administration could reflect the residual B cell function (Faber and Binder, 1977), we used the increase in C-peptide at 6 minutes after glucagon administration as an index of residual B cell function because some of the patients had been treated with insulin for a long time and the presence of insulin antibody interfering with C-peptide radioimmunoassay was expected (Maruyama et al., 1979). Serum C-peptide response to glucagon in patients treated with sulfonylurea or insulin in the present study was substantially the same as the reported values (Matsuda et al., 1985) and it was suggested that the residual B cell function was not lowered in long-standing NIDDM, being consistent with previous studies (Lev-Ran et al., 1986; Snehalatha et al., 1986).
Some reports on IDDM indicated that the more active the residual B cell function, the better the metabolic control (Gonen et al., 1979; Clarson et al., 1987; Sjöberg et al., 1987). The present study on NIDDM, however, differed from them in that the residual B cell function did not significantly correlate with the glycemic levels at the first visit, through the observation period and at present. The reason for this difference may be that in NIDDM patients other factors except endogenous insulin secretion such as insulin resistance play a major role in metabolic control. Furthermore, since this study was undertaken in a retrospective manner, a number of biases did exist, for example, very poorly controlled patients could not survive for 20 years or more. However, the present study showed that NIDDM patients with poor residual B cell function could be controlled as well as those with good residual B cell function regardless of their initial hyperglycemia.

In long-standing IDDM patients, the persisting residual B cell function is associated with a decreased incidence of proliferative retinopathy (Eff et al., 1978) or proteinuria (Sjöberg et al., 1987). In the present study, however, the prevalence of retinopathy which needed photocoagulation therapy and neuropathy was not increased in NIDDM patients with poor residual B cell function compared with those with good residual B cell function and the diabetic complications could develop even though the pancreatic B cell function was well preserved. In con-
trast, glycemic control during the observation period was associated with the prevalence of diabetic complications. Therefore, diabetic retinopathy and neuropathy were related with long term metabolic control but not with the residual B cell function in long-standing NIDDM patients.

In conclusion, the residual B cell function assessed by glucagon load test in long-standing NIDDM patients was correlated with the type of treatment and BMI but not with the long term glycemic level, and it had no direct relationship to the prevalence of diabetic complications such as advanced retinopathy and neuropathy. Therefore, it was suggested that the residual B cell function was not a predominant determinant for glycemic control and diabetic complications in NIDDM patients, in contrast with IDDM patients.

References


