The Characteristics of Japanese Diabetics

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(A) Diabetes Coma and Ketosis of Japanese Diabetes

The most significant characteristic of Japanese diabetics is that the occurrence of coma is very rare compared with that of Europeans and Americans.

From 1920 to 1963 in total only 111 cases of coma were reported in Japan, of which 15 cases were observed in our clinic. Out of many severe diabetic patients observed in Japan, however, only a small number of patients were found to be in coma.

In order to solve this significant and paradoxical characteristic of Japanese diabetics, the blood acetone bodies from 160 diabetics of various severity were examined.

(1) The Levels of Acetone Bodies in Blood Non-Coma.

The levels of acetone bodies in blood were measured by the method of Frommer. The mean levels of acetone bodies of 160 patients (non-coma) classified according to the degrees of severity are shown in Table 1.

The degree of severity was determined from the results following twice oral administrations of 50g glucose.

(a) Excessively severe group: The peak value of blood sugar curve exceeded 400mg/100cc.
(b) Severe group: Do. exceeded 300mg/100cc.
(c) Moderate group: Do. exceeded 200mg/100cc.
(d) Mild group: Do. between 200-130 mg/100cc.

According to Table 1, the levels of blood acetone bodies are generally significantly low even in the excessively severe cases, and do not exhibit definitely any difference among the degrees of severity of diabetes.

Table I. Mean Levels of Serum Acetone Bodies Except Coma

<table>
<thead>
<tr>
<th>Severity of diabetes</th>
<th>Excessively severe group mg%</th>
<th>Severe group mg%</th>
<th>Moderate group mg%</th>
<th>Mild group mg%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total acetone</td>
<td>10.00</td>
<td>6.83</td>
<td>2.96</td>
<td>3.30</td>
</tr>
<tr>
<td>Acetone + Acetoacetic acid</td>
<td>4.96</td>
<td>2.03</td>
<td>1.40</td>
<td>1.45</td>
</tr>
<tr>
<td>β-hydroxybutylic acid</td>
<td>5.04</td>
<td>4.80</td>
<td>1.56</td>
<td>1.85</td>
</tr>
<tr>
<td>Number of Cases observed</td>
<td>37</td>
<td>53</td>
<td>45</td>
<td>25</td>
</tr>
</tbody>
</table>
(2) The Levels of Acetone Bodies in Blood from Coma Diabetics.

The levels of blood acetone bodies of patients during and after coma are presented in Table II.

Where does this peculiar ketonemia in Japanese diabetics come from? No satisfactory interpretation of this fact can here be given, but it may be connected with the taking of the diet low in animal fat in Japan.

Table II. The Values of Blood Acetone Bodies during and after Coma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Total acetone bodies mg%</th>
<th>Blood sugar mg/100cc</th>
<th>Total acetone bodies mg%</th>
<th>Blood sugar mg/100cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.K.</td>
<td>M</td>
<td>8</td>
<td>69.6</td>
<td>343</td>
<td>26.3</td>
<td>267</td>
</tr>
<tr>
<td>Y.A.</td>
<td>M</td>
<td>24</td>
<td>45.9</td>
<td>407</td>
<td>4.5</td>
<td>269</td>
</tr>
<tr>
<td>S.K.</td>
<td>W</td>
<td>40</td>
<td>24.4</td>
<td>276</td>
<td>6.3</td>
<td>151</td>
</tr>
<tr>
<td>C.F.</td>
<td>W</td>
<td>37</td>
<td>55.0</td>
<td>607</td>
<td>29.0</td>
<td>250</td>
</tr>
<tr>
<td>A.O.</td>
<td>W</td>
<td>24</td>
<td>156.0</td>
<td>1000</td>
<td>(died)</td>
<td></td>
</tr>
<tr>
<td>T.M.</td>
<td>M</td>
<td>28</td>
<td>52.0</td>
<td>575</td>
<td>(died)</td>
<td></td>
</tr>
</tbody>
</table>

(B) Comparison and Correlation on the Clinical Effectiveness between Insulin and Sulfonylurea in Japanese Diabetics

(1) Comparative Studies on the Clinical Effectiveness following Insulin or Sulfonylurea Therapy in Japanese Severe Diabetics.

(1) Clinical Material

Altogether, 250 severe diabetic patients in our hospital were selected for the treatment with insulin or sulfonylurea during 5 years (from 1959 to 1963). Nearly all the patients were maturity onset, showed the blood sugar peak exceeding 300 mg per cent, following two administrations of 50g glucose. Several causes of juvenile onset and ketoacidotic diabetics were included.

All the patients, at first, were treated with insulin (usually 30 U daily, in excessively severe patients 45 U daily) from 1 to 3 months. When Insulin therapy was over, a treatment with sulfonylurea was begun, and in a few cases, the order of the treatments were reversed.

(2) The Method of Comparison on the Responsiveness to each Agent.

The degree of responsiveness to insulin or SU was evaluated from the reduction of blood and urine glucose within a given time due to insulin or SU therapy.

In all the patients, levels of sugar in the blood (fasting and postprandial) weekly and urine sugar daily were determined.

The decreased FBS and postprandial sugar values were expressed by percentage changes, and the mean of these values was compared after each therapy.

To compare the responses of urine sugar to each agent, we used the method of
estimating the insulin-(or SU) urinary-glucose-equivalent, which means the total glucose disappeared from the urine daily with insulin or SU therapy, and the mean values with each therapy were expressed in terms of a unit of insulin or 0.05 g tolbutamide.

For the two evaluations following schemas were adopted. (Table III)

The practical evaluation of the therapeutical effect was done with the combinations of the above A and B series, giving at the same time considerations due to the results of oral glucose tolerance test before and after the therapy and the decreased percentage of postprandial blood sugar. The practical evaluations we used finally are seen in Table IV.

(3) Results

As shown in Table V, in a total of 250 severe patients who were treated previously with insulin and SU separately in our hospital, 132 patients (53%) revealed good effect
with both insulin and SU, while in 47 cases (19%) were non-responsive to each drug.

To insulin alone, 34 patients (14%) were resistant, though they were responsive to SU; and 37 patients (15%) failed to respond to SU, but responded to insulin alone.


Attempts were made to use insulin in conjunction with SU in 46 patients who had been previously treated with insulin and SU separately, and were proved non-responsive to both or single drug. They were divided into three groups and were given combined insulin and SU therapy with 30 U insulin and SU daily (1.5g. tolbutamide or 0.5g. chlorpropamide) from one to 6 months.

The first group, 17 patients also were previously minimally or none responsive to both insulin and SU, showed 11 beneficial cases after the long-term insulin and SU combined therapy.

Out of the second group, 10 insulin resistant patients, favorable responses were obtained in 3 cases by the combined treatment.

The third group consisting of 19 non-responsive to SU, good effects were obtained in 10.

All these are tabulated below.

Table VI. Results of combined Insulin and SU therapy to both or each Resistant Diabetics

<table>
<thead>
<tr>
<th>Non-responsive to</th>
<th>Number of cases treated</th>
<th>Cases of good response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both insulin and SU</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Insulin alone</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>SU alone</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

(III) Correlation on the Effectiveness between Insulin and Sulfonylurea Therapy.

During our trials on the responsiveness to insulin or SU separately, we found an interesting fact that to some patients who had been previously proved to be resistant to SU, and responsive to insulin, we carried out another insulin therapy of long periods, and confirmed a new beneficial effectiveness of SU alone in some of those SU resistant patients. To such patients the name 'pseudo-sulfonylurea-resistant diabetics' was coined by us.

On the other hand, there is another group of patients who show non-responsiveness to SU alone, which was not affected from long-term repeated insulin therapy. Another term 'true sulfonylurea-resistant diabetics' seems to be appropriate to these cases.
In total, 38 SU alone refractory cases came under our observations, 16 patients were found to be pseudo-sulfonlurea-resistant diabetics, and the remaining were true-sulfonlurea resistant.

(IV) Observation on Long-term Treatment with SU alone at the Outpatient Clinic of our Hospital.

From about 500 diabetic patients attending the outpatient clinic, 240 patients were selected who were continuously treated between 3 months to 4 years.

They were divided into 2 groups. In the first group of 113, previously hospitalized severe patients, however, excellent results were obtained with insulin and SU therapy and did not require insulin. The latter group consisted of 127 mild patients and were treated from the beginning at the outpatient clinic.

All patients of the two groups were treated with SU alone in long-term under usual dietary restriction.

Among the 240 patients who were well controlled on SU therapy alone there appeared, however, in the course of the continuation, 44 cases who failed to respond to SU, and it became necessary to apply insulin therapy.

Out of these 44 patients of secondary failures, 40 were found previously hospitalized insulin dependent patients, who had obtained good response to SU after insulin and SU therapy in our hospital previously.

This fact indicates that among mild and moderate patients of Japanese diabetics only 18% had secondary failures and required insulin treatment during single SU therapy of long-term.

It is of interest to note that among 44 patients of secondary failures most of them (40 patients) were previously insulin dependent hospitalized patients.

(C) Conclusion

(1) In spite of the fact that many severe diabetics were found in Japan, the occurrence of coma among them was significantly rare. To solve this paradoxical fact, blood acetone bodies of 160 patients were measured.

The extraordinary low levels of blood acetone bodies even in the severe patients except coma patients were found, and there were no definite differences due to the degrees of severity.

(2) Sulfonlurea compounds were excellently effective as well as insulin, to almost half of our hospitalized severe patients a totaling 250, when these were separately administered.

(3) With insulin and sulfonlurea separately treated patients a totaling 46 who had failed to respond to both or each, almost half of them showed beneficial effects with combined insulin and SU therapy.

(4) In a group refractory to SU alone (38 refractory with SU alone), termed by
us 'pseudo-SU-resistant diabetics', 42% of them gave good response to SU after repeated insulin administrations, indicating an intimate correlation between insulin and SU.

(5) Out of 240 mild or moderate outpatients, one group who were once in severe condition and insulin dependent showed good response to SU and required no more insulin after hospitalized therapy. The other group responded well from the beginning to SU, and no hospitalization was required.

In the course of long-term SU therapy, alone, 44 (18%) of the 240 patients who firstly responded well to SU, began to fail to respond to SU.

In this secondary failures we found that almost of them (40 patients) had been insulin dependent hospitalized patients previously. It is also important to point out that among 240 patients from the outpatient clinic only 18% suffered from secondary failures and eventually required insulin.

From the above comparative clinical observations on insulin and SU (II to V), we may assume that an intimate relation exists between the functional activity of pancreatic cells and SU, and furthermore that a stimulation of endogenous insulin secretion occurs following the administration of sulfonylurea.