Dietary Therapy and Insulin Secretory Response to Glucose in Adult-Onset Non-Obese Diabetic Subjects

KIKUO ICHIHARA*, KENJI SHIMA**, KYOHEI NONAKA* and SEICHIRO TARUI*

*The Second Department of Internal Medicine, Osaka University Medical School, Osaka, Japan 553
and
**The Central Laboratory for Clinical Investigation, Osaka University Medical School, Osaka, 553

Synopsis

The effect of a 4-week diet regulation on non-obese, adult-onset diabetics was studied. The diet, which was prescribed for them, was composed of 60% carbohydrate, 15-20% protein and 20-25% fat. The total caloric intake was restricted to 30, 35 and 40 Cal/kg ideal body weight depending on their physical activity.

In the group whose calculated diet showed over 10% reduction in total caloric intake and carbohydrate intake, fasting glucose was decreased and glucose tolerance was improved significantly after the 4-week dietary therapy. Insulin response to oral glucose loading was improved, particularly in the later stage of oral glucose tolerance test. As a result, insulin area, i.e. the total area under the insulin curve was increased to almost two times. The sensitivity to insulin did not show any significant changes after diet regulation.

The present data indicate that the therapeutic effect of the diet restriction should be at least in part ascribed to the increased secretion of insulin. In the treatment of diabetics, a restricted diet is essential and beneficial from the point of view that it could improve the pancreatic β-cell function.

Diet regulation is a basic means for the treatment of diabetes mellitus. It seems to be the consensus that there should be some restrictions in the intake of total calorie for diabetics except for thin children who are growing. A striking lessening of hyperglycemia and glycosuria is not infrequently encountered when the appropriate diabetic diet is consistently adhered to. None the less, the primary effect of diet regulation on diabetic metabolism has not yet been fully clarified.

Two lines of thought have been proposed in regard to the effect of diet regulation. Allen (1922) showed that in a partially depancreatized dog a high carbohydrate diet leads to overstimulation of the remaining islet tissue, eventually resulting in degeneration, while a restricted diet preserves the function of the islets. This observation speaks strongly for a close relationship between a preservation of insulin secretory capacity and avoidance of overloading of the islet tissue.

Conversely, Brunzell et al. (1971) suggested the possibility that a continuation of a high carbohydrate diet results in an increase in the sensitivity of peripheral tissues to circulating insulin, which in turn causes an improved glucose tolerance in diabetics.

This study was undertaken to examine the changes in insulin secretory response to oral glucose and blood glucose response to exogenous insulin after the restriction of dietary intake. Non-obese adult-onset dia-
betics were subjected to this investigation in order to exclude the influence of obesity on the islet function, since it has been shown that insulin response to oral glucose decreases in subjects with simple obesity when their body weights are reduced (Salans et al., 1968; Farrant et al., 1969; Kalkhoff et al., 1971) and it increases in normal adults when they grow fat (Kosaka et al., 1972).

Materials and Methods

Twenty-two, non-obese adult-onset non-ketotic diabetic subjects (Table 1) aged from 30 to 68 were selected from the outpatient clinic of the Second Department of Internal Medicine, Osaka University Medical School. They were newly diagnosed and free of other diseases which might affect carbohydrate metabolism, such as liver diseases, infectious diseases and other endocrine disorders. Their body weights were within plus-minus 20% of ideal body weight, calculated by the Jones’ formula (Nocker, 1956). The values calculated by this formula coincides well (Tarui, 1965) with the maximum longevity table of medium frame issued by Metropolitan Life Insurance Company (1959). In all cases, diagnosis of diabetes mellitus was made on the basis of an abnormal response to a 100 g oral glucose load, using the criteria of Japan Diabetic Society (Kuzuya et al., 1970): diagnostic of diabetes if the 1-hour venous blood sugar value was over 160 mg% and the 2-hour value was over 150 mg%. Low or delayed insulin response to glucose loading was demonstrated in all the subjects.

The diet prescribed for these patients consisted of 60% carbohydrate, 15-20% protein and 20-25% fat. The total caloric intake was restricted to 30, 35 or 40 Calories per kg of ideal body weight depending on their physical activity. The patients were instructed to weight and record their daily meals for the calculation of their diet composition. The contents of pretreatment and the prescribed therapeutic diets were recorded for at least three days each. Daily intake of carbohydrate, protein, fat and total calorie during these two periods were calculated on the basis of “Table of Standard Composition of Japanese Food” (Japanese Science and Technology Agency, 1963). No anti-diabetic drugs were administered, and physical activity of each subject was not markedly changed during the period of study.

After the prescription of therapeutic diets, the total caloric intake was more than 10 percent less than their regular intake in the other 7 patients (Group B) (Figure 1). There were no statistical differences between Group A and Group B in age, percent of ideal body weight, fasting blood sugar or “total blood sugar area” (defined in Result) before diet instruction as judged by the Student’s t-test (Table 1).

In these patients, blood sugar, plasma FFA and serum insulin response to oral loading of a 100 g glucose and blood sugar response to intravenous insulin injection (0.1 unit of regular insulin, Isuzilin “Simizu”, per kg body weight) were compared before and after a 4-week dietary therapy.

Blood sugar and plasma FFA were measured by the method of Somogyi & Nelson (1944) and Dole & Meinerz (1960), respectively. Serum insulin was determined by the method of Hales & Randle (1963) using the commercial kits obtained from the Radiochemical Center, Amersham, U.K. Until the insulin assay, serum was stored at -20°C and the two samples, before and after the dietary therapy, of the same patient were assayed at the same time so as to minimize the variations.

Insulinogenic indices were calculated according to the method of Seltzer et al. (1963), by dividing plasma insulin enhancement above fasting value by corresponding net increase of blood sugar.

Statistical analyses were performed using the rank-order technic of Wilcoxon (1945), unless otherwise mentioned.

Results

In Group A, total calorie and carbohydrate caloric intake were lowered on dietary therapy from 2,039±83 Cal/day to 1,693±83 Cal/day (P<0.01) and 1,350±80 Cal/day to 1,013±47 Cal/day (P<0.01), respectively. There were no significant changes in caloric intakes of protein and fat. In Group B, intakes on therapy of total calories and those of three nutrients were not changed from the patients’ habitual diet (Figure 1). Body weight was reduced slightly in major part of Group A (Table 1), but no more reduction of body weight was observed during the further continuation of the same dietary therapy.

Figure 2 shows glucose tolerance curves in the two periods. In Group A, mean fasting blood sugar was decreased from 164.1±16.4 mg% to 121.7±7.1 mg% (P<
Table 1. Clinical features of the patients studied, and the effect of dietary therapy on total blood sugar area and total insulin area

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Body Weight (kg) Before Dietary Therapy (±)</th>
<th>After 4 Weeks</th>
<th>F.B.S. (mg%) Before Dietary Therapy</th>
<th>After 4 Weeks</th>
<th>B.S. Area (mg·min%) Before Dietary Therapy</th>
<th>After 4 Weeks</th>
<th>Insulin Area (µg·min/ml) Before Dietary Therapy</th>
<th>After 4 Weeks</th>
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<td>After 4 Weeks</td>
<td>Before Dietary Therapy</td>
<td>After 4 Weeks</td>
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<td>After 4 Weeks</td>
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<td>After 4 Weeks</td>
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<td>120</td>
<td>100</td>
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<td>3.0</td>
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<td>60,465</td>
<td>57,630</td>
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* Parenthesis indicates percent of ideal body weight before dietary therapy.
and blood sugar response to oral glucose load estimated by measuring the total area under the curve, i.e. blood sugar area, was also decreased from $52,346 \pm 5,911$ mg-min% to $35,375 \pm 3,903$ mg-min% ($P < 0.01$, Table 1) after diet regulation.

On the other hand, in Group B there were no statistical differences in the blood sugar values at the fasting and during oral glucose loading between before and after the dietary therapy.

Insulin secretory response to oral glucose load was found to be augmented in Group A after the dietary therapy. The concentrations of serum insulin demonstrated at 90, 120 and 180 min. of the test performed after the dietary therapy were significantly higher than the corresponding values before the therapy (Figure 3). Insulin area, which was estimated by the same method as blood sugar area, was increased from $6,807 \pm 958 \mu$-min/ml to $10,392 \pm 1,657 \mu$-min/ml in Group A after the 4-week dietary therapy ($P < 0.01$, Table 1).

Insulinogenic index was significantly elevated at 180 min. after oral glucose load in Group A (Figure 4). These results suggest that the improved insulin secretion occurs at the later stage of the glucose tolerance test, and sluggishness of early insulin response still remains after dietary therapy.

The plasma FFA response to oral glucose is depicted in Figure 5. There were no differences in fasting FFA values between two periods in either group, but a significantly lowered plasma FFA value was demonstrated at 120 min. after the dietary therapy in Group A than before.

Figure 6 shows the relationship between the percent changes in blood sugar area and insulin area in oral glucose tolerance test after a 4-week dietary therapy in Group A. The two values showed negative cor-

![Cal./day](cal/day.png)

**Fig. 1.** Changes in intakes of total calorie, carbohydrate, protein and fat after diet instruction. Vertical bars in this and subsequent figures represent standard errors of mean.
**Fig. 2.** Effect of dietary therapy on glucose tolerance in non-obese diabetics of the two groups.

- Before Dietary Therapy
- After 4 weeks

* p<0.05  ** <0.01

Group A  n=15
Group B  n=7

**Fig. 3.** Effect of dietary therapy on insulin secretion in non-obese diabetics of the two groups.

- Before Dietary Therapy
- After 4 weeks

* p<0.05  ** <0.01

Group A  n=14
Group B  n=5
In order to examine whether the improved glucose tolerance of Group A was due to increased insulin sensitivity or not, insulin sensitivity tests were performed in Group A. As shown in Figure 7, there were no significant differences at all between the insulin tolerance curves in these two periods.

Fig. 4. Effect of dietary therapy on insulinogenic index in non-obese diabetic subjects of the two groups.

Fig. 5. Effect of dietary therapy on plasma FFA response to oral glucose in non-obese diabetic subjects of the two groups. Left columns indicate fasting FFA value before (■■) and after 4 week dietary therapy (■■). Right graphs show the plasma FFA response to oral glucose loading.
Fig. 6. Correlation between percent changes in total glucose area and total insulin area after 4 week dietary therapy.

Fig. 7. Effect of dietary therapy on insulin sensitivity tests in Group A. Regular insulin was administered intravenously at a dose level of 0.1 u/kg body weight to each subjects.

Discussion

A noticeable improvement in glucose tolerance and an increase in insulin secretory response to oral glucose load were demonstrated when non-obese adult-onset diabetics were treated for 4 weeks only with dietary therapy of over 10% reduction in total caloric intake and carbohydrate intake. However, no significant improvements in glucose tolerance and insulin secretory response to glucose were observed in Group B, in which intakes of total calorie and carbohydrate as calculated were the same as its regular intake. Since Group B is not different from Group A in regard to its mean age, percent of ideal body weight, fasting blood sugar or total blood sugar area before diet instruction, the findings observed in Group A should be attributed to the restriction of dietary intake, per se.
Plasma FFA was suggested by Randle et al. (1963) to have a causal relationship to the development and exacerbation of diabetes mellitus. In our present data, plasma FFA and serum insulin in fasting were not affected by diet regulation but FFA decreased more markedly in response to oral glucose load, associating with a more increased serum insulin secretion. Those results suggest that our dietary therapy had no direct effect on the FFA release from peripheral tissue and the change in FFA response to oral glucose should be rather a result of the inhibition of hormone-sensitive lipase activity by the more elevated circulatory insulin.

It is generally accepted that in simple obesity, the glucose tolerance is improved in association with increased insulin sensitivity when the body weight is reduced (Salans et al., 1968; Farrant et al., 1969; Kalkhoff et al., 1971). In the present study, most of the subjects in Group A showed a slight reduction of their body weights after the 4-week dietary therapy (Table 1). However, insulin tolerance tests did not show any significant changes. Besides, the body weights of Case 2, 7 and 15 (Table 1) were rather increased in spite of the improvement of glucose tolerance after the dietary therapy. It is, therefore, reasonably assumed that an improvement in glucose tolerance was induced not by an increased insulin sensitivity due to the reduction of body weight but rather by the increased insulin secretion on glucose loading after dietary therapy. Wrenshall and his associates (Wrenshall et al., 1965; Vranic et al., 1968) suggested that the supply of additional insulin is indispensable for the maintaining of glucose tolerance in experimental animals being insulin-deficient or receiving a portal infusion of insulin at a rate comparable to the endogeneous basal secretion after pancreatectomy, whereas glucose tolerance was demonstrated not to be impaired in normal dogs immediately after total pancreatectomy (Kosaka et al., 1966). These observations might indicate the importance of additional secretion of insulin in achieving the normal glucose tolerance in relatively or absolutely insulin-deficient subjects. The above assumption could be also supported by the observation that a negative linear relationship between the percent changes in blood sugar area and insulin area after the 4-week diet was demonstrated.

The responses of serum insulin to oral glucose were markedly elevated after diet regulation but mainly in the later stage of glucose loading test, suggesting that β-cell function could be improved but sluggishness of early insulin response to glucose is not markedly ameliorated by dietary therapy, which is characteristic in diabetes mellitus as pointed out by Luft & Cerasi (1967).

The reason why the function of the pancreatic β-cells was improved by our dietary therapy is not clear at present. However, in diabetic subjects with a defective insulin secretory capacity, and over-stimulation by excessive caloric intake is assumed to impair further the β-cell function. Seltzer & Harris (1964) showed that insulin secretion was decreased when prolonged hyperglycemic stimulus was given to adult-onset diabetic patients. Considering the fact that the insulin content of β-cells is decreased in adult-onset diabetics (Gept et al., 1970), the β-cells of diabetics is assumed to be easily exhausted by over-stimulation. Therefore, we suppose that it is particularly important for diabetics to reduce the insulin secretory stimulus. The concept, “Resting the Pancreas”, which was proposed by Naunyn in the 19th century should be reevaluated.

In Group A, 7 of 15 patients had a fasting blood sugar of over 150 mg% and 4 of these 7 patients could be controlled with dietary therapy alone (the fasting blood sugar being kept under 130 mg%). These data indicate again the importance
and wide indication of dietary therapy.

Karam et al. (1965) reported that after a weight reduction an obese diabetic subject showed an improved glucose tolerance and a decreased insulin secretory response to glucose loading. Rudnick & Taylor (1965) demonstrated increased insulin response after prolonged carbohydrate restriction in diabetics including both obese and non-obese subjects. However, it was suggested that obese subjects with impaired glucose tolerance should be divided into at least two groups, one associated with hyperinsulinemia and the other associated with hypoinsulinemia (Kosaka et al., 1971; Ichihara et al., 1974). According to our observations (Ichihara et al., 1974), the insulin secretory response to glucose was inclined to decrease in the former, and to increase in the latter after the dietary therapy. Therefore, it might be concluded that dietary therapy could change the insulin secretory capacity of diabetics in the direction of normalization not only in non-obese subjects but in obese subjects, even if the normalization frequently remains imperfect.

Acknowledgement

We wish to express our thanks to Prof. M. Nishikawa, the Director of the Second Department of Internal Medicine, Osaka University Medical School, for his constant interest and guidance in this investigation.

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