tion between ARC/IRC and the presence of nephropathy, neuropathy and retinopathy in the 4 groups were examined. Responses of aldosterone and its precursors, 11-desoxycorticosterone (DOC), corticosterone (B) and 18-hydroxy-corticosterone (18-OH-B) to ACTH or angiotensin II (A II) were measured in normal subjects and in the 4 groups of diabetic patients in order to examine adrenal biosynthesis in this disorder.

PRA in the diabetic patients was elevated to 2.4±2.2 from 0.8±0.6 ng/ml/h (3.2±1.7 from 1.2±0.7 in normals) 2 h after furosemide (1 mg/kg) in an upright position. ARC was 15.8±3.3, 9.0±3.0, 13.7±2.2 and 17.4±3.0 pg/ml in diabetic groups I–IV, respectively (23.7±4.6 pg/ml in normals and 17.2±3.9 pg/ml in chronic glomerulonephritis). On the other hand, IRC showed a high value of 323.1±87.5 pg/ml only in group IV (141.8±35.6 in normals, 149.5±17.2 in chronic glomerulonephritis). The ARC/IRC ratio after captopril administration was, therefore, low in group IV, but not in the other groups of diabetics. The factor most strongly correlated with the ARC/IRC ratio was the creatinine clearance in the nephritis group but not in diabetic group IV. PAC was 7.5±2.6, 6.0±1.6, and 4.7±2.4 ng/100 ml in groups I, II, and III and IV (N 7.7±2.2 ng/100 ml), respectively, despite normal potassium concentrations (4.3±0.1 meq/l). 18-OH-B in diabetic patients with neuropathy and nephropathy (8.8±3.2 ng/100 ml) was significantly lower than that in controls. No difference in B, DOC, or F (cortisol) was observed between diabetic patients and controls.

Infusions of ACTH or A II were associated with low aldosterone and 18-OH-B responses in group IV. B, DOC and F were increased both in diabetic patients and in controls; there was no significant difference between diabetic patients and controls in these 3 steroids after ACTH and A II, also suggesting that the defect is probably at the level of the zona glomerulosa cell. HSHA was found in 3 elderly diabetic patients with nephropathy or autonomic neuropathy of group IV and there was no significant difference in female/male ratio. A HSHA patient, in whom renal function was extremely weakened and hyperkalemia persisted, underwent an examination after 2 yr. PAC was within the normal range (6.0–10.9 ng/100 ml) and was positively correlated with the serum potassium level (r = 0.62, n = 22). PAC rose from 10.9 to 15.8 ng/100 ml after A II and from 6.0 to 14.2 ng/100 ml after ACTH. In another HSHA patient, microscopic examination at autopsy showed severe atrophy of the zona glomerulosa and the outer layer of the zona fasciculata of the adrenals, hyalinization of the glomeruli, and destruction of the juxtaglomerular apparatus.

These findings suggest that, in diabetic patients, first impairment of the A II receptor occurs, and secondly corticosterone methyloxidase I and II are reduced by depletion of the renin-angiotensin system, associated with diabetic neuropathy and/or nephropathy. The development of these abnormalities in adrenal cells may depress aldosterone biosynthesis and induce symptoms of HSHA in diabetic patients.

2. Determination of the Glycemic Threshold for the Regression or Prevention of Diabetic Microangiopathies, and the Insulin Injection Regimen to Establish Strict Glycemic Control in NIDDM

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Since it is not yet clear whether strict glycemic control can prevent the onset or progression of diabetic microangiopathies and the point of glycemic threshold to arrest the progression of microangio-
pathies remains undetermined, a randomized prospective study was conducted to clarify the relationship between the degree of glycemic control and the progression of diabetic microangiopathies. In addition, the method of insulin injection to non-obese non-insulin dependent diabetic patients (NIDDM) with secondary failure on sulfonylureas in order to strictly glycemas was investigated.

Four-year randomized prospective study

A randomized prospective study was undertaken to determine the glycemic threshold in 50 insulin-treated patients showing an early stage of diabetic microangiopathies who had been treated with once or twice daily intermediate-acting insulin injection for an average period of 6.3 yr. These were divided randomly into 2 groups. Twenty-two patients, maintained on intermediate-acting insulin (once daily injection) therapy, were used as the control group (CIT). The other 28 patients were given multiple insulin injection therapy (MIT). In the latter group, all patients were treated with multiple insulin injections, receiving either short-, intermediate-, or long-acting insulin. During the experimental period, in both groups, insulin doses were frequently adjusted to accomplish as strict glycemic control as possible. At the time of randomization, there were no statistical differences in age, known duration of diabetes, duration of insulin therapy or insulin dose between the two groups. In CIT, for 48 months there was no significant improvement in any index of glycemic regulation for 48 months (Fig. 1). In MIT, HbA1c markedly improved from 12.5 ± 0.4% to 8.2 ± 0.3 after 3 months, and thereafter, it was maintained at levels around 8.5%. The insulin dose in CIT did not change throughout the period from 20.0 ± 1.0 U/day to 22.3 ± 1.3 U/day at 48 months. In MIT it increased significantly, from 23.2 ± 1.8 U/day to 39.8 ± 2.6 U/day at 48 months. In CIT, there was no significant change in urinary excretion of total protein. In MIT, it decreased markedly from the control value of 587 ± 112 mg/day to 130 ± 39, 128 ± 46, and 65 ± 25 mg/day at 3, 12 and 48 months later. Since systolic and diastolic blood pressure did not change during the period in either group, these improvements seemed to be affected by glycemic control. On the other hand, the urinary excretion of β2-microglobulin did not change significantly in either group. The motor nerve conduction velocity between the elbow and the wrist showed no significant change at any point and maintained a low value in CIT. In MIT, it showed a gradual but significant improvement at every point; from 47.1 ± 1.2 m/s, to 52.0 ± 0.9, 52.2 ± 0.4, and 53.9 ± 1.1 m/s at 3, 12, and 48 months later, respectively. However, the value at each point was still lower than that of 15 healthy controls. 59.0 ± 0.6 m/s. The postural change in systolic blood pressure did not change significantly in either group over the 48-month period. No significant changes in R-R intervals of electrocardiogram were observed in either group. Regarding the changes in ocular fundus photography and fluorescein angiography judged subjectively by an ophthalmologist, in the 4-yr
period there were no cases whose retinopathy improved in CIT: rather, in 11 cases retinopathies worsened: In contrast, in MIT, 4 cases of improvement in degree of retinopathy, 2 cases with disappearance of microaneurysms, and 2 cases of decreased permeability of fluorescence, were observed. It was revealed that in the 4 improved cases, HbA1 levels were maintained in the range from 7.0 to 7.6% throughout the observation period. On the other hand, even in MIT, 5 cases of deterioration of retinopathy were recognized: 1 case of dot hemorrhage, 1 case of macula edema, 1 case of microaneurysm, and 2 cases of introduction of photocoagulation. HbA1 levels just prior to deterioration in these 5 patients were revealed to range from 8.0 to 8.6% (1).

From these results, it was demonstrated that the glycemic threshold is an HbA1 level of lower than 8%. These results may be indicative that strict glycemic control should be initiated at an early stage or at the functionally abnormal stage of microangiopathies.

**Effectiveness of prandial insulin supplementation in NIDDM with secondary failure to sulfonylurea**

It is of no doubt that a therapeutic tool which enhances hepatic glucose uptake, especially after meal-intake, should be utilized for strict glycemic control in diabetics. In animal experiments, we demonstrated that portally administered insulin enhances a much greater hepatic uptake than that administered peripherally (2). We also showed that the hepatic glucose uptake obtained with intraportal or intrahepatic artery glucose infusion was markedly higher than that with peripheral glucose infusion, indicating that the hepatic-general circulatory glucose gradient might be an indicator of hepatic glucose uptake (3). In addition, we recently found that the hepatic glucose uptake is greater if the peripheral glucose concentration is maintained euglycemic rather than hyperglycemic, even though the gradient was equivalent (unpublished).

From the viewpoint of insulin secretion, NIDDM is characterized by a decreased glycemic rise-related insulin secretion but with substantial amount of basal insulin is preserved (4). Recently, we have clearly demonstrated that sufficient insulin supplements before each meal in NIDDM normalized meal-related glycemic excursions, prevent beta cell exhaustion followed by restoration of endogenous basal insulin secretion (5).

From these combined results, we have proposed the following working hypothesis in the treatment regime of non-obese NIDDM with secondary failure on sulfonylureas (Fig. 2). This hypothesis was tested in 77 non-obese NIDDM with secondary failure on long-term sulfonylurea treatment. The age of the patients was 58.3 ± 11.4 (mean ± SD) yr. The duration of diabetes averaged 18.4 ± 6.5 yr and duration of sulfonylurea treatment was 8.4 ± 3.5 yr. Averaged fasting blood glucose level and HbA1c was 201.6 ± 7.6 mg/dl and 11.2 ± 0.7%, respectively. Patients were given regular insulin 30 min preprandially for 3 meals. Insulin injections were initiated at doses of 10 U, 8 U, and 6 U for breakfast, lunch and dinner, respectively. Then according to the daily profile of blood glucose taken every 3–4 days, insulin doses were adjusted to obtain normal pre- and 2-h postprandial glycemias. At 4 wk after the initiation of insulin treatment, if the pre-breakfast glycemia level was greater than 150 mg/dl, in spite of a normoglycemia after meals and before sleep, 1.25–5 mg of glibenclamide was administered at bedtime in addition to pre-meal insulin.

Perfect normalization of both meal-related and pre-breakfast glycemia levels was established in 56 cases with insulin doses of 10.9 ± 0.8 U, for...
breakfast, 7.0 ± 0.5 U for lunch, and 7.4 ± 0.6 U for dinner, respectively. Urinary C-peptide excretion rate (UCPR), during the period from 11 PM to 7 AM in these patients was 1.83 ± 0.11 µg/h before insulin treatment and 1.85 ± 0.18 µg/h at 4 wk of treatment. However, UCPR divided by plasma glucose area (11 PM–7 AM) was increased by twofold in 4 wk.

In 21 cases, even though pre- and post-meal glycemas were regulated, pre-breakfast glycemas were higher than 150 mg/dl. In 14 out of 21 cases with combined insulin and bedtime glibenclamide therapy, the perfect glycemic excursions were established. In those 14 patients, with insulin injection alone, UCPR was 0.56 ± 0.49 µg/h. However, after adding glibenclamide, UCPR during night increased to 1.50 ± 0.64 µg/h, showing that glibenclamide again stimulates basal insulin secretion. In the other 7 patients, pre-dinner or bedtime intermediate-acting insulin injection was obligatory in addition to pre-meal regular insulin to perfectly regulate the glycemia level. With these treatments, even though insulin requirements decreased week by week, HbA1c decreased rather rapidly; 9.5 ± 0.6, 7.9 ± 0.6, 7.2 ± 0.4%, after 1, 3, and 6 months, respectively.

Thus, these studies clearly demonstrate that in NIDDM, endogenous basal insulin secretory ability is reversed dynamically and insulin sensitivity is modified in response to glycemic regulation as well.

In summary, to prevent onset or progress in diabetic microangiopathies, it is of necessity to regulate the blood glucose excursions to the same extent as healthy subjects, even in the early stage of diabetes. Maintenance of strict glycemic regulation, in turn, facilitates ease in the treatment of diabetes with the aid of preserved insulin secretion and diminished insulin resistance.

REFERENCES


