Evidence of Beneficial Effects of Strict Glycemic Control on Diabetic Vascular Complications-A Prospective Study with Artificial Devices

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SHICHIRI, M., KAWAMORI, R., GORIYA, Y., KIKUCHI, M., BANDO, K. and ABE, H. Evidence of Beneficial Effects of Strict Glycemic Control on Diabetic Vascular Complications—A Prospective Study with Artificial Devices Tohoku J. exp. Med., 1983, 141, Suppl., 719-722—This prospective study was undertaken to examine whether glycemic normalization could have beneficial on the course of diabetic vascular complications in 6 insulin-dependent diabetics. A significant amelioration of glycemic regulation was achieved by intensive glycemic control with artificial devices and multiple injections for 3 months, which also resulted in an improvement in conduction velocity, a regression in retionvascular permeability and a decrease in urinary total protein excretion. These results indicate that even after short-term treatment, glycemic near-normalization can have a beneficial effect on the early stage of diabetic vascular complications. ——— diabetes mellitus, vascular complication, prospective study

There has been some controversy as to whether or not improvement of glycemic regulation can delay the onset of diabetic microangiopathies. Glycemic normalization or near-normalization has been made possible by the recent development of the artificial endocrine pancreas and preprogrammable insulin infusion pumps. Therefore, the following prospective study was undertaken in diabetic patients to examine the effects of strict glycemic control on the course of diabetic microangiopathies.

MATERIALS AND METHODS

The subjects were 6 insulin-dependent diabetics (3 females and 3 males) who were known to have exhibited diabetic microangiopathic findings.

On admission, each subject was initially controlled for one week with subcutaneous injections at the conventional dosage of intermediate-acting insulin for the base-line study. Afterwards, each subject was put on a 3 month-program of intensive glycemic control which consisted of the following 3 insulin therapies:
1. Closed-loop control by artificial endocrine pancreas
   For whole-day glycemic normalization, the bed-side type artificial endocrine pancreas system originally developed by the authors19 was used.
2. Open-loop control by insulin infusion pump
Our own preprogrammable insulin infusion system\textsuperscript{2}, was used for this study. The algorithm of the continuous subcutaneous insulin infusion consisted of the basal insulin infusion and the postprandial insulin infusions, details of which have been published elsewhere\textsuperscript{3}.

3. Multiple insulin injections

Multiple insulin injections of short-acting and intermediate-acting insulin were administered to every subject so that was controlled to the same extent as by open-loop control for a period of up to 3 months.

Glycemic control by each insulin therapy was evaluated from the glucoregulatory indices of M-value, mean blood glucose, mean amplitude of glycemic excursions and hemoglobin A\textsubscript{1c}.

The following examinations were performed for the investigation of diabetic microangiopathies before and after intensive glycemic control: fluorescein retinal angiography for retinopathy, excretion of urinary total protein and beta-2-microglobulin for nephropathy and nerve conduction velocity of the median nerve and postural changes in systolic blood pressure for neuropathy. The statistical significance was evaluated by a Student's paired t-test.

**RESULTS**

Comparison of glycemic control before and after 3 months of intensive treatment is shown in Table 1. Conventional insulin injection therapy showed significantly poorer results ($p < 0.05$) in every index than intensive glycemic control therapy. The 3 months of glycemic near-normalization by intensive glycemic control caused hemoglobin A\textsubscript{1c} to fall from an initial value of $13.7 \pm 0.8$ to $9.3 \pm 0.4\%$ ($p < 0.05$)

| Table 1. Alterations in indices of glycemic regulation and diabetic microangiopathies before and after 3 months of intensive glycemic control |
|-------------------------------------------------|-------------------|-------------------|
| Glycemic control                               | Conventional insulin injection | Intensive glycemic control |
| M-value                                        | $109 \pm 33$      | $24 \pm 9^*$      |
| MBG (mg/100 ml)                                | $314 \pm 46$      | $168 \pm 32^*$    |
| MAGE (mg/100 ml)                               | $248 \pm 45$      | $112 \pm 24^*$    |
| HbA\textsubscript{1c} (%)                      | $13.7 \pm 0.8$    | $9.3 \pm 0.4^*$   |
| Diabetic microangiopathies                     | Urinary excretion of total protein (mg/day) | $412 \pm 188$      | $197 \pm 136$        |
| Urinary excretion of beta-2-microglobulin (µg/day) | $157 \pm 48$      | $139 \pm 56$      |
| Nerve conduction velocity (m/sec)              | $38.7 \pm 2.4$    | $44.5 \pm 0.9^*$  |
| Orthostatic hypotension (ΔBP mmHg)             | $-30.0 \pm 3.7$   | $-23.5 \pm 13.1$  |

* $p < 0.05$, compared to conventional insulin injection.

($N = 6$, Mean ± s.e.m.)
Concerning diabetic retinopathy, a remarkable reduction in retinovascular permeability was observed in 1 patient, a slight reduction of capillary permeability in 2 patients and no changes in the other 2 cases. The evaluation was difficult in 1 case with proliferative retinopathy because of previous laser-coagulation.

Urinary total protein excretion decreased remarkably in every patient as shown in Table 1. However, excretion of urinary beta-2-microglobulin showed inconsistent results.

Nerve conduction velocity of the median nerve improved individually from the initial mean value of $38.7 \pm 2.4$ to $44.5 \pm 0.9$ m/sec. ($p < 0.05$). The postural changes in systolic blood pressure improved from the initial mean value of $-30.0 \pm 3.7$ to $-23.5 \pm 13.1$ mmHg. Improvements were observed in 4 cases out of 6.

**DISCUSSION**

Despite many reports to dealing with the relationship of diabetic microangiopathy to glycemic control its pathogenetic conclusion has been unclear. From this viewpoint, a prospective study in diabetic patients would seem to be very significant.

In this study, intensive glycemic control showed apparently better glycemic regulation than conventional insulin therapy and it also showed glycemic control as good as in 2 other insulin therapies with artificial devices. (unpublished data)

Intensive glycemic control resulted in remarkable improvements in all subjects in nerve conduction velocity and urinary excretion of total protein. These results were in good agreement with other studies\(^4,5\). However, results of urinary beta-2-microglobulin were inconsistent, and improvement in retinovascular permeability and orthostatic hypotension was not observed in all subjects. This may be attributable to the imperfect glycemic control reflected by a somewhat high level of hemoglobin A\(_1\) after the treatment or to the relatively short period of treatment.

Moreover, more study is necessary to see if a distinct point exists which divides the reversible and irreversible stages of each diabetic microangiopathy. For that purpose, further longer and complete glycemic control studies should be undertaken employing an artificial endocrine pancreas system which can be worn by the subject. These are now under development by the authors\(^6\).

**References**


