

# Induction of Long-Term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients by Transient Intensive Insulin Treatment

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**OBJECTIVE** — Type 2 diabetes is a slowly progressive disease, in which the gradual deterioration of glucose tolerance is associated with the progressive decrease in  $\beta$ -cell function. Hyperglycemia per se has deleterious effects on both  $\beta$ -cell function and insulin action, which are partially reversible by the short-term control of blood glucose levels. We hypothesized that the induction of euglycemia, using intensive insulin therapy at the time of clinical diagnosis, could lead to a significant improvement in insulin secretion and action and thus alter the clinical course of the disease.

**RESEARCH DESIGN AND METHODS** — Thirteen newly diagnosed diet-unresponsive type 2 diabetic patients were treated with continuous subcutaneous insulin infusion (CSII) for 2 weeks and followed longitudinally while being treated with diet alone.

**RESULTS** — Four patients were considered therapeutic failures since CSII failed to induce euglycemia ( $n = 1$ ) or glucose control deteriorated within 6 months after CSII ( $n = 3$ ). The remaining nine patients were maintained on diet alone with adequate control from 9 to  $>50$  months (median  $\pm$  SE,  $26 \pm 4.8$  months). In five patients, glycemic control deteriorated after 9–36 months, but a repeat 2-week CSII treatment reestablished control in four patients. One of these patients underwent a third CSII treatment 13 months later. At the time this article was written, six patients of the initial group were still controlled without medication 16–59 months (median  $\pm$  SE,  $45.5 \pm 6.6$  months) after the initiation of treatment. Body weight remained unchanged in all patients.

**CONCLUSIONS** — These findings suggest that in a significant proportion of type 2 diabetic patients who fail to respond to dietary measures, short-term intensive insulin treatment can effectively establish responsiveness, allowing long-term glycemic control without medication. Further studies are required to establish whether simpler treatment regimens could be equally effective. If the hypothesis offered here finds support, present approaches to the management of newly diagnosed type 2 diabetes may need to be revised.

Type 2 diabetes is a slowly progressive disease regarding onset and severity. Treatment begins with dietary intervention and increased physical exercise. When these measures fail to control the blood glucose levels adequately, oral agents and eventually insulin are added (1). This

approach, although widely practiced and often successful, is not ideal since there is growing concern that sulfonylureas may have deleterious cardiovascular effects (2) and since insulin therapy is inconvenient, expensive, and sometimes associated with potentially dangerous hypoglycemic events

(3), a problem also faced with sulfonylureas (4). It is therefore considered preferable to control the disease with diet and exercise alone. However, these measures often fail to restore satisfactory metabolic control. Although the initial defects that cause type 2 diabetes have been debated (5), there is agreement that the deterioration of glucose tolerance over time is associated with a progressive decrease in  $\beta$ -cell function (6). The deleterious effects of hyperglycemia per se on  $\beta$ -cell function and insulin action have been well described (7,8). Some, at least, are reversible after the induction of a relatively short period of normoglycemia.

We hypothesized that intensive insulin therapy could improve insulin secretion and/or insulin action in diet-unresponsive type 2 diabetic patients and could allow glycemic control by diet therapy alone. To test this hypothesis, we recruited 13 patients with newly diagnosed type 2 diabetes who could not be controlled with diet alone and treated them with intensive insulin therapy for 2 weeks.

## RESEARCH DESIGN AND METHODS

Thirteen newly diagnosed type 2 diabetic patients (11 men and 2 women) with a mean  $\pm$  SE age of  $50.6 \pm 2.9$  years (range, 34–67 years) and BMI of  $26.9 \pm 0.8$  kg/m<sup>2</sup> (range, 24–34 kg/m<sup>2</sup>) participated in the study. The diagnosis of type 2 diabetes was based on World Health Organization criteria. All patients were instructed to engage in regular exercise and to adhere to a diet of 30 kcal/kg ideal body weight. Compliance was monitored by weekly sessions with clinic staff. Failure to achieve at least fair glycemic control, as defined below, after 3–6 weeks of adequate diet was the primary inclusion criterion. At inclusion, patients had fasting plasma glucose levels of  $12.1 \pm 1.1$  mmol/l, 2-h postprandial glucose levels of  $16.9 \pm 1.8$  mmol/l, glycated hemoglobin levels of  $11.0 \pm 0.7\%$ , and glycosylated serum protein (GSP) levels of  $359 \pm 58\%$ .

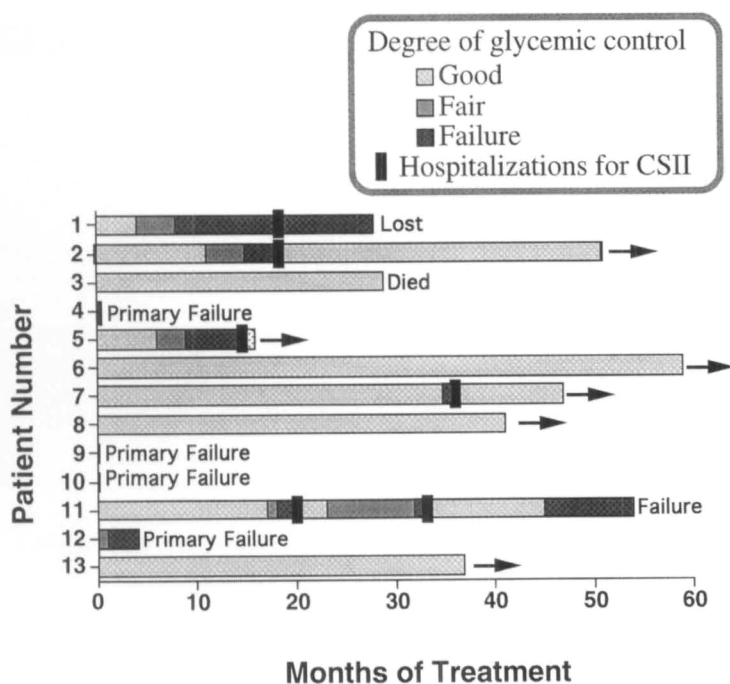
Patients were admitted to the hospital, and glucose, insulin, and C-peptide profiles

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**Abbreviations:** CSII, continuous subcutaneous insulin infusion; GSP, glycosylated serum protein.



**Figure 1**—Long-term follow-up of 13 patients. See results for a description of individual patients and Table 1 for a summary.

were monitored for 48 h (7 daily determinations). Intensive insulin treatment by continuous subcutaneous insulin infusion (CSII) was initiated using an insulin pump (Nordisk Infuser MK2; Novo-Nordisk, Copenhagen, Denmark), with the goal of rapidly achieving and maintaining near euglycemia. After 2 weeks of optimal control, insulin treatment was stopped, and glucose, insulin, and C-peptide levels were monitored for 1 day in the hospital, after which the patients were discharged and instructed to continue their previous diet and exercise regimen. Pre- and 1- and 2-h postprandial glucose, insulin, and C-peptide levels were monitored at 1, 2, and 4 weeks after discharge and monthly thereafter. Glycated hemoglobin and GSP levels were determined monthly. Excellent blood glucose control was defined as fasting levels  $<7.8$  mmol/l, with postprandial levels  $<10$  mmol/l. The corresponding values for fair control were  $<8.9$  and  $11.1$  mmol/l, respectively. Diabetic control was judged to have deteriorated when two consecutive profiles failed to meet either of these criteria. The treatment was considered to have failed if at least 6 months of fair glycemic control could not be obtained after the CSII course. If glycemic control deteriorated after more than 6 months, the patient was offered a repeat CSII treatment cycle.

#### Laboratory methods

Glucose was determined in venous blood by glucose oxidase method. Insulin levels were determined by radioimmunoassay using an antibody (Linco, St. Louis, MO) that has  $\sim 70\%$  cross-reactivity with proinsulin. C-peptide was determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA), glycated hemoglobin by affinity chromatography (Glyc-Affin GHb; Isolab, Akron, OH), and GSP by an immunoradiometric assay developed in our laboratory (normal values,  $50$ – $150\%$ ) (9). Results are expressed as means  $\pm$  SE, and  $P$  values were calculated using the paired Student's  $t$  test.

**RESULTS** — Of the 13 patients admitted to the study, one (patient 9) could not be controlled satisfactorily on CSII and was therefore considered an early therapeutic failure and excluded from further analysis. In the remaining 12 patients, glycemic control was readily attained after  $1.9 \pm 0.8$  days of CSII, using insulin doses of  $0.27 \pm 0.06$  and  $0.34 \pm 0.15$  U  $\cdot$  kg $^{-1} \cdot$  day $^{-1}$  for the basal infusion and premeal boluses, respectively. Fasting and 2-h postprandial glucose levels were under excellent control, while insulin concentrations were only modestly increased (Table 1). During CSII, there was a partial suppression of fasting

and 2-h postprandial C-peptide levels (fasting,  $2.4 \pm 0.8$  vs.  $1.6 \pm 0.4$  nmol/l; postprandial,  $2.6 \pm 0.8$  vs.  $1.5 \pm 0.3$  nmol/l for the basal infusion and during CSII, respectively). Twenty-four hours after the cessation of CSII, glucose and insulin levels remained essentially unchanged from those measured during insulin treatment (Table 1), while postprandial C-peptide levels increased to  $2.2 \pm 0.4$  nmol/l.

After CSII (Table 1, Fig. 1), patients 4, 10, and 12 were accepted as early failures when glycemic control became inadequate within 1 month after CSII. At the time this article was written, three of the remaining nine patients were in adequate glycemic control without medication 37, 44, and 59 months after CSII. Patient 3 was in good glycemic control for 29 months after CSII, at which time she died of an acute myocardial infarction. In the remaining five patients, glucose control became inadequate 9–36 months after CSII. At that time, the patients were hospitalized for a second 2-week CSII treatment, after which adequate glycemic control was maintained in three of these patients 1, 11, and 33 months later. Patient 11 was well controlled for 13 months when glycemia deteriorated. A third CSII treatment was given, and the patient was again well controlled for an additional 10 months, at which time control deteriorated, and elected not to pursue a fourth CSII course. During follow-up, no patient experienced significant change in body weight. At the time of the deterioration of glycemic control in the five patients, weight had increased by  $0.3 \pm 0.2$  kg (range,  $0$ – $1$  kg) when compared with initial weight. At the time of last visit, while under good glycemic control, weight had increased by  $0.4 \pm 0.4$  kg (range,  $-3.5$  to  $3.0$  kg) relative to initial weight. Thus, neither the ability to maintain good glycemic control nor the deterioration of glycemic control was associated with significant changes in body weight.

In the nine patients who maintained good glycemic control for  $>6$  months, we compared 1- and 2-h postbreakfast glucose and insulin levels before CSII with those immediately after CSII and at the last visit during which glycemic control was maintained. The marked reduction in postbreakfast glucose levels documented after CSII ( $15.2 \pm 1.9$  vs.  $8.2 \pm 0.4$  mmol/l) persisted ( $8.3 \pm 0.7$  mmol/l), while the insulin levels ( $228 \pm 41$ ,  $389 \pm 65$ , and  $592 \pm 77$  pmol/l) and the insulinogenic index (insulin-to-glucose ratio,  $16.8 \pm 3.3$ ,  $47 \pm$

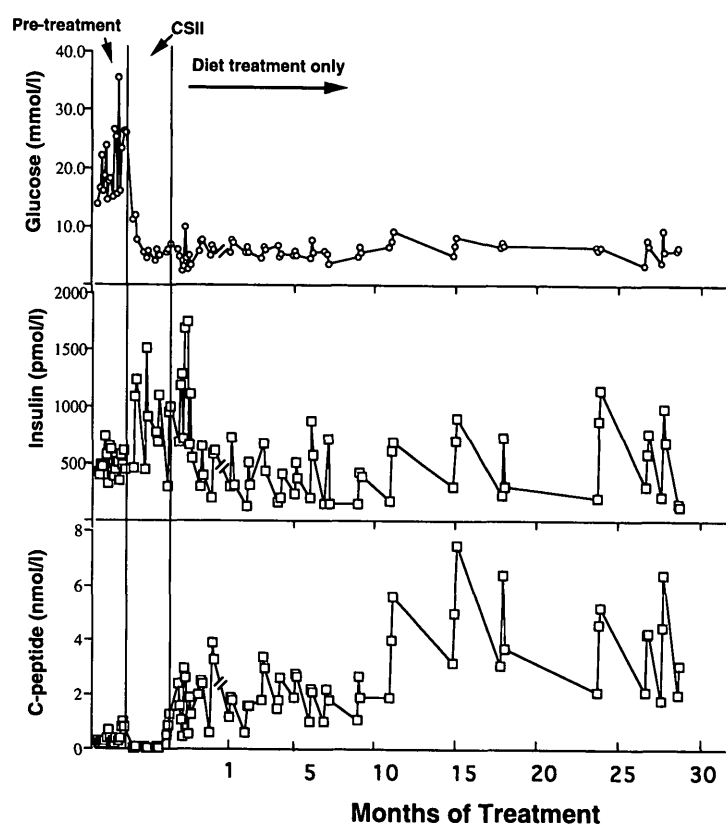
Table 1—Clinical course after CSII on diet treatment alone

	n	Post-CSII duration (months)	FBG (mmol/l)	PPBG (mmol/l)	FPI (pmol/l)	PPPI (pmol/l)	GHb (%)
Initial CSII	12						
Before CSII		—	11.8 ± 1.4	16.9 ± 1.8	182 ± 38	309 ± 57	11.0 ± 0.7
During CSII		—	4.7 ± 0.5	6.2 ± 0.6	235 ± 28	578 ± 111	—
24 h after CSII			4.8 ± 0.3	6.1 ± 0.8	382 ± 117	533 ± 81	
P value, pre-CSII levels vs. levels during CSII			<0.001	<0.001	0.05	0.04	
P value, pre-CSII levels vs. levels after CSII			<0.001	<0.001	NS	0.03	
Following initial CSII	9						
Before CSII		—	11.6 ± 1.1	16.7 ± 2.0	155 ± 39	252 ± 48	11.2 ± 0.9
After CSII		27 ± 17	6.6 ± 0.4	7.4 ± 0.4	201 ± 25	453 ± 48	6.1 ± 0.5
P value			0.01	0.001	NS	NS	0.0001
Following second CSII	4						
Before CSII		—	10.4 ± 1.3	9.9 ± 0.7	359 ± 89	577 ± 57	7.9 ± 1
After CSII		15 ± 11.5	7.0 ± 1.6	9.0 ± 2.0	312 ± 230	709 ± 520	6.7 ± 0.4
P value			0.05	NS	NS	NS	.03
Following third CSII	1						
Before CSII		—	15.8	17.2	170	194	6.8
After CSII		10	7.9 ± 1.9	9.7 ± 2.3	83 ± 10	309 ± 47	5.1

Data are means ± SE of all measurements before each CSII treatment and during the period of good glycemic control after each CSII treatment. FBG, fasting blood glucose; FPI, fasting plasma insulin; NS, not significant; PPBG, 2-h postprandial blood glucose; PPPI, 2-h postprandial plasma insulin.

8, and  $72.4 \pm 8.3$ ) increased progressively over the three time points, respectively. An example of the remarkable improvement in glucose control achieved by some patients is given in Fig. 2. Marked hyperglycemia, associated with severely elevated GSP (734%), and low C-peptide levels were observed at diagnosis. Excellent glycemic control during CSII was associated with the suppression of plasma C-peptide levels. After stopping CSII, excellent glycemic control was maintained for 44 months, while C-peptide increased gradually in parallel with a slight decrease in fasting and a pronounced increase in postprandial insulin concentrations. These changes thus reflect diminished overall hyperinsulinemia with improved  $\beta$ -cell responsiveness to nutrient intake. As with all patients, there was no change in body weight throughout the study, thus excluding weight loss or improved dietary compliance as possible causes for this remarkable improvement.

**CONCLUSIONS** — Prolonged hyperglycemia per se has been shown to cause  $\beta$ -cell secretory defects (10) and resistance to insulin action (8). Both can be reversed if hyperglycemia is controlled for a short period. Indeed, we and others have shown that induction of normoglycemia in type 2 diabetes results in both improved  $\beta$ -cell



**Figure 2**—Long-term follow-up in patient 8, showing pretreatment, CSII, and follow-up levels of glucose, insulin, and C-peptide. Data is for first 29 months of follow-up. At each visit, glucose, insulin, and C-peptide levels were determined before and 1 and 2 h after a standard breakfast. Glucose levels continued to be under excellent control for 15 additional months. However, insulin and C-peptide values were not available for this period.

function and improved insulin action (11–13). In the present study, we obtained evidence suggesting that  $\beta$ -cell function was improved in type 2 diabetic patients by CSII-induced near euglycemia and that this improvement could persist over a long time and have important clinical implications.

The treatment of new-onset type 2 diabetes always begins with diet and exercise (14). In this study, we used a period of diet treatment of only 3–6 weeks, since many of our patients were severely hyperglycemic and failed to demonstrate any tendency toward improvement on diet therapy. Prolonged treatment with an ineffective diet was considered unethical. According to standard practice, when diet fails, oral agents and/or insulin are added in increasing doses as needed to control hyperglycemia. Here, we demonstrate that long-term drug therapy is not necessarily required. The transient normalization of blood glucose using intensive insulin treatment may reestablish diet responsiveness in a significant percentage of patients for up to several years, with the possibility of recuperating “secondary failures” with repeated transient intensified insulin treatment. Of the 13 patients who entered this study, nine responded successfully to diet treatment after CSII. Although two of the failures had the highest fasting glucose values of the group, the other two were indistinguishable from the patients who responded. Therefore, in this small group, we could not predict which subjects would be most likely to benefit from the proposed treatment. The rate of deterioration in glucose control after the CSII period was variable and was not associated with weight gain, poor dietary compliance, or any other discernible factor. In fact, we were unable to identify any criterion that could be used to predict or explain the loss of glycemic control. Additional studies are needed to address this issue specifically.

In the present study, which represents a first attempt at a radical modification of the treatment for type 2 diabetes, we hospitalized our patients for a 2-week CSII course. We do not know if a full 2-week period of euglycemia is necessary, neither are we convinced that hospitalization and the use of an insulin pump are needed. It is mainly the transient nature of the intensified treatment that deserves emphasis. Besides the long-term savings in drug costs, this approach avoids the potential side-effects of chronic sulfonylurea, metformin,

or exogenous insulin treatment. Similar findings were reported by Banerji et al. (15,16) who were able to induce long-term near normoglycemia after intensive inpatient and outpatient treatment in African-Americans with severe new-onset type 2 diabetes.

Since type 2 diabetes is associated with insulin resistance and hyperinsulinism has been associated with accelerated atherosclerosis, it has been suggested that insulin treatment in type 2 diabetes may exacerbate this problem (3). During the 2 weeks of CSII, excellent blood glucose control was readily achieved and maintained with a total daily insulin dose 0.6 U/kg, which is less than the endogenous insulin production in nondiabetic subjects (17) and identical to the dose required to control type 1 diabetic patients (18). Our finding of essentially normal peripheral insulin levels during CSII suggests that the concern of treatment-induced hyperinsulinemia is unwarranted if insulin replacement is given in near physiological ways. Furthermore, the transient nature of the treatment should alleviate such fears.

To conclude, the proposed transient insulin treatment has the merit to induce long-term metabolic control, reminiscent of the “honeymoon” period of type 1 diabetes, reducing simultaneously the two factors incriminated for macrovascular complications, hyperglycemia and hyperinsulinemia.

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