Hypoglycemia and Counterregulation in Insulin-Dependent Diabetic Patients: A Comparison of Continuous Subcutaneous Insulin Infusion and Conventional Insulin Injection Therapy

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Eleven insulin-dependent diabetic patients were treated in random order by 2-mo continuous subcutaneous insulin infusion (CSII) or 2-mo conventional injection treatment (CIT) with crossover to the alternative regimen. Mean plasma glucose concentrations throughout the day were significantly lower during CSII than during CIT, but the percentage of plasma glucose values <2.5 mmol/L, obtained from outpatient self-collected diurnal profiles, was similar for both treatments (CSII vs. CIT: 5.9 and 4.8%, respectively). Reported symptomatic hypoglycemia at home was not significantly different in the whole group of patients treated by CSII or CIT but was reduced by a mean of 57% ($P < .02$) in the five patients on CSII who experienced frequent symptomatic hypoglycemic episodes (>4/2 mo) during CIT. Neither the plasma glucose concentration at which the patients recognized induced hypoglycemia nor the glycemic or counterregulatory hormone responses for 60 min thereafter were changed by CSII treatment. DIABETES CARE 1986; 9:221–27.

The increasing use of intensified insulin regimens, such as continuous subcutaneous insulin infusion (CSII), for the management of diabetic patients[1] has raised the question of whether overall glycemic control might only be improved by such strategies at the expense of an increased risk of hypoglycemia.[2] A number of mechanisms might predispose to hypoglycemia in CSII-treated patients,[2] including overinsulinization during the night (or at other times) to produce fasting euglycemia in patients with the dawn glycemic increase[3–5] and the impairments of counterregulatory hormone responses to and symptoms of hypoglycemia, which are present in many diabetic patients (and may be altered by a period of strict metabolic control).[6–8]

In this study, we compare the frequency and severity of biochemical and reported symptomatic hypoglycemia during CSII and conventional injection therapy (CIT) in a group of insulin-dependent diabetic patients. We also report the blood glucose threshold for symptomatic hypoglycemia, the rate of glucose recovery, and the counterregulatory hormone responses after deliberate insulin-induced hypoglycemia in this group of patients during both insulin regimens.

PATIENTS AND METHODS

The clinical features of the 11 insulin-dependent diabetic patients studied are shown in Table 1. Plasma C-peptide concentrations were measured by radioimmunoassay (Novo, Basingstoke, UK) before and 6 min after 1 mg of intravenously (i.v.) administered glucagon and were <0.1 pmol/ml in all subjects. All patients had been receiving CIT for at least 2 mo before the study. Patients 1, 4, 5, and 11 had received CSII previously.

Patients were randomly allocated to an initial treatment period by their unchanged CIT (see Table 1) or by CSII; each treatment lasted 2 mo. At the end of 2 mo, patients received the alternative treatment regimen for another 2 mo. CSII was performed as described previously,[9,10] by use of either a Mill Hill Infuser model 1001 HM (Muirhead Medical, London, UK) or a Nordisk Infuser (Nordisk, Gentofte, Denmark). Purified porcine insulin (Actrapid, Novo, Basingstoke, UK, or Velosulin, Nordisk) was used in the infusion pumps, and the delivery cannulas were 25-gauge winged needles ("Butterfly," Abbott, Sligo, Ireland). Patients were instructed

TABLE 1
Clinical features of patients

Case no.	Age (yr)	Sex	BMI	Duration of diabetes (yr)	Daily insulin dose CIT (U)	CIT regimen (all twice daily)
1	56	M	25.8	9	66	AR/MT
2	27	M	25.0	6	59	AR/IT
3	30	M	25.5	5	44	AR/MT
4	42	M	25.4	38	73	AR/MT
5	31	M	26.0	8	52	Mix
6	33	M	26.3	4	34	AR
7	26	M	22.8	24	66	AR/MT
8	34	F	25.3	25	56	AR/MT
9	19	F	21.7	12	56	AR/MT
10	25	M	22.6	13	56	AR/MT
11	20	M	20.6	9	46	AR/MT

Abbreviations: BMI, body mass index: wt (kg)/ht^2 (m); AR, porcine Actrapid (Novo); MT, porcine Monotard (Novo); IT, Insulatard (Nordisk); Mix, Mixtard (Nordisk).

to record all episodes of what they regarded as hypoglycemic symptoms during each treatment according to severity: moderate hypoglycemia was defined as symptoms resulting in intake of extra food; severe, as symptoms requiring i.v. glucose or parenteral glucagon administration by another person. The glycemic goals for CSII treatment were a fasting plasma glucose of 3.5–6.5 mmol/L and values <9 mmol/L 90 min after main meals. Management on CIT was unchanged, without specific recommended goals. A seven-sample diurnal profile of plasma glucose concentration was performed by each patient on 1 day of each week of the study. Capillary blood obtained by finger prick was collected by the patients into heparinized, fluoridated plastic tubes[11] (Walter Sarstedt, Leicester, UK) before and 90 min after breakfast, lunch, and the evening meal, and at bedtime. The samples were sent to Guy's Hospital for plasma glucose analysis with a Yellow Springs Instruments glucose analyzer (YSI model 23 M, Yellow Springs, OH). Patients were also requested to collect blood samples during symptomatic hypoglycemia at home.

At the end of each 2-mo treatment period, patients were admitted to a metabolic ward for assessment of counterregulatory responses to hypoglycemia. After an overnight fast, an indwelling Teflon cannula was inserted into an antecubital vein for blood sampling and kept patent with 0.154 mol/L saline. A cannula in an antecubital vein of the other arm was used for insulin infusion (6-U bolus of Actrapid insulin followed by 6 U/h Actrapid insulin via a Treonic IP3 syringe pump; Vickers Medical, Basingstoke, UK).

Insulin infusion was started after a 20-min "run-in" period during which 0.154 mol/L saline was slowly infused into the cannula, and insulin infusion continued until the patients reported that they recognized hypoglycemia. At this time, the physician recorded the reported symptoms and checked for signs of hypoglycemia, including pallor, tachycardia, and sweating. Also, insulin administration was discontinued at this point and recovery from hypoglycemia allowed to occur spontaneously. Venous blood samples were withdrawn at −20, −10, and 0 min (the start of infusion) and then at 5-min intervals until hypoglycemia occurred for rapid glucose estimation at the bedside (YSI analyzer). Blood samples for plasma-free insulin, growth hormone, cortisol, glucagon, epinephrine, and norepinephrine concentrations were taken at −20, −10, and 0 min, at the time of hypoglycemia, and, with a

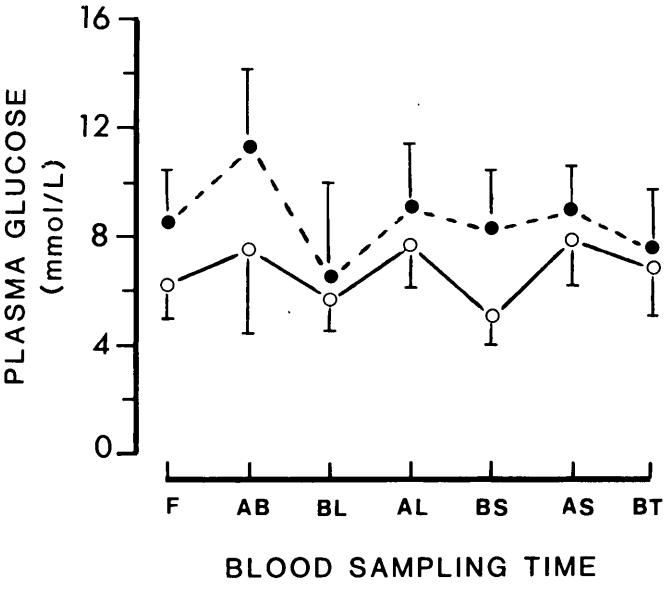

FIG. 1. Mean ± SD plasma glucose concentrations throughout day in patients treated by CSII (○——○) or conventional insulin injections (●- - - -●). Samples were collected by patients at home with heparinized-fluoridated tubes and analyzed later in the laboratory. F, fasting; AB, 90 min after breakfast; BL, before lunch; AL, 90 min after lunch; BS, before evening meal (supper); AS, 90 min after evening meal; BT, immediately before going to bed.

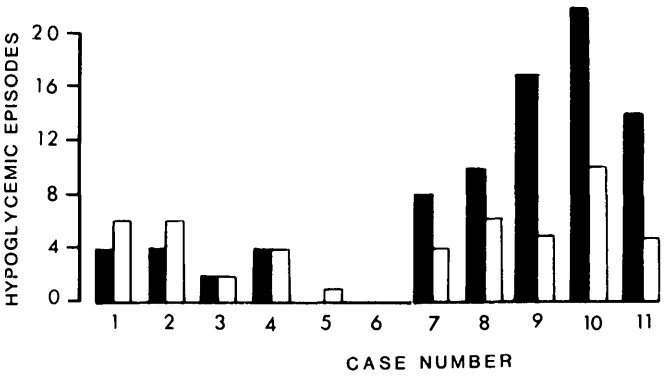

FIG. 2. Frequency of reported symptomatic hypoglycemic episodes (total number/2 mo) at home during CSII and CIT in individual patients. Black bars, frequency during CIT; white bars, during CSII.

sample for plasma glucose level, at the following intervals afterward: 5 min (insulin and glucose only), 10 min, 15 min (insulin and glucose), 30 min, 45 min (insulin and glucose), and 60 min. The experiment was then terminated and the patients given an oral glucose drink and meal.

Standardized tests for the detection of autonomic neuropathy (mean of two measurements of lying and standing blood pressure, and the difference between maximum and minimum heart rate from expiration to inspiration at a rate of 6 breaths/min calculated from the electrocardiogram) were performed on all patients after each treatment regimen.[12] None had any evidence of proteinuria (negative testing to Albustix, Ames-Miles, Stoke Poges, UK).

Plasma-free insulin concentration was measured by radioimmunoassay with a modification of the method of Gerbitz and Summer.[13,14] Radioimmunoassay was also used for the measurement of growth hormone, cortisol, and glucagon levels. Epinephrine and norepinephrine concentrations were assayed by a radioenzymatic method.[15]

Statistical comparisons between groups were made by Student's *t* test or the Wilcoxon rank test, as appropriate. All patients gave their written consent to the study, which was approved by the Guy's Hospital Ethical Committee.

RESULTS

Plasma glucose control during CSII and CIT. Figure 1 shows the mean ± SD plasma glucose concentrations throughout the day in the 11 diabetic patients during treatment by CSII and CIT. Results were calculated from the outpatient capillary blood samples measured in the hospital laboratory. The profile for a given patient was the mean of the weekly profile values for a treatment regimen. Mean plasma glucose levels were lower during CSII compared with CIT, significantly so before breakfast ($P < .02$), 90 min after breakfast ($P < .05$), and before the evening meal ($P < .01$).

The percentage of all recorded individual outpatient plasma glucose values <2.5 mmol/L was not significantly different

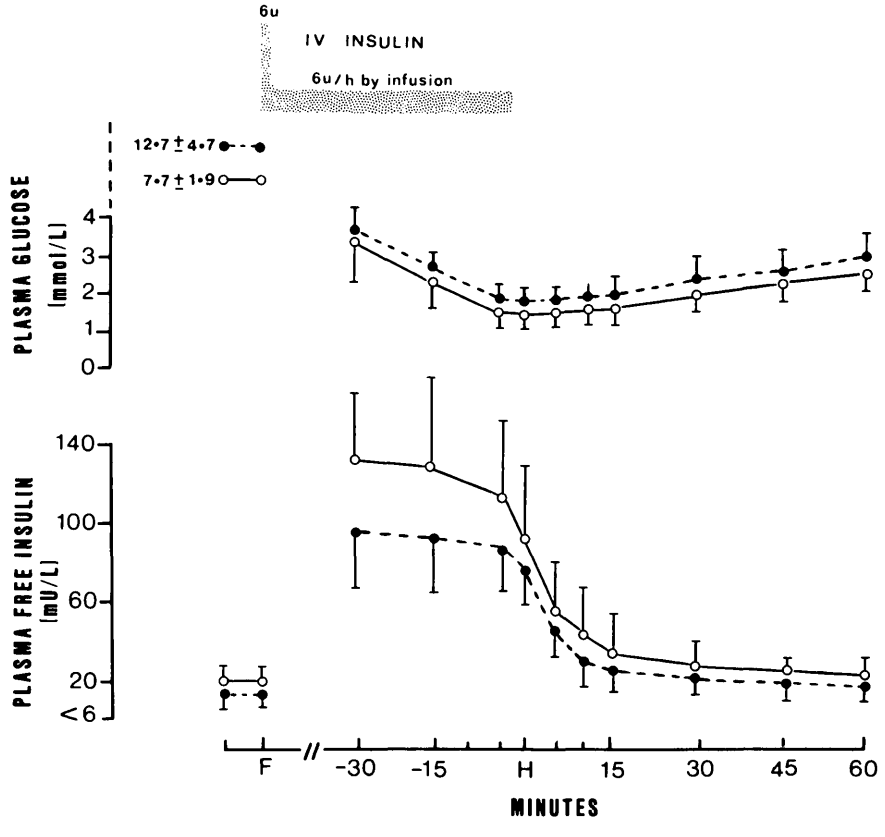

FIG. 3. Mean ± SD plasma glucose and free-insulin concentrations before and during recovery from induced hypoglycemia. After CSII, o——o; after CIT, ●-----●. H, time of reported symptomatic hypoglycemia; F, fasting levels before insulin infusion. Note: because time taken to achieve hypoglycemia varied between patients, complete data (N = 11) are shown for only the 30 min preceding hypoglycemia and at baseline (fasting).

TABLE 2
Symptoms reported by patients as signaling definite hypoglycemia during intravenous insulin infusion after CSII or CIT

Case no.	Symptoms	
	CSII	CIT
1	Impaired concentration, sweating	Hunger, sleepiness, sweating
2	Impaired concentration, hunger, sweating*	Dizziness, drowsiness, sweating
3	Hunger, drowsiness, sweating	Hunger, palpitations, dizziness, sweating
4	Hunger, palpitations, drowsiness, sweating	Hunger, palpitations, sweating, muscle twitching
5	Sleepiness	Drowsiness, sweating
6	Headache, drowsiness, palpitations, sweating	Sleepiness, palpitations, sweating
7	Drowsiness, sweating	Hunger, light-headedness, sweating
8	Drowsiness	Drowsiness, sweating*
9	Muscle twitching, palpitations, drowsiness	Muscle twitching, hunger, drowsiness
10	Hunger, weakness	Hunger, drowsiness, sweating*
11	Dizziness, impaired concentration	Headache, hunger, palpitations, blurred vision

*Sweating detected by physician within 10 min of symptomatic hypoglycemia but not reported by patients.

during CSII and CIT (mean and range 5.9 and 0–12.2%, 4.8 and 0–9.7%, respectively). Although patients were instructed to obtain a blood sample during episodes of symptomatic hypoglycemia at home, few did so during moderate hypoglycemia; therefore, these profiles do not include values of hypoglycemia occurring at times not included in the weekly profile. No patient experienced severe hypoglycemia requiring i.v. glucose or parenteral glucagon administration.

Symptomatic hypoglycemia at home. Figure 2 shows the frequency of reported symptomatic moderate hypoglycemia in each patient during CSII and CIT. There was no significant difference in the frequency of symptomatic hypoglycemia on the two regimens for the entire group of patients. However, for the five patients who reported the highest frequency of symptoms during CIT (>4 episodes/2 mo), there was a mean reduction of 57% in the number of hypoglycemic episodes on CSII compared with CIT (mean and range 5.8 and 4.0–10, 13.6 and 7.0–21 episodes/2 mo, respectively, $P < .02$).

Induced hypoglycemia. During hypoglycemia deliberately induced by i.v. infusion of insulin, there was no significant difference in the plasma glucose concentration at which symptomatic hypoglycemia was recognized by the patients after either CSII or CIT (Figure 3). Table 2 shows the symptoms that the patients reported as signaling definite hypoglycemia on each regimen. There was also no significant difference in the rate of fall of plasma glucose concentrations during the 40 min preceding hypoglycemia (0.090 and 0.047–0.14 $mmol \cdot L^{-1} \cdot min^{-1}$, 0.072 and 0.042–0.13 $mmol \cdot L^{-1} \cdot min^{-1}$; mean and range, CSII vs. CIT). The time taken to reach hypoglycemia was 109 ± 56 min (CIT) and 55 ± 15 min (CSII).

Figure 3 also shows that the spontaneous rate of plasma glucose recovery after hypoglycemia was low for both treatment regimens. There was no significant difference in plasma glucose values at any time point for either the CSII or CIT groups. In addition, the change in plasma glucose concentration between the time of hypoglycemia and the termination of the experiment was not significantly different after CSII or CIT (mean and range 1.15 and 0.5–2.3 mmol/L, 1.34 and 0.5–3.1 mmol/L, respectively). Plasma free-insulin concentrations were also similar (NS) at the time of hypoglycemia and did not differ between CSII and CIT at any time point during recovery (Figure 3).

Figure 4 shows the mean ± SD plasma concentrations of growth hormone, cortisol, glucagon, epinephrine, and norepinephrine at baseline and at the time of and during recovery from hypoglycemia. Again, there was no significant difference between CSII and CIT regimens at any time point.

Autonomic nervous system function tests. No patient had abnormal autonomic nervous system function tests during CSII or CIT. The range of systolic blood pressure changes on standing was −6 to +9 mmHg (CSII) and −5 to +30 mmHg (CIT). A fall of >30 mmHg was considered abnormal.

The change in heart rate on deep breathing was 15–29 and 14–38 beats/min (CSII vs. CIT). A variation of <10 beats/min was considered abnormal.

DISCUSSION

This study shows that the frequency of biochemical hypoglycemia (arbitrarily, a plasma glucose concentration <2.5 mmol/L) and the frequency and severity of recorded symptoms of hypoglycemia were not increased during outpatient treatment by CSII compared with CIT, despite a significant reduction of overall plasma glucose concentrations during pump therapy. Moreover, in the patients reporting frequent hypoglycemic episodes (>4/2 mo during CIT), the number of such symptomatic attacks was more than halved during CSII. However, one must interpret the latter finding with caution because of the small number of patients and the failure to detect differences in hypoglycemia for the entire group. It may indicate that in the subgroup of five patients there was a marked change in the perception of hypoglycemia by the brain.

Hypoglycemia is a well-recognized and ever-present risk of CIT. For example, hypoglycemic coma occurred in 10% of the insulin-treated patients in the 8-mo prospective study of Barnett et al.,[16] and 200 severe hypoglycemic episodes requiring hospital treatment were recorded in 130 insulin-treated diabetic patients in a 12-mo prospective study in the Nottingham area.[17] In a retrospective study, Goldgewicht et al.[18] noted at least one episode of severe hypoglycemia in the previous 1-yr period in 26% of insulin-treated patients. Hy-

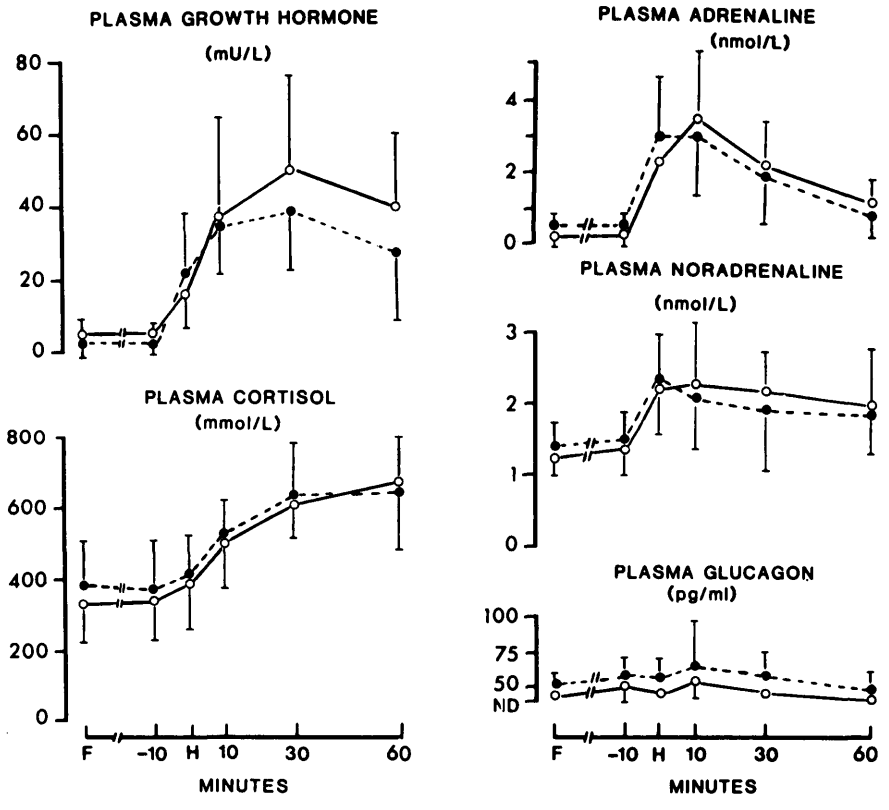

FIG. 4. Mean ± SD plasma growth hormone, cortisol, epinephrine, norepinephrine, and glucagon levels during and after induced hypoglycemia. After CSII, o——o; after CIT, ●-----●. ND, not detectable; H, time of reported hypoglycemia; F, fasting sample.

poglycemia was the cause of death in 4% of diabetic patients who died at <50 yr of age in England and Wales in 1979.[19]

Several uncontrolled case studies of severe hypoglycemia during CSII have been reported recently,[20,21] and the potential risks of intensified insulin regimens have been discussed,[2] with particular reference to the hazards of striving to improve control in patients with already impaired counterregulatory hormone responses to hypoglycemia or of changing insulin requirements throughout the 24 h (the "dawn phenomenon"[3-5]). However, the study of Teutsch et al.[22] indicates that mortality from hypoglycemia or other causes in 3500 CSII-treated patients in the United States was not greater than the number expected by comparison with the separate study of Tunbridge,[19] concerning deaths in patients on injection treatment, and that hypoglycemic episodes decreased in about four times the number of patients that reported an increase. Also, in a recent retrospective review of all patients at Guy's Hospital who underwent outpatient CSII for >6 mo (N = 40), the frequency of hypoglycemic coma in patients on CSII was less than one-third that of a closely matched group of 40 injection-treated patients studied over the same period at the same hospital.[23] Therefore, the present prospective study is in accord with the view that hypoglycemia is not usually increased during pump therapy. Moreover, we were unable to confirm the recent report of Chisholm et al.,[24] which found an increased rate of fall of blood glucose concentrations in the period preceding induced hypoglycemia in patients treated with CSII.

There are conflicting reports on the influence of CSII-induced strict control on the counterregulatory hormone responses to induced hypoglycemia. In unrandomized studies, counterregulatory hormone levels have been reported as being diminished,[25] unchanged,[26] or, with respect to glucose but not hormones, increased[27] by a period of CSII. These studies differ from each other in a number of ways, including the definition of hypoglycemia (2.8 mmol/L, for example, in the study of Simonson and Sherwin,[25] in which not all patients may have experienced symptoms of hypoglycemia), the presence or absence of autonomic neuropathy in the patients, and the duration of study after hypoglycemia. It should also be noted that Bergenstal et al.[28] measured counterregulatory hormone responses to hypoglycemia in patients after 4–18 mo of CSII but did not study the patients during injection therapy.

In the present study, we found that neither the plasma glucose level at which the patients recognized hypoglycemia nor the glucose and hormonal response thereafter was significantly changed by a period of CSII. It is relevant that Bolli et al.[29] reported that, up to 9 mo, near normalization of glycemic control with an intensive insulin injection regimen failed to alter glucose counterregulation and hormonal responses after induced hypoglycemia. Therefore, it is unlikely with controlled hypoglycemia that the marked reduction in reported symptomatic hypoglycemia during outpatient CSII in the patients experiencing frequent attacks during CIT was due to a decreased glycemic threshold level for symptoms

of hypoglycemia. However, at home, the rate of fall of blood glucose levels may be slower during CSII than CIT. The influence of the rate of decline of glycemia on symptoms and responses to hypoglycemia is controversial, although some studies suggest no difference between fast and slow falls.[30,31]

A related consideration is that CIT patients received more insulin during the induction of hypoglycemia because their starting plasma glucose level was generally higher. Both the infusion rate of insulin and the absolute amount of insulin administered may, of course, influence glycemic recovery from hypoglycemia, and this possibility should be investigated.

Although the frequency of biochemical hypoglycemia during the limited number of seven-point profiles was reported to be similar during CSII and CIT, patients rarely collected a blood sample for analysis during an actual hypoglycemic attack (contrary to instruction), and it must be acknowledged that the true frequency of biochemical values <2.5 mmol/L may be different from that reported and that some episodes may have occurred at glycemic levels >2.5 mmol/L. It is also possible that a placebo mechanism may account for any reduction in hypoglycemia during CSII in these patients.

In conclusion, hypoglycemia remains a risk of intensified treatment by CSII, and careful instruction and supervision of patients must continue to be exercised. Under the conditions of this study, it did not seem that hypoglycemia was significantly more common during CSII than during CIT, and the marked symptomatic improvement during CSII may indicate pump therapy as a treatment option in this type of patient. However, periods of strict control longer than the 2 mo may have other effects on glycemic recovery and, indeed, the frequency of hypoglycemia; these possibilities require further investigation.

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