Induction of Long-term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients Is Associated With Improvement of β-Cell Function

YANBING LI, MD
WEN XU, MD
ZHIHONG LIAO, MD, PHD
BIN YAO, MD
XIAHUA CHEN, MD
ZHIMIN HUANG, MD
GUOLIANG HU, MD
JIANPING WENG, MD, PHD

OBJECTIVE — To investigate whether long-term optimal glycemic control can be achieved without medication by transient continuous subcutaneous insulin infusion (CSII) and the possible mechanisms responsible for this remission.

RESEARCH DESIGN AND METHODS — Newly diagnosed type 2 diabetic patients (n = 138, fasting glucose >11.1mmol/l) were hospitalized and treated with CSII for 2 weeks. Intravenous glucose tolerance tests (IVGTTs) were performed, and blood glucose, HbA_{1c}, lipid profiles, proinsulin, insulin, and C-peptide were measured before and after CSII. Patients were followed longitudinally on diet alone after withdrawal of insulin.

RESULTS — Optimal glycemic control was achieved within 6.3 ± 3.9 days by CSII in 126 patients. The remission rates (percentages maintaining near euglycemia) at the third, sixth, twelfth, and twenty-fourth month were 72.6, 67.0, 47.1, and 42.3%, respectively. Patients who maintained glycemic control >12 months (remission group) had greater recovery of β-cell function than those who did not (nonremission group) when assessed immediately after CSII. Homeostasis model assessment of β-cell function (HOMA-B) and the area under the curve (AUC) of insulin during IVGTT were higher in the remission group (145.4 ± 89.6 vs. 78.5 ± 68.5, P = 0.002, and 1,423.4 ± 523.2 vs. 1,159.5 ± 476.8 pmol · l^{-1} · min^{-1}, P = 0.044). Change in acute insulin response was also greater in the remission group than that in the nonremission group (621.8 ± 430.4 vs. 387.3 ± 428.8 pmol · l^{-1} · min^{-1}, P = 0.033).

CONCLUSIONS — Short-term intensive insulin therapy can induce long-term glycemic control in newly diagnosed type 2 diabetic patients with severe hyperglycemia. The improvement of β-cell function, especially the restoration of first-phase insulin secretion, could be responsible for the remission.

Diabetes Care 27:2597–2602, 2004

β-Cell dysfunction and decreased insulin sensitivity are the main pathophysiological defects responsible for the development of hyperglycemia (1). With continuous presence of insulin resistance, progressive loss of β-cell function is the crucial defect. The continuous decline in β-cell function is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis (2). The vicious cycle of elevated glucose further impairs and possibly destroys β-cells, finally stopping insulin production completely (3). Therefore, optimal metabolic control, especially early intensive glycemic control, plays a role in the prevention of progressive β-cell dysfunction and worsening of diabetes. Many reports have shown (4–6) that induction of normoglycemia in type 2 diabetes resulted in both improved β-cell function and insulin resistance. Ryan, Imes, and Wallace (7) recently reported that, in severe newly diagnosed type 2 diabetic patients, a 2- to 3-weeks' course of intensive insulin therapy by multiple daily insulin injection could successfully lay a foundation for prolonged good glycemic control. So the potential benefits of early, aggressive intervention with insulin treatment to counter both β-cell dysfunction and insulin resistance must be considered.

Our previous (8,9) and Zhu et al.'s (10) studies showed that 2 weeks' continuous subcutaneous insulin infusion (CSII) could induce adequate glycemic control accompanied with improvement of β-cell function in newly diagnosed type 2 diabetic patients with severe hyperglycemia. We therefore designed this prospective study in consecutive newly diagnosed type 2 diabetic patients to investigate whether long-term optimal glycemic control can be achieved without medication by transient CSII treatment and the possible mechanisms responsible for the development of this remission.

RESEARCH DESIGN AND METHODS

— Consecutive newly diagnosed type 2 diabetic patients with severe fasting hyperglycemia (>11.1 mmol/l) were recruited. The patients with acute and severe chronic complications were excluded. Patients receiving antidiabetic treatment before the study, having

From the Department of Endocrinology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

Address correspondence and reprint requests to Professor JianPing Weng, Department of Endocrinology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China 510080. E-mail: gzwengjp@pub.guangzhou.gd.cn.

Received for publication 28 June 2004 and accepted in revised form 17 August 2004.

Abbreviations: AIR, acute insulin response; AUC, area under the curve; CSII, continuous subcutaneous insulin infusion; FBG, fasting blood glucose; FFA, free fatty acid; FPG, fasting plasma glucose; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, HOMA of insulin resistance; IVGTT, intravenous glucose tolerance test; PPG, postprandial plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

other diseases, or taking pharmacologic agents known to affect carbohydrate homeostasis were also excluded. A total of 138 patients (88 men and 50 women), aged 48.9 ± 11.8 years (from 21 to 75 years), with BMI 25.0 ± 3.7 kg/m^2 were enrolled into the study from November 2001 to May 2004. Their fasting plasma glucose (FPG) was 13.6 ± 4.5 mmol/l, 2-h postprandial (postbreakfast) plasma glucose (PPG) 19.0 ± 6.1 mmol/l, and HbA_{1c} 10.1 ± 2.2%.

All patients were admitted to the hospital. Fasting blood samples were collected for measuring FPG, HbA_{1c}, proinsulin, free fatty acids (FFAs), and lipid profiles. Then subjects underwent intravenous glucose tolerance tests (IVGTTs) using 25 g of glucose (50 ml of 50% glucose). Serum samples were obtained before and 1, 2, 4, 6, and 10 min after injection for insulin and C-peptide determination. PPG levels were evaluated on the previous day. After completing the baseline assessment, intensive insulin treatment by CSII was initiated with an insulin pump (H-Tron Plus V100; Disetronic Medical System, Burgdorf, Switzerland). The basal and boluses of insulin infusion were adjusted according to the fasting and postprandial of three meals capillary blood glucose (fasting blood glucose [FBG] and postprandial blood glucose). Excellent blood glucose control was defined as FBG <6.1 mmol/l and postprandial blood glucose <8.0 mmol/l. After 2 weeks of CSII, insulin treatment was stopped and patients were guided with diet and physical exercise only. The initial investigations were repeated on the following day at least 15 h after insulin cessation. No antidiabetic agents or antihyperlipidemic agents were used during the CSII.

After discharge from the hospital, patients were scheduled to visit the hospital every 3 months (every month for the first 3 months). FPG and PPG were measured at each clinical visit. Dietary and exercise instructions were reinforced at each time. Patients were encouraged to contact the medical staff with intercurrent problems. A hyperglycemic relapse was defined as either FPG >7.0 mmol/l or PPG >10.0 mmol/l, which was confirmed on another weekday.

All patients participated in diabetes education programs during hospitalization and gave written informed consent before treatment. The study was approved by the Medical Research and Ethics Committee of Sun Yat-Sen University.

Plasma glucose levels were determined by an enzymatic colorimetric test. Radioimmunoassay was used for measurement of insulin (Diagnostic Products, Los Angeles, CA), proinsulin (Linco Research, St. Charles, MO), and C-peptide (Diagnostic Products). HbA_{1c} was assayed using microcolumn (Variant II; Bio-Rad, Hercules, CA). FFA levels were determined enzymatically using a Wako NEFA C test kit (Wako Chemicals, Dallas, TX). Total cholesterol and triglycerides were assayed by enzymatic colorimetric test with lipid clearing factor. HDL and LDL were measured enzymatically by direct method.

The area under the curve (AUC) of insulin and C-peptide and acute insulin response (AIR) during IVGTT were used to evaluate the first-phase insulin secretion of β-cell. AUCs of insulin and C-peptide were calculated using trapezoidal estimation. AIR represented the incremental area above baseline over the 10 min. Homeostasis model assessment (11) was used to estimate insulin resistance (HOMA-IR) and β-cell function (HOMA-B). HOMA-IR = FPG × fasting insulin/22.5. HOMA-B = 20 × fasting insulin/(FPG − 3.5). Paired-samples *t* test was used to compare BMI, glucose, HbA_{1c}, FFA, lipid profiles, AUCs of insulin and C-peptide, AIR, proinsulin, proinsulin-to-insulin ratio, HOMA-B, and HOMA-IR before and after CSII. Independent-samples *t* test was performed to compare the difference between the remission group and the nonremission group. Statistical significance was defined as $P < 0.05$. The data were described as means ± SD.

RESULTS — Twelve patients who failed to achieve excellent glycemic control on CSII within 2 weeks were considered as early therapeutic failure and excluded from further analysis. The remaining 126 patients (78 men and 48 women) were aged 48.6 ± 11.7 years, with BMIs of 25.1 ± 3.7 kg/m^2.

The effect of optimized metabolic control by transient CSII on β-cell function

Glycemic control. Before CSII, the glycemic control was poor in the 126 diabetic patients, with average FPG of 13.3 ± 4.4 mmol/l, PPG 18.7 ± 6.1 mmol/l, and HbA_{1c} 10.0 ± 2.2%. With CSII, excellent blood glucose control was achieved in 6.3 ± 3.9 days. After treatment, FPG and PPG levels were significantly reduced (13.3 ± 4.4 vs. 6.3 ± 1.3 mmol/l and 18.7 ± 6.1 vs. 8.6 ± 2.3 mmol/l, respectively; $P < 0.001$), with a maximal total daily insulin dose of 0.7 units/kg (0.25–1.58). After 2 weeks' CSII, there was a marked decrease in HbA_{1c} (from 10.0 ± 2.2 to 8.7 ± 1.9%, $P < 0.001$).

Lipid profile. Intensive treatment with CSII resulted in an improvement in all of the lipid parameters measured. Total cholesterol level decreased from 5.8 ± 1.1 to

Table 1—*Insulin and C-peptide concentrations of the patients during IVGTT in the whole group* (n = *126*)

Item/time (min)	Before CSII	After CSII	*P*
Insulin concentration (pmol/l)			
0	102.8 ± 45.9	104.8 ± 91.0	0.836
1	98.3 ± 45.8	128.3 ± 60.7	<0.001
2	100.5 ± 63.9	139.4 ± 67.1	<0.001
4	84.3 ± 40.2	126.6 ± 62.9	<0.001
6	80.7 ± 38.2	123.6 ± 63.3	<0.001
10	90.8 ± 47.3	137.7 ± 67.7	<0.001
C-peptide concentration (pmol/l)			
0	0.8 ± 0.4	0.7 ± 0.3	0.023
1	0.7 ± 0.3	0.9 ± 0.4	<0.001
2	0.7 ± 0.3	0.9 ± 0.5	<0.001
4	0.67 ± 0.3	0.8 ± 0.4	<0.001
6	0.7 ± 0.3	0.9 ± 0.4	<0.001
10	0.7 ± 0.3	1.0 ± 0.5	<0.001

Data are means ± SD.

Table 2—*Clinical characteristics in the remission and nonremission groups*

Item	Remission	Nonremission	*P*
n	32	36	—
Age (years)	50.6 ± 10.4	51.6 ± 13.1	0.718
BMI before CSII (kg/m^2)	25.9 ± 4.3	24.3 ± 3.1	0.069
BMI after CSII (kg/m^2)	26.0 ± 4.2	24.3 ± 3.0	0.051
HbA_{1c} before CSII (%)	10.3 ± 1.9	10.0 ± 1.9	0.647
HbA_{1c} after CSII (%)	9.2 ± 2.0	8.6 ± 1.5	0.207
FPG before CSII (mmol/l)	14.9 ± 3.0	14.7 ± 5.0	0.852
FPG after CSII (mmol/l)	6.1 ± 1.2	6.7 ± 1.1*	0.035
PPBG before CSII (mmol/l)	21.7 ± 5.1	19.7 ± 5.5	0.141
PPBG after CSII (mmol/l)	8.8 ± 2.2	9.9 ± 2.4	0.064
Duration to achieve glycemic control (days)	8.5 ± 3.1	8.8 ± 3.9	0.757
Maximal total daily insulin dose to achieve glycemic control (units/kg)	0.7 ± 0.2	0.7 ± 0.2	0.744
LnHOMA-IR before CSII †	2.3 ± 0.5	2.1 ± 0.5	0.117
LnHOMA-IR after CSII †	1.3 ± 0.5	1.2 ± 0.5	0.456
LnHOMA-B before CSII †	3.3 ± 0.6	3.2 ± 0.5	0.631
LnHOMA-B after CSII †	4.8 ± 0.6	4.4 ± 0.7*	0.002
AUC of insulin before CSII (pmol · l^{-1} · min^{-1})	834.8 ± 352.3	853.6 ± 365.4	0.837
AUC of insulin after CSII (pmol · l^{-1} · min^{-1})	1,423.4 ± 523.2	1,159.5 ± 476.8*	0.044
AUC of C-peptide before CSII (pmol · l^{-1} · min^{-1})	7.0 ± 3.2	6.3 ± 3.4	0.384
AUC of C-peptide after CSII (pmol · l^{-1} · min^{-1})	9.9 ± 4.3	7.8 ± 3.4*	0.036
AIR before CSII (pmol · l^{-1} · min^{-1})	−316.1 ± 214.9	−152.2 ± 311.2*	0.020
AIR after CSII (pmol · l^{-1} · min^{-1})	326.45 ± 413.1	255.2 ± 307.7	0.447
ΔAIR (pmol · l^{-1} · min^{-1})	621.8 ± 430.4	387.3 ± 428.8*	0.033

Data are means ± SD. *$P < 0.05$ vs. the remission group; †HOMA-IR and HOMA-B were nonnormally distributed, so the data were logarithmically transformed before analysis. PPBG, postprandial plasma blood glucose.

5.3 ± 1.0 mmol/l ($P < 0.001$) and triglycerides from 2.2 ± 1.7 to 1.5 ± 0.8 mmol/l ($P < 0.001$). LDL cholesterol decreased from 3.3 ± 1.1 to 3.0 ± 1.0 mmol/l ($P = 0.003$), while HDL cholesterol increased from 1.1 ± 0.3 to 1.2 ± 0.3 mmol/l ($P = 0.001$). A marked decrease also was observed for FFAs (from 0.6 ± 0.3 to 0.5 ± 0.2 mmol/l, $P = 0.001$).

β-Cell function. *The AIR and AUC of insulin and C-peptide.* Before CSII treatment, none of the patients had first-phase insulin secretion, and insulin secretion was inhibited by intravenous glucose stimulus. After 2 weeks' CSII, most of the patients had a partial restoration. The mean insulin concentrations at each point during IVGTT were increased, while the fasting insulin concentration remained unchanged. The AIR after CSII was significantly higher than that before CSII treatment (239.2 ± 84.9 vs. −135.6 ± 29.4 pmol · l^{-1} · min^{-1}, $P < 0.001$). The AUC of insulin and C-peptide were also elevated significantly (1,286.6 ± 594.1 vs. 892.6 ± 408.0 pmol · l^{-1} · min^{-1}, $P < 0.001$, and 8.7 ± 3.9 vs. 6.9 ± 3.2 pmol · l^{-1} · min^{-1}, $P < 0.001$, respectively). The mean insulin and C-peptide levels during IVGTT before and after CSII treatment are shown in Table 1.

HOMA-B. HOMA-B was used for evaluating β-cell function. The indexes were markedly improved after CSII (36.1 ± 25.1 before CSII versus 121.3 ± 96.3 after CSII, $P < 0.001$).

Proinsulin and proinsulin-to-insulin ratio. Proinsulin decreased from 31.2 ± 19.4 to 15.8 ± 10.0 pmol/l ($P < 0.001$), thus the proinsulin-to-insulin ratio decreased from 31.7 ± 20.2 to 16.6 ± 7.6% ($P < 0.001$).

Insulin resistance. HOMA-IR was used to evaluate the degree of insulin resistance. In the study, HOMA-IR decreased from 8.3 ± 4.1 to 4.3 ± 3.4 ($P < 0.001$).

Side effects. There were no obviously pump-related side effects, including hypoglycemia and subcutaneous infection, during 2 weeks' CSII treatment. The BMI of the patients was not changed before and after CSII (25.09 ± 3.73 vs. 25.05 ± 3.68 kg/m^2, $P = 0.513$).

Follow-up

Of the 126 patients, 113 completed at least three visits at the time this study was written. During follow-up, the remission rates (percentages of the subjects maintaining near euglycemia on diet alone) at the third, sixth, twelfth, and twenty-fourth months were 72.6% (82 of 113), 67.0% (61 of 91), 47.1% (32 of 68), and 42.3% (11 of 26), respectively. The patients who failed to maintain euglycemia were treated with either oral hypoglycemic agents or insulin based on clinical practice guidelines.

To determine patients who would most likely benefit from this treatment, we defined the patients who had long-term optimal glycemic control (>12 months) without medication as the remission group (32 of 68) and those who relapsed within 12 months as the nonremission group (36 of 68) in order to compare the differences between their clinical characteristics (Table 2).

First, there were no differences in age, BMI, FPG, PPG, HbA_{1c}, and lipid profiles between two groups at baseline. The maximal total daily insulin doses used to achieve glycemic control were not different either, but lower FPG was achieved in the remission group after CSII (6.1 ± 1.2 vs. 6.7 ± 1.1 mmol/l, $P = 0.035$). Although the insulin, C-peptide levels, and AUCs of insulin and C-peptide during IVGTT before CSII were not different between the two groups, the AUCs of insulin and C-peptide were significantly higher in the remission group after CSII (1,423.4 ± 523.2 vs. 1,159.5 ± 476.8, $P = 0.044$, for insulin, and 9.9 ± 4.3 vs. 7.8 ± 3.4 pmol · l^{-1} · min^{-1} for C-peptide, $P = 0.036$) (Fig. 1). HOMA-B in the remission group after CSII was higher than that in the nonremission group (145.4 ± 89.6 vs. 78.5 ± 68.5, $P = 0.008$). Although the AIR of the remission group was significantly lower than that of the nonremission group (−316.1 ± 214.9 vs. −152.2 ± 311.2 pmol · l^{-1} · min^{-1}, $P = 0.02$) before CSII, there was

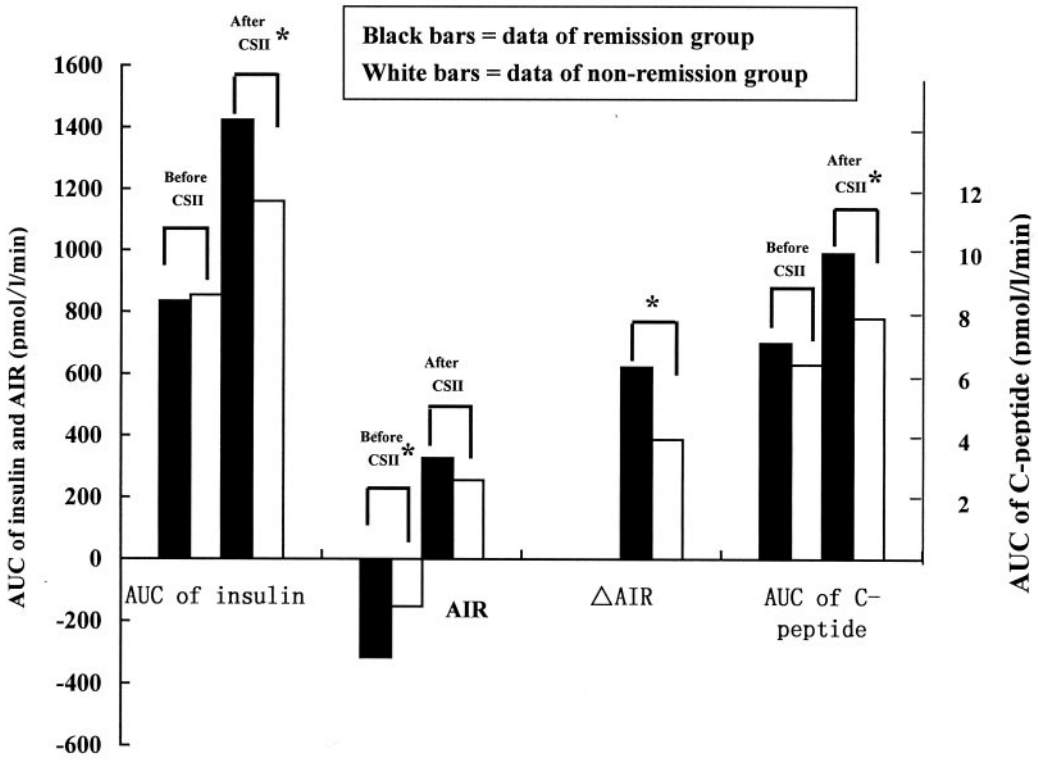

Figure 1—*The comparison of β-cell function before and after CSII between the remission* (n = *32) and nonremission* (n = *36) groups.* *$P < 0.05$.

no difference between the two groups after treatment (Fig. 1). As a result, ΔAIR (the AIR after CSII during IVGTT subtracted from that before CSII) was much greater in the remission group than that in the nonremission group (621.8 ± 430.4 vs. 387.3 ± 428.8 pmol·l^{-1}·min^{-1}, P = 0.033).

CONCLUSIONS— Our present study showed that excellent glycemic control was successfully achieved in 6.3 ± 3.9 days by CSII in newly diagnosed diabetic patients with severe hyperglycemia. FPG were reduced by 7 mmol/l, PPG by 10 mmol/l, and HbA_{1c} by 2.3%, accompanied with the great improvement of lipid profiles and lowering of FFAs without undesirable weight gain. The insulin-secretion function of β-cells, represented by the AUC of insulin or C-peptide, AIR, and HOMA-B, distinctly increased after CSII treatment. Gorden, Hendricks, and Roth (12) hypothesized that in severe, poorly controlled, type 2 diabetic patients, the diseased β-cell was forced to secrete immature granules, in which the conversion of proinsulin to insulin was incomplete. In our study, the concentration of proinsulin and the proinsulin-to-insulin ratio were greatly reduced after CSII treatment, indicating that once hyperglycemia was corrected, the β-cell stress was diminished. Therefore, both quantitatively and qualitatively, improvement of glucose-stimulated insulin secretion was associated with the relief of hyperglycemia.

Glucose toxicity has been demonstrated clinically and has been investigated extensively in the laboratory. A blunted first-phase insulin secretion can been seen in subjects with FBG ≥5.6 mmol/l and is virtually absent when FBG is ≥6.4 mmol/l (13). In Pima Indians, impaired first-phase insulin secretion was an independent and additive predictor of the progression from normal glucose tolerance to impaired glucose tolerance and to overt diabetes (14). Glucotoxicity hampers first-phase insulin secretion (15), leading to decreased second-phase insulin secretion and perhaps increased β-cell apoptosis chronically. Thus, the shorter the period of antecedent glucotoxicity, the more likely the full recovery of β-cell function (16). Our results showed that rapid correction of hyperglycemia could greatly improve β-cell function, especially in partially recovering first-phase insulin secretion. The lowering of FFAs and triglycerides, indicating the ease of lipolysis, might also contribute to the improvement of β-cell function and insulin resistance. Therefore it is rational to think that new-onset patients will derive more benefit from treatment because of the shorter period of antecedent glucotoxicity and lipotoxicity, hinting at the reversible function of β-cells and that euglycemia can be maintained for a prolonged period of time.

The present prospective study on a relatively large number of patients showed that most patients can develop normoglycemic or near normoglycemic remission on diet alone following the initial period of excellent glycemic control by 2 weeks' CSII. The remission rates at the third, sixth, twelfth, and twenty-fourth month after CSII were 72.6, 67.0, 47.1, and 42.3%, respectively. In 1997, Ilkova et al. (17) did a similar study in 13 newly diagnosed type 2 diabetic patients with less severe hyperglycemia (mean FPG 11.8 mmol/l) and found that remission of hyperglycemia can be induced in 9 of 13 (69.2%) patients for >6 months. But that study (17) merely focused on glycemic control and did not investigate the mechanisms responsible for it. McFarlane et al. (18) found in 2001 that 11 of 26 newly diagnosed African-American type 2

diabetic patients with severe hyperglycemia (mean presenting plasma glucose of 31.0 mmol/l), who were initially treated with insulin and then intensive pharmacological agents (most remained on insulin treatment), developed near-normoglycemic remission for 248–479 days. The remission was associated with a greater recovery of oral glucose-stimulated insulin secretion. Recently, Ryan, Imes, and Wallace (7) reported that 2–3 weeks of intensive insulin therapy with multiple daily injection could maintain glycemic control on diet alone for 1 year in 7 of 16 (43.8%) newly diagnosed type 2 diabetic patients. The ease with which normoglycemia was achieved on insulin treatment might predict those who may later succeed in controlling blood glucose on diet alone.

To identify those who would gain prolonged good glycemic control, we compared the clinical characteristics and laboratory parameters between subjects in the remission group and the nonremission group. We found that there were no differences in age, BMI, PPG, HbA_{1c}, and lipid profiles between the two groups before and after CSII treatment. The maximal total daily insulin doses to achieve targeted glycemic control were not different either. The remission group achieved lower FPG, concomitant with higher HOMA-B and greater improvement in the AUC of insulin and C-peptide after CSII treatment. Of particular importance, we found that there was significant difference in the restoration of AIR between the two groups. Although the AIR before CSII of the remission group was weaker than that of the nonremission group, which meant that the higher suppression of β-cell function at baseline in the remission group was caused by glucotoxicity, ΔAIR (representing the improvement of the AIR) was markedly greater in the remission group than in the nonremission group. When comparing subjects who maintained euglycemia with those who did not at the third and sixth months, the differences remained (data not shown). It is well recognized that impaired first-phase insulin secretion is an early marker of β-cell dysfunction, appearing long before significant changes in absolute glucose concentrations, much like that observed during the beginning stages of impaired glucose tolerance or gestational diabetes (19,20). Recovery of first-phase insulin secretion could even partially be very helpful in maintaining prolonged near normoglycemia. Based on our results, we considered that better glycemic control and greater improvement of β-cell function, especially partial restoration of AIR, could be responsible for the long-term euglycemia.

In the natural course of type 2 diabetes, the progressive worsening of β-cell function mainly affected by uncontrolled hyperglycemia is accountable for the loss of efficacy of oral hypoglycemic agents over time. The U.K. Prospective Diabetes Study found that 3 years after the diagnosis of diabetes, ~50% of the patients treated with monotherapy did not achieve targeted glycemic control (21). But the study by Della Casa et al. (22) showed that it was conceivable that sulfonylurea therapy, when initiated in near-normoglycemic patients with "rested" β-cells induced by CSII, might have an augmented therapeutic effect lasting for a considerably long period of time. It is exciting to find that high remission rates in our newly diagnosed type 2 diabetic patients treated by 2 weeks' CSII were associated with the improvement of β-cell function. These patients were regarded as being in a remission stage without requiring antidiabetic agents, which was similar to the "honeymoon" in type 1 diabetic patients. It is undoubtedly true that this remission rate will decrease over time, but our study demonstrates that newly diagnosed type 2 diabetic patients with severe hyperglycemia might obtain benefits from short-term intensive insulin treatment. The recovery in insulin-secretion function raises the possibility that the natural history of type 2 diabetes, with a relentless decline in insulin secretion, may be altered by intervention with early intensive insulin treatment targeting excellent blood glucose control.

In conclusion, transient CSII can be effectively used in achieving adequate glycemic control accompanied with significant improvement of β-cell secretion in newly diagnosed type 2 diabetic patients with severe hyperglycemia. Nearly one-half of the patients can maintain euglycemia on diet only for >12 months. The present study, based on a relatively large number of patients, confirms a remission stage in newly diagnosed type 2 diabetic patients treated with short-term intensive insulin therapy and shows that the mechanism responsible for this remission could be the improvement of β-cell function, especially the partial restoration of AIR. It is unclear whether any other intervention (e.g., oral hypoglycemic agents) inducing optimal glycemic control in a short period of time can have the same effect. As a corollary, a large sample, prospective, randomized, controlled study will be needed to further prove and clarify our findings.

Acknowledgments— This study was supported by grants from the Natural Science Foundation of Guangdong Province Government (2001 and 2002).

We thank Professor Linong Ji from the People's Hospital of Beijing University for his suggestions in the initiation of this study. We appreciate Dr. Mary Ann Banerji from State University of New York (SUNY) Health Science Center at Brooklyn in New York for her kind help in the revision and fluency of this manuscript. We thank all of the nurses and technicians in the clinic and laboratory: Jiyan Wu, Shenlan Deng, Xiaojuan Zhao, Yonghong Yuan, Xiangzhong Ou, Ying Liao, Shaomei Hu, Yibin Xiao, and especially head nurse Wanping Deng for their excellent work. We also thank all of the subjects involved for their dedication to the study.

This work was presented in part at the American Diabetes Association 64th Annual Meeting, 7 June 2004, Orlando, Florida, and also presented at the 40th European Association for the Study of Diabetes (EASD) Annual Meeting, which was held from 5–9 September 2004 in Munich, Germany.

References

1. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. *Am J Med* 90:229–235, 1991
2. Robertson RP, Harmon J, Tran PO, Poitout V: β-Cell glucotoxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 53 (Suppl. 1):S119–S124, 2004
3. Yki-Jarvinen H: Glucose toxicity. *Endocr Rev* 13:415–431, 1992
4. Samanta A, Burden AC, Jones GR, Clarkson L: The effect of short-term intensive insulin therapy in non-insulin-dependent diabetes who had failed on sulphonylurea therapy. *Diabetes Res* 3:269–271, 1986
5. Yki-Jarvinen H, Esko N, Eero H, Taskmo MR: Clinical benefits and mechanisms of sustained response to intermittent insulin therapy in type 2 diabetic patients with secondary drug failure. *Am J Med* 84:185–192, 1988
6. Glaser B, Leibovich G, Nesher R, Hartling S, Binder C, Cerasi E: improved beta-cell function after intensive insulin treatment

in severe non-insulin-dependent diabetes. *Acta Endocrinol* 118:365–373, 1988
7. Ryan EA, Imes S, Wallace C: Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 27: 1028–1032, 2004
8. Li Y, Xu W, Liao Z, Yao B, Huang Z, Weng J: The effect of continuous subcutaneous insulin infusion (CSII) on glucose metabolism and induction of long-term glycemic control in newly diagnosed type 2 diabetic patients (Abstract). *Diabetes* 53 (Suppl. 2):A112, 2004
9. Weng J, Li Y, Xu W, Chen X, Liao Z, Yao B, Deng W, Ou X, Hu G: The effect of short-term continuous subcutaneous insulin infusion treatment on beta-cell function in newly diagnosed type 2 diabetic patients. *Chinese Journal of Diabetes* 11:10–15, 2003
10. Zhu F, Ji L, Han X, Zhu Y, Zhang H, Zhou X, Chen J, Cai X, Zhang M: Induction of long-tern glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Chinese Journal of Diabetes* 11:5–9, 2003
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412–419, 1985
12. Gorden P, Hendricks CM, Roth J: Circulating proinsulin-like component in man: increased proportion in hypoinsulinemia state *Diabetologia* 10:469–474, 1974
13. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 42:222–229, 1976
14. Weyer C, Tataranni PA, Bogardus C, Pratley RE: Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care* 24:89–94, 2001
15. Leahy JL, Bonner-Weir S, Weir GC: β-Cell dysfunction induced by chronic hyperglycemia: current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care* 15:442–455, 1992
16. Gleason CE, Gonzalez M, Harmon JS, Robertson RP: Determinants of glucotoxicity and its reversibility in the pancreatic islet beta-cell line, HIT-T15. *Am J Physiol Endocrinol Metab* 279:E997–E1002, 2000
17. Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 20:1353–1356, 1997
18. McFarlane SI, Chaiken RL, Hirsch S, Harrington P, Lebovitz HE, Banerji MA: Near-normoglycaemic remission in African-Americans with type 2 diabetes mellitus is associated with recovery of beta cell function. *Diabet Med* 18:10–16, 2001
19. Byrne MM, Sturis J, Sobel RJ, Polonsky KS: Elevated plasma glucose 2 h postchallenge predicts defects in beta-cell function. *Am J Physi* 270:E572–E579, 1996
20. Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J: Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes* 44:506–512, 1995
21. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 281: 2005–2012, 1999
22. Della Casa L, del Rio G, Glaser B, Cerasi E: Effect of 6-month gliclazide treatment on insulin release and sensitivity to endogenous insulin in NIDDM: role of initial continuous subcutaneous insulin infusion-induced normoglycemia. *Am J Med* 90 (Suppl. 6A):37S–45S, 1991