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RESEARCH ARTICLE

Improvement of β-cell function after achievement of optimal glycaemic control via long-term continuous subcutaneous insulin infusion therapy in non-newly diagnosed type 2 diabetic patients with suboptimal glycaemic control

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Abstract

Background Achieving euglycaemia by continuous subcutaneous insulin infusion (CSII) therapy alone has been shown to restore β-cell function in patients with newly diagnosed type 2 diabetes. However, the efficacy has not been evaluated in patients with non-newly diagnosed type 2 diabetes and suboptimal glycaemic control.

Methods Of the 1220 patients with type 2 diabetes who began CSII therapy from March 2000 to March 2007, we retrospectively selected patients using the following inclusion criteria: glycosylated haemoglobin (HbA_{1c}) ≥ 7.0%, diabetes duration ≥ 1 year before CSII therapy, and duration of CSII therapy ≥ 6 months. We evaluated sequential changes in HbA_{1c} and serum C-peptide levels measured at a 6- to 12-month intervals during CSII therapy.

Results In the 521 subjects included in this study [median diabetes duration 10 years; interquartile range (IQR) 6.0–17.0; CSII therapy ≤30 months], median HbA_{1c} decreased from 8.7% (IQR 7.7–10.0) at baseline to 6.3% (IQR 5.9–6.9) after 6 months of CSII therapy ($p < 0.0001$). During the subsequent 24 months, median HbA_{1c} levels were maintained between 6.3% and 6.5% ($p < 0.0001$ for all time points *vs* baseline). At 12 months after CSII therapy, median C-peptide levels began to increase compared with baseline (fasting level 23% increase, $p < 0.0001$; 2-h postprandial level 26% increase, $p = 0.022$), and the increase was maintained at 30 months (fasting level 39%; 2-h postprandial level 53%; $p < 0.0001$ for all *vs* baseline).

Conclusions β-Cell function was significantly improved in patients with non-newly diagnosed and suboptimally controlled type 2 diabetes after achieving and maintaining optimal glycaemic control with long-term CSII therapy alone.

Keywords β-cell function; C-peptide; CSII; HbA_{1c}; type 2 diabetes

Abbreviations CSII, continuous subcutaneous insulin infusion; IQR, interquartile range; M_BMI, posttreatment mean body mass index; M_Cpep, posttreatment mean serum C-peptide; M_CpepF, posttreatment mean

fasting serum C-peptide; M_CpepPP2, posttreatment mean 2-h postprandial serum C-peptide; M_HbA_{1c}, posttreatment mean serum HbA_{1c}; TDD, total daily dose of insulin; TG, triglyceride

Introduction

In patients with type 2 diabetes, glycaemic control and β-cell function progressively deteriorate over time [1,2]. Results of trials testing the efficacy of available pharmaceutical interventions suggest that it is difficult to achieve and maintain the glycosylated haemoglobin (HbA_{1c}) target of ≤6.5% and improve β-cell function in patients with type 2 diabetes [3–8].

However, several recent studies of patients with newly diagnosed type 2 diabetes have demonstrated that normoglycaemia or even long-term remission can be achieved with short-term early intensive insulin therapy using CSII or multiple daily injections [9–12]. Restoration of β-cell function has been reported as the mechanism underlying this effect [9,11,12]. We previously reported that long-term CSII therapy achieved normoglycaemia and induced remission in 31 patients (mean diabetes duration 3.3 ± 2.7 years) of a total of 91 patients with type 2 diabetes (mean diabetes duration 7.2 ± 4.9 years) [13].

Taken together, these findings suggest that β-cell function may be restored in patients with newly or recently diagnosed type 2 diabetes as long as optimal glycaemic control is achieved and maintained by early intensive insulin therapy. However, few studies have been conducted to determine whether optimal glycaemic control and improved β-cell function can be achieved by intensive insulin therapy in patients with non-newly diagnosed type 2 diabetes. Therefore, in this study, we examined whether a target HbA_{1c} of ≤6.5% can be achieved and maintained and β-cell function improved by long-term CSII therapy alone in patients with non-newly diagnosed type 2 diabetes (duration of diabetes ≥1 year), especially in patients with suboptimal glycaemic control (HbA_{1c} ≥7.0%) on other therapeutic modalities before CSII therapy.

Materials and methods

Subjects and study design

We selected subjects among the Korean patients with type 2 diabetes admitted for CSII therapy from March 2000 to March 2007 at the Diabetes Center at the Konkuk University Hospital and the Yangjae Diabetes Clinic, South Korea. Inclusion criteria were HbA_{1c} level of ≥7% despite previous treatment, duration of diabetes of ≥1 year, absence of significant renal impairment (serum creatinine ≤1.5 mg/dL) before CSII therapy, and available follow-up data for at least 6 months after initiation of CSII therapy. We retrospectively analysed sequential changes in HbA_{1c} levels during CSII therapy and the proportion of patients who achieved the HbA_{1c} goal of ≤6.5%. We also analysed sequential changes in serum C-peptide levels as a marker for β-cell function (i.e. endogenous insulin biosynthesis and secretion) [14].

In addition, we evaluated M_Cpep levels, taking into account all observations recorded for a patient during the duration of CSII therapy. Patients were divided into two groups on the basis of glycaemic control: good glycaemic control was defined as M_HbA_{1c} during the duration of CSII therapy of ≤6.5%, and poor glycaemic control was defined as M_HbA_{1c} of ≥8.0%. To determine whether improvement in β-cell function was associated with glycaemic control, M_Cpep levels of the two patient groups were compared. We also compared posttreatment mean values of other biochemical parameters with baseline values and between the two patient groups. All protocols were approved by the institutional review board of Konkuk University Hospital.

Most patients were admitted for 1–2 weeks to learn appropriate diet and exercise and how to use the insulin pumps (Dana insulin pump, Sooil Development Co., Seoul, Korea) and deal with hypoglycaemia during CSII therapy. Medications for glycaemic and lipidemic control were discontinued on admission. CSII therapy was initiated using the rapid-acting insulin analogues insulin aspart (NovoRapid®, Novo Nordisk, Bagsværd, Denmark) or insulin lispro (Humalog®, Eli Lilly, Indianapolis, IN, USA). Strategies to adjust insulin doses with insulin pumps were published previously [15,16]. Briefly, patients received a bolus of insulin (2–4 U) no more than 15 min before each meal, and the initial basal rate was set at 2–4 U/day. Blood glucose levels were measured seven times a day by finger-prick tests before and 2 h after all three meals and at bedtime. We adjusted bolus and basal insulin doses by trial and error every day or every other day on the basis of blood glucose levels to achieve normoglycaemia [preprandial glucose level 4.5–5.6 mmol/L; 2-h postprandial (PP2) glucose level 5.6–6.7 mmol/L]. During this period, patients were served a balanced diet (three meals per day with no regular snacks) composed of 65% carbohydrates, 15% protein, and 20% fat by calories (female patients, 2000 kcal/day; male patients, 2400 kcal/day). Mild to moderate exercise for at least 30 min after each meal was highly recommended, but patients were instructed to avoid exercise before breakfast to prevent fasting hypoglycaemia. We instructed the patients to eat and exercise regularly and to monitor their blood glucose levels seven times a day for

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at least 6 months after discharge until they understood how their glycaemic control with a given insulin dose was affected by the types and amounts of foods consumed, physical activity, emotional stress, and other medical conditions.

Before and during CSII therapy, blood specimens were collected after overnight (12-h) fasting and 2-h after consuming a mixed meal composed of 65% carbohydrates, 15% protein, and 20% fat by calories. Intervals for collecting blood specimens during routine check-ups were 6–12 months (at least 12-h after the patient had removed the insulin pump).

The HbA_{1c} level was determined by high-performance liquid chromatography (HA-8160 HbA_{1c} Analyser, Arkray Inc., Kyoto, Japan), and serum C-peptide concentrations were quantified by electrochemiluminescence immunoassays (Roche/Hitachi Modular analytics, Roche Diagnostic GmbH, Mannheim, Germany). Levels of plasma glucose, serum albumin, TG, and low-density lipoprotein cholesterol were measured with an automated analyser (TBA-200 FR NEO, Toshiba Medical Systems Corporation, Tochigi, Japan). High-density lipoprotein (HDL) cholesterol was quantified using a polyethylene glycol precipitation kit (Young Dong, Seoul, Korea) combined with the cholesterol oxidase method for cholesterol measurement. Haemoglobin levels were determined by using flow cytometry (XE-2100, Sysmex, Kobe, Japan). All biochemical analyses other than PP2 serum C-peptide levels were performed with fasting blood samples.

Statistical analysis

Our sample size was calculated to have >90% power to detect significant differences in HbA_{1c} level as a primary endpoint (alpha = 0.05). Normally distributed variables are expressed as mean ± standard deviation, and non-normally distributed variables as median (IQR). Non-normally distributed variables at baseline and after CSII therapy were compared by Wilcoxon signed rank test. Significant sequential changes in variables were compared with baseline values by paired *t*-test for normally distributed variables or the Holm–Sidak test for non-normally distributed variables. Variables were compared between patient groups (good glycaemic control *vs* poor glycaemic control) after CSII therapy by the Mann–Whitney *U*-test for non-normally distributed variables or unpaired *t*-test for normally distributed variables. Stepwise multiple linear regression analysis was performed to identify variables independently associated with PP2 serum C-peptide. A two-sided *p*-value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, USA) and SigmaPlot version 11 (Systat Software Inc., San Jose, USA).

Results

Of the 1220 patients screened, 521 matched our inclusion criteria (Figure 1). Table 1 shows their clinical and biochemical characteristics at baseline and after long-term CSII therapy (median follow-up, 24 months [IQR 12.0–30.0]). The findings after CSII therapy presented in Table 1 were median values of the individual patients' mean clinical and biochemical values during the entire follow-up period. Most patients (94%) had received other treatments before CSII therapy (Table 1). Diabetic complications at baseline were neuropathy (47%), retinopathy (26%), nephropathy (6%), cardiovascular disease (8%), stroke (8%), and diabetic foot ulcers (2%).

We found that median HbA_{1c} decreased from 8.7% (IQR 7.7–10.0) at baseline to 6.3% (IQR 5.9–6.9) after 6 months of CSII therapy ($p < 0.0001$). Median HbA_{1c} levels were maintained between 6.3% and 6.5% during the subsequent period of CSII therapy (Figure 2A, $p < 0.0001$ for all time points *vs* baseline). Compared with baseline, median M_HbA_{1c} was decreased to 6.5% (IQR 6.0–7.3) after long-term CSII therapy (Table 1, $p < 0.0001$).

The proportion of patients achieving the HbA_{1c} target of ≤6.5% increased from 0% at baseline to 63.7% after 6 months of CSII therapy. During the subsequent period of CSII therapy, 52.4–60.1% of patients achieved HbA_{1c} of ≤6.5% at each time point (Figure 2B). At baseline, 69.9% of patients had poor glycaemic control (HbA_{1c} ≥8.0%), but this percentage decreased to 6.3% after 6 months of CSII therapy and was between 12.7% and 14.8% during the subsequent period of CSII therapy (Figure 2B).

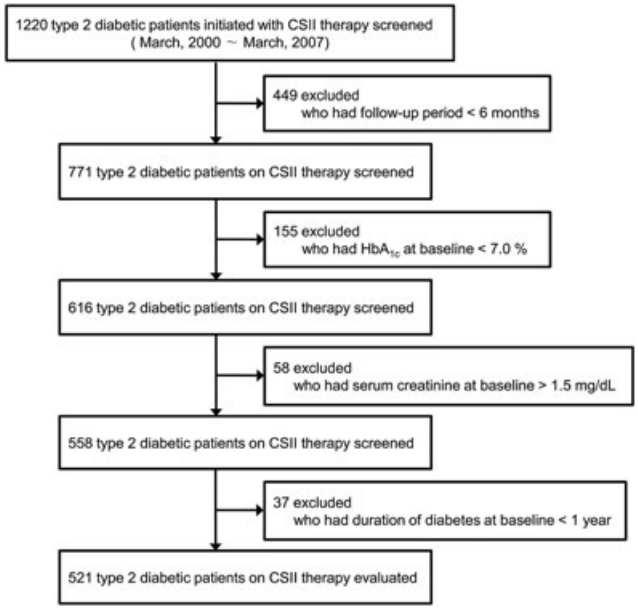

Figure 1. Selection of study participants. CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycosylated haemoglobin

Table 1. Comparison of clinical and biochemical characteristics between baseline and after CSII therapy

	At baseline	After CSII[a]	*p*-value[b]
Number	521		
Men (%)	267 (51.2)		
Age (years)	60 (52–67)		
Diabetes duration (years)	10.0 (6.0–17.0)		
BMI (kg/m^2)	23.6 (21.5–25.8)	25.7 (23.5–27.4)	<0.0001
Blood pressure (mmHg)			
Systolic	130.0 (120.0–140.0)	128.3 (119.6–138.7)	0.006
Diastolic	80.0 (72.0–90.0)	72.0 (66.9–78.1)	<0.0001
HbA_{1c} (%)	8.7 (7.7–10.0)	6.5 (6.0–7.3)	<0.0001
Number of subjects			
HbA_{1c} ≤6.5% (%)	0 (0)	269 (51.6)	
HbA_{1c} ≤7.0% (%)	18 (3.5)	371 (71.2)	
HbA_{1c} ≥8.0% (%)	364 (69.9)	56 (10.7)	
Plasma glucose (mmol/L)			
Fasting	9.2 (7.1–12.1)	8.5 (7.6–10.2)	<0.0001
2-h postprandial	19.8 (16.0–23.2)	17.1 (14.4–20.2)	<0.0001
Serum C-peptide (nmol/L)			
Fasting	0.47 (0.30–0.70)	0.62 (0.44–0.85)	<0.0001
2-h postprandial	1.08 (0.62–1.73)	1.48 (0.99–1.99)	<0.0001
Serum albumin (g/dL)	4.0 (3.7–4.3)	4.3 (4.1–4.4)	<0.0001
Haemoglobin (g/dL)	13.3 (12.3–14.5)	13.5 (12.5–14.6)	0.001
Triglycerides (mmol/L)	1.25 (0.85–1.97)	1.50 (0.97–2.30)	<0.0001
HDL-C (mmol/L)	1.19 (1.01–1.40)	1.31 (1.11–1.53)	<0.0001
LDL-C (mmol/L)	2.90 (2.38–3.60)	3.06 (2.52–3.74)	0.059
Free fatty acids (mmol/L)	0.68 (0.42–0.95)	0.67 (0.48–0.85)	0.838
Previous treatment (%)			
Diet only	6.0		
OADs	65.6		
Insulin	21.9		
Combined (OADs + Insulin)	6.5		

Data are median (interquartile range) or *n* (%).
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; OADs, oral anti-diabetic drugs.
[a]Data are median (interquartile range) of posttreatment mean outcome measures calculated using all observations recoded during the entire period of CSII therapy in a patient.
[b]Wilcoxon signed rank tests between baseline and after CSII.

We evaluated serum C-peptide levels to determine whether β-cell function improved when HbA_{1c} was maintained at or below 6.5% with long-term CSII therapy. We found that the median fasting serum C-peptide level increased by 23%, from 0.47 nmol/L (IQR 0.30–0.70) at baseline to 0.58 nmol/L (IQR 0.41–0.83) after 12 months of CSII therapy ($p < 0.0001$); this increase was maintained between 39% and 41% during the subsequent period of CSII therapy (Figure 2C, $p < 0.0001$ for all time points *vs* baseline). Similarly, the median PP2 serum C-peptide level increased by 26%, from 1.08 nmol/L (IQR 0.62–1.73) at baseline to 1.36 nmol/L (IQR 0.99–1.77) after 12 months of CSII therapy ($p = 0.022$); this increase was maintained between 43% and 53% during the subsequent period of CSII therapy (Figure 2D, $p < 0.0001$ for all time points *vs* baseline). Compared with baseline, M_CpepF increased by 32% and median M_CpepPP2 by 37% after long-term CSII therapy (Table 1, $p < 0.0001$ for both).

To determine whether β-cell function was associated with glycaemic control after CSII therapy, we compared M_CpepF and M_CpepPP2 of patients with good glycaemic control (M_HbA_{1c} ≤6.5%; $n = 269$) with those of patients with poor glycaemic control (M_HbA_{1c} ≥8.0%; $n = 56$). Compared with baseline values, median M_HbA_{1c} was significantly improved by long-term CSII therapy in both patient groups ($p < 0.0001$ for both, Table 2). However, the mean M_CpepPP2 increased significantly in the good glycaemic control group compared with baseline (48%, $p = 0.017$) but not in the poor glycaemic control group (27%, $p = 0.292$). Although the median M_CpepF did not differ between patient groups, mean M_CpepPP2 was significantly higher in the group with good glycaemic control ($p < 0.0001$, Table 2).

Stepwise multiple linear regression analysis showed that baseline PP2 serum C-peptide and M_CpepF were positive independent predictors of M_CpepPP2, and M_HbA_{1c} was a negative independent predictor ($R^2 = 0.56$, $p < 0.0001$).

Compared with median baseline values, group median values of the posttreatment means for blood pressure (systolic and diastolic), plasma glucose (fasting and PP2), haemoglobin, serum albumin, and HDL cholesterol were also significantly improved after long-term CSII

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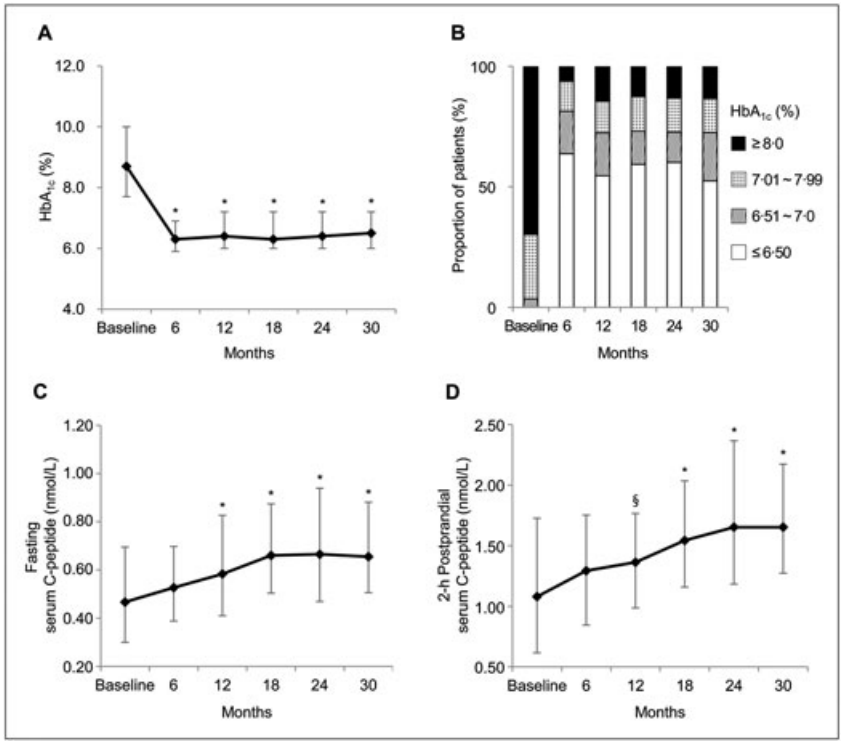

Figure 2. Changes in glycaemic level and β-cell function during long-term continuous subcutaneous insulin infusion therapy. (A) Changes in glycosylated haemoglobin (HbA_{1c}) levels; (B) changes in the proportion of patients with optimal or suboptimal glycaemic control; (C) changes in fasting serum C-peptide levels; (D) changes in 2-h postprandial serum C-peptide levels. Data are expressed as median values, and error bars indicate interquartile range. *$p < 0.0001$ or §$p = 0.022$ compared with baseline values

therapy (Table 1). In addition, group median values of the M_BMI and TG significantly increased compared with their baseline median values after long-term CSII therapy (Table 1).

Besides better glycaemic control and β-cell recovery, patients with good glycaemic control also showed improved diastolic blood pressure, serum albumin, TG, and low-density lipoprotein cholesterol after long-term CSII therapy compared with patients who had poor glycaemic control (Table 2).

Severe cases of hypoglycaemia resulting in coma or seizure did not occur during admission. Unexpected adverse events requiring hospital admission regarding the use of insulin pumps were not reported during the follow-up period.

Discussion

In the present study, we demonstrated that β-cell function represented by serum C-peptide secretion improved after achieving and maintaining optimal glycaemic control with long-term CSII therapy, even in non-newly diagnosed patients with type 2 diabetes who had previously failed to control hyperglycaemia with other treatment modalities.

The results of the UK Prospective Diabetes Study showed that β-cell function deteriorates over time in patients with type 2 diabetes; however, hyperglycaemia in that study was not corrected but increased continuously during the study period despite intensive interventions [1,2]. In contrast, we found that the target HbA_{1c} goal of ≤6.5% could be maintained in >50% of patients with previously suboptimally controlled type 2 diabetes during 30 months of CSII therapy, which delivers rapid-acting insulin analogues as on-demand bolus dosing plus continuous basal infusion. These patients did not eat a restricted diet or take oral anti-diabetic drugs. During 12 months after the initiation of CSII therapy, median HbA_{1c} levels were maintained between 6.3% (IQR 5.9–6.9) and 6.4% (IQR 6.0–7.2), and from the 12th month after the therapy, median serum C-peptide levels (fasting and PP2) began to increase steadily compared with baseline levels (Figure 2C and D, $p < 0.0001$).

We further evaluated the relationship between β-cell function improvement and glycaemic control. Compared with median values at baseline, improved PP2 serum C-peptide levels ($p = 0.017$) and plasma glucose levels (fasting and PP2, $p < 0.0001$ for both) were shown by the good glycaemic control group after CSII therapy (Table 2), but improvements were not observed

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Table 2. Comparison of clinical and biochemical findings between good and poor glycaemic control groups after CSII therapy

	Posttreatment mean HbA_{1c}		
	Good (≤6.5%)	Poor (≥8.0%)	*p*-value[a]
Number (%)	269 (51.6)	56 (10.7)	
Men (%)	161 (59.9)	22 (39.3)	0.005
Age at baseline (years)	60 (52–65)	58 (50–67)	0.910
Diabetes duration at baseline (years)	10.0 (6.0–17.0)	12.1 (7.1)[b]	0.654
HbA_{1c} (%)			
At baseline	8.3 (7.4–9.5)	10.3 (8.8-12.1)	<0.0001
Posttreatment mean	6.1 (5.8-6.3)*	8.9 (8.3–9.8)*	<0.0001
Serum C-peptide (nmol/L)			
Fasting			
At baseline	0.48 (0.32–0.73)	0.40 (0.30–0.62)	0.035
Posttreatment mean	0.61 (0.45–0.80)	0.55 (0.36–0.79)*	0.133
2-h postprandial			
At baseline	1.14 (0.63–1.82)	0.88 (0.50–1.26)	0.014
Posttreatment mean[b]	1.69 (0.70)**	1.12 (0.63)	<0.0001[c]
BMI (kg/m^2)[b]			
At baseline	23.6 (3.2)	23.8 (4.0)	0.763[c]
Posttreatment mean	25.3 (2.8)***	25.7 (3.8)***	0.416[c]
Blood pressure posttreatment mean			
Systolic (mmHg)	127.7 (119.8–138.2)	132.3 (16.3)[b]	0.147
Diastolic (mmHg)	71.0 (66.6–77.4)	75.2 (9.5)[b]	0.036
Plasma glucose (mmol/L)			
Fasting			
At baseline	8.6 (6.7–11.1)	11.1 (9.1–16.6)	<0.0001
Posttreatment mean	7.8 (6.7–8.5)*	11.7 (3.3)[b]	<0.0001
2-h postprandial[b]			
At baseline	19.2 (6.0)	22.1 (7.2)	0.061[c]
Posttreatment mean	15.3 (3.9)***	23.6 (6.4)	<0.0001[c]
Serum albumin (g/dL)			
At baseline	4.2 (3.8–4.4)	3.8 (0.5)[b]	<0.0001
Posttreatment mean	4.3 (4.1–4.4)*	4.2 (4.0–4.4)*	0.038[c]
Haemoglobin posttreatment mean (g/dL)[b]	13.6 (1.6)	13.5 (1.8)	0.723[c]
Triglycerides (mmol/L)			
At baseline	1.23 (0.84–1.91)	1.22 (0.84–1.83)	0.913
Posttreatment mean	1.34 (0.93–1.92)	2.20 (1.02–2.94)*	0.005
HDL-C posttreatment mean (mmol/L)	1.32 (1.10–1.54)	1.31 (0.46)[b]	0.804
LDL-C (mmol/L)			
At baseline	2.92 (2.5–3.6)	2.56 (0.91)[b]	0.048
Posttreatment mean[b]	3.0 (0.82)	3.36 (1.19)	0.042[c]
Free fatty acids (mmol/L)			
Posttreatment mean	0.65 (0.49–0.84)	0.66 (0.33)[b]	0.765

Data are median (interquartile range) or mean (standard deviation) of posttreatment mean levels of clinical and biochemical parameters calculated using all observations recoded in each patient during the entire period of CSII therapy (for up to 30 months).
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]Mann–Whitney *U*-tests.
[b]Mean (SD).
[c]Unpaired *t*-tests between the two groups.
*$p < 0.0001$ (Wilcoxon signed rank tests).
**$p = 0.017$ (Wilcoxon signed rank tests).
***$p < 0.0001$ (paired *t*-tests compared with data at baseline in the same group).

in the poor glycaemic control group. Furthermore, the median M_CpepPP2 level was higher in the good glycaemic control group than in the poor glycaemic control group (Table 2, $p < 0.0001$), and multiple linear regression analysis showed that M_HbA_{1c} was inversely related to M_CpepPP2. Taken together, these findings indicate that long-term correction of hyperglycaemia within near physiologic ranges by intensive insulin therapy can rescue β-cell function, even in patients with non-newly diagnosed type 2 diabetes, as reported previously for patients with newly diagnosed type 2 diabetes, whose β–cell function is restored through normalization of blood glucose level via early intensive insulin therapy [9–12].

Interestingly, other studies have reported that postprandial insulin and C-peptide deficiency independently contribute to deteriorating glucose control in patients with type 2 diabetes [17,18]. These findings appear to support the relationship between optimal glycaemic control with CSII therapy and improved PP2 serum C-peptide

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levels. In contrast, a study of β-cell function in Korean patients with type 2 diabetes ($n = 1170$) treated with usual diabetic therapies showed that the following biochemical parameters worsened with disease duration: HbA_{1c} (from $7.7 \pm 1.8\%$ at <5 years to $8.6 \pm 1.6\%$ at >10 years, $p < 0.05$), fasting C-peptide levels (from 0.54 nmol/L [range 0.16–1.9] at <5 years to 0.47 nmol/L [range, 0.14–1.09] at >10 years, $p < 0.05$), and PP2 C-peptide levels (from 1.41 nmol/L [range 0.28–4.94] at <5 years to 0.96 nmol/L [range 0.31–2.83] at >10 years, $p < 0.05$) [19]. However, CSII therapy significantly improved HbA_{1c} and C-peptide levels (Table 1), supporting again the relationship between optimal glycaemic control and β-cell function improvement.

Consistent with our findings, a 3-year study evaluating complex regimens with insulin analogues (biphasic, prandial, or basal alone or in combination) reported that the HbA_{1c} goal of ≤6.5% was achieved in 32–45% of patients with suboptimally controlled type 2 diabetes at baseline [20]. A meta-analysis of 16 randomized controlled trials concluded that the basal–bolus regimen is the best insulin analogue regimen for attaining HbA_{1c} goals [21]. However, no other study has reported β-cell function recovery in terms of improved serum C-peptide secretion after achieving optimal glycaemic control by long-term CSII therapy in patients with non-newly diagnosed type 2 diabetes and suboptimal glycaemic control.

One possible mechanism for the improved β-cell function observed in our study may be β-cell rest provided by insulin replacement [22,23]. This mechanism was reported by a previous study of patients with newly diagnosed type 2 diabetes, in which patients who underwent intensive insulin therapy by CSII or multiple daily injections maintained a higher remission rate 1 year after the intervention began compared with patients who received sulphonylurea (which overstimulates β-cells) or metformin (which improves insulin sensitivity) [9]. Indeed, the TDD of insulin required for optimal glycaemic control in our study decreased from 83 ± 29 IU/day (highest mean TDD at initiation of CSII therapy) to 48 ± 25 IU/day at 24 months ($n = 51$, $p < 0.0001$; unpublished results). This finding demonstrates that β-cell rest provided by CSII therapy can support β-cell recovery.

In contrast, the median TDD in the 3-year study with complex insulin regimens increased steadily during the second and third years despite a significant decrease in median HbA_{1c} to 6.9% in the third year [20]. This increase in TDD over time suggests that continuous infusion of rapid-acting insulin via insulin pumps, which mimics physiologic basal insulin secretion, may be more effective than once-daily or twice-daily injections with long-acting insulin analogues for restoring β-cell function, especially in patients with long-standing type 2 diabetes.

Another possible mechanism underlying improved β-cell function in our study may be that long-term CSII therapy protects β-cells from apoptosis by maintaining long-term normoglycaemia, because glucotoxicity resulting from hyperglycaemia is considered a major factor in the loss of β-cell function and mass over time in type 2 diabetes [22]. Accordingly, only patients with good glycaemic control showed significantly improved M_CpepPP2 and plasma glucose levels (fasting or PP2) with long-term CSII therapy in our study (Table 2). However, the median M_HbA_{1c} of the poor glycaemic control group was 8.9% (IQR 8.3–9.8) after long-term CSII therapy, which was significantly lower than the median value of 10.3% at baseline (IQR 8.8–12.1; $p < 0.0001$; Table 2). These results indicate that a significant improvement in blood glucose level is not sufficient to recover β-cell function in patients with type 2 diabetes – the achievement of normoglycaemia is needed.

We performed stepwise multiple linear regression analysis using M_CpepPP2 as a dependent variable to explain improvement of β-cell function after CSII therapy. We found that baseline PP2 C-peptide and M_CpepF were positive independent predictors of M_CpepPP2, and M_HbA_{1c} was a negative independent predictor ($R^2 = 0.56$, $p < 0.0001$). These results suggest that improvement of β-cell function after CSII therapy seems more likely dependent on baseline PP2 C-peptide rather than on other baseline parameters, including glycaemic control. Our previous study on long-term CSII therapy also showed that the remission group has a higher baseline PP2 C-peptide level than the nonremission group but not baseline fasting C-peptide [13]. Indeed, the PP2 C-peptide level is known to significantly decrease from the normal range earlier before fasting C-peptide level does as duration of type 2 diabetes increases [19], suggesting that PP2 C-peptide can be a better surrogate marker for β-cell function reserve than fasting C-peptide. Meanwhile, in a study of newly diagnosed type 2 diabetes with severe hyperglycaemia (HbA_{1c} $10.0 \pm 2.2\%$) treated by early intensive insulin therapy, β-cell function (represented by the area under the curve of C-peptide during an intravenous glucose tolerance test) was not significantly different at baseline between remission and nonremission groups [12]. However, the remission group achieved greater improvement in β-cell function than the nonremission group after the intervention. In contrast with our results, it appears that other parameters rather than baseline PP2 C-peptide might be needed to predict improvement of β-cell function in new-onset type 2 diabetes with severe hyperglycaemia, for magnitude of β-cell function reserve may not be differentiated by using baseline PP2 C-peptide because of the short duration of diabetes.

The inability to control hyperglycaemia with CSII therapy in the poor glycaemic control group requires further analysis, especially in terms of glycaemic control and β-cell function at baseline, for patients with poor glycaemic control had significantly worse glycaemic control and lower median

levels of fasting and PP2 serum C-peptide even at baseline than patients with good glycaemic control (Table 2). These results suggest that β-cell function reserve represented by PP2 C-peptide may have a threshold level to obtain β-cell function improvement and normoglycaemia when using CSII therapy in type 2 diabetes. Another finding we observed clinically was that many patients in the poor glycaemic control group showed low compliance with CSII therapy. For example, many did not wear their insulin pumps continuously or follow recommendations about diet and exercise when using insulin pumps. Their poor glycaemic control may therefore be attributed to low compliance with any treatments for glycaemic control, including CSII therapy, although this warrants further investigation.

In our study population, median body mass index (BMI) increased continuously during the first 12 months of CSII therapy and then remained unchanged for the remaining period of CSII therapy. As a measure of BMI throughout the entire study period, median M_BMI level increased significantly (25.7 kg/m^2 [IQR 23.5–27.4]) compared with median BMI at baseline (23.6 kg/m^2 [IQR 21.5–25.8], $p < 0.0001$; Table 1). However, this increase is not considered as undesirable as in Western patients with type 2 diabetes, because Asian patients with type 2 diabetes are less overweight than Western patients [24]. In a previous study, patients with newly diagnosed type 2 diabetes who achieved remission were more obese at baseline (BMI 25.5 ± 2.8 kg/m^2) than patients who did not achieve remission (BMI 24.3 ± 3.1 kg/m^2) [9], and in our study, M_BMI was positively correlated with M_CpepPP2 ($r = 0.23$, $p = 0.001$), even after adjusting for age and diabetes duration. Moreover, among Chinese, Japanese, and Koreans, the BMI range of 22.6–27.5 kg/m^2 is associated with the lowest mortality [25].

Unexpectedly, we found an improvement in blood pressure after long-term CSII therapy in all subjects (Table 1), where the improvement was more prominent in patients with good glycaemic control than in patients with poor glycaemic control (Table 2). And even the poor glycaemic control group showed a significant improvement in diastolic pressure as compared with its baseline level (data not shown). Although the poor glycaemic control group did not achieve optimal glycaemia, both groups showed significant improvement in glycaemic control as compared with their baseline levels (Table 2). Therefore, we speculate that resolution of glucotoxicity at any amount by using long-term CSII therapy may be related to the improvement in blood pressure, on the basis of the following backgrounds: first, hyperglycaemia-induced reactive oxygen species production impairs bioavailability of NO, a potent vasodilator [26,27]. Second, the endothelial function to regulate vascular tone is impaired in diabetic condition because of an imbalance between endothelial mediators [28]. Third, insulin, which we used through insulin pumps to control hyperglycaemia, is considered to exert important roles in maintenance of vascular tone by means of regulating many vascular mediators, including induction of NO synthesis [29,30]. To elucidate the exact mechanisms for lowering blood pressure after long-term CSII therapy, further investigation will be warranted.

After long-term CSII therapy, posttreatment mean values of haemoglobin, serum albumin, and HDL cholesterol increased significantly compared with median baseline values (Table 1), suggesting that improved nutrition may accompany CSII therapy. We advise our patients to avoid the restricted diet that is frequently recommended to control postprandial hyperglycaemia on other therapeutic modalities.

Although posttreatment mean serum TG significantly increased in all subjects compared with the baseline level, the level was still within the normal range (Table 1). Moreover, the level was not changed in patients with good glycaemic control but increased only in patients with poor glycaemic control, as compared with that of baseline (Table 2). Therefore, it appears that as long as optimal glycaemia is achieved, the TG level does not increase above the normal range after long-term CSII therapy. Meanwhile, we took the overnight (12-h) fasting serum sample at least 12-h after the patient had removed the insulin pump. In this condition where no exogenous insulin was supplied, the TG level was inappropriately controlled in patients with poor glycaemic control but not in patients with good glycaemic control. These results suggest that the magnitude of β-cell function reserve and the concomitant fasting glycaemic level may determine the serum TG level in our study patients, for insulin regulates serum TG level by promoting the metabolism of very low-density lipoprotein transferring TG in the serum [31], and serum TG level increases in hyperglycaemic condition because TG synthesis in the liver is accelerated as the glycaemic level increases [32].

In contrast to the serum TG, the posttreatment mean of HDL was significantly improved in all subjects (Table 1), where there is no significant difference between patients with good and those with poor glycaemic control (Table 2). These results suggest that the improvement in serum HDL level may not be affected by glycaemic level in patients treated with long-term CSII therapy, which warrants further investigation.

Our study has several limitations. First, this study is retrospective, therefore, there is no control group other than the comparison of changes before and after the treatment. Second, the study population consisted of Korean patients with type 2 diabetes, who are typically less overweight than Western patients with type 2 diabetes. Third, cultural or ethnic factors may have affected our results. However, other studies evaluating intensive insulin

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therapy in Western patients with type 2 diabetes [20,21] or short-term CSII or multiple daily injection therapy in patients with newly diagnosed type 2 diabetes [9–12] have demonstrated the efficacy of intensive insulin therapy.

In conclusion, the target HbA_{1c} goal of ≤6.5% was maintained with long-term CSII therapy in more than 50% of Korean patients with non-newly diagnosed type 2 diabetes and suboptimal glycaemic control before CSII therapy. In addition, a correction of hyperglycaemia was followed by improved β-cell function. These results demonstrate that CSII therapy may represent a major therapeutic option for treating type 2 diabetes at any duration of the disease (newly diagnosed or long-standing) to prevent or reverse the progressive deterioration of type 2 diabetes over time.

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Conflict of interest

Dr Choi has the ownership of stock of Sooil Development Co. Dr Noh is the recipient of a grant from Konkuk University. All the other authors have no conflict of interest to disclose.

Author contributions

S. Choi researched data, wrote the manuscript, and contributed to discussion. J. Lee researched data and contributed to discussion. J. Lee researched data and contributed to discussion. S. Kim researched data and contributed to discussion. S. Han researched data and reviewed/edited the manuscript. I. Kim researched data and reviewed/edited the manuscript. Y. Noh researched data, wrote the manuscript, contributed to discussion, and reviewed/edited the manuscript.

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