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RESEARCH ARTICLE

Induction of long-term normoglycemia without medication in Korean type 2 diabetes patients after continuous subcutaneous insulin infusion therapy

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Abstract

Background Our previous studies showed that some Korean type 2 diabetic patients could maintain long-term normal blood glucose control without any medication, referred to as remission after a certain period of normalization of blood glucose level by continuous subcutaneous insulin infusion (CSII) treatment. In this study we determined the clinical characteristics that influenced the induction of remission.

Methods Ninety-one type 2 diabetes mellitus (DM) patients were treated with CSII therapy. Follow-up examinations took place monthly, for sixteen months, at an outpatient clinic where blood glucose levels and insulin dosage were monitored.

Results Overall, in 34.4% of all subjects, remission was induced after 53.6 ± 38.9 days of CSII therapy and lasted for an average of 13.6 ± 8.9 months during the study period. The total daily insulin dosage given to normalize blood glucose levels reached a maximum dosage at 7.3 ± 1.2 days and gradually decreased in all subjects. It did not significantly decrease beyond 14.4 ± 2.7 days of therapy in patients who did not experience remission, but did continuously decrease and reached zero in patients with remission. Remission rates were higher when patients started CSII therapy with a shorter history of diabetes, lower postprandial blood glucose levels, higher body mass index (BMI), and fewer chronic diabetic complications.

Conclusions These findings suggest that CSII therapy can induce remission in a significant proportion of Korean type 2 DM patients. The possibility of remission is higher if the severity of glucose toxicity is lower at the initiation stage of the therapy. It is suggested that CSII therapy might be considered as an early treatment for type 2 diabetic patients. Copyright © 2002 John Wiley & Sons, Ltd.

Keywords insulin pump; intensive glycemic control; hemoglobin A_{1c}; serum c-peptide; insulin dosage

Introduction

It is known that insulin deficiency as well as insulin resistance is a pathogenetic mechanism of type 2 DM. It is also well known that type 2 DM has an asymptomatic insulin resistant phase preceding the onset of clinical diabetes [1]. Treatment of type 2 DM is usually initiated with dietary intervention and gradually progresses to administration of medications of

oral hypoglycemic agents. However, in many cases, these measures fail to achieve normoglycemic control [2]. Insulin therapy is generally not recommended for type 2 DM especially in the early phases of the disease [3,4].

Progressive decrease in insulin residual secretory capacity in type 2 diabetic patients is associated with a gradual deterioration of glucose tolerance as is seen in several publications such as the United Kingdom Prospective Diabetes Study and the Belfast studies [5,6]. Chronic hyperglycemia, as well as playing a role in the pathogenesis of micro- and macrovascular complications [7,8] may also aggravate the defective insulin secretion and insulin action, and thereby contribute to the progressive deterioration of glycemic control [9]. CSII via an insulin pump, can normalize blood glucose levels and improve insulin secretion and/or insulin action in type 2 DM [10,11]. CSII therapy has also resulted in decreased prevalence and delayed progression of microvascular complications in type 1 and type 2 DM [12,13].

Ilkova *et al*. [10] reported that in 46.2% of newly diagnosed type 2 DM patients who failed to respond to dietary and exercise measures, short-term intensive insulin treatment by CSII induced long-term normoglycemia without medication. We have previously conducted studies that indicated a gradual decrease in the need for insulin dosage in most type 2 DM patients treated with CSII therapy [14,15]. In the clinical setting, some patients experienced the insulin dosage decrease markedly, to the point where it was no longer necessary and they were able to maintain normal glucose levels without any pharmacological intervention – a state referred to as remission.

The purpose of this study was to examine the long-term glycemic control pattern, without medication, following CSII therapy in type 2 DM patients and to determine the clinical and metabolic characteristics that are related to the induction of remission.

Patients and methods

Selection of subjects and study design

Type 2 DM patients who visited the Konkuk University Diabetic Center and were unable to control blood glucose levels by dietary intervention, oral hypoglycemic agents and/or intermediate acting insulin were candidates for CSII therapy using an insulin pump (Dana insulin pump, Sooil Development Co., Seoul, Korea). Regular insulin (Humulin R, Eli Lilly, Indianapolis, IN, USA) was used for the insulin pump. The following is a list of criteria that was used to exclude patients from the CSII therapy: (1) proliferative retinopathy, (2) significant renal impairment (more than 2.0 mg/dL of serum creatinine concentrations), (3) coronary heart disease, (4) chronic liver disease, (5) diabetic foot ulceration and gangrene, and (6) pulmonary infections. Since slow onset insulin dependent DM was known to affect only 1 to 2% of Korean type 2 DM patients, it was rejected as a criterion for exclusion or inclusion in the study [16]. Over a period of one year (from 1 May 1995 to 30 April 1996), 117 newly hospitalized patients were randomly selected as subjects for this study when either of the numbers, 3 or 6 was generated by rolling a dice. Most subjects were admitted to Konkuk University Diabetic Center for four to six weeks. Some patients were admitted for as little as two weeks and others for as much as eight weeks. Hospitalization is not necessary for the commencement of CSII provided adequate education is given as an outpatient on how to use the insulin pump, how to eat properly, how to exercise, and other health related issues. Each subject's lifestyle, including food intake and exercise, was discussed with a dietician. Subjects received individualized instruction in a regimen of regular exercise and diet to maintain normal body weight. The experimental protocol was approved by the Committee on Human Investigation of KonKuk University.

Blood glucose levels were adjusted with appropriate insulin dosage. The usual initial dosage of insulin was 2 to 4 units in each meal and 2 to 4 unit/day in basal insulin delivery. Basal rates and premeal boluses of insulin were adjusted everyday to achieve euglycemia, as defined by preprandial and 2-h postprandial glucose levels of less than 5.5 and 7.8 mmol/L, respectively. The criterion for determining remission was that pharmacological medication was not needed for maintaining fasting and postprandial blood glucose levels of less than 6.0 and 10.0 mmol/L, respectively. Compliance was also monitored for diet and exercise at subsequent follow-up visits. The subjects consulted with a dietician and had 24-h diet and physical activity recall at every visit. The main purpose of this consultation was to help the patient maintain compliance. The patients who maintained normoglycemia without medication checked blood glucose levels before and after each meal. Follow-up examinations were conducted every month at an outpatient clinic for patients who were not successful in inducing remission. Those patients who needed CSII therapy for the normoglycemic control measured blood glucose levels seven times a day, before and after all meals, and at bedtime. Twenty-six patients were lost to tracking during the follow-up.

Body mass index, the levels of fasting and postprandial serum c-peptide, glycated hemoglobin (HbA_{1c}), and serum lipid profiles were measured at baseline, the 6th week and the 16th month following the initiation of CSII therapy. Daily fasting and postprandial blood glucose levels and insulin dosage were recorded.

Blood collection and biochemical analysis

Blood glucose levels were measured with a portable blood glucose meter (Accutrend, Boehringer Mannheim, Mannheim, Germany). At baseline, the 6th week and 16th month of the study periods, CSII therapy was stopped overnight and blood was collected with vacutainers at the fasting state and at the postprandial state 2 h after

ingestion of a standardized mixed meal composed of 65% carbohydrate, 15% protein, 20% fat in calories. Following centrifugation of the blood at 3000 rpm for 30 min, the supernatant fractions were separated and stored at −70 °C until further analysis. Serum c-peptide levels were evaluated by radioimmunoassay (Linco Research, St Charles, MO, USA) [17], and HbA_{1c} contents were measured by high performance liquid chromatography [18]. Total cholesterol and triglyceride levels were measured by enzymatic methods [19,20]. High-density lipoprotein (HDL) cholesterol levels were quantified by a polyethylene glycol precipitation kit (Young Dong, Seoul, Korea) combined with a cholesterol oxidase method for cholesterol measurement [21]. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation [22].

Statistical analysis

Results are expressed as mean ± standard deviation. Statistical analysis was performed using the Statistical Analysis System (SAS) program. Comparison of means between the remission and nonremission groups was specified by unpaired two-sample Student's t-tests. Paired t-tests were used to compare means before and after CSII therapy in both remission and nonremission groups, respectively. The difference of frequencies in categorical variables was determined by Chi-square test. Backward stepwise logistic regression analysis was performed for selecting the clinical and metabolic variables that influence the induction of remission. Pearson correlation analysis was also done for determining the relationship between remission status and clinical and metabolic variables. Remission status was treated as an indicative variable (a set of dummy variables). A value of $P < 0.05$ was considered to be statistically significant.

Results

Clinical features of subjects

The clinical characteristics of the subjects prior to CSII are presented in Tables 1 and 2. The subjects were nonobese and their fasting serum c-peptide levels were not significantly different from that of healthy Korean people (0.8 nmol/L). Their postprandial serum c-peptide levels were a little lower than those of the healthy population (3.1 nmol/L). The average duration of diagnosed type 2 DM in all subjects was 7.2 ± 6.9 years. Their average HbA_{1c} values were 13.2 ± 4.9%. Of these subjects, 73.2% had chronic diabetic complications, neuropathy (69.2%), retinopathy (27.5%), and nephropathy (14.3%), respectively. Approximately half the number of subjects controlled their blood glucose levels by diet alone. While 27.5% of the subjects took oral hypoglycemic agents, 12.3% of the subjects took neutral protamine Hagedorn (NPH) insulin, everyday. A combination of oral hypoglycemic agents and NPH insulin was followed by 8.7% of the subjects.

Remission pattern

Figure 1 gives the remission pattern in patients who maintained normoglycemia without any medication. Among all the subjects, 34.4% showed decreased insulin dosage to normalized blood glucose levels and eventually, they showed normoglycemic remission after 9 to 219 (53.6 ± 38.9) days of CSII therapy. After remission, normal blood glucose levels were sustained for 13.6 ± 8.9 months. In 3 out of 31 remitted patients, a temporary elevation of blood glucose levels occurred after remission. These patients restarted CSII therapy to normalize their blood glucose levels. After 15 to 30 days, they maintained

Table 1. Clinical features prior to CSII therapy in the remission and nonremission groups

	All subjects ($n = 91$)	Remission group ($n = 31$)	Nonremission group ($n = 60$)
Age (years)	53.8 ± 8.9	49.5 ± 9.7	56.0 ± 8.4*
Gender (male %)	56.7	50.0	60.0
Duration (years)	7.2 ± 4.9	3.3 ± 2.7	9.1 ± 4.3**
Previous treatment			
Diet only (%)	51.7	80.6	36.7*
Oral hypoglycemic agent (%)	27.5	19.4	31.6
NPH insulin (%)	12.3	0	18.3*
Combination (%)[1]	8.5	0	13.4*
Complication			
Peripheral neuropathy (%)	69.2	54.8	78.3*
Retinopathy (%)	27.5	3.2	40.0*
Nephropathy (%)	14.3	0	21.7*
Serum total cholesterol (mmol/L)	5.1 ± 1.7	4.8 ± 1.1	5.2 ± 1.7
Serum HDL-cholesterol (mmol/L)	1.2 ± 0.5	1.2 ± 0.6	1.1 ± 0.6
Serum LDL-cholesterol[2] (mmol/L)	3.0 ± 1.9	2.6 ± 1.0	3.2 ± 1.7
Serum triglyceride (mmol/L)	2.1 ± 1.2	2.1 ± 1.2	2.0 ± 1.2

Note: Data are shown as mean ± standard deviation.
*Significantly different from the remission group at $p < 0.01$; ** $p < 0.001$.
[1]The combination treatment of hypoglycemic agent and neutral protamine Hagedorn (NPH) insulin.
[2]Calculated by the Friedewald equation.

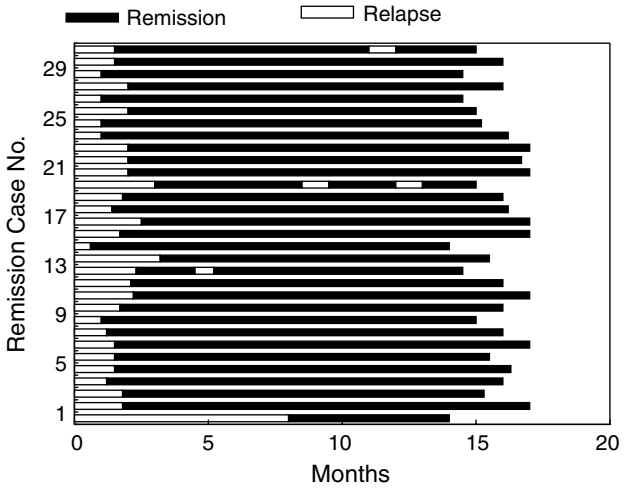

Figure 1. Remission pattern of patients who maintained normoglycemia without medication after CSII treatment. The open bar represents the periods of CSII treatment and the solid bar represents the periods of good glycemic control without any medication, that is, remission

normoglycemia without further medication until the end of the study.

Changes in insulin dosage and blood glucose during CSII therapy

Total daily insulin dosage did not significantly decrease after 14.4 ± 2.7 days of therapy in nonremitted patients. It did continuously decrease in remitted patients until exogenous insulin and/or any other medication was no longer needed for normalizing blood glucose levels (Figure 2A). The decreasing slope of insulin dosage was steeper in the remission group than in the nonremission group. Blood glucose levels were significantly lower in the remission group than in the nonremission group, even though blood glucose levels in both groups fell within the normal ranges (Figure 2B).

Changes of fasting and postprandial glucose, c-peptide and HbA_{1c}, and BMI at baseline, 6 weeks, and 16 months of CSII therapy

Tables 1 and 2 give the clinical characteristics of the patients in the remission and nonremission groups prior to CSII therapy. Initial postprandial blood glucose levels were higher in the nonremission group than in the remission group ($p < 0.01$). Postprandial serum c-peptide levels were higher in the remission group ($p < 0.01$). HbA_{1c} values were remarkably higher than normal at baseline, but did not differ between the groups. BMI was higher in the patients of the remission group than in those of the nonremission group ($p < 0.05$).

After six weeks of CSII therapy, fasting and postprandial blood glucose levels significantly decreased compared to

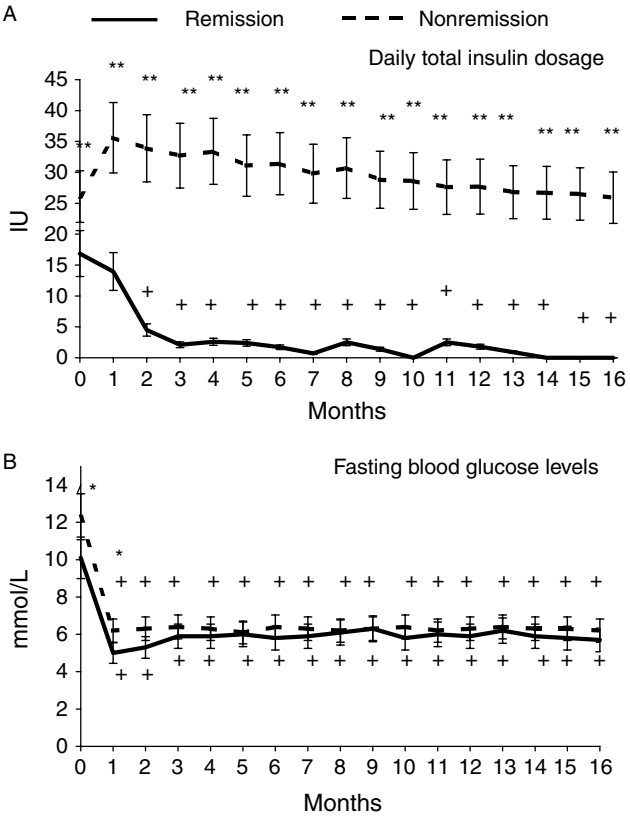

Figure 2. Changes of daily insulin dosages (A) and fasting blood glucose levels (B) after CSII by insulin pump in the remission and nonremission groups during 16 months of follow-up periods. ——— – Remission group; - - - - – Nonremission group. Remission versus nonremission: *$p < 0.05$, **$p < 0.001$, $^{+}p < 0.001$ versus day 1

the baseline. Significantly, they did not differ between the remission and nonremission groups (Table 2). The HbA_{1c} values decreased at six weeks, but were not yet normalized. They also did not differ between the two groups. Fasting and postprandial c-peptide levels did not change in both the remission and nonremission group in the period from baseline to six weeks. However, after CSII treatment, these levels were higher in the remission group than in the nonremission group. BMI was higher in the remission group than in the nonremission group after six weeks of CSII therapy ($p < 0.05$).

The follow-up at 16 months showed that serum glucose and c-peptide levels in fasting and postprandial state were consistent with the 6-week results (Table 2). Postprandial c-peptide levels indicated an increase from the baseline at 16 months in the remitted group; however, the increase was not significant ($p = 0.08$). The HbA_{1c} values were maintained below 7.0% in both groups. BMI of the remission group did not change during CSII treatment or after remission. On the contrary, BMI of the nonremission group showed a significant increase from the baseline at 16 months and maintained the plateau at 23.5 kg/m^2. BMI did not differ between the remission and nonremission groups at 16 months.

Table 2. Body mass index, fasting and postprandial blood glucose, fasting hemoglobin A_{1c}, and fasting serum c-peptide levels in the remission and nonremission groups before and after CSIItherapy

	Remission group ($n = 31$)			Nonremission group ($n = 60$)		
	At day 1	At 6 weeks	At 16 months	At day 1	At 6 weeks	At 16 months
Body mass index (kg/m^2)	23.8 ± 1.2	24.2 ± 1.1	24.0 ± 1.1	$22.6 \pm 1.1^{*}$	$23.2 \pm 1.2^{*}$	$23.5 \pm 0.9^{\dagger}$
Fasting blood glucose (mmol/L)	10.3 ± 2.5	$5.0 \pm 1.5^{\ddagger}$	$5.7 \pm 2.6^{\ddagger}$	12.1 ± 3.0	$6.2 \pm 1.4^{\ddagger}$	$6.2 \pm 1.5^{\ddagger}$
Postprandial blood glucose (mmol/L)	15.4 ± 3.2	$6.6 \pm 1.7^{\ddagger}$	$7.1 \pm 2.2^{\ddagger}$	$19.0 \pm 4.2^{**}$	$7.6 \pm 2.1^{\ddagger}$	$7.5 \pm 1.7^{\ddagger}$
Hemoglobin A_{1c} (%)	12.6 ± 4.0	$7.2 \pm 2.5^{\ddagger}$	$6.4 \pm 3.1^{\ddagger}$	13.5 ± 5.0	$7.8 \pm 2.9^{\ddagger}$	$6.8 \pm 2.1^{\ddagger}$
Fasting serum c-peptide (nmol/L)	0.8 ± 0.3	0.9 ± 0.4	1.0 ± 0.4	0.6 ± 0.4	$0.5 \pm 0.3^{*}$	$0.4 \pm 0.3^{*}$
Postprandial serum c-peptide (nmol/L)	2.4 ± 0.9	2.8 ± 1.2	3.0 ± 1.1	$1.6 \pm 0.8^{**}$	$1.4 \pm 0.8^{*}$	$1.2 \pm 0.7^{**}$

Note: Data are shown as mean $\pm$ standard deviation.
*Significantly different from the remission group at $p < 0.05$; ** $p < 0.01$.
†Significantly different from day 1 at $p < 0.05$; ‡ $p < 0.001$.

Clinical factors influencing the induction of remission

Clinical and metabolic factors that influenced the induction of remission were selected with logistic regression analysis. The factors that influenced the induction of remission were the duration of diabetes ($\beta = -0.34$, $p < 0.05$), postprandial blood glucose levels ($\beta = -1.75$, $p < 0.01$), BMI ($\beta = 1.13$, $p < 0.05$), and presence of diabetic complications ($\beta = -1.28, p < 0.05$). The rate of remission was higher when the patients had a shorter duration of diabetes, lower postprandial glucose levels, higher BMI, and fewer and/or less severe complications. There was no difference in total, HDL and LDL cholesterol levels of serum between the remission and nonremission groups.

Correlation analysis gave information about the relationship between each clinical/metabolic factor and the induction of remission. Remission occurred more frequently in patients who started CSII therapy at a younger age ($r = -0.41$, $p < 0.01$). Patients with shorter duration of diabetes had a higher chance of remission after CSII therapy ($r = -0.55$, $p < 0.01$). When duration of diabetes was divided into less than 1 year, 2 to 5 years, 6 to 10 years, 11 to 15 years, and more than 16 years, the remission rates were 62.0%, 52.9%, 22.6%, 20.0%, and 0%, respectively ($p < 0.05$). Previous treatment, as well as duration of diabetes influenced remission. This was mainly due to the different treatment modalities selected by the severity and duration of diabetes. Thus, patients who controlled their blood glucose levels by diet alone had more frequent episodes of remission than those with oral hypoglycemic agent and/or NPH insulin.

Remission occurred more frequently in patients whose postprandial blood glucose levels were lower at the beginning of CSII therapy ($r = -0.51$, $p < 0.01$) and postprandial c-peptide levels were higher ($r = 0.42$, $p < 0.01$). When BMI was under 20 kg/m^2, 21 to 26 kg/m^2, and over 27 kg/m^2 prior to CSII, the remission rates were 9.0%, 31.4%, and 50%, respectively ($p < 0.05$). Thus, leaner patients at the start of CSII therapy showed less remission ($r = 0.36$, $p < 0.05$). Remission occurred more frequently in patients without diabetic complications than in those with complications. None of the patients with nephropathy prior to CSII treatment experienced remission after intensive insulin therapy.

Discussion

Asian type 2 DM patients are mostly nonobese and experience severe weight loss during the course of the disease. They are not hyperinsulinemic. The insulin secretory capacity of Korean people is less than that of Western people [23]. It is possible that the pancreatic beta cells of Korean people cannot secrete enough insulin to compensate for the insulin resistance imposed by recent changes toward a westernized diet. Most Korean type 2 DM patients have difficulty maintaining normal blood glucose levels using pharmacological agents except in the case of patients with physiological delivery of insulin, that is, CSII.

Several clinical studies about the glucotoxicity effect on insulin secretion and insulin resistance have been reported in Western type 2 DM patients [10,24,25]. In the study conducted by Ilkova *et al*. [10], the remission rate of the patients appeared to be higher than in our study. This may be ascribed to a shorter duration of DM and less diabetic complications compared to those of the subjects in our study. Glaser *et al*. reported that maximum incremental c-peptide response improved from both the glucagon and the intravenous glucose bolus injection after seven days of CSII therapy in obese type 2 DM patients [24]. These studies suggest that short-term intensive glycemic control decreases and/or eliminates glucotoxicity of the pancreatic beta cell and improves the insulin secretion capability. In our study, postprandial serum c-peptide levels in the remission group increased after 16 months of CSII therapy, which implies that there is recovery of pancreatic insulin secretory function. However, in the nonremission group, both fasting and postprandial serum c-peptide levels did not change, whereas the fasting and postprandial blood glucose levels decreased at 16 months. Some studies also show that intensive insulin therapy reverses insulin resistance in type 2 DM [25,26]. Thus, intensive insulin treatment may correct the abnormalities of insulin secretory function of the pancreatic beta cell

and/or insulin resistance in both lean and obese type 2 DM patients.

In this study, the factors that influenced the induction of remission were the duration of diabetes, BMI, postprandial blood glucose levels, and the presence of diabetic complications. All these factors can be explained by glucose toxicity. The longer the duration of chronic hyperglycemia and the higher the level of hyperglycemia, the stronger is the deteriorating effect on pancreatic beta cell function and insulin action in peripheral tissue. This leads to lower BMI and accelerated diabetic complications, which could be explained by the concept of glucose desensitization and glucose toxicity as proposed by Robertson *et al*. [27]. Glucose desensitization refers to a pharmacological event involving a temporary, readily induced, physiological and reversible state of cellular refractoriness. This state is due to repeated or prolonged exposure to high concentrations of glucose. Glucose toxicity is reserved for nonphysiological, irreversible alterations in cellular function caused by chronic exposure to hyperglycemia. Thus, it is worth reemphasizing that intensive blood glucose normalization is needed for early stage type 2 DM patients to prevent the irreversible alteration in cellular function called 'glucose toxicity', and to reverse the 'glucose desensitization' of Robertson's proposal.

Remission of diabetes following initiation of treatment with oral hypoglycemic agents and/or NPH is rare in Korea. The present study was not designed as a formal randomized controlled trial either to determine remission patterns or to examine the effects of specific therapies, and a major limitation of the trial is the absence of a control group. However, factors affecting remission in response to CSII may be the physiological effects of infused insulin, the normalization of blood glucose, or a combination of both, and further studies are required to elucidate the mechanism underlying this apparent therapeutic benefit.

A major clinical feature of obese type 2 DM is hyperinsulinemia, which may contribute to cardiovascular disease [28]. Because of concerns that exogenous insulin treatment may exacerbate hyperinsulinemia, insulin therapy was not recommended for obese type 2 DM patients even though hyperinsulinemia may appear to be a compensatory mechanism for insulin resistance [29]. However, no epidemiological study in type 2 DM, nor any data from intervention studies with insulin or insulin secretagogues have given any evidence of toxicity of insulin *per se*. Barrett *et al*. has reviewed the available epidemiological data [30] with the conclusion that there is a clear absence of deleterious cardiovascular effect of high plasma insulin levels in patients with diabetes or impaired glucose regulation. Moreover, long-term results of the Bedford Study indicate in type 2 diabetic patients an inverse correlation between insulin plasma levels at the beginning of the study and the incidence of cardiovascular events including death [31]. The United Kingdom Prospective Diabetes Study showed no increase in cardiovascular disease events or mortality in type 2 diabetic patients assigned insulin therapy, even though their fasting serum insulin levels were higher than those of conventionally treated patients [8]. These conclusions are further supported by the results of the Kumamoto Study of a Japanese population [13]. Our own previous studies have also shown that serum insulin levels increased to 91.5 ± 12.3 nmol/L during CSII therapy from 43.5 ± 10.4 nmol/L at baseline [32]. The beneficial effects of decreasing glucose toxicity by intensive insulin therapy may outweigh their purported risks.

In conclusion, long-term maintenance of normoglycemia by CSII increases the likelihood of long-term normoglycemic control without any medication in Korean type 2 DM patients who have shorter duration of diabetes, lower postprandial blood glucose levels, higher BMI, and fewer chronic diabetic complications. Intensive insulin therapy may need to be considered as an early phase treatment for type 2 DM.

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