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Research Article

COMPARISON OF MULTIPLE DAILY INSULIN INJECTION USING BASAL INSULIN DETEMIR AND CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN JAPANESE PATIENTS WITH TYPE 1 DIABETES

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ABSTRACT

The aim of this study is to evaluate the outcomes of two intensified insulin therapies, continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) using a long-acting insulin analogue, detemir, in Japanese patients with type 1 diabetes in clinical practice. To compare outcomes of CSII and MDI, a retrospective study was carried out at Otsu Municipal Hospital (Otsu, Shiga, Japan). A total of 24 type 1 diabetic patients on intensified insulin therapy (MDI with detemir, *n* = 18; CSII with lispro, *n* = 6) were enrolled in the study. The changes in hemoglobin A1c (HbA1c), total daily insulin dose, bodyweight, fasting blood glucose levels (FBG) and blood glucose levels (BG) before meals, within-patient day-to-day variability in FBG and BG before meals, prevalence of hypoglycemia and lipid profiles were followed up for 12 months. In group CSII, HbA1c, FBG, BG before meals, variability in FBG and BG before meals were improved compared with those in group MDI. In addition, the bodyweight increased in group CSII despite the total insulin dose being reduced, while the total insulin dose and bodyweight in group MDI remained unchanged throughout the study. The frequency of hypoglycemic episodes in group CSII was higher than that in group MDI. There were no differences in the lipid profiles between MDI and CSII therapy. These findings show that CSII therapy using lispro reduces the within-patient variability in BG and improves glycemic control. In contrast, detemir-based MDI achieves stable effects for glycemic control, insulin dose adjustment and bodyweight control. In switching from detemir-based MDI to CSII with lispro, it should be noted that CSII therapy causes weight gain and increased risk of hypoglycemia.

Keywords; Insulin detemir, Insulin lispro, Insulin therapy, MDI, CSII, Japanese patients with type 1 diabetes

INTRODUCTION

Type 1 diabetes patients with deficient insulin secretion are routinely treated with multiple daily injection (MDI) therapy using insulin analogue to reproduce endogenous insulin secretion [1]. The importance of intensive glycemic control in reducing the long-term microvascular and macrovascular complications associated with type 1 diabetes has been shown in several clinical trials [1-4]. MDI and continuous subcutaneous insulin infusion (CSII) therapy are two current methods of intensive insulin therapy for patients with type 1 diabetes. The ideal insulin therapy achieves two aims of both maintenance of glycemic control and reduction of frequent and severe hypoglycemia, simultaneously. MDI therapy requires bolus injection of regular or rapid-acting insulin at each meal, along with long-acting insulin once or twice daily for basal insulin. The long-acting insulin analog, insulin detemir, has pharmacokinetic and pharmacodynamic efficacy to prolong hypoglycemic action, which makes it suitable for use as basal insulin. Its prolonged duration of action is attributable to a combination of increased self-association and albumin binding as a result of acylation of the amino acid at position B29, lysine, by myristic acid [5, 6]. It is well known that CSII is the most physiological method of insulin delivery to improve glycemic control of diabetic patients [7-14]. Recently, it has been reported that the use of an analog-only glargine-based MDI therapy closely mimics CSII therapy. However, the prevailing view is that CSII is more effective than the use of an analog-only glargine-based MDI therapy [9-14].

In recent years, Heis *et al.* reported that detemir showed significantly lower within-subject variability effects in comparison with neutral protamine Hagedorn (NPH) insulin or insulin glargine in patients with type 1 diabetes [15]. Moreover, Tone *et al.* demonstrated low within-subject variability of insulin detemir compared with that of insulin glargine, suggesting that basal insulin replacement with detemir could provide a useful therapeutic strategy for uncontrolled Japanese patients with type 1diabetes with high glucose variability [16]. In our previous study, we reported the usefulness of changing the dosage regimen of detemir from once-daily to twice-daily administration, which improves within-subject variability of BG and reduces the risk of hypoglycemia in Japanese patients with insulin-dependent diabetes who received MDI with detemir [17]. However, it has not been reported whether CSII offers lower within-subject variability of FBG and BG than detemir-based MDI in patients with type 1 diabetes.

In addition, we reported that Japanese patients with type 1 diabetes treated with detemir in MDI therapy exhibited less weight gain [18]. Recently, Fujii *et al.* reported that administration of detemir reduces or maintains bodyweight in Japanese diabetic patients with a lower body mass index [19]. Increasing evidence has shown that insulin therapy using detemir is associated with less weight gain in Japanese patients with diabetes. Therefore, we hypothesized that switching from detemir-based MDI to CSII would be associated with increased bodyweight if detemir involves less weight gain. Moreover, Derosa *et al.* reported that CSII therapy allows better glycemic control and also improves the lipid profiles, thereby reducing cardiovascular risk [14]. Similarly, we assumed that switching from detemir-based MDI to CSII improves the lipid profiles in Japanese patients with diabetes. To our knowledge, there are no published reports comparing detemir-based MDI with CSII in patients with type 1diabetes. Given this background, we carried out a retrospective study to compare the clinical outcomes between detemir-based MDI therapy and CSII therapy with insulin lispro.

METHODS

Patients

A total of 26 adult outpatients with type 1 diabetes who received detemir-based MDI at Otsu Municipal Hospital (Otsu, Shiga, Japan) between January 2008 and March 2011were enrolled in the study. Of these patients, 6 patients (23.1%) were switched from detemir-based MDI to CSII with lispro, and 20 patients continued detemir-based MDI. The main reasons for switching from detemir-based MDI to CSII therapy were to improve glycemic control and to reduce variability in BG. Two patients were excluded because of changing hospitals during the study period, and the remaining 18 patients (8 men and 10 women) were analyzed in this study. To compare the outcomes of detemir-based MDI and CSII with lispro, the clinical

course for each patient was divided into five 3-monthly periods. In the CSII groups, these 3-monthly periods were defined as follows: baseline before switching to CSII, that is, receiving detemir-based MDI (baseline), 1-3 months (period 1), 4-6 months (period 2), 7-9 months (period 3) and 10-12 months (period 4) after switching to CSII. Meanwhile, in the detemir-based MDI groups, the clinical course for each patient between October 2009 and December 2010 was divided into five 3-monthly periods, namely, the first 3 months (baseline) and second 3 months (period 1), third 3 months (period 2), fourth 3 months (period 3), and fifth 3 months (period 4). All patients had received the MDI using detemir for at least 6 months before the study. Throughout the study period, the dose of insulin was adjusted by a physician according to the blood glucose profiles recorded at each hospital visit. If necessary, insulin dose was increased or reduced to meet the target BG. The dosages of oral anti-diabetic and lipid-lowering drugs were unchanged throughout the study period in all patients. Retinopathy was classified as either no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), pre-proliferative diabetic retinopathy (PPDR) or proliferative diabetic retinopathy (PDR). Nephropathy stage was classified into three groups of normoalbuminuria, microalbuminuria or macroalbuminuria. This study was conducted in accordance with the Declaration of Helsinki and the Japanese government's "Ethical Standards for Clinical Research". The Ethics Committee of Otsu Municipal Hospital gave its approval for this study.

Insulin products and apparatus used for the patients

In detemir-based MDI therapy, the patients received regular insulin (Novorin-R Flex pen™, NovoNordisk, Bagsvaerd, Denmark), ultra-rapid insulin including insulin lispro (Humalog™, Eli Lilly, Indianapolis, USA) or insulin aspart (Novo Rapid Flex pen™, NovoNordisk, Bagsvaerd, Denmark) for bolus insulin injection, and received detemir (Revemir Flex pen™, NovoNordisk, Bagsvaerd, Denmark) for basal insulin injection. In CSII therapy, patients were treated with MiniMed Paradigm 712 pump (Medtronic Inc., Northridge, CA) with insulin lispro (Humalog Vial ™, Eli Lilly, Indianapolis, USA).

Biochemical tests and monitoring indexes

HbA1c was measured by a latex agglutination immunoassay using the Determiner HbA1c kit (Kyowa Medex Co., Ltd., Tokyo, Japan) and an automatic analyzer (DM-JACK; Kyowa Medex Co., Ltd., Tokyo, Japan). Self-measured blood glucose (SMBG) was measured using a glucose meter (Glutest Ace, Sanwa Kagaku, Nagoya, Japan). Total cholesterol (TC), triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C) and low-density-lipoprotein cholesterol (LDL-C) were measured using a clinical biochemistry analyzer (Bio Majesty JCA-BM6050, JEOL Ltd., Tokyo, Japan). The following kits were used for several clinical measurements: L-Type CHO M (Wako Pure Chemical Industries, Ltd., Osaka, Japan) for TC, L-Type TG M (Wako Pure Chemical Industries, Ltd., Osaka, Japan) for TG, Cholestest LDL (Sekisui Chemical Co., Ltd., Tokyo, Japan) for LDL-C, and Cholestest N HDL (Sekisui Chemical Co., Ltd., Tokyo, Japan) for HDL-C. Bodyweight was measured at the hospital using a calibrated scale. Basic clinical information on the patients was collected by reviewing medical records and included medical history, clinical progress, laboratory tests, concurrent drugs and time-dependent changes in insulin dose. FBG, BG before meals and incidence of hypoglycemia were collected from patients' SMBG records. Hypoglycemia was defined as a confirmed blood glucose level < 70 mg/dL. Hypoglycemia that occurred during sleep from bedtime to getting up in the morning was defined as nocturnal. Severe hypoglycemia was defined by impaired consciousness or convulsions requiring assistance from another person and the need for an intramuscular injection of glucagon or intravenous glucose. Using these data, changes in HbA1c values, daily insulin dose, bodyweight, FBG, BG before meals, within-patient variability in FBG and BG before meals, frequency of hypoglycemia, TC, TG, HDL-C and LDL-C were analyzed. HbA1c values, daily insulin dose and bodyweight were evaluated in all patients, whereas the other values were evaluated in patients for whom detailed records were obtained. We evaluated these parameters at the baseline and after periods 1, 2, 3 and 4.

Calculations and statistics

The mean values for each parameter were calculated for each period and the results are expressed with standard error of the mean (SEM) unless otherwise stated. Within-patient day-to-day variabilities in FBG and BG before meals were calculated as the standard deviations of FBG and BG before meals, respectively. Japan Diabetes Society (JDS), National Glycohemoglobin Standardization Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values of HbA1c were calculated according to Consensus and Statement on International Standardization of HbA1c in Japan [20].

As each data set did not assume a normal distribution or the same variance, to compare between-group differences, statistical testing was carried out using Mann-Whitney's U-test; to compare differences between baseline and each period, Wilcoxon's signed rank test was carried out. A *P*-value of < 0.05 was considered statistically significant. All analyses were performed with the statistical software Statview ver 5.0 (SAS Institute Inc., Cary, NC, U.S.A.).

Table 1: Characteristics of the patients at baseline

Parameter	MDI	CSII	P value
	n=18	n=6	
Male/Female (No.)	8/10	3/3	-
Age (years)	45.2 (16.6)	40.4 (12.0)	N.S.
Duration of diabetes (years)	15.9 (11.5)	9.7 (6.2)	N.S.
Bodyweight (kg)	58.6 (12.2)	63.1 (6.9)	N.S.
Body mass index (kg/㎡)	22.5 (3.7)	22.8 (3.6)	N.S.
JDS HbA1c (%)	7.22 (0.84)	7.68 (0.51)	N.S.
NGSP HbA1c (%)	7.66 (0.86)	8.12 (0.51)	N.S.
IFCC HbA1c (mmol/mol)	58.3 (8.8)	62.9 (5.2)	N.S.
Retinopathy (NDR/SDR/PPDR/PDR), No.	13/2/0/3	4/1/0/1	-
Nephropathy stage (normoalbuminuric/microalbuminuric/ macroalbuminuric), No.	14/4/0	4/1/1	-
Injection Number of detemir injections (once-/twice-daily)	10/8	1/5	-

Each value represents the mean (SD).
JDS HbA1c, Japan Diabetes Society values; NGSP HbA1c, National Glycohemoglobin Standardization Program values; IFCC HbA1c, International Federation of Clinical Chemistry and Laboratory Medicine values.
NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy

RESULTS

Patient characteristics

Table 1 shows the clinical characteristics of the subjects at baseline. There were no patients with proliferative retinopathy requiring acute treatment, impaired renal or hepatic function, severe cardiac problems, uncontrolled hypertension, recurrent major hypoglycemia, allergy to insulin or pregnancy. Eight patients (44.4%) received twice-daily detemir in group MDI, and 5 patients (83.3%) received twice-daily detemir in group CSII at baseline. Of the 18 patients in group

MDI, only one patient received regular insulin before breakfast and lunch because postprandial glucose level dropped markedly when ultra-rapid insulin was used as bolus insulin. In group MDI, one patient was treated with α-glucosidase inhibitors and four patients were treated with HMG-CoA reductase inhibitors. In group CSII, one patient was treated with HMG-CoA reductase inhibitors. No patient was prescribed additional oral anti-diabetic drugs or lipid-lowering medications during the study.

Changes in HbA1c

Table 2 shows changes in the mean values of HbA1c at baseline and during periods 1, 2, 3 and 4; here, HbA1c represents JDS, NGSP and IFCC values. Although no significant difference was observed in HbA1c levels between groups CSII and MDI, the values of HbA1c in group CSII showed a tendency to improve toward the end of the study period. Meanwhile, in group MDI, there was no remarkable improvement during the study periods. Furthermore, the values of HbA1c in group CSII were higher than those in group MDI at baseline. These values in group CSII were lower than in group MDI in period 4.

Changes in FBG, BG before meals, variability in FBG and BG before meals

Figures 1 a), b), c) and d) show the changes in mean values of FBG, BG before meals, variability in FBG and BG before meals at baseline and during the four periods, respectively. FBG and BG before meals of group CSII improved after switching from MDI to CSII therapy and these improvements were sustained during the study periods, while those of group MDI showed no remarkable improvement. Moreover, the values of FBG and BG before meals of group CSII were higher than those of group MDI at baseline; these values were lower than those of group MDI after switching from MDI to CSII (Fig. 1 a, b). There were no significant differences between the two groups.

Similarly, the day-to-day within-patient variability in FBG and BG before meals of group CSII also improved after switching from MDI to CSII therapy, while that of the MDI group remaining unchanged throughout the study. The variability in FBG of group CSII was significant higher ($P < 0.05$) than that of the MDI group at baseline (72.9 vs. 43.6 mg/dL) and during period 2 (71.4 vs. 47.1 mg/dL); no significant difference of the variability in FBG was observed in periods 3 and 4 between the CSII and MDI groups (Fig. 1 c). In addition, the variability in BG before meals of group CSII improved after switching from MDI to CSII therapy, while that of group MDI remained unchanged throughout the study. There were significant reductions ($P < 0.05$) in the variation in BG before meals during periods 3 (75.0 vs. 63.8 mg/dL) and 4 (75.0 vs. 61.7 mg/dL) in comparison with the baseline in CSII (Fig. 1 d). There was no significant difference of the variability in BG before meals between the two groups.

Table 2: Changes in mean HbA1c at baseline and in periods 1, 2, 3 and 4

Parameter	Groups	Baseline	Period 1 1-3 months	Period 2 4-6 months	Period 3 7-9 months	Period 4 10-12 months
JDS HbA1c (%)	MDI, n=18	7.23 (0.20)	7.43 (0.24)	7.44 (0.27)	7.22 (0.24)	7.29 (0.25)
	CSII, n=6	7.68 (0.21)	7.50 (0.22)	7.56 (0.29)	7.38 (0.27)	7.18 (0.33)
NGSP HbA1c (%)	MDI, n=18	7.66 (0.20)	7.87 (0.25)	7.89 (0.28)	7.66 (0.25)	7.73 (0.25)
	CSII, n=6	8.12 (0.21)	7.94 (0.23)	8.00 (0.30)	7.82 (0.27)	7.61 (0.33)
IFCC HbA1c (mmol/mol)	MDI, n=18	58.3 (2.1)	60.4 (2.5)	60.5 (2.8)	58.2 (2.5)	58.9 (2.6)
	CSII, n=6	62.9 (2.1)	61.1 (2.3)	61.7 (3.0)	59.9 (2.8)	57.7 (3.4)

JDS HbA1c, Japan Diabetes Society values; NGSP HbA1c, National Glycohemoglobin Standardization Program values; IFCC HbA1c, International Federation of Clinical Chemistry and Laboratory Medicine values.
Each value represents the mean (SEM).

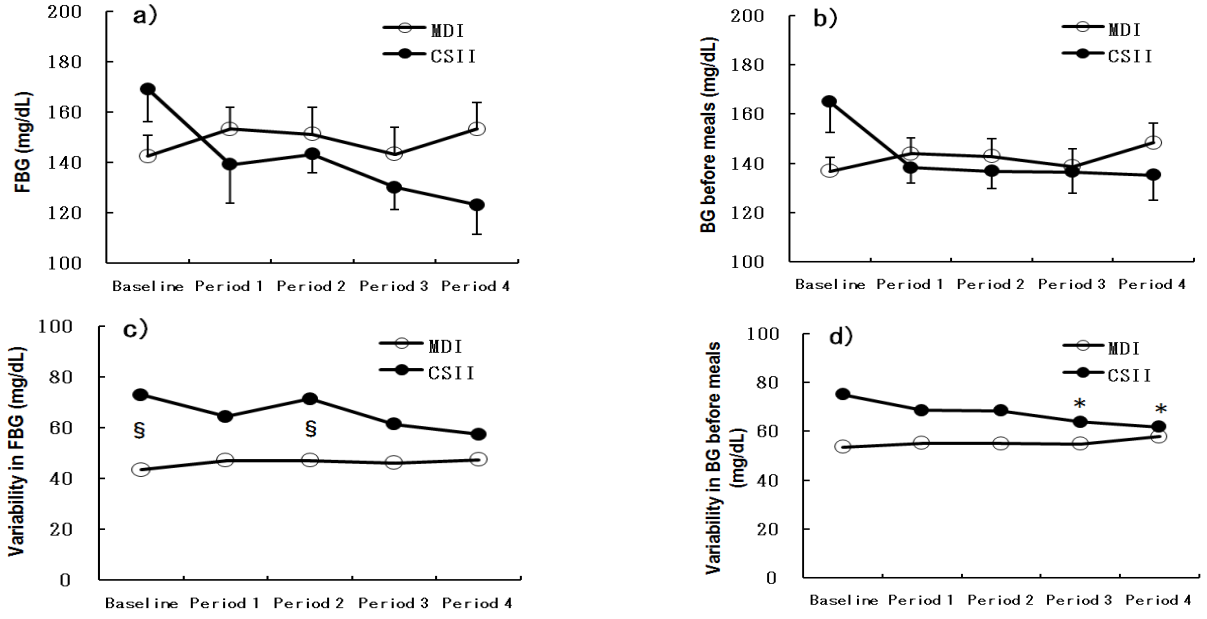

Fig. 1: Comparison of the changes in mean values of FBG (a), BG before meals (b), variability in FBG (c) and BG before meals (d) of groups MDI and CSII at baseline and in periods 1, 2, 3 and 4.

Each open circle with bar represents the mean (SEM) for 15 patients in MDI therapy.
Each closed circle with bar represents the mean (SEM) for 6 patients in CSII therapy.
FBG represents fasting blood glucose levels.
BG represents blood glucose levels.
Variability in FBG was calculated as the standard deviation of FBG.
Variability in BG before meals was calculated as the standard deviation of BG before meals.
*) $p < 0.05$ vs baseline (Wilcoxon's signed rank test)
§) $p < 0.05$, between the MDI and CSII groups (Mann-Whitney's U-test).

Results of insulin dose adjustment

Figure 2 shows the changes in the mean daily insulin doses at baseline and during the four study periods. Although the mean daily insulin dose of the MDI group remained unchanged (approximately 0.72 IU/kg/day), the dose of the CSII group tended to decrease from 0.71 ± 0.05 IU/kg/day to 0.58 ± 0.04 IU/kg/day during the study. There was no significant difference between the two groups.

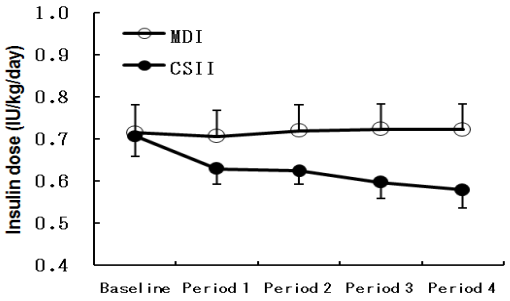

Fig. 2: Comparison of changes in mean total insulin dose of groups MDI and CSII at baseline and in periods 1, 2, 3 and 4

Each open circle with a bar represents the mean (SEM) for 18 patients in MDI therapy.
Each closed circle with a bar represents the mean (SEM) for 6 patients in CSII therapy.

Changes in bodyweight

Figure 3 shows changes in the mean bodyweight at baseline and during the four periods. Although the mean bodyweight of group MDI remained unchanged, that of group CSII increased after switching from MDI to CSII therapy. There was significant weight gain ($P < 0.05$) in group CSII during periods 1 (63.1±2.8 vs. 64.3 ± 3.1 kg), 3 (63.1 ± 2.8 vs. 65.1 ± 2.8 kg) and 4 (63.1 ± 2.8 vs. 65.2 ± 2.8 kg) compared with that at baseline.

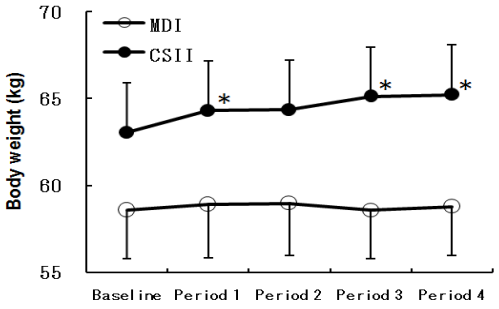

Fig. 3: Comparison of the changes in mean bodyweight of groups MDI and CSII at baseline and in periods 1, 2, 3 and 4

Each open circle with a bar represents the mean (SEM) for 18 patients in MDI therapy.
Each closed circle with a bar represents the mean (SEM) for 6 patients in CSII therapy.
*) $p < 0.05$ vs. baseline (Wilcoxon's signed rank test)

Frequency of hypoglycemia and other side effects

Table 3 shows the mean frequency of hypoglycemic episodes at baseline and during the four periods. Significant increases in the mean frequency of overall and daytime hypoglycemia in group CSII during period 1 (both $P < 0.05$) were found compared with those at baseline, and there were tendencies to decrease in periods 2, 3 and 4. In contrast, the mean frequency of nocturnal hypoglycemia was unchanged throughout the study period. Meanwhile, significant increases in the mean frequency of overall and daytime hypoglycemia in group MDI during period 3 (both $P < 0.05$) were found compared with those at baseline. No severe hypoglycemic episodes that required external help occurred during the study period. Furthermore, no other adverse events were caused by treatment with detemir-based MDI or CSII therapy during the study period.

Table 3: Changes in mean frequency of hypoglycemia at baseline and in periods 1, 2, 3 and 4

Hypoglycemia (events/patient/3months)	Groups	Baseline	Period 1 1-3 months	Period 2 4-6 months	Period 3 7-9 months	Period 4 10-12 months
Overall	MDI, n=15	22.7 (9.3)	23.1 (9.0)	23.5 (8.9)	26.6 (9.8)*	22.5 (9.6)
	CSII, n=6	22.5 (7.1)	41.9 (13.1)*	37.5 (13.5)	35.0 (9.4)	31.3 (9.7)
Daytime	MDI, n=15	22.6 (9.3)	22.9 (9.0)	23.3 (8.9)	26.5 (9.8)*	22.4 (9.5)
	CSII, n=6	22.5 (7.1)	41.7 (13.1)*	37.5 (13.5)	35.0 (9.4)	31.3 (9.7)
Nocturnal	MDI, n=15	0.1 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)
	CSII, n=6	0	0.2 (0.2)	0	0	0

Each value represents the mean (SEM).
*) $p<0.05$ vs. baseline (Wilcoxon's signed rank test)

Changes in lipid profiles

Table 4 shows the changes in mean values of TC, TG, HDL-C and LDL-C at baseline and during the four periods. There was a significant decrease ($P < 0.01$) in TC and HDL-C of group MDI during period 3 compared with that at baseline. No significant difference was observed in group CSII compared with that at baseline throughout the study period. There were no significant differences of the values of TC, TG, HDL-C and LDL-C between the two groups.

Table 4: Changes in mean lipid profiles at baseline and in periods 1, 2, 3 and 4

Parameter (mg/dL)	Groups	Baseline	Period 1 1-3 months	Period 2 4-6 months	Period 3 7-9 months	Period 4 10-12 months
TC	MDI, n=17	206.2 (7.7)	209.2 (8.0)	207.1 (7.6)	192.6 (6.6)†	207.0 (8.8)
	CSII, n=6	189.3 (9.6)	190.7 (11.3)	192.7 (8.9)	190.4 (9.9)	190.6 (10.0)
TG	MDI, n=17	106.9 (20.2)	101.8 (15.6)	100.1 (24.1)	93.3 (12.4)	106.6 (25.1)
	CSII, n=6	89.2 (18.8)	74.2 (10.3)	82.4 (12.4)	107.5 (32.5)	88.9 (10.4)
HDL-C	MDI, n=17	70.5 (4.5)	71.3 (4.5)	71.5 (5.1)	64.3 (4.2)†	68.9 (4.4)
	CSII, n=6	62.7 (6.3)	64.2 (5.7)	64.3 (4.8)	62.9 (5.3)	62.7 (5.8)
LDL-C	MDI, n=17	111.3 (6.8)	114.0 (6.5)	112.0 (6.7)	104.6 (6.2)	114.9 (6.9)
	CSII, n=6	107.8 (13.0)	106.9 (12.7)	108.9 (11.8)	102.7 (9.6)	107.1 (12.1)

TC, total cholesterol; TG, triglycerides; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.
Each value represents the mean (SEM).
†) $p<0.01$ vs. baseline (Wilcoxon's signed rank test).

DISCUSSION

The results obtained in this study revealed that glycemic control was improved after switching from detemir-based MDI to CSII therapy. As shown in Fig. 1, FBG, BG before meals, variability in FBG and BG before meals in group CSII improved after switching from MDI to CSII therapy. It is considered that these beneficial effects of CSII therapy eventually lead to improvement of HbA1c levels (Table 2).

In our previous study, we reported that changing the dosage regimen of detemir from once-daily to twice-daily administration improves within-subject variability of BG in Japanese patients with insulin-dependent diabetes who received MDI therapy with detemir [17]. In this study, most patients in the CSII group (83.3%) received twice-daily detemir before switching from MDI to CSII (Table 1). The data shown in Table 2 and Fig. 1 provide evidence that CSII is more effective in terms of glycemic control than detemir-based MDI. In addition, our results in this study are consistent with those of previous studies implying that CSII is more effective than the use of an analog-only glargine-based MDI therapy [9-14].

As shown in Fig. 2, the total insulin dose in the CSII group decreased, whereas that of the MDI group remained unchanged throughout the study periods. Several reports showed that insulin detemir required a higher dose than NPH insulin or insulin glargine [18, 19, 21]. In our previous studies, even though the majority of patients required increases in doses of detemir to achieve better glycemic control, the total insulin dose remained unchanged [17, 18]. The reduction of the total insulin in group CSII was independent of treatment with detemir before switching CSII therapy. The results in this study are in accordance with those of previous studies implying a reduction in the total insulin dose requirement of most patients. This might be related to more reliable absorption of insulin with CSII by using a single injection site for several days. In addition, it is likely that CSII enables more precise adjustment of insulin dose and delivery of a small amount of insulin to facilitate insulin deficiency.

The present study also showed that bodyweight was increased by CSII treatment regardless of temporary decreases in the total insulin dose (Figs. 2, 3). Weight gain is a common problem during insulin therapy and presents a major concern for many patients in clinical practice [22, 23]. In previous reports, the prevailing view is that weight gain is similar for CSII with lispro and glargine-based MDI therapy in type 1 or type 2 diabetes mellitus [13, 24]. We previously reported that Japanese insulin-dependent patients with diabetes treated with detemir in basal-bolus therapy exhibited less weight gain [18, 19]. There are several possible explanations for this phenomenon: reduction of the frequency of intermittent food intake provides fewer hypoglycemic attacks [25, 26, 28]; the high affinity of detemir to suppress hepatic glycogenesis [27-29]; detemir activating the insulin receptor signaling cascade causing neurological anorexia [27, 28, 30]; and detemir being less adipogenic in comparison with human insulin because of its lower affinity for the insulin receptor [31]. In our previous paper, we stated that the weight loss observed in detemir treatment might not be the result of reduced calorie intake associated with fewer hypoglycemic attacks [19]. In addition, a very recent reported study demonstrated that detemir provides stronger acute effects on brain functions than human insulin, and detemir becomes a trigger of a relative decrease in food consumption; that is, detemir enhances anorexigenic effects on the central nervous networks that control nutrient uptake compared with human insulin [32]. It is also possible that increased intake of snacks as defense against hypoglycemia, normalization of glucose metabolism because of stable insulin absorption, or flexibility of diet could explain the weight gain in CSII therapy. These are still only hypotheses and further experiments are needed to establish the mechanism responsible for less weight gain. Nonetheless, these findings suggest that detemir-based MDI is associated with less weight gain than other insulin regimens for long-term treatment.

Although the prevalence of hypoglycemia showed a tendency to decrease gradually toward the end of the study periods, the frequency of overall and daytime hypoglycemic attacks increased significantly after switching from MDI to CSII (Table 3). The reason for this was assumed to be that patients must acquire basic knowledge on insulin pharmacodynamics, carbohydrate counting and insulin pump technology in CSII therapy. Since a switch to a new injection pump technology requires frequent insulin adjustment, so patients must be able to assess their physical conditions and operate a computerized insulin pump. In general, it takes several months after switching to CSII for sufficient competence in these techniques to be obtained. As shown in Fig. 2, CSII required lower doses of insulin than MDI throughout the study period. We conclude that the increase in the risk of hypoglycemia is related to the possibility of excess insulin infusion. We propose that enthusiasm and motivation of patients, as well as of medical and nursing staff, for CSII therapy are the most important factors for the achievement of better glycemic control.

Derosa *et al.* concluded that CSII therapy also improves TC, TG, HDL-C and LDL-C because of the steady insulinization [15]. In our results, improvement of lipid profile in group CSII was not observed during the study periods (Table 4). In contrast, there were significant decreases ($P < 0.01$) in TC and HDL-C during period 3 in group MDI compared with those at baseline. Since these declines recovered to previous levels in period 4, these results raise the possibility of seasonal variation in Japan [33-34].

From these observations, we conclude that CSII therapy reduces the within-patient variability in BG and could improve glycemic control in Japanese patients with type 1 diabetes with unstable glycemic control using detemir-based MDI. In light of these considerations, the results in this study are essentially consistent with the recent findings regarding comparative studies between MDI and CSII therapy as prospective randomized studies in other countries [7-14]. In switching from detemir-based MDI to CSII, however, we must be careful about weight control and insulin dose adjustment. In contrast, MDI using detemir achieves stable results of insulin dose adjustment and bodyweight control. CSII using rapid-acting insulin therapy improves quality of life in terms of fewer injections and more flexibility for everyday activities [35-36]. On the other hand, CSII therapy is more expensive than MDI therapy because of the pump and cost of supplies, so CSII therapy is not applicable for all diabetic patients [14]. Finally, a limitation of this study was the small number of patients. Further studies are required on a large population to evaluate the advantages or disadvantages of these two intensified insulin treatments in Asian patients with type 1 diabetes.

In conclusion, beneficial effects of CSII using lispro, including both improvements of blood glucose control and variability in blood glucose levels, were observed in Japanese patients with type 1 diabetes inadequately treated with detemir-based MDI. In contrast, MDI using detemir has advantages of less weight gain. In switching from detemir-based MDI to CSII with lispro, it should be noted that CSII therapy causes weight gain and increased risk of hypoglycemia.

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