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SHORT COMMUNICATION

Effect of switching from conventional continuous subcutaneous insulin infusion to sensor augmented pump therapy on glycemic profile in Japanese patients with type 1 diabetes

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Abstract

Aims Evidence suggests that sensor augmented pump (SAP) therapy is superior to conventional continuous subcutaneous insulin infusion (CSII) for achieving glycemic control in patients with type 1 diabetes. However, the clinical benefit of SAP therapy in East Asians has not yet been demonstrated.

Methods The effect of switching from conventional CSII to SAP therapy on glycemic profile was examined in 18 Japanese patients with type 1 diabetes. The glycemic profile of the patients was determined by retrospective continuous glucose monitoring (CGM) within 1 month before the treatment switch, whereas that at 6 and 12 months after the switch was evaluated with the CGM function of the SAP device. Hemoglobin A1c levels were also measured before and after the switch to SAP therapy.

Results The duration of hypoglycemia was significantly decreased at both 6 and 12 months after the change in treatment (6.6 ± 4.5, 3.2 ± 4.1, and 3.0 ± 2.8 min/h for before and 6 and 12 months, respectively), as was the HbA1c level at 12 months (7.8 ± 1.0 and 7.4 ± 0.9%, respectively). The duration of hyperglycemia did not differ between before and after the treatment switch. The decline in HbA1c level at 12 months after the switch to SAP was negatively correlated with age.

Conclusion Switching from conventional CSII to SAP therapy was associated with a decrease in both the duration of hypoglycemia and the level of HbA1c in Japanese patients with type 1 diabetes.

Keywords Continuous subcutaneous insulin infusion · Sensor augmented pump · Type 1 diabetes · Hypoglycemia

Introduction

Although a reduction in blood glucose concentration is fundamental to the prevention of diabetic complications [1, 2], the achievement of optimal glycemic control is often challenging for individuals with diabetes mellitus. One obstacle for such patients is the concern over and fear of the development of hypoglycemia during treatment [3]. The recent development of new drugs and devices for the treatment of diabetes has improved this situation. Evidence suggests that continuous subcutaneous insulin infusion (CSII) is beneficial for the treatment of type 1 diabetes in terms of reducing hemoglobin A1c (HbA1c) levels without increasing the frequency of hypoglycemia [4]. Although recognition of daily changes in blood glucose concentration by frequent home monitoring has a favorable effect on achievement of target HbA1c levels [5, 6], many individuals with type 1 diabetes do not measure their blood glucose at a sufficient frequency [7, 8]. Continuous glucose monitoring (CGM) is advantageous for providing a comprehensive picture of daily fluctuations in blood glucose concentration, with such devices also helping to reduce both HbA1c levels and the risk of hypoglycemia [9].

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A sensor augmented pump (SAP), a CSII pump equipped with real-time CGM, was recently launched on the market in Japan. Although previous studies have shown beneficial effects of SAP therapy for type 1 diabetes mellitus [10–12], the clinical utility of the device in East Asians has remained unknown. Moreover, these previous studies did not analyze changes in the frequency of daytime and nocturnal hypoglycemia separately [10–12], with the latter sometimes leading to potentially lethal events [13].

We have now investigated the effect of switching from conventional CSII to SAP therapy on glycemic profile in Japanese patients with type 1 diabetes. We analyzed glycemic profile with the use of CGM before and after the change in treatment and found that SAP therapy was beneficial for reducing both HbA1c levels and the duration of hypoglycemia.

Methods

Patients, treatment, and evaluation of glycemic profile

The study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 160123, approval date 6 October 2016). After MiniMed 620G (Medtronic, Northridge, CA, USA), a SAP therapy devise, had become available in Kobe University Hospital (October 2014), we introduced all the type 1 diabetes subjects who had been treated with CSII (a total of 112 subjects) with the use of Paradigm 712 or 722 (Medtronic) to SAP therapy. Twenty-four subjects wanted to change their pump to MiniMed 620G by April 2015. We excluded 3 subjects with pregnant and 3 with severe renal dysfunction. We thus analyzed the data of 18 subjects.

Within 1 month before the change of treatment, the glycemic profile of the patients was investigated with the use of a retrospective CGM system (iPro2, Medtronic) for 5 days. After the change in treatment, insulin titration was performed according to the instruction of the attending physician or the patient's own judgment. The duration of hypoglycemia (< 70 mg/dl) and hyperglycemia (> 180 mg/dl), the area under the curve (AUC) for hypoglycemia and hyperglycemia, mean blood glucose levels, as well as the mean amplitude of glycemic excursions (MAGE) and standard deviation (SD) of glucose level were evaluated over 30 days with the CGM function of the SAP device at 6 and 12 months after the change in treatment. We defined nighttime as 23:00–6:00, and daytime as 6:00–23:00. Retrospective CGM data obtained with iPro2 were analyzed with the CGM analysis software (CareLink iPro Therapy Management Software for Diabetes, Medtronic). The CGM and pump data for the SAP system were analyzed with the diabetes management software (CareLink Therapy Management System for Diabetes-Clinical, Medtronic).

Statistical analysis

Data are presented as mean ± SD. Differences in parameters measured before and after the change in treatment were analyzed with the paired Student's *t* test. The relation between the reduction in either HbA1c level or the duration of hypoglycemia after the switch in treatment to age, baseline HbA1c, the time of sensor usage, or the frequency of self-monitoring of blood glucose (SMBG) or of hypoglycemic or hyperglycemic alarms, the frequency of bolus, the frequency of correction bolus was evaluated with Pearson's correlation coefficient (*r*). Glycemic variability (MAGE and SD of glucose level) was calculated with the use of EASY GV software [14]. All statistical analyses were performed with SPSS software version 22 (IBM SPSS statistics). A *P* value of < 0.05 and an *r* value of $> |\pm 0.4|$ were considered statistically significant.

Results

The baseline characteristics of the 18 study subjects are shown in Table 1. The capacity for insulin secretion as assessed by the response to glucagon infusion was almost completely exhausted. No diabetic ketoacidosis or episodes of severe hypoglycemia (defined as events associated with central nervous system manifestations during which the patient required the assistance of another person) were reported during the study period.

After the change in treatment from conventional CSII to SAP therapy, the duration of hypoglycemia for all day or daytime decreased significantly from 6.6 ± 4.5 and 7.1 ± 4.5 min/h, respectively, to 3.2 ± 4.1 and 3.1 ± 4.0 min/h at 6 months and to 3.0 ± 2.8 and 3.2 ± 3.0 min/h at 12 months (Table 2). Although the

Table 1 Baseline characteristics of the 18 study patients

Characteristic	
Males/females	2/16
Age (years)	41.2 ± 16.9
Body mass index (kg/m^2)	22.7 ± 3.7
Duration of diabetes (years)	11.6 ± 8.3
Duration of conventional CSII treatment (years)	3.7 ± 1.7
HbA1c (%)	7.8 ± 1.0
ΔCPR_{6min} (ng/ml)	0.07 ± 0.15

Data are mean ± SD. ΔCPR_{6min}, the difference in serum C-peptide levels between 6 min after and before the intravenous infusion of 1 mg of glucagon

Table 2 CGM results and other clinical parameters before as well as 6 and 12 months after the switch from conventional CSII to SAP therapy

Parameter	Before the change to SAP	6 months after the change to SAP	12 months after the change to SAP
Duration of glucose range (min/h)			
< 70 mg/dl			
All day	6.6 ± 4.5	3.2 ± 4.1*	3.0 ± 2.8*
Daytime	7.1 ± 4.5	3.1 ± 4.0*	3.2 ± 3.0*
Nighttime	5.6 ± 7.2	3.1 ± 4.2	2.4 ± 2.9
70–180 mg/dl	35.7 ± 6.8	36.8 ± 7.8	38.1 ± 9.0
> 180 mg/dl	17.6 ± 8.5	20.0 ± 9.8	18.9 ± 10.2
AUC for glucose range [(min × mg/dl)/day]			
< 70 mg/dl	1.4 ± 1.2	0.7 ± 1.1*	0.6 ± 0.7*
> 180 mg/dl	16.2 ± 9.2	18.3 ± 12.7	16.6 ± 14.4
Mean glucose level (mg/dl)	146.0 ± 24.8	158.3 ± 28.3	155.7 ± 28.5
SD of glucose level (mg/dl)	63.2 ± 12.1	59.6 ± 11.4	57.7 ± 11.9
MAGE (mg/dl)	117.9 ± 26.7	114.6 ± 20.4	106.4 ± 20.5
HbA1c (%)	7.8 ± 1.0	7.7 ± 0.9	7.4 ± 0.9*
TDD (U/day)	33.5 ± 12.7	34.3 ± 12.6	38.9 ± 15.2
TBD/TDD ratio (%)	29 ± 10	29 ± 7	28 ± 8

Data are mean ± SD

MAGE mean amplitude of glycemic excursions, *TDD* total daily dose of insulin, *TBD* total basal dose of insulin

*$P < 0.05$ versus before the switch to SAP therapy (paired Student's *t* test)

duration of hypoglycemia during nighttime also tended to be decreased from 5.6 ± 7.2 before to 3.1 ± 4.2 and 2.4 ± 2.9 min/h at 6 and 12 months, respectively, after the switch in treatment, these changes were not statistically significant ($P = 0.21$ and 0.10, respectively). The AUC of hypoglycemia for all day was also significantly decreased from 1.4 ± 1.2 before to 0.7 ± 1.1 and 0.6 ± 0.7 (mg/dl) at 6 and 12 months, respectively, after the change in treatment. The duration and AUC for hyperglycemia did not differ between before and after the change in treatment.

The HbA1c level declined from 7.8 ± 1.0% before to 7.7 ± 0.9% at 6 months and 7.4 ± 0.9% at 12 months after the switch from conventional CSII to SAP therapy, with only the change at 12 months achieving statistical significance ($P = 0.41$ and < 0.05, respectively) (Table 2). The mean glucose level was similar before and after the change of treatment. Parameters for glycemic variability including MAGE and the SD of glucose level were also not altered after the therapy switch.

The percentage sensor usage time over the 12 months after the switch to SAP therapy was 75 ± 22%, with the values for the 1st (78 ± 20%) and 12th (76 ± 22%) months not being significantly different. The frequency of self-monitoring of blood glucose declined significantly from 6.4 per day for the 1st month to 4.3 and 4.9 per day for the 6th and 12th months of SAP usage, respectively ($P < 0.01$ and < 0.05, respectively).

The total daily dose of insulin tended to be increased after the change in treatment, although the differences did not achieve statistical significance [33.5 ± 12.7 U/day before to 34.3 ± 12.6 U/day at 6 months ($P = 0.73$) and 38.9 ± 15.2 U/day at 12 months ($P = 0.08$)] (Table 2). The total daily dose of insulin standardized by body mass did not significantly differ after the change in treatment [0.61 ± 0.24 U/kg/day before to 0.61 ± 0.21 U/kg/day at 6 months ($P = 0.89$) and 0.69 ± 0.24 U/kg/day at 12 months ($P = 0.14$)]. The ratio of the total basal dose of insulin to the total daily dose was not altered after the treatment switch. Although the hourly rates of basal insulin at 12 months after the change of the therapy tended to be greater than those before the change of the therapy at most of the time of the day, no significant change was observed at each time point (Fig. 1). The carbohydrate to insulin ratio at lunch, but not those at breakfast and dinner, was significantly decreased at 12 months after the change of the therapy (Fig. 1).

The frequency of bolus increased from 4.8 ± 2.1 (before the change of the therapy) to 6.9 ± 1.7 per day (at 12 months after the change of the therapy) ($P < 0.05$). The frequency of correction bolus tended to be increased from 3.6 ± 2.2 to 4.6 ± 1.9 per day; the difference did not reach to statistical significance.

Among the various parameters measured, the reduction in HbA1c level at 12 months after the change in treatment was negatively correlated with age ($r = -0.49$, $P < 0.05$) and

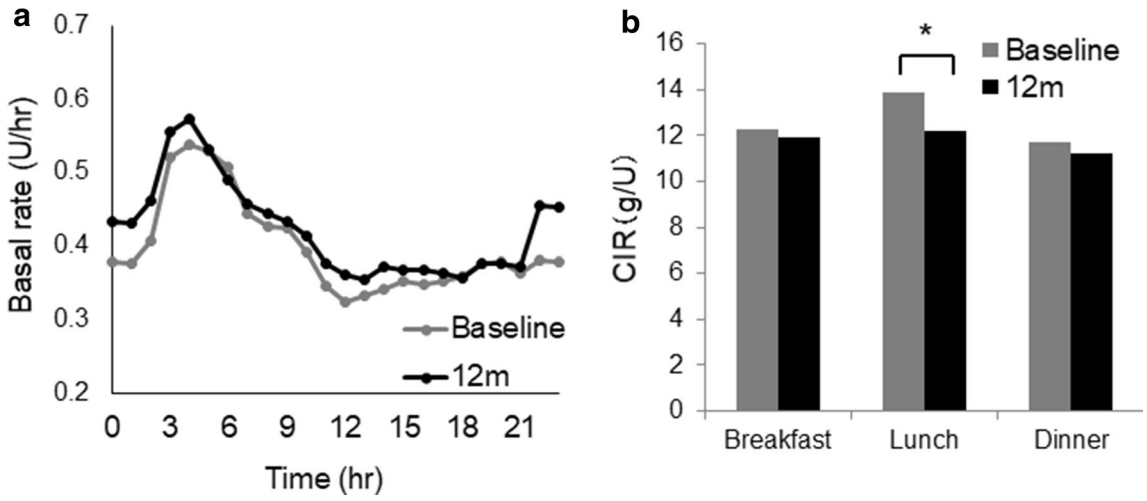

Fig. 1 Daily profile of basal insulin rate (**a**) and carbohydrate to insulin ratio (CIR) for each meal (**b**) at baseline and 12 months after the switch from conventional CSII to SAP therapy. *$P < 0.05$, baseline vs. 12 months after

tended to be correlated with the frequency of hyperglycemic alarms ($r = 0.47$, $P = 0.05$) as well as with baseline HbA1c level ($r = 0.41$, $P = 0.09$) (Table 3). The reduction in the duration of hypoglycemia was neither correlated with any of the parameters measured (Table 3), nor the reduction in HbA1c level ($r = -0.25$, $P = 0.31$).

At the initiation of SAP therapy, all the subjects used hypoglycemic, hyperglycemic alarms and predictive alerts with 70 and 250 mg/dl for the low and the high limits, respectively. At 12 months after the switch of the therapy, 16 subjects had changed the initial setting either by the instruction of the attending physicians or by the self-decision: 3 and 3 subjects lowered and raised the low limit, respectively; 3 and 1 subjects lowered and raised the high limit, respectively; and 6 and 9 subjects ceased the usage of hypoglycemic and hyperglycemic predictive alerts, respectively. Frequency of hypoglycemic alarms was not correlated with the reduction in the duration of hypoglycemia or in HbA1c level (Table 3). Although frequency of hyperglycemic alarms was not correlated with the reduction in the duration of hypoglycemia, it tended to be correlated with the reduction in HbA1c level ($P = 0.05$, Table 3).

Table 3 Correlation between the reduction in the duration of hypoglycemia or in HbA1c level at 12 months after the switch to SAP therapy and other parameters

Parameter	Reduction in duration of hypoglycemia	Reduction in HbA1c level
Age	$P = 0.44$ $r = 0.19$	$P < 0.05$ $r = -0.49$
Baseline HbA1c level	$P = 0.19$ $r = 0.32$	$P = 0.09$ $r = 0.41$
Frequency of self-monitoring of blood glucose (SMBG)	$P = 0.20$ $r = -0.31$	$P = 0.35$ $r = -0.23$
Sensor usage	$P = 0.69$ $r = -0.10$	$P = 0.53$ $r = -0.16$
Frequency of hypoglycemic alarms	$P = 0.68$ $r = -0.11$	$P = 0.43$ $r = 0.20$
Frequency of hyperglycemic alarms	$P = 0.91$ $r = -0.03$	$P = 0.05$ $r = 0.47$
Bolus frequency	$P = 0.27$ $r = -0.28$	$P = 0.46$ $r = 0.19$
Frequency of correction bolus	$P = 0.38$ $r = -0.22$	$P = 0.53$ $r = -0.16$

Discussion

We analyzed the glycemic profile of Japanese patients with type 1 diabetes with the use of CGM before and after the switch from conventional CSII to SAP therapy. We found that the change in treatment was associated with a reduction both in the duration of hypoglycemia and in HbA1c level. As far as we are aware, this is the first demonstration of the superiority of SAP therapy over conventional CSII therapy for glycemic control in Japanese individuals with type 1 diabetes.

The duration of hypoglycemia for all day and daytime, but not for nighttime, was significantly reduced after the change in treatment. Although the exact reason for the reduction of the duration of hypoglycemia is unknown, it is likely that continuous glucose monitoring by SAP therapy was useful for appropriate change of the pump setting and thus contributed to the favorable outcome. The effect of the use of real-time CGM on nocturnal hypoglycemia has been found to vary. The use of real-time CGM over 3 days reduced the duration of hypoglycemia to a greater extent at nighttime than in daytime for patients with type 1 diabetes treated with multiple daily injections or CSII therapy [15]. Use of a real-time CGM device in such patients for 6 months resulted in a reduction in the duration of hypoglycemia both for all day and to a lesser extent at nighttime [16]. No previous study has directly compared the influence of conventional CSII therapy and SAP therapy on daytime and nocturnal hypoglycemia separately. It is unclear why SAP therapy did not reduce nocturnal hypoglycemia in the present study. It is possible that real-time glucose monitoring during SAP therapy enabled the immediate self-management of hypoglycemia at daytime, whereas patients might miss alarms during sleep.

Although previous studies have shown that longer sensor usage was correlated with a greater decline in HbA1c levels [17–20], the time of sensor usage was not correlated with the reduction in HbA1c after the switch from conventional CSII to SAP therapy in the present study. Sensor usage time was relatively long throughout the present study, with the mean percentage value over 12 months being 75%, whereas the values for previous studies were either shorter (30–62.5%) [19, 20] or varied according to age (30–83%) [17]. We found that younger age was associated with a greater reduction in HbA1c level, suggesting that younger adults recognize the benefit of SAP to a greater extent than older individuals. However, previous studies in which the effects of SAP were evaluated in cohorts containing younger patients including children showed that age was directly correlated with the reduction in HbA1c level [17–19]. Alarm/alert setting is an important factor that potentially influences the outcome of the therapy. We have shown that frequencies of hyperglycemic and hypoglycemic alarms were not correlated with the reduction of hypoglycemia or of HbA1c level. We did not use a standardized alarm/alert setting protocol and the study subjects set the alarm/alert in various conditions, which may explain the lack of the correlation between alarm frequencies and the outcome of the study.

The HbA1c level reduced after the change in treatment, but the mean glucose level did not. We currently do not know the reason for this apparent inconsistency. We cannot exclude the possibility that monitoring of glucose with CGM immediately altered self-care behaviors of the study subjects during the pre-treatment evaluation period. Indeed, the estimated HbA1c values calculated by the mean glucose levels (6.7 ± 0.9%) were lower than the real HbA1c values (7.8 ± 1.0%) at this period. At 12 months after the change of the therapy, the difference between the estimated HbA1c values (7.1 ± 1.0%) and the real HbA1c values (7.4 ± 0.9%) had become smaller. It is thus possible that the mean glucose levels during the pre-treatment evaluation period were lower than the baseline conditions of the subjects.

One limitation of the current study is its design, which is that of a retrospective observational study with a relatively small number of patients. Moreover, we did not determine the sample size before the initiation of the study, and analyzed the data of all subjects obtained during a certain time period. A post hoc power analysis, however, revealed that our sample size possesses a sufficient power (83% with α value 5%) to detect the difference in the reduction of the duration of hypoglycemia. The number of patients treated with CSII is much smaller in Japan than in the US or many European countries, with a large proportion of Japanese individuals with type 1 diabetes being treated by multiple daily injections [21–23]. Our study subjects, for whom the average duration of conventional CSII therapy was 3.7 years, thus may not be truly representative of Japanese patients with type 1 diabetes. Moreover, the study subjects wanted to change their pump to the SAP devise immediately after its launch in Japan. It is possible that those subjects were highly motivated by its treatment of diabetes, which could raise some bias. To evaluate the effects of SAP therapy under the real-world clinical practice, we did not use a standardized titration algorism, which is also a limitation of the study. We also evaluated glycemic profile before and after the initiation of SAP therapy with different devices (iPro2 and the CGM function of the SAP device, respectively). Little information regarding the differences in measurement accuracy between different CGM devices is available [24].

In summary, our results suggest that SAP therapy has a beneficial effect on the glycemic profile of adult Japanese patients with relatively well controlled type 1 diabetes, with the observed reduction in both HbA1c levels and the duration of hypoglycemia being similar to that previously

described for subjects of different ethnicities and different age groups [10–12, 25]. Further studies with larger numbers of subjects are required to confirm the clinical superiority of this newly developed treatment device.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. All subjects provided written informed consent to analyze and publish their data for scientific purpose.

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