JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
SHORT REPORT

Comparison of continuous subcutaneous insulin infusion treatment and multiple daily injection treatment on the progression of diabetic complications in Japanese patients with juvenile-onset type 1 diabetes mellitus

Takafumi Masuda[1], Naoto Katakami[1]*, Naohiro Taya[1], Kazuyuki Miyashita[1], Mitsuyoshi Takahara[1,2], Ken Kato[3], Akio Kuroda[4], Munehide Matsuhisa[4], Iichiro Shimomura[1]

[1]Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, [3]Diabetes Center, NHO Osaka National Hospital, Osaka, Japan, and [4]Diabetes Therapeutics and Research Center, Institute of Advance Medical Sciences, Tokushima University, Tokushima, Japan

Keywords
Continuous subcutaneous insulin infusion, Diabetic complication, Type 1 diabetes mellitus

***Correspondence**
Naoto Katakami
Tel.: +81-6-6879-3732
Fax: +81-6-6879-3739
E-mail address:
katakami@endmet.med.osaka-u.ac.jp

J Diabetes Investig 2022; 13: 1528–1532

doi: 10.1111/jdi.13819

ABSTRACT

To evaluate whether continuous subcutaneous insulin infusion attenuates the progression of diabetic complications, we retrospectively extracted data from 35 individuals who had developed type 1 diabetes mellitus aged ≤20 years and whose treatment had been changed from multiple daily injections to continuous subcutaneous insulin infusion. The annual changes in estimated glomerular filtration rate, urinary albumin excretion rate, carotid intima-media thickness and brachial-ankle pulse wave velocity during each treatment period were calculated. Although mean glycated hemoglobin under the continuous subcutaneous insulin infusion treatment was lower than that under the multiple daily injection treatment, there were no significant differences in annual changes in diabetic nephropathy and atherosclerosis between the two treatment periods. This pilot study showed that, in Japanese patients with juvenile-onset type 1 diabetes mellitus, there was no significant difference in the progression of diabetic nephropathy and atherosclerosis, at least in the early stage, between the two treatments.

INTRODUCTION

Compared with multiple daily injection (MDI) therapy, continuous subcutaneous insulin infusion (CSII) therapy improves glycemic control in patients with type 1 diabetes mellitus[1]. In addition, several studies carried out in Western countries showed that CSII was associated with a reduced risk of diabetic complications, such as nephropathy, retinopathy and macroangiopathy [2–4]. The aim of the present study was to evaluate whether CSII, as compared with MDI, attenuates the progression of diabetic complications in Japanese patients with juvenile-onset type 1 diabetes mellitus.

Received 2 February 2022; revised 14 April 2022; accepted 25 April 2022

MATERIALS AND METHODS

This was a retrospective observational study using a dataset obtained from a health-check program for patients with type 1 diabetes mellitus. This program targeted patients who developed type 1 diabetes mellitus aged ≤20 years, and was carried out annually at Osaka University Hospital and Osaka Police Hospital, Osaka Japan, from 2000 to 2019. A total of 170 patients participated in the study. Of these, 35 patients who met the following eligibility criteria were included in this study: (i) treatment was changed from MDI to CSII (detailed in Tables S1 and S2); and (ii) periods of MDI treatment and CSII treatment were both over 2 years.

We used clinical data from four visiting points for each patient: the first and last visits during both the MDI and CSII

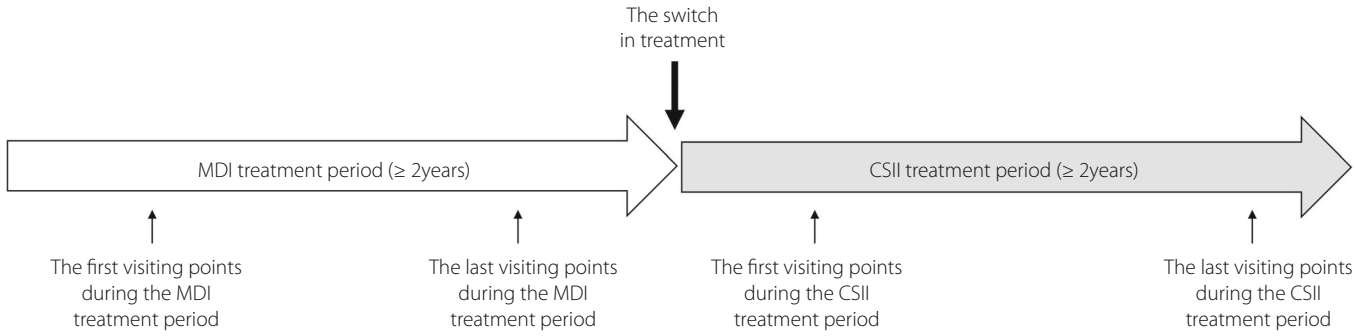

Figure 1 | Timeline of treatment changes and data collection. The switching of the treatment was carried out between the last visiting points during the multiple daily injections (MDI) treatment period and the first visiting points during the continuous subcutaneous insulin infusion (CSII) treatment period. The period between the last visiting points during the MDI treatment period and the first visiting points during the CSII treatment period was within 2 years (31 patients were 1 year and four patients were 2 years).

treatment periods (Figure 1). To evaluate glycemic control, we used average glycated hemoglobin (HbA1c) values measured during each treatment period. Urinary albumin excretion rate (UAE) was calculated as urinary albumin per day and urinary creatinine per day, which were obtained by 24-h urine collection. Carotid intima-media thickness (CIMT) was evaluated using B-mode imaging ultrasonography with a high-frequency linear probe (>7.5 MHz) according to the guidelines of the Japan Society of Ultrasonics[5]. CIMT was defined as the average value of three points measured at 10-mm intervals around the maximum thickening point on the distal wall of the common carotid artery. Brachial-ankle pulse wave velocity (baPWV) was evaluated as previously reported[6–8]. A higher value of either the left or right baPWV was adopted as a representative value. Detailed methods are outlined in Tables S1 and S2.

To assess progression, we calculated the annual changes in the estimated glomerular filtration rate (eGFR) in each treatment period using the following equation:

$$\text{Annual change in eGFR} = (\text{last eGFR} - \text{initial eGFR})/\text{observation period}$$

We calculated the annual changes in UAE, CIMT and baPWV in each treatment period by using equivalent formulas.

Summary statistics at baseline of the two treatment periods are shown as mean ± standard deviation for continuous data, and as *n* (%) for categorical data. UAE was subjected to a logarithmic conversion. Paired *t*-tests were used to compare glycemic control and progress of diabetic complications between the two treatment periods. Two-sided *P*-values of <0.05 were considered statistically significant. All statistical tests were carried out using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Table 1 shows the characteristics at the first visit during the MDI and CSII treatment periods separately (reference values are presented in the Tables S1 and S2). HbA1c level was significantly lower and baPWV was significantly higher at the first visit during the CSII period than during the MDI treatment period. There were no significant differences between the other variables.

The median treatment periods of MDI and CSII were 5.5 and 7.6 years, respectively. As shown in Table 2, the mean HbA1c level under CSII treatment was lower than that under MDI treatment. There were no significant differences in annual changes in eGFR, $\log_{10}$UAE, CIMT and baPWV between the two treatment periods.

DISCUSSION

The results of the present study are consistent with those of previous studies in that switching from MDI to CSII was associated with a reduction in HbA1c levels[9–12]. Previous studies showed that the annual age-related decline in eGFR in the general population and patients with type 1 diabetes mellitus were estimated at <1 mL/min/1.73 m^2 and 1.25 mL/min/1.73 m^2, respectively [13–15]. As the annual decline in eGFR during the MDI treatment period and that during CSII treatment in the present study were 0.59 ± 4.00 and 0.79 ± 2.03 mL/min/1.73 m^2, respectively, these annual declines were considered as almost within normal range, irrespective of treatment type. One possible explanation for this phenomenon is that the participants of the present study were relatively young, and the decline in their eGFR remained too small for detection of the difference between treatment periods.

Similarly, the progression of UAE was quite minor in both treatment periods, and there was no significant difference between the treatment periods. In contrast, treatment with CSII over 4 years significantly reduced UAE compared with treatment with MDI in Danish patients with type 1 diabetes mellitus[2], although age, duration of type 1 diabetes mellitus and baseline UAE levels of the study participants were greater than those of the present study. The differences in the background of the study participants between the studies might account for the discrepancy in the findings.

Table 1 | Characteristics at baseline according to treatment

Parameters (n = 35)	Baseline of MDI treatment	Baseline of CSII treatment	P-value
Age (years)	22.2 ± 3.2	28.8 ± 4.5	<0.001
Male (%)	5 (14.3%)	5 (14.3%)	–
Duration of diabetes (years)	12.8 ± 5.2	19.4 ± 5.8	<0.001
Smoking (%)	4 (11.4%)	4 (11.4%)	1.00
BMI (kg/m^2)	22.6 ± 2.4	23.0 ± 2.6	0.10
HbA1c (%)	8.48 ± 1.40	7.51 ± 1.11	0.001
LDL-C (mg/dL)	95.7 ± 20.7	101.5 ± 28.9	0.23
Statin (%)	0 (0%)	1 (2.9%)	1.00
Systolic blood pressure (mmHg)	112.8 ± 11.1	114.3 ± 11.8	0.41
Antihypertensives (%)	0 (0%)	3 (8.6%)	0.25
eGFR (mL/min/1.73 m^2)	104.5 ± 20.6	98.4 ± 14.6	0.09
UAE (mg/g·Cre)	5.95 (4.57, 7.64)	4.67 (2.67, 7.46)	0.37
Log_{10}UAE (mg/g·Cre)	0.83 ± 0.35	0.77 ± 0.60	0.45
Albuminuria (%)	2 (5.7%)	4 (11.4%)	0.50
CIMT (mm)	0.62 ± 0.08	0.61 ± 0.09	0.44
baPWV (cm/s)[†]	1,171.5 ± 206.7	1,228.4 ± 154.0	0.03

Categorical data are expressed as n (%), and continuous data as the mean ± standard deviation or geometric mean (interquartile range). Antihypertensives include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium antagonists. [†]n = 17. baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CIMT, carotid intima-media thickness; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; MDI, multiple daily injections; UAE, urinary albumin excretion rate.

Table 2 | Mean glycated hemoglobin and progress of each complication before and after treatment change

Parameters	n	Period of MDI treatment	Period of CSII treatment	P-value
Mean HbA1c (%)	35	8.26 ± 1.29	7.47 ± 0.99	<0.001
ΔeGFR (mL/min/1.73 m^2/year)	35	−0.56 ± 4.02	−0.79 ± 2.03	0.77
ΔLog_{10}UAE (mg/g·Cre/year)	35	0.016 ± 0.108	−0.025 ± 0.121	0.13
ΔCIMT (mm/year)	35	−0.001 ± 0.018	−0.002 ± 0.013	0.83
ΔbaPWV (cm/s/year)	17	10.50 ± 37.56	14.65 ± 21.43	0.67

Average numbers of the glycated hemoglobin (HbA1c) values used to calculate the "mean HbA1c" values were 5.9 in the period of multiple daily injections (MDI) treatment and 8.0 in the period of continuous subcutaneous insulin infusion (CSII) treatment, respectively. baPWV, brachial-ankle pulse wave velocity; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion rate.

The mean annual progression of CIMT after treatment with MDI and CSII was −0.001 ± 0.018 and − 0.002 ± 0.013 mm/year, respectively, and there was no significant difference. These values were comparable to those in the general population[16], whereas previous studies showed that the progression of carotid atherosclerosis was accelerated in patients with type 1 diabetes mellitus[17–21].

Although the mean annual progression value of baPWV in the general population has not been established yet, a previous study reported an age coefficient of 7.3 cm/s/age[22]. In this study, the mean annual progression of baPWV under treatment with MDI and CSII was 10.50 ± 35.76 and 14.65 ± 21.63 cm/s/year, respectively, without significant differences. Therefore, the elasticity of the arterial walls might be impaired more rapidly in individuals with type 1 diabetes mellitus than in the general population.

The strengths of the present study were that the observation period was relatively long, and that the annual progression of nephropathy and atherosclerosis during each treatment period was quantitatively measured in individuals.

The present study had some limitations. First, it was a retrospective study with a small sample size. Second, the follow-up period differed according to the patients. Third, as discussed in a review article[23], long-term glycemic variability is associated with diabetic macrovascular complications regardless of the method of insulin administration. Several studies also showed associations between glycemic variability assessed by continuous glucose monitoring system and progression of diabetic complications[24,25]. However, we have no data relating to glycemic variability indices. Finally, the acceleration of the progression of complications related to aging, if any, was not considered in the present study. Further studies with larger sample sizes and longer observation periods are necessary.

In conclusion, the present pilot study showed that in Japanese patients with juvenile-onset type 1 diabetes mellitus, there

was no significant difference in the progression of diabetic nephropathy or atherosclerosis, at least in the early stage after switching treatment, between the MDI and CSII treatment periods.

ACKNOWLEDGMENTS

This project did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. All authors thank Advisory Doctors of Osaka Association for Diabetes Education and Care.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study was approved by the Ethics Committee of Osaka University Hospital, Japan (approval number: 14328–9).

Informed consent: The participants provided written consent to participate in the study.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2002; 324: 705.
2. Rosenlund S, Hansen TW, Andersen S, *et al*. Effect of 4 years subcutaneous insulin infusion treatment on albuminuria, kidney function and HbA1c compared with multiple daily injections: a longitudinal follow-up study. *Diabet Med* 2015; 32: 1445–1452.
3. Steineck I, Cederholm J, Eliasson B, *et al*. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. *BMJ* 2015; 350: h3234.
4. Tołwińska J, Głowińska-Olszewska B, Bossowski A. Insulin therapy with personal insulin pumps and early angiopathy in children with type 1 diabetes mellitus. *Mediators Inflamm* 2013; 2013: 791283.
5. Terminology and Diagnostic Criteria Committee, Japan Society of Ultrasonics in Medicine. Standard method for ultrasound evaluation of carotid artery lesions. *Jpn J Med Ultrasonics* 2009; 36: 219–226.
6. Suzuki E, Kashiwagi A, Nishio Y, *et al*. Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients. *Diabetes Care* 2001; 24: 2107–2114.
7. Turin TC, Kita Y, Rumana N, *et al*. Brachial-ankle pulse wave velocity predicts all-cause mortality in the general population: Findings from the Takashima study. *Japan Hypertens Res* 2010; 33: 922–925.
8. Yamashina A, Tomiyama H, Takeda K, *et al*. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; 25: 359–364.
9. Boland EA, Grey M, Yu C, *et al*. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999; 22: 1779–1784.
10. Hannaire-Broutin H, Melki V, Bessieres-Lacombe S, *et al*. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. *Diabetes Care* 2000; 23: 1232–1235.
11. Ahern JH, Boland EA, Doane R, *et al*. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA1c levels across all age groups. *Pediatr Diabetes* 2002; 3: 10–15.
12. Sulli N, Shashaj B. Continuous subcutaneous insulin infusion in children and adolescents with diabetes mellitus: decreased HbA1c with low risk of hypoglycemia. *J Pediatr Endocrinol Metab* 2003; 16: 393–399.
13. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; 33: 278–285.
14. Baba M, Shimbo T, Horio M, *et al*. Longitudinal study of the decline in renal function in healthy subjects. *PLoS One* 2015; 10: e0129036.
15. Thomson HJ, Ekinci EI, Radcliffe NJ, *et al*. Elevated baseline glomerular filtration rate (GFR) is independently associated with a more rapid decline in renal function of patients with type 1 diabetes. *J Diabetes Complications* 2016; 30: 256–261.
16. Lorenz MW, Polak JF, Kavousi M, *et al*. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012; 379: 2053–2062.
17. Nathan DM, Lachin J, Cleary P, *et al*. Epidemiology of diabetes interventions and complications research group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003; 348: 2294–2303.
18. Järvisalo MJ, Putto-Laurila A, Jartti L, *et al*. Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 2002; 51: 493–498.
19. Dalla Pozza R, Bechtold S, Bonfig W, *et al*. Age of onset of type 1 diabetes in children and carotid intima medial thickness. *J Clin Endocrinol Metab* 2007; 92: 2053–2057.
20. Rabago Rodriguez R, Gómez-Díaz RA, Tanus Haj J, *et al*. Carotid intima-media thickness in pediatric type 1 diabetic patients. *Diabetes Care* 2007; 30: 2599–2602.
21. Palombo C, Kozakova M, Morizzo C, *et al*. Circulating endothelial progenitor cells and large artery structure and function in young subjects with uncomplicated type 1 diabetes. *Cardiovasc Diabetol* 2011; 10: 88.

22. Sugawara J, Hayashi K, Yokoi T, *et al*. Brachial-ankle pulse wave velocity: an index of central arterial stiffness. *J Hum Hypertens* 2005; 19: 401–406.
23. Kusunoki Y, Konishi K, Tsunoda T, *et al*. Significance of glycemic variability in diabetes mellitus med. *Intern Med* 2022; 61: 281–290.
24. Beck RW, Bergenstal RM, Riddlesworth TD, *et al*. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 2019; 42: 400–405.
25. Ranjan AG, Rosenlund SV, Hansen TW, *et al*. Improved time in range over 1 year is associated with reduced albuminuria in individuals with sensor-augmented insulin pump-treated type 1 diabetes. *Diabetes Care* 2020; 43: 2882–2885.
26. American Diabetes Association professional practice committee. 6. Glycemic targets: standards of medical Care in Diabetes—2022. *Diabetes Care* 2022; 45(Suppl_1): S83–S96.
27. Battelino T, Danne T, Bergenstal RM, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019; 42: 1593–1603.
28. Kashiwagi A, Kasuga M, Araki E, *et al*. Committee on the standardization of diabetes mellitus - related laboratory testing of Japan diabetes society: international clinical harmonization of glycated hemoglobin in Japan: from Japan diabetes society to National Glycohemoglobin Standardization Program values. *J Diabetes Investig* 2012; 3: 39–40.
29. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
30. YanaseT NS, Mukuta Y, *et al*. Evaluation of a new carotid intima-media thickness measurement by B-mode ultrasonography using an innovative measurement software, intimascope. *Am J Hypertens* 2006; 19: 1206–1212.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Characteristics at baseline and the last visit of multiple daily injection treatment.

Table S2 | Characteristics at baseline and the last visit of continuous subcutaneous insulin infusion treatment.