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ORIGINAL ARTICLE

Comparison of the clinical effects of intermittently scanned and real-time continuous glucose monitoring in children and adolescents with type 1 diabetes: A retrospective cohort study

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ABSTRACT

Aims/Introduction: The aim of the study was to compare two continuous glucose monitoring (CGM) systems, intermittently scanned CGM (isCGM) and real-time CGM (rtCGM), to determine which system achieved better glycemic control in pediatric patients.

Materials and Methods: We carried out a retrospective cohort study of children and adolescents with type 1 diabetes, and compared the time in range (70–180 mg/dL), time below range (<70 mg/dL) and time above range (>180 mg/dL), and estimated glycated hemoglobin levels between patients on isCGM and rtCGM.

Results: Of the 112 participants, 76 (67.9%) used isCGM and 36 (32.1%) used rtCGM for glycemic management. Patients on rtCGM had significantly greater time in range (57.7 ± 12.3% vs 52.3 ± 12.3%, $P = 0.0368$), and had significantly lower time below range (4.3 ± 2.7% vs 10.2% ± 5.4%, $P < 0.001$) than those on isCGM, but there was no significant difference in the time above range (37.4 ± 12.9% vs 38.0% ± 12.5%, $P = 0.881$) or the glycosylated hemoglobin A1c levels (7.4 ± 0.9% vs 7.5 ± 0.8%, $P = 0.734$) between the two groups.

Conclusions: Pediatric patients with type 1 diabetes on rtCGM also showed more beneficial effects for increase of time in range, with a notable reduction of time below range compared with those on isCGM. Real-time CGM might provide better glycemic control than isCGM in children with type 1 diabetes.

INTRODUCTION

In patients with type 1 diabetes, blood glucose monitoring is essential for glycemic control and making decisions regarding therapy. Self-monitoring of blood glucose (SMBG) is the mainstay for glycemic management; however, frequent testing, usually more than four times a day with finger-stick blood, is required to assess glucose patterns and to recognize critically high and low glucose levels. Continuous glucose monitoring (CGM), which uses a subcutaneous tissue sensor that provides an interstitial fluid glucose measurement every 1–5 min, has become widely used as an alternative to SMBG in recent years in many countries. CGM is more useful for glycemic management than SMBG in terms of providing real-time, continuous and predictive glycemic data without the burden of frequent finger-sticks. CGM is also useful for reviewing glycemic variability over time and identifying asymptomatic hyper- and hypoglycemia. Furthermore, reviewing CGM data can reveal the therapeutic impact of glycemic management strategies, and provide opportunities for education of users and healthcare providers in CGM[1]. CGM data are interpreted in an ambulatory glucose profile report, which provides a graphical and quantitative display of glycemic patterns. The ambulatory

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glucose profile shows the dynamic glucose activities, and provides information on periods of appropriate glucose (time in range [TIR]), and high and low glucose (time below range [TBR] and time above range [TAR], respectively), which are important metrics for glycemic management. The Advanced Technologies and Treatments for Diabetes Congress proposed a glycemic range of 70–180 mg/dL for assessing TIR in non-high-risk patients with type 1 and type 2 diabetes[2].

There are two basic types of CGM: professional CGM, in which patients are blinded to the results at the time of measurement and the results are retrospectively reviewed with the patients by healthcare providers; and personal CGM, in which patients who require more engagement with their glycemic management view data on their glucose patterns in real time. Furthermore, there are two types of devices used for personal CGM: intermittently scanned CGM (isCGM) and real-time CGM (rtCGM). Patients on isCGM can monitor their glucose values by scanning the sensor transmitter with a receiver or a smartphone, whereas those on rtCGM can continually view real-time glucose levels and patterns on a receiver or a smartphone. Unlike isCGM, rtCGM has the advantage of providing high- and low-glucose alerts/alarms, which warn patients and healthcare providers of immediate or impending hyperglycemia or hypoglycemia. Several clinical studies have shown the superiority of isCGM and rtCGM to SMBG for glycemic outcomes and quality of life in patients with type 1 diabetes treated with multiple daily injections of insulin (MDI) or continuous insulin infusion[3–6]. In addition, some comparative studies have shown that rtCGM is better than isCGM at reducing hypoglycemia and improving glycemic control in adults with type 1 diabetes[7–11].

Maintaining appropriate glycemic control is more difficult in pediatric patients than in adult patients, because physical activities, eating habits and lifestyles are variable, adherence to diabetes management is often inadequate, and most children with type 1 diabetes have no β-cell function. Furthermore, the occurrence of hypoglycemia is a serious problem in pediatric patients, and is a barrier to achieving sustained optimal glycemic control, particularly in younger children[12]. Therefore, knowing glucose patterns and variability in real time might be useful for glycemic management in children and adolescents with type 1 diabetes. In the present study, we compared the time spent in each glucose range (TIR, TBR and TAR) and estimated glycosylated hemoglobin A1c (eA1c) levels from CGM data and laboratory measured glycosylated hemoglobin A1c (HbA1c) levels in children and adolescents with type 1 diabetes on isCGM and rtCGM to evaluate the relative benefits of each system for glycemic management of pediatric patients.

MATERIALS AND METHODS

Study design and setting

The present retrospective cohort study was carried out in the Department of Pediatrics at Nihon University Hospital in Tokyo, Japan, from January to May 2021.

Study participants

The study participants included children and adolescents with type 1 diabetes using either isCGM (FreeStyle Libre; Abbott Diabetes Care, Alameda, CA, USA) or rtCGM (Dexcom G4 PLATINUM; Dexcom, San Diego, CA, USA) for glycemic management. Selection of the type of CGM was dependent on the preference and demands for glycemic management of each patient. The bolus insulin doses were decided by a carbohydrate-counting method based on the carbohydrate intake at each meal. The basal insulin doses were adjusted to maintain fasting glucose levels between 90 and 145 mg/dL. The patients visited the outpatient clinic once a month.

Assessments

In Japan, isCGM with FreeStyle Libre, and rtCGM with Dexcom G4 PLATINUM have been available for use, covered by medical insurance, since September 2017 and February 2019, respectively. Sensor insertion was allowed on the abdomen, upper arm or thigh for both devices. Patients on rtCGM were required to calibrate sensors using capillary blood glucose measured on finger-stick blood according to the manufacturer's instructions, whereas calibration was not required with isCGM, because it is a factory-calibrated system. Patients wore the sensors for up to 14 days in isCGM, and up to 7 days in rtCGM. Patients on isCGM obtained their glucose data by scanning a sensor at any time, and they were requested to scan a minimum of once every 8 h to capture all of the glucose data, because the sensor only stored 8 h of glucose data at a time. Optional real-time high- and low-glucose alerts were available to patients using rtCGM, and were set according to the needs of each patient. A low-glucose alarm was set to trigger in each user if the glucose level dropped to <54 mg/dL. All patients were asked to report any adverse events, including severe hypoglycemia, defined as impaired consciousness or a seizure, and the need for third-party assistance with treatment.

For the CGM metrics, TIR, TBR and TAR were defined as the percentage of time spent within the glucose level of 70–180 mg/dL, <70 mg/dL and >180 mg/dL, respectively, on the basis of measures used in previous studies[2]. The eA1c value was calculated based on the mean glucose level on CGM as (mean glucose [mg/dL] + 46.7) / 28.7, as recommended by the A1c-Derived Average Glucose Study Group of the American Diabetes Association[13]. HbA1c was measured by a high-performance liquid chromatography method.

We compared the mean values of CGM metrics, TIR, TBR and TAR, and eA1c between patients on isCGM (the isCGM group) and patients on rtCGM (the rtCGM group). In addition, the frequencies of CGM metrics in TIR of >70%, TBR of <5% and eA1c of <7.0%, which were proposed as standard target levels of glycemic management in type 1 and type 2 diabetes by an Advanced Technologies and Treatments for Diabetes Congress panel in 2019[2], were compared between the two groups. We analyzed the glucose management indicators by using all monthly CGM data during the study period from

January to May 2021. Adverse events, including severe hypoglycemia, were also compared between the two groups.

Statistical analysis

The results were expressed as means and standard deviations. All analyses were carried out using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Two-tailed *P*-values <0.05 were considered statistically significant.

RESULTS

Participant characteristics

A total of 112 children and adolescents with type 1 diabetes with a mean age of 11.1 ± 2.4 years were included in the analysis, of whom 76 patients used isCGM, and 36 patients used rtCGM for glycemic management. The mean age of the participants was 11.7 ± 2.8 years and 10.8 ± 2.6 years for the isCGM and the rtCGM groups, respectively. There was no loss to follow up. The ratio of MDI/continuous insulin infusion for insulin treatment was 42/6 and 32/4 in patients on isCGM and rtCGM, respectively, and this ratio did not differ significantly between groups. None of the patients used a sensor-augmented pump, a predictive low-glucose suspend-function pump or a hybrid closed-loop therapy. The participant characteristics are shown in Table 1. The mean period of use of CGM was 3.0 ± 0.5 years for isCGM and 1.1 ± 0.5 years for rtCGM. The mean utilization rate of CGM was 83.8 ± 17.6% and 93.9 ± 5.4% for isCGM and rtCGM, respectively, a non-statistically significant difference. The mean frequency of scanning a sensor was 12.5 ± 0.5 per day.

Comparison of continuous glucose monitoring metrics, eA1c levels and laboratory-measured HbA1c levels between groups

Patients in the rtCGM group had significantly greater TIR (57.7 ± 12.3% vs 52.3 ± 12.3%, $P = 0.0368$), and had significantly shorter TBR (4.3 ± 2.7% vs 10.2 ± 5.4%, $P < 0.0001$) than those in the isCGM group (Figures 1 and 2), but there was no significant difference in the TAR (37.4 ± 12.9% vs 38.0 ± 12.5%, $P = 0.881$; Figure 3) or the eA1c levels (7.4 ± 0.9% vs 7.5 ± 0.8%, $P = 0.734$; Figure 4) between the two groups. In addition, laboratory-measured HbA1c levels were similar between the two groups (7.6 ± 0.7% vs 7.7 ± 0.7%, $P = 0.758$).

Comparison of the proportion of measures in the target time in range and time below range, and eA1c levels between groups

The proportion of participants with values in the target TIR of >70% was 3.9% (3/76) in the isCGM group and 13.9% (5/36) in the rtCGM group, a non-significant difference ($P = 0.108$). The proportion of participants with values in the target TBR of <5% was significantly lower in the isCGM group than in the rtCGM group (18.4% [14/76] vs 72.2% [26/36], $P < 0.001$). The proportion of participants with an appropriate eA1c of <7.0% was similar between the isCGM and rtCGM groups (31.6% [24/76] vs 38.9% [14/36], $P = 0.523$).

Adverse events during the study period

Five patients in the isCGM group and one patient in the rtCGM group experienced skin reactions, redness and/or irritation at the site of the attachment of the sensors; however, this did not influence the wearing of the CGM device or data collection. No patients in either group experienced severe hypoglycemia during the study period.

DISCUSSION

Reduction of hypoglycemia and minimization of severe hypoglycemia are critical issues in the management of type 1 diabetes[14]. Severe hypoglycemia is still a lethal complication, with

Table 1 | Participant characteristics

	isCGM (*n* = 76)	rtCGM (*n* = 36)
Age (years)	Mean 11. 7 (SD 2.8) Median 11.6 (SE 0.5) Range (7–15), quantile (9.8, 13.3)	Mean 11. 7 (SD 2.8) Median 11.5 (SE 0.5) Range (7–15), quantile (9.9, 13.4)
Male/female	36/40	16/20
BMI	Mean 19.0 (SD 2.2) Median 18.5 (SE 0.4) Range (16.5–22.5), quantile (18.5, 20.5)	Mean 18.8 (SD 2.1) Median 18.2 (SE 0.3) Range (15.8–23.0), quantile (18.2, 21.0)
BMI SD-score	Mean 0.7 (SD 0.6) Median 0.6 (SE 0.3) Range (–0.2–1.3), quantile (0.4, 0.9)	Mean 0.7 (SD 0.5) Median 0.6 (SE 0.3) Range (–0.1–1.4), quantile (0.5, 0.9)
MDI/CSII	42/6	32/4
Insulin dose (/kg/day)	Mean 0.8 (SD 0.4) Median 0.7 (SE 0.2) Range (0.4–1.2), quantile (0.6, 1.0)	Mean 0.8 (SD 0.4) Median 0.8 (SE 0.2) Range (0.5–1.1), quantile (0.6, 0.9)

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections of insulin; SD, standard deviation; SE, standard error.

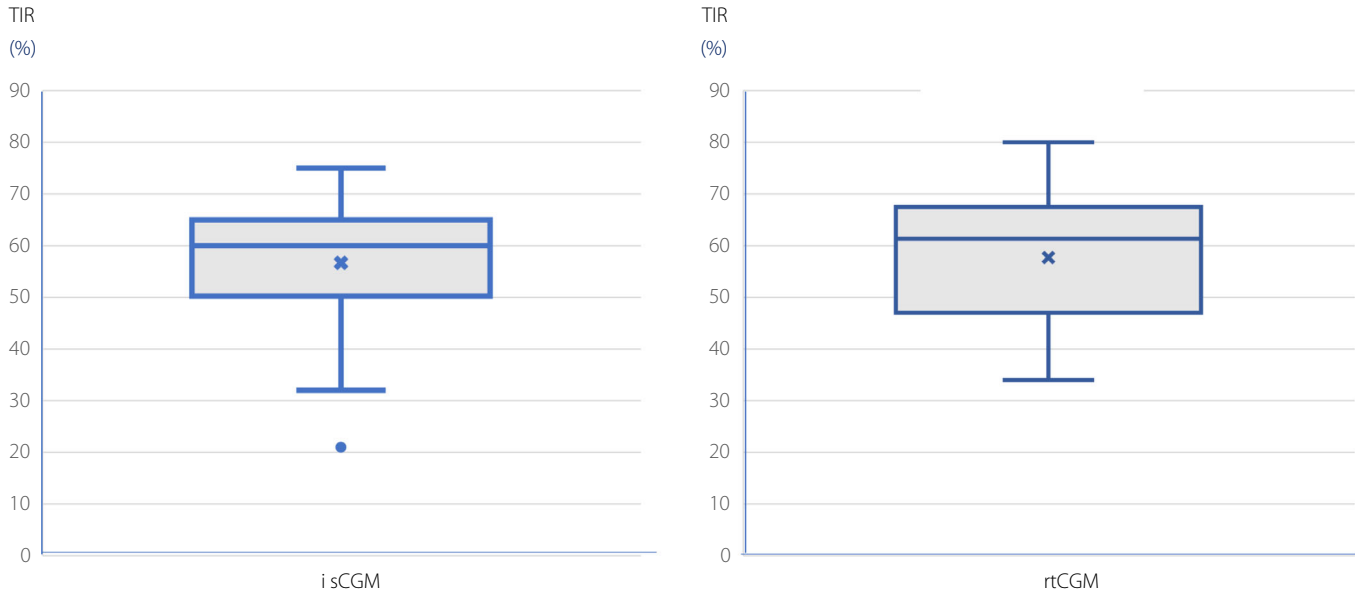

Figure 1 | Comparison of time in range (TIR) between the intermittently scanned continuous glucose monitoring (isCGM) group and the real-time CGM (rtCGM) group.

Figure 2 | Comparison of time below range (TBR) between the intermittently scanned continuous glucose monitoring (isCGM) group and the real-time CGM (rtCGM) group.

a 4–10% case fatality rate[15, 16]. It can cause permanent brain damage and mental retardation, which is a serious problem, particularly in young children[17–20]. We previously reported that Japanese children with type 1 diabetes, the majority of whom were treated with MDI, had greater TBR of 10.8 ± 5.4% than that of the proposed TBR level of <5.0% with isCGM, particularly during sleep[21]. This proportion was similar to that of children who used isCGM in the present study. High-sensitivity glucose monitoring is required to detect hypoglycemia accurately and early, and to reliably prevent the development of severe hypoglycemia in patients at risk of severe hypoglycemia, such as young children and individuals with irregular eating habits, physical activity and lifestyles[14]. The Advanced Technologies and Treatments for Diabetes panel emphasized that

Figure 3 | Comparison of time above range (TAR) between the intermittently scanned continuous glucose monitoring (isCGM) group and the real-time CGM (rtCGM) group.

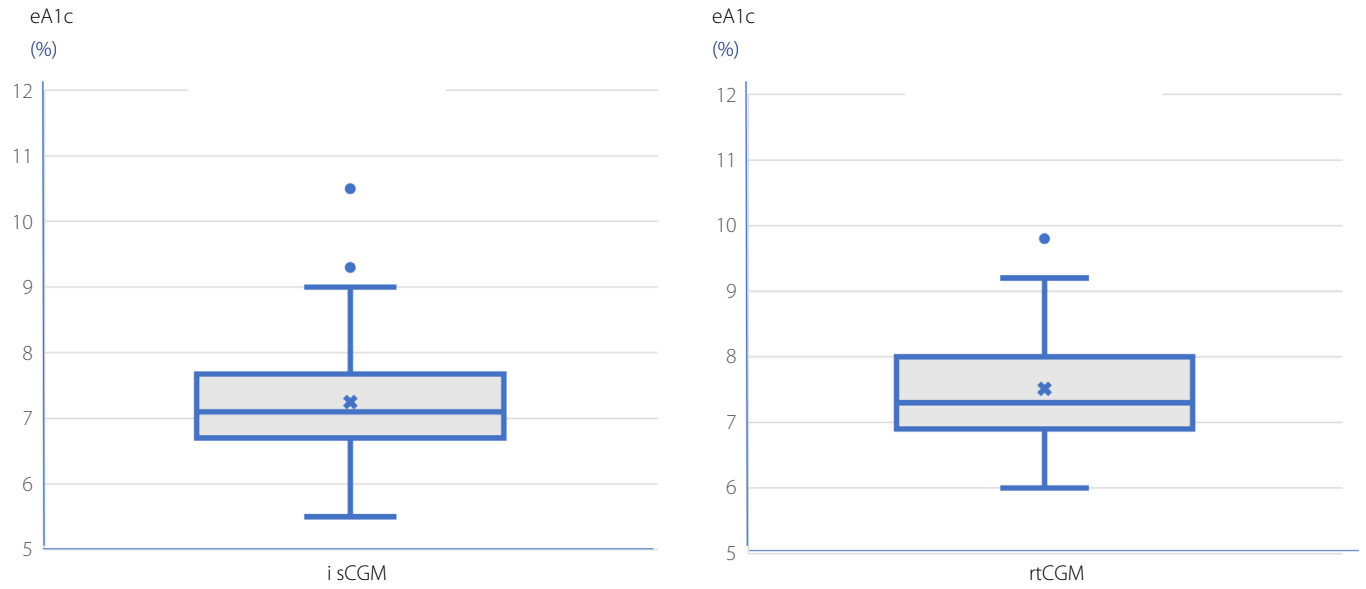

Figure 4 | Comparison of estimated glycosylated hemoglobin A1c (eA1c) between the intermittently scanned continuous glucose monitoring (isCGM) group and the real-time CGM (rtCGM)group.

the primary objective of glycemic management should be to minimize TBR to a target level and to then address the TIR and TAR targets[2].

In the present study, patients who used rtCGM had significantly lower TBR and significantly higher TIR than patients who used isCGM. To our knowledge, this study is the first study to show the superiority of rtCGM to isCGM in pediatric patients with type 1 diabetes. Of note, the reduction of TBR was more marked among patients using rtCGM, and almost three-quarters of patients on rtCGM achieved the target TBR of <5.0%, whereas fewer than one-fifth of patients using isCGM achieved this target level. Several randomized controlled trials showed that use of either isCGM or rtCGM is more effective than SMBG at achieving glycemic control in patients with

type 1 diabetes treated with either MDI or continuous insulin infusion, with significant reduction of hypoglycemia[3–6]. Both isCGM and rtCGM provide dynamic glucose profiles shown in an ambulatory glucose profile report[3]. Both types of CGM improve glycemic control, with a reduction of the severity of hypoglycemia and hyperglycemia, glucose variability, and provide greater patients satisfaction with their treatment[1, 22–24]. Large glucose variability might increase oxidative stress and inflammation, which cause endothelial cell damage[25] and increase cardiovascular risk[26]. Several studies have shown that rtCGM is superior to isCGM in terms of reducing the TBR, and improving the TIR and HbA1c levels in adult patients with type 1 diabetes[7–11]. Reddy *et al.*[7] and Préau *et al.*[10] reported that switching from isCGM to rtCGM reduced TBR and increased TIR in patients with type 1 diabetes, and suggested switching from isCGM to rtCGM as an alternative to changing the insulin delivery system in patients with suboptimal glycemic control. A 6-month multicenter randomized controlled trial carried out by Visser *et al.*[11] showed that switching from isCGM to rtCGM was associated with an improvement in health and quality of life. Maiorino *et al.*[27] carried out a meta-analysis of randomized controlled trials of the effects of CGM on glycemic control in patients with type 1 and type 2 diabetes. This review found that TBR was significantly lower and TIR was significantly higher in patients on rtCGM than in patients on isCGM, except in studies in which the patients were treated with a sensor-augmented pump. Studies that used CGM for increasing hypoglycemia awareness had a lower incidence of TBR. Furthermore, use of a hypoglycemia alert/alarm in patients on rtCGM led to a greater reduction in the TBR. These results suggest that rtCGM is generally better than isCGM for improving glycemic control, with lower TBR and higher TIR.

There are several possible reasons for the superiority of rtCGM to isCGM. First, unlike isCGM, CGM data are automatically visible in real time in rtCGM, and patients can directly view their glucose trends without frequent scanning. This enables patients to evaluate the data for glucose trend and make therapeutic decisions more easily. For example, when glucose increases after meals, patients can adjust the rate of glycemic change, or when glucose decreases, they can act to prevent the development of hypoglycemia. Second, some studies have shown that the Dexcom G4 device provides more accurate data, as measured by the mean absolute relative difference in blood glucose, than other CGM devices, with a low level of 10–14%, particularly for blood glucose values in the hypoglycemic range[28–33]. CGM with isCGM using FreeStyle Libre, might show a higher frequency of TBR values than CGM with rtCGM using Dexcom G4, due to the difference in the accuracy of the two devices. Third, several reports have shown the hypo- and hyperglycemia alert systems and an alert system against excessive hypoglycemia available with rtCGM have beneficial effects[7–11, 27]. In particular, the low-glucose alert with rtCGM can greatly contribute to reducing TBR because patients can respond in a timely manner to hypoglycemia during exercise and in daily self-management[9, 10], and during the night when they would otherwise be unaware of hypoglycemia[7, 8]. Visser *et al.*[11] showed that patients on rtCGM were less concerned about developing hypoglycemia, because the low-glucose alert and urgent low-glucose alarm reduced their risk of developing hypoglycemia. Patients with type 1 diabetes who lacked an awareness of the symptoms of hypoglycemia also reported less concern about hypoglycemia on rtCGM than on isCGM[8]. For pediatric patients, severe hypoglycemia is a particular threat and is more problematic than in adults, because it can cause brain damage and decreased intelligence[14]. The alert/alarm system can contribute to preventing severe hypoglycemia, which is the primary objective of glycemic management in pediatric patients.

The present study had some limitations. First, it was a retrospective observational study. Therefore, the primary end-point was not specified, a sample size target was not set, and most results were descriptive in nature. Second, it was a single-center study; therefore, the results might not be generalizable to all pediatric patients with type 1 diabetes in Japan. Third, the study sample was too small to carry out detailed analyses. Consequently, a multicenter randomized controlled trial would be useful to determine the difference of clinical effects on glycemic control between isCGM and rtCGM in children and adolescents with type 1 diabetes. Finally, TIR >70% seems to be stringent for a portion of younger pediatric patients (i.e., infants). Therefore, analyses using stratified targets according to age-groups might be more adequate for the purpose of comparing effectiveness between the two types of CGM. However, we did not compare the results according to age-groups, but the present study did not include infants and young children aged <6 years, because they were treated with a sensor-augmented pump in our hospital. In contrast, to our knowledge, this is the first study to compare the clinical effects of the two types of CGM device in pediatric patients with type 1 diabetes, so it provides useful information on the relative benefits of the two types of CGM devices for glycemic management in children and adolescents with type 1 diabetes who are prone to fluctuations in their glucose level and are at risk of developing hypoglycemia.

In conclusion, the present study suggests that use of rtCGM is more effective than isCGM at reducing TBR and increasing TIR in children and adolescents with type 1 diabetes. The real-time alert/alarm system for hyper- and hypoglycemia that is available with rtCGM might be the main reason for the greater effectiveness of rtCGM. However, CGM metrics should be individualized according to the age, level of comprehension, treatment options and the needs of each patient[2, 34]. Nevertheless, minimization of the number of hypoglycemic events and prevention of severe hypoglycemia are critical issues for glycemic management in children and adolescents with type 1 diabetes. More advanced technology, such as closed-loop systems with more accurate glucose sensor and more sensitive alert/alarm

system for hyper- and hypoglycemia, can help to reduce dysglycemia in pediatric patients with type 1 diabetes[35].

DISCLOSURE

TU received honoraria from Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., Terumo Corp. and JCR Pharmaceuticals Co., Ltd. IM received study grants from Atom Medical Corp., and lecture fees from MSD Co., Ltd. and AbbVie LLC. The other authors declare no conflict of interest.

Approval of the research protocol: This study was approved by the Human Ethics Review Committee of Nihon University School of Medicine (No. 20210102, 21 January 2021), and was carried out in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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