Individualization of recommendations from the international consensus on continuous glucose monitoring-derived metrics in Japanese children and adolescents with type 1 diabetes

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Abstract. We assessed the significance of recommendations from the international consensus on continuous glucose monitoring (CGM)-derived metrics in Japanese children and adolescents with type 1 diabetes. Eighty-five patients (age, 13.5 ± 4.7 years) who wore the FreeStyle® Libre for a 28-day period were enrolled in this study. Seventy-three patients were treated with multiple daily injections of insulin and 12 with insulin pump therapy without using a sensor-augmented pump or a predictive low-glucose suspend-function pump. We evaluated the relationship between CGM-derived metrics: time in range (TIR: 70–180 mg/dL), time below range (TBR: <70 mg/dL), and time above range (TAR: >180 mg/dL), and laboratory-measured HbA1c and estimated HbA1c (eA1c) levels calculated from the mean glucose values. The TIR was 50.7 ± 12.2% (23–75%), TBR was 11.8 ± 5.8% (2–27%), and TAR was 37.5 ± 13.5% (9–69%). The TIR was highly correlated with HbA1c level, eA1c level, and TAR, but not with TBR. An HbA1c level of 7.0% corresponded to a TIR of 55.1% (95% CI: 53.7–56.5%), whereas a TIR of 70% corresponded to an HbA1c level of 6.1% (95% CI: 5.9–6.3%). The results of eA1c levels were similar to those observed for HbA1c levels. From these findings, we conclude that low rates of a recommended TIR of 70% may be due to less use of advanced technology and insufficient comprehensive diabetes care. Ethnic characteristics including lifestyle and eating customs may have contributed to the result. CGM-derived targets must be individualized based on ethnic characteristics, insulin treatment and diabetes care, and needs of individuals with diabetes.

Key words: Children, Adolescents, Type 1 diabetes, Intermittently scanned continuous glucose monitoring, Time in range

THE ADVANCED TECHNOLOGIES and Treatments for Diabetes (ATTD) Congress of 2019 convened an international global panel that comprised individuals with diabetes as well as clinicians and researchers with expertise in continuous glucose monitoring (CGM). The aim of the congress was to develop clinical CGM targets to supplement the standard metrics for CGM-derived times in glucose target ranges in an effort to offer guidelines for individuals with diabetes, clinicians, and researchers who use CGM data in routine clinical care and diabetes research. The CGM-derived metrics include three key measurements during a 24-h period: the frequency of time spent in the target glucose range (TIR: 70–180 mg/dL), time spent below the target glucose range (TBR: <70 mg/dL), and time spent above the target glucose range (TAR: >180 mg/dL) [1]. The primary goal for optimal glucose control is to increase the TIR while simultaneously reducing the TBR. The ATTD consensus panel concurred on the need to personalize CGM-derived metrics to match the needs of individuals with diabetes. Moreover, the panel reached a consensus on the glycemic cutoff point of TIR of 70%–180 mg/dL for individuals of all age groups with type 1 or 2 diabetes [1]. The CGM metrics include TIR, TBR, and TAR, although achieving the goals for both TIR and TBR would consequently result in decreased TAR and thereby improve glycemic control. Therefore, the first therapeutic objective should be to minimize the TBR to target levels, followed by addressing the TIR and TAR targets [1]. However, several studies have shown that potential glycemic targets differ among insulin-treatment regimens: individuals treated with multiple daily injections of insulin (MDI) and using CGM or intermittently scanned continuous glucose monitoring (isCGM) tend to have shorter
TIR, whereas patients with advanced therapeutic options, such as hybrid closed-loop therapy, are more likely to achieve greater TIR and satisfactory glycemic control [2].

In Japan, the prevalence of children with type 1 diabetes is quite low compared with that in the United States and European countries [3]. Therefore, there are limited advanced insulin treatment and diabetes care options, with a lower frequency of use of insulin pumps, CGM, and isCGM than that in Caucasian populations; furthermore, hybrid closed-loop therapy is not approved for use in Japan. Glycated hemoglobin (HbA1c) measurement remains the gold standard for assessing glycemic control, but fails to identify patterns of hypo- and hyperglycemia and magnitudes of inter-day glucose variations [4, 5]. Unlike HbA1c measurement, CGM facilitates direct observation of glycemic excursions and daily profiles. Therefore, the utility of CGM-derived metrics should be enhanced in the Japanese population with type 1 diabetes. This study was undertaken to assess the significance of the consensus recommendations from the ATTD on CGM-derived metrics in Japanese children and adolescents with type 1 diabetes—a population that is likely to experience glycemic excursions—based on an analysis of glucose profiles recorded on CGM.

**Materials and Methods**

**Subjects**

This study enrolled 85 children and adolescents (36 males and 49 females) with type 1 diabetes, including 80 with acute-onset type 1 diabetes and 5 with slowly progressive type 1 diabetes. They were using FreeStyle® Libre (Abbott Diabetes Care, Witney, Oxfordshire, UK) for isCGM; the designated reader scanned glucose values at least 4 times per day. The mean age at the time of study was 13.5 ± 4.7 (4.0–17.9) years with the mean duration of diabetes of 6.5 ± 4.4 (1.2–14.0) years. The mean value of 1 to 2-h postprandial serum C-peptide was 0.08 ± 0.11 ng/mL. In our study population, 73 patients were treated with MDI of rapid-acting and long-acting insulin analogs and 12 with insulin pump therapy using rapid-acting insulin analog. They continued wearing FreeStyle® Libre during the entire study period of 28 days. They were instructed to scan the sensors using the designated reader at least 4 times per day. None of our patients used a sensor-augmented pump or a predictive low-glucose suspend-function pump. Bolus insulin doses were determined using a carbohydrate counting method that assessed the consumption of carbohydrate at each meal. Patients regularly visited the outpatient clinic once a month, and HbA1c levels were measured at each visit at the laboratory of the Nihon University Hospital. The study participants had nearly uniform lifestyles, without excessive physical activities, eating disorders, or psychosocial problems. In the year preceding study enrolment, one patient experienced severe hypoglycemia due to failed management of a sick day, although none of our patients developed diabetic ketoacidosis or other serious health problems. None of the patients had macro- and/or micro-vascular complications.

**Assessments**

We assessed the relationship between CGM-derived metrics, including TIR, TBR, and TAR, and HbA1c levels based on laboratory measurements and estimated HbA1c (eA1c) levels, which were calculated from mean sensor glucose values obtained via isCGM among the study participants. For the purposes of this study, we specified TIR (70–180 mg/dL), TBR (<70 mg/dL), and TAR (>180 mg/dL) on the basis of previously reported CGM metrics [1].

The HbA1c value was measured by high-performance liquid chromatography and expressed as the National Glycohemoglobin Standardization Program unit (%; reference value: 4.6–6.1%). The eA1c level was calculated as [mean glucose, mg/dL + 46.7]/28.7, as recommended by the A1c-derived average glucose (ADAG) Study Group of the American Diabetes Association (ADA) [6].

**Statistical analysis**

The associations of HbA1c and eA1c levels with TIR, TBR, and TAR were assessed with Pearson’s product-moment correlation coefficients. Point estimates and 95% confidence intervals (CIs) of TIR, TBR, and TAR corresponding to an HbA1c/eA1c level of 7.0% were calculated using simple linear regression models. Assumptions for linear regression were confirmed by residual analyses. We undertook estimation of HbA1c and eA1c values corresponding to a TIR of 70% in the same manner. Results were compared between the two groups using a Mann–Whitney U-test. A *p*-value <0.05 was considered indicative of a statistically significant difference. All statistical analyses were conducted in IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp. Released 2017. Armonk, NY).

**Study approval**

This study was approved by the Human Ethics Review Committee of Nihon University Hospital (approval no. 20191204) and was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.
Results

The mean (range) of age and diabetes duration for the overall study population (n = 90) was 13.3 ± 4.8 (3.8–17.9) and 6.4 ± 4.5 (1.0–14.0) years, respectively. In these patients, 85 patients continued to wearing FreeStyle® Libre for the entire study duration of 28 days, whereas 5 participants dropped out of the study because of sensor troubles, skin peeling off, and skin irritation. Accordingly, the final analysis dataset included 85 patients (36 males, 49 females; mean age 13.5 ± 4.7 [4.0–17.9] years; diabetes duration 6.5 ± 4.4 [1.2–14.0] years). The number of times the glucose values were scanned daily ranged from 5 to 20 (mean: 11.5 ± 3.5).

Mean values of CGM-derived metrics, HbA1c levels, and eA1c levels

In our study participants, the mean glucose value was 162.8 ± 25.5 (109–244) mg/dL with FreeStyle® Libre, whereas the laboratory-measured HbA1c and CGM-derived eA1c levels were 7.4 ± 0.9% (5.6–9.9%) and 7.3 ± 0.9% (5.4–10.1%), respectively. The eA1c level was highly correlated with HbA1c levels (r = 0.979, p < 0.0001). In contrast, the mean TIR was 50.7 ± 12.2% (23–75%), mean TBR was 11.8 ± 5.8% (2–27%), and mean TAR was 37.5 ± 13.5% (9–69%). No significant differences were observed on subgroup analyses by sex and age.

Correlation between HbA1c levels and all CGM-derived metrics

HbA1c levels showed a highly inverse correlation with TIR (r = −0.869, p < 0.0001, Fig. 1a), a highly positive correlation with TAR (r = 0.934, p < 0.0001, Fig. 1b), and a weakly inverse correlation with TBR (r = −0.351, p = 0.001, Fig. 1c).

Correlation between eA1c levels and all CGM-derived metrics

Similarly, the eA1c levels showed a highly inverse correlation with TIR (r = −0.844, p < 0.0001, Fig. 2a), a highly positive correlation with TAR (r = 0.919, p < 0.0001, Fig. 2b), and a weakly inverse correlation with TBR (r = −0.370, p < 0.0001, Fig. 2c).
Correlation among all the CGM-derived metrics

The TIR showed a highly inverse correlation with the TAR ($r = -0.862$, $p < 0.0001$), and the TBR showed a weakly inverse correlation with the TAR ($r = -0.352$, $p = 0.0026$). However, there was no significant correlation between the TIR and TBR ($r = -0.130$, $p = 0.2836$).

Frequency of the CGM-derived metrics corresponded to the recommended levels in HbA1c of 7.0% and eA1c of 7.0%

The recommended HbA1c level of 7.0% corresponded to a TIR of 55.1% (95% CI: 53.7–56.5%), TBR of 12.7% (95% CI: 11.4–13.9%), and TAR of 32.2% (31.1–33.4%). The eA1c level of 7.0% was equivalent to a TIR of 54.4% (95% CI: 52.8–55.9%), TBR of 12.6% (95% CI: 11.3–13.8%), and TAR of 33.1% (95% CI: 31.9–34.3%) (Table 1).

HbA1c and eA1c levels corresponded to the recommended frequency in TIR of 70%

In contrast, the recommended TIR of 70% corresponded to an HbA1c level of 6.1% (95% CI: 5.9–6.3) and an eA1c level of 6.1% (95% CI: 5.9–6.3) as shown in Table 2.

Discussion

The widespread use of CGM has rapidly accelerated in the past few years to replace classical fingerstick blood glucometers. The frequency of individuals with type 1 diabetes who use CGM increased from 7% in 2010–2012 to 30% in 2016–2018 [7]. Greater convenience, including ease of use and less invasion, and improvement in sensor accuracy may underlie the increased use of CGM [8]. The CGM systems comprise a few types of measuring systems: retrospective CGM, real-time CGM, and isCGM. The FreeStyle® Libre, an isCGM system, offers real-time interstitial glucose levels by scanning and reading continuous and dynamic glucose profiles to present ambulatory glucose profiles (AGP) [9, 10]. The FreeStyle® Libre was approved for use in Japan in 2017, and it is currently used broadly in mainly individuals with type 1 diabetes treated with MDI or insulin-pump therapy. Several studies have demonstrated significant clinical benefits of use of FreeStyle® Libre in individuals with diabetes [9-12].

The CGM-derived TIR is recognized as a key metric of the quality of glycemic control. Compared with HbA1c measurement, the TIR offers more sensitive and accurate data: TIR assessment can record hypo- or hyper-glycemic events at any time, and dynamic glucose profiles and glycemic variations can be observed [4, 5, 13], which cannot be obtained on HbA1c assessment. Several reports have indicated that TIR is highly correlated with HbA1c levels [14-16], suggesting that TIR has potential value as a novel and promising metric in assessing not only short-term glycemic control but also the risk for diabetes complications in individuals with diabetes [1]. A cross-sectional study has demonstrated the association of current retrospective 3-day TIR with varying degrees of retinopathy [14]. An analysis of the 7-point data in self-monitoring of blood glucose in the Diabetes Control and Complications Trial (DCCT) showed a significant correlation between TIR and microvascular complications [15]. Beck, et al. [16] demonstrated a strong association between TIR and microvascular complications, including microalbuminuria and retinopathy. Moreover, the relationship between TIR and severe or moderate hypoglycemia has been reported [17-21]. Therefore, TIR is a potentially promising indicator of comprehensive glycemic control beyond HbA1c measurement.

The ADA recommended the use of eA1c levels in diabetes management. However, CGM users can access eA1c results routinely with AGP reports in a direct

Table 1  Frequency of the CGM-derived metrics corresponded to the recommended levels in HbA1c of 7.0% and eA1c of 7.0%

| TIR (%) | TBR (%) | TAR (%) |
|---------|---------|---------|
| HbA1c: 7.0% | 55.12 (53.70–56.54) | 12.66 (11.38–13.93) | 32.22 (31.08–33.36) |
| eA1c: 7.0% | 54.35 (52.84–55.85) | 12.57 (11.33–13.81) | 33.08 (31.85–34.31) |

Table 2  HbA1c and eA1c levels corresponded to the recommended frequency in TIR of 70%

| HbA1c (%) | eA1c (%) |
|-----------|----------|
| TIR: 70% | 6.11 (5.92–6.30) | 6.10 (5.89–6.30) |

Point estimate (the 95% CI)
HbA1c, glycated hemoglobin; eA1c, estimated HbA1c; CGM, continuous glucose monitoring; TIR, time spent in the target glucose range; TBR, time spent below the target glucose range; TAR, time spent above the target glucose range
approach to diabetes management. There may be discordance between the results of laboratory-measured HbA1c and eA1c levels, which may be attributed to interindividual differences in red blood cell lifespan or other factors that could affect HbA1c levels unrelated to the degrees of glycemic control [6, 22]. Nonetheless, CGM or isCGM may show some out-of-range values, possibly due to sensor errors and a compression artifact during sleep, particularly with regard to low glucose levels; this can influence the eA1c value [17]. Nevertheless, we found that the eA1c level was highly correlated with HbA1c levels, suggesting there might be no or few factors influencing HbA1c values that are unrelated to glucose levels or that are present in the absence of acute problematic events, such as severe hypoglycemia and ketoacidosis, which can affect short-time glycemic control. In contrast, several reports have demonstrated that the correlation between mean glucose and eA1c levels is reasonably constant at all times and the relationship between TIR and eA1c levels could also be constant [6, 22-24]. The ADAG Study Group of the ADA proposed that the eA1c level be termed the glucose management indicator (GMI) [25]. Thus, the eA1c level will likely become an essential indicator for glycemic control as the GMI in the near future [17, 25].

It has been recommended that the TIR should be 70–180 mg/dL for individuals with type 1 and type 2 diabetes and 63–140 mg/dL during pregnancy [1]. Moreover, this recommendation specifies conservative CGM targets for individuals with diabetes who are older and/or at a high risk of hyper- and hypoglycemia, with a strong focus on the reduction of the time spent in TIR [1]. However, achieving the target TIR of 70–180 mg/dL seems substantially difficult in children and adolescents with type 1 diabetes. Data of TIR derived from 7-point glucose profiles in the DCCT demonstrated that the TIR in the conventional therapy group was 31% (mean HbA1c level 9.1%) whereas the TIR in the intensive treatment group was 52% (mean HbA1c level 7.3%) [16]. Edge et al. [26] reported a frequency of 50% for TIR in 89 children and adolescents aged 4–17 years with type 1 diabetes or type 2 diabetes. Campbell, et al. [27] reported the frequency of TIR as 46% in children with type 1 diabetes aged 4–17 years with a duration of diabetes of more than 1 year. We found the frequency of TIR was 50.7% (mean HbA1c level 7.4%), which was similar to that reported by previous studies in children and adolescents with type 1 diabetes, but there was a wide interindividual variation (23–75%) in the TIR. Moreover, the frequencies of a TAR of 37.5% (9–69%) and particularly a TBR of 11.8% (2–27%), which should be less than 5.0%, were higher than recommended. Children and adolescents with type 1 diabetes are likely to show high magnitudes in postprandial glucose levels and remarkable interindividual and day-to-day glycemic variations. In contrast, the recommended CGM-derived targets are more frequently achieved with advanced insulin treatment, such as hybrid closed-loop therapy. However, the majority of our patients were treated with MDI despite using FreeStyle® Libre for diabetes management. The mean TIR ranged from 51% in individuals treated with MDI using CGM in the DIAMOND trial [28] to approximately 70% in those receiving hybrid closed-loop therapy [29-31]. Therefore, analysis of TIR data in individuals treated with both MDI and with more advanced therapy is needed in a large number of Japanese pediatric patients with type 1 diabetes.

The mean TIR has been reported to show a significantly inverse linear correlation with the mean HbA1c level in various clinical trials. Vigersky and McMahon [14] compared TIR data with paired HbA1c data from 18 different studies including more than 1.137 patients with type 1 diabetes and type 2 diabetes and found a strongly inverse linear relationship between the two parameters ($r = -0.84, r^2 = 0.72$). Furthermore, another recent study reported a similarly high inverse correlation between HbA1c levels and TIR in at least 2-week CGM data from 530 patients with type 1 and type 2 diabetes treated with insulin [15]. In contrast, various studies have reported an association between the recommended levels for these two parameters. Beck, et al. [17] analyzed data from four randomized trials in 545 adults with type 1 diabetes that used laboratory-measured HbA1c data, and found that TIRs of 70% and 50% were strongly related with HbA1c levels of approximately 7.0% (95% CI 5.6–8.3) and 7.9% (95% CI 6.6–9.2), respectively. Vigersky and McMahon [14] found that a TIR of 70% corresponded to an HbA1c level of 6.7% and a TIR of 50% to an HbA1c level of 8.3%. Peterson, et al. [32] reported that a TIR of 70% corresponded to an HbA1c level of 7.1% in 133 Swedish children and adolescents with type 1 diabetes using CGM or isCGM. This result is satisfactory and similar to that in adult patients, because pediatric patients reported by Petersson, et al. exhibited excellent glycemic control with a mean HbA1c level of 7.1% and a mean TIR of 60.8%. In contrast, we found that an HbA1c level of 7.0% corresponded to a TIR of 55.1%, whereas a TIR of 70% corresponded to an HbA1c level of 6.1%. Moreover, a TAR of 32.2% was equivalent to an HbA1c level of 7.0%, and TAR was significantly correlated with TIR, although there was no significant association between TBR and TIR. These results suggest that achieving the recommended TIR of 70% seems to be difficult in Japanese children and adolescents with type 1 diabetes despite an optimal HbA1c level of 7.0% recommend by the International Society for Pediatric and Adolescent Diabetes (ISPAD) [33]. Possible reasons for the inability
to achieve the target could be as follows: insulin treatment and diabetes care in our patients differed from those in Caucasian patients who are treated with advanced technology and sufficient comprehensive diabetes care, whereas our patients were mostly treated with MDI with a low frequency of use of insulin pump and without any use of a closed-loop therapy. Comprehensive diabetes care with the diabetes team may be inappropriate compared with diabetes care in the United States and European countries. Second, Japanese individuals tend to consume more carbohydrates in each meal than Caucasians, and eating habits are irregular, particularly in younger children and adolescents. Therefore, they are likely to exhibit postprandial hyperglycemia, which is reflected by a high rate of TAR despite an adequate HbA1c level. Moreover, the mean TBR of 11.8% is greater than the recommended rate of less than 5%. Consequently, the HbA1c level becomes apparently appropriate as a result of combination with higher rates of TAR and TBR; nonetheless, there actually exists a fluctuation in glycemic profiles. The primary goal for CGM-derived metrics is to increase TIR while reducing TBR; therefore, shortening of time spent in TBR is critical for achieving satisfactory glycemic control.

It has been recommended that individualized goals of CGM-derived metrics are important, particularly in pediatric patients with type 1 diabetes [1]. The ISPAD has emphasized that the glycemic target for pediatric patients should be an achievable HbA1c level without an episode of severe hypoglycemia or negative effects on quality of life and burden of care [33]. The goals of the metrics, HbA1c level of 7.0% and TIR of 70%, should be adapted in pediatric patients who can access comprehensive diabetes care and advanced technology. However, a more relaxed target is required in individuals with unawareness regarding hypoglycemia, history of severe hypoglycemia, and those unable to access advanced technology and comprehensive care [33]. CGM-derived targets must be personalized according to the patient’s background, such as ethnicity, lifestyles, insulin treatment, and diabetes management, and needs of individuals with diabetes.

There are some limitations in the present study. First, study subjects background, such as education degrees, socioeconomic statuses, lifestyles, eating customs and physical activities, can affect TIR, which were not assessed in the present study. Second, we did not assess the association between serum C-peptide values and TIR. Residual β-cell function may influence on glycemic control. However, the majority of our patients were acute-onset type 1 diabetes and they almost lost β-cell function at the time of study. Third, we did not evaluate the association between scanning frequency with FreeStyle® Libre and TIR. Various studies have demonstrated that the scanning frequency is associated with glycemic control and frequency of hypoglycemia in patients with diabetes [9, 10, 34]. Forth, the sensor accuracy in FreeStyle® Libre seems imperfect particularly at extremes of glucose levels (hypoglycemia and hyperglycemia), or when the rate of glucose change is rapid [35]. Moreover, glucose levels tend to be unstable on the first day with FreeStyle® Libre. Under these conditions, there may be difference between glucose levels with FreeStyle® Libre and conventional self-monitored blood glucose levels. However, it has been reported that the accuracy of FreeStyle® Libre, evaluated by mean absolute relative difference, is considered acceptable (<15%) in routine environmental conditions [36]. Therefore, we used all measured data with FreeStyle® Libre for the analyses. Finally, our study sample was too small to confirm the results and conclusions with adequate statistical power. Therefore, a large study population is required to confirm the results and conclusions.

In conclusion, we found that approximately half of the Japanese children and adolescents with type 1 diabetes could achieve a TIR of 70–180 mg/dL with a mean HbA1c level of 7.4%. An HbA1c level of 7.0% corresponded to a TIR of 55.1%, whereas a TIR of 70% corresponded to an HbA1c level of 6.1%. The lower rate of achievement of the recommended TIR may be secondary to less use of advanced technology and insufficient comprehensive diabetes care as compared with that in the United States and European countries. Ethnic characteristics, including lifestyle and eating habits, can contribute to these results. Therefore, CGM-derived targets must be personalized according to the patients’ background and the needs of individuals with diabetes.

Disclosure

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Author Contributions

Tatsuhiko Urakami conceived and designed the study and wrote the manuscript. Kei Yoshida, Remi Kuwabara, Yusuke Mine and Masako Aoki collected the data. Junichiro Suzuki performed the data analysis. Ichiro Morioka critically revised the manuscript. All authors read and approved the final manuscript.
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