Evaluation of the Association of CGM Metrics with Antihyperglycemic Drugs in Insulin-Treated Diabetics

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FGM · CGM metrics · Incretin · Hypoglycemia

Abstract

Introduction: Intermittent flash glucose monitoring (FGM) and real-time continuous glucose monitoring (CGM) are used to monitor glycemic excursions for 14 days and can demonstrate time in range (TIR), time above range (TAR), and time below range (TBR). The utility of CGM metrics, such as TIR, TAR, and TBR, in diabetics treated with insulin combined with antihyperglycemic drugs is uncertain. Methods: In a cross-sectional and retrospective study, we investigated the relationship between target metrics from CGM/FGM and HbA1c or glucose variabilities in 80 type 1 and 2 diabetic patients receiving insulin treatment with ≥1 injections per day. The proportions of TIR, TAR, and TBR from FGM in relation to HbA1c and coefficient of variation (CV)\% in types 1 and 2 diabetics were analyzed. Multivariable analyses were performed regarding the associations of TIR with biochemical factors and glycemic variabilities. TBR was also examined in relation to antidiabetic agents and diabetic type in multiple regression analyses. Finally, the association of retinopathy with FGM-CGM metrics was examined using a logistic analysis. Results: When patients were grouped by sex and diabetic type, significant differences in age, TIR, TBR, high-density lipoprotein cholesterol (HDLC), and insulin dose were detected using Kruskal-Wallis analyses. HbA1c significantly correlated with TIR ($p < 0.001$) and TAR ($p < 0.001$) using Pearson’s correlation analysis. TBR significantly correlated with CV\% ($p < 0.001$). Multivariable analysis of TIR showed a significant negative association with HbA1c ($p = 0.02$). Incretin combined with insulin therapy reduced the TBR proportion significantly according to the multivariate analysis. Retinopathy tended to be related to HbA1c ($p = 0.059$) and duration ($p = 0.078$) but not TIR ($p = 0.891$), according to the logistic analysis. Conclusions: These results demonstrate that CGM metrics reflect glucose control for 2 weeks using TIR. In addition, combined therapy with incretin and insulin therapy is superior for reducing hypoglycemia, based on TBR. Thus, TBR is also useful for monitoring hypoglycemia. However, FGM/CGM metrics do not predict retinopathy accurately.

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Introduction

The limitation of HbA1c is that it is undetectable during hypo- and hyperglycemia and HbA1c fluctuates during glucose excursions. Moreover, anemia influenc-
es the HbA1c value. In contrast to HbA1c, continuous glucose monitoring (CGM) metrics, such as time in range (TIR), can provide information to assist with immediate therapy decisions and/or lifestyle modifications. In 2019, the use of CGM was discussed in the Advanced Technologies & Treatments for Diabetes Study [1]. Flash glucose monitoring (FGM) was used to check for hypoglycemia in a diet and medication interventional study [2]. CGM also provides the ability to assess glucose variability and identify patterns of hyper- and hypoglycemia [3]. The effects of CGM on metrics of glycemic control diabetes were reviewed by a meta-analysis of randomized control studies [4]. This meta-analysis demonstrated that CGM improves glycemic control by expanding TIR and decreasing time below range (TBR), time above range (TAR), and glucose variability in both type 1 and type 2 diabetes. In older adults with type 1 diabetes, the use of CGM-derived coefficient of variation (CV) and glucose management indicators improved the identification of individuals at higher risk for hypoglycemia compared with HbA1c alone [5].

CGM metrics should be useful in detecting hyper- and hypoglycemia and improving diabetes management when glucose control is insufficient [6]. In the present study, we investigated the relationship between target metrics from CGM/FGM and HbA1c or CV%. TIR was analyzed in relation to biochemical factors and glycemic variabilities in patients with type 2 diabetes treated with insulin in addition to type 1 diabetic patients. TBR was also examined in relation to the reduction of antidiabetic agents for hypoglycemic patients undergoing combination therapy with DPP-4I, GLP-1RA, SGLT2I, or glinide based on insulin in multivariate analyses. Additionally, the association of CGM/FGM metrics with retinopathy was investigated.

Materials and Methods

Study Design

A total of 80 participants (42 males and 38 females) with type 1 or 2 diabetes undergoing treatment at the Tokyo Metropolitan Health and Medical Toshima Hospital (TMHMTH) and Ome Municipal General Hospital outpatient clinics were recruited for the study. The FGM examination was explained to each patient by a doctor or nurse and only patients who agreed to the examination were studied. This cross-sectional and retrospective study was conducted at the TMHMTH and approval was obtained from the Ethical Committee (Application No. 30-20). Exclusion criteria were the presence of complications, such as cancer, autoimmune disease, apoplexy, steroid use, and pregnancy.

HbA1c levels (National Glycohemoglobin Standardization Program) were measured with a Tosoh high-performance liquid chromatograph (Tosoh Bioscience, Tokyo, Japan) and glucose levels were measured using the hexokinase ultraviolet method. Participants were fitted with an FGM sensor (Free Style Libre Pro) on the back of their arm, which was used to monitor blood glucose levels 24 h/day for approximately 14 days. The data were stored automatically every 15 min. After 2 weeks, the sensors were removed from the arm and the cumulative data were transferred into Excel software (Microsoft Corp., Redmond, WA, USA).

Glycemic variability (GV), including mean, standard deviation (SD), and the mean amplitude of glycemic excursions (MAGE), were calculated by Easy GV (available in the public domain at https://www.phc.ox.ac.uk/research/technology-outputs/easygv) [7]. The percent CV (CV%) was calculated as SD divided by 14 days mean glucose value multiplied by 100. Median was expressed as an interquartile range. GV was also compared in patients treated with DPP-4I, GLP-1RA, sodium glucose transporter 2 inhibitors (SGLT2I), and glinide. Complications were defined as follows. Retinopathy included simple, preproliferative stage, and proliferative stage.

Data Collection and Statistical Analysis

The relationships between proportions of TIR, TAR, and TBR from FGM and retinopathy in insulin-treated type 1 and 2 diabetics were examined. Multivariable analysis was performed to analyze the associations of TIR with biochemical factors and glycemic variabilities. Logistic analysis was used to evaluate the association of retinopathy with TIR, HbA1c, GV, and duration. Furthermore, multiple regression analysis was used to examine the associations of TBR with antidiabetic agents, adjusted by diabetes type and insulin dose. Antidiabetic agents included DPP-4I, SGLT2I, Glinide, and GLP-1RA. The FGM data were entered into SPSS software (SPSS, Inc., Chicago, IL, USA) and analyzed.

Results

Characteristics of Male/Female Type 1 and 2 Diabetics

The baseline characteristics of patients are shown in Table 1. When grouping patients according to sex and diabetic type, significant differences in TIR, TBR, high-density lipoprotein cholesterol (HDLC), and insulin dose were detected using a nonparametric test (Kruskal-Wallis method). The other parameters did not differ significantly between the groups.

The Correlations between CGM/FGM Metrics and HbA1c or CV%

TRs are shown in Table 2. HbA1c correlated with TIR ($p < 0.001$) and TAR ($p < 0.001$), but not TBR. CV% significantly correlated with TIR ($p = 0.04$) and TBR ($p < 0.001$), but not TAR.
Association of CGM Metrics with Antihyperglycemic Drugs

**Multivariate Analysis for TIR**
According to the multivariate analysis, HbA1c negatively associated with TIR (\(p = 0.02\)). One standard deviation (SD) increase in HbA1c was accompanied by a 0.3 decrease of SD in TIR (Table 3). No other significant associations with TIR were detected.

**Multivariate Analysis of TBR with Diabetic Therapies**
Incretin combined with insulin therapy reduced the TBR proportion significantly according to the multivariate analysis (Table 4). The other drug treatments did not significantly associate with TBR.

**Logistic Analysis for Retinopathy**
Retinopathy was not significantly associated with any diabetes-related factors, according to the logistic analysis, as shown in Table 5. However, HbA1c tended to associate with retinopathy (\(p = 0.059\)) and duration (\(p = 0.078\)), but not TIR (\(p > 0.05\)).

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**Table 1.** Comparison of baseline characteristics using the Kruskal-Wallis test

|                         | Male/type 1 (n = 10) | Male/type 2 (n = 32) | Female/type 1 (n = 14) | Female/type 2 (n = 24) | \(p\) value |
|-------------------------|----------------------|----------------------|------------------------|------------------------|-------------|
| BMI, kg/m\(^2\)         | 24.9 (20.7–26.9)     | 25.1 (22.5–26.6)     | 23.4 (21.7–25.2)       | 22.5 (19.3–25.9)       | 0.26        |
| BP, systolic mm Hg      | 118 (115–121)        | 134.5 (119.0–150.0)  | 111.0 (108.0–126.0)    | 143.0 (116.3–155.5)    | 0.55        |
| HbA1c, %                | 7.6 (6.7–8.3)        | 7.5 (7.0–8.7)        | 8.6 (8.0–9.6)          | 8.1 (6.8–8.9)          | 0.058       |
| TIR, %                  | 32.0 (16.5–43.5)     | 36.0 (29.5–61.3)     | 25.5 (16.8–33.8)       | 43.5 (29.0–54.0)       | 0.01        |
| TBR, %                  | 14.0 (19.5–43.5)     | 2.0 (0.7–6.5)        | 11.5 (2.8–19.5)        | 6.5 (0.5–14.0)         | 0.001       |
| TAR, %                  | 44.0 (20.5–71.0)     | 61.0 (32.5–68.0)     | 60.0 (48.8–77.0)       | 52.5 (34.0–61.3)       | 0.33        |
| PPG, mg/dL              | 171.5 (56.3–349.8)   | 166.5 (117.0–206.0)  | 187.0 (125.0–299.5)    | 181.0 (127.5–231.0)    | 0.84        |
| HDLC, mg/dL             | 76.0 (57.5–81.8)     | 48.0 (44.5–57.0)     | 82.5 (66.8–104.8)      | 61.0 (52.5–79.5)       | 0.001       |
| Triglyceride, mg/dL     | 88.0 (48.5–221.0)    | 112.0 (85.0–165.0)   | 83.0 (60.5–100.0)      | 93.0 (74.8–133.3)      | 0.08        |
| LDLC, mg/dL             | 105.0 (88.5–133.0)   | 108.0 (82.0–117.0)   | 91.0 (72.5–114.0)      | 11.0 (87.5–120.1)      | 0.29        |
| Insulin dose, U         | 40.0 (34.5–71.0)     | 14.0 (10.0–35.0)     | 41.5 (35.0–55.8)       | 19.5 (12.5–27.5)       | 0.001       |

Range means 1 quarter to 3 quarters of each value. Italicized \(p\) values indicate statistically significant differences. BMI, body mass index; BP, blood pressure; HbA1c, glycosylated hemoglobin A1c; TIR, time in range; TAR, time above range; TBR, time below range; PPG, postprandial glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

**Table 2.** Correlation of FGM/CGM metrics with HbA1c and CV%

| TIR (\(N = 80\)) | TAR (\(N = 80\)) | TBR (\(N = 80\)) |
|-------------------|------------------|------------------|
| HbA1c             | −0.513 (<0.001)  | 0.534 (<0.001)   | −0.199 (NS)         |
| CV%               | −0.233 (0.04)    | 0.288 (NS)       | 0.688 (<0.001)     |

Numerical values are correlation coefficients. Values in parentheses are \(p\) values. NS, not significant; CV%, percent of coefficient variation; FGM, fast glucose monitoring; CGM, continuous glucose monitoring; HbA1c, glycosylated hemoglobin A1c; TIR, time in range; TAR, time above range; TBR, time below range.

**Table 3.** The association of TIR with biochemical factors on multivariate analysis

| Model     | Standardized regression coefficient (\(\beta\)) | 95% CI for the unstandardized coefficient | \(p\) value |
|-----------|-----------------------------------------------|------------------------------------------|-------------|
| Age       | −0.085                                        | (−0.296, 0.130)                          | 0.44        |
| Sex       | 0.204                                         | (−0.734, 13.41)                          | 0.07        |
| HbA1c     | −0.309                                        | (−7.204, −0.612)                         | 0.02        |
| PPG       | −0.057                                        | (−0.052, 0.031)                          | 0.62        |
| HDLC      | −0.086                                        | (−0.781, 0.267)                          | 0.54        |
| LDLC      | 0.158                                         | (−0.041, 0.238)                          | 0.16        |
| TG        | −0.010                                        | (−0.035, 0.033)                          | 0.93        |
| SD        | −0.359                                        | (−0.781, 0.267)                          | 0.33        |
| MAGE      | −0.161                                        | (−0.240, 0.146)                          | 0.63        |

Dependent factor, TIR (time in range); italicized \(p\) values are statistically significant. 95% CI, 95% of confidential interval; HbA1c, glycosylated hemoglobin A1c; TIR, time in range; PPG, postprandial glucose; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; MAGE, mean amplitude of glycemic excursion; SD, standard deviation.

**Discussion/Conclusion**
TIR resulting from CGM data in type 2 diabetic patients was higher than TIR in type 1 diabetic patients in our study. On the other hand, TBR was lower in type 2 diabetes than that in type 1 diabetes. CV% reflects the variability of glucose excursions. In type 1 diabetes, GV relative to mean glucose (i.e., CV%) explains the higher hypoglycemia than mean glucose alone when the glucose threshold is 3.0 mmol/L [8]. CV% is a good predictor of...
hypoglycemia in both type 1 and 2 diabetes treated with insulin in our study. Our results demonstrated that TIR is a surrogate marker for glycemic control and glycemic variabilities, since TIR changes positively with glucose levels (70–180 mg/dL), while TIR changes negatively with CV%. HbA1c is not able to detect hyper- and hypoglycemia. CV% reflects the incidences of hypoglycemia.

One advantage of CGM is that the metrics can be collected in a shorter time period facilitating the management of diabetic patients. TIR is a metric of 7–14 days of glucose levels collected by CGM or FGM, which is shorter than the 3–4 months for HbA1c, as a marker for glycemic control. However, there are several disadvantages of measuring CGM with the Libre device. This device does not have an alert and alarm system for hypoglycemia. Furthermore, glucose levels in interstitial fluid in the subcutaneous tissue are measured with the Libre device. These measurements may be less precise than capillary glucose testing [9]. Caution should be used when using CGM in diabetics because CGM cannot indicate severe hypoglycemia below 2.22 mmol/L of glucose.

We showed that incretin reduced the proportion of TBR in relation to hypoglycemia when used with insulin for diabetic treatment. Incretin prevents hypoglycemia in patients with type 1 and 2 diabetes during treatment with insulin. DPP-4 inhibitors prevent hypoglycemia by augmenting glucagon counter-regulation through the GIP-glucagon counter-regulatory axis [10]. GLP-1RA also prevents severe hypoglycemia with a single injection of long-acting insulin, such as Gargline or Degludec [11]. GLP-1RA is thought to prevent hypoglycemia in diabetics compared to non-GLP-1RA users as a counter-regulatory hormone. Two studies were conducted to assess whether glucose-dependent insulin secretion and the counter-regulatory response are preserved during hypoglycemia. During hypoglycemic events, exenatide resulted in a preserved glucose-dependent insulin secretory response and counter-regulatory response during hypoglycemia. During hypoglycemic events, exenatide produced a higher secretory glucagon response compared to a placebo [10]. Diabetics show a low glucagon secretory response during hypoglycemia in the absence of GLP1-RA, while GLP1-RA improves the glucagon response. Furthermore, the mechanism of recovery of glucagon secretion in diabetics, whether or not it is due to a decrease in insulin or some other reason, must be elucidated. SGLT2I prevents hypoglycemia if administered alone, since SGLT2I stimulates glucagon secretion via α cells [14].

### Table 4. The association of TBR with biochemical factors on multivariate analysis

| Model     | Standardized regression coefficient (β) | 95% CI for the unstandardized coefficient | p value |
|-----------|-----------------------------------------|------------------------------------------|---------|
| Age       | 0.281                                   | (5.336, 44.391)                          | 0.036   |
| Sex       | 0.135                                   | (0.013, 0.353)                           | 0.193   |
| HbA1c     | −0.252                                  | (−4.550, −0.179)                         | 0.034   |
| SD        | −0.051                                  | (−0.151, 0.100)                          | 0.62    |
| Glinide   | 0.028                                   | (−5.999, 7.936)                          | 0.782   |
| Incretin  | −0.301                                  | (−11.894, −1.371)                        | 0.014   |
| SGLT2I    | 0.045                                   | (−0.4620, 7.052)                         | 0.679   |
| Insulin dose | 0.324                                  | (0.043, 0.284)                           | 0.009   |
| Type      | −0.275                                  | (−2.108, −0.329)                         | 0.039   |

Dependent factor, TBR; italicized p values are statistically significant. 95% CI, 95% of confidential interval; SD, standard deviation; HbA1c, glycosylated hemoglobin A1c; TBR, time below range.

### Table 5. Association of retinopathy with diabetes-related factors by logistic analysis

| Regression coefficient (β) | OR  | 95% CIs  | p value |
|----------------------------|-----|----------|---------|
| Age                        | 0.032 | 1.033     | (0.996, 1.071) | 0.081   |
| Sex                        | −0.145 | 0.865     | (0.285, 2.622) | 0.797   |
| HbA1c                      | 0.571 | 1.770     | (0.980, 3.197) | 0.059   |
| TIR                        | −0.003 | 0.997     | (0.960, 1.036) | 0.891   |
| Duration                   | 0.048 | 1.050     | (0.995, 1.108) | 0.078   |
| SD                         | 0.003 | 1.003     | (0.965, 1.041) | 0.894   |
| Mean                       | −0.012 | 0.988     | (0.968, 1.008) | 0.236   |

β is regression coefficient; HbA1c shows a trend of association with retinopathy. OR, odds ratio; 95% CIs, 95% of confidence interval; HbA1c, glycosylated hemoglobin A1c; TIR, time in range; SD, standard deviation.
plications. HbA1c is a glycation end product. Therefore, HbA1c changes indicate changes not only in the mean glucose control for 2–3 months, but also imply an advance glycation end product [17]. On the other hand, TIR does not measure glycation end products. Thus, these 2 surrogate markers are basically different. Therefore, in this cross-sectional retrospective study, there was not a significant association of TIR with diabetic complications. Although it has been reported that TIR is strongly associated with microvascular complications [18], CGM/FGM metrics could not predict retinopathy like HbA1c, according to our results. For future research, there are some tasks to resolve in the usage of FGM/CGM metrics to predict diabetic complication issues.

In conclusion, HbA1c reflects a longer period and at present, it is the measure associated with chronic complications, while TBR from FGM was useful in detecting hypoglycemia in diabetics treated with insulin combined with incretin. We must accumulate more CGM and FGM data to endorse their use for the management of insulin-treated diabetics in terms of glycemic control, hypoglycemia, and complications.

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Statement of Ethics

“The protocol of the following studies was approved by the Ethical Committee on human research at Tokyo Metropolitan Health and Medical Toshima Hospital (TMHMTH) (approval no. 30-20) according to the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to enrollment.”

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors were involved in examining patients who used FGM. All data were collected by 4 participating doctors.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
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