Accuracy of a Professional Continuous Glucose Monitoring Device in Individuals with Type 2 Diabetes Mellitus

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Among continuous glucose monitoring (CGM) devices, which continuously measure glucose concentration in subcutaneous interstitial fluid for comprehensive monitoring of blood glucose profile, only FreeStyle Libre Pro® (Abbott Diabetes Care) is currently available in Japan as a professional system. FreeStyle Libre Pro® is easy to use because it does not require calibration by self-monitoring of blood glucose (SMBG), but information on its accuracy has been insufficient. To evaluate the measurement accuracy of FreeStyle Libre Pro®, we have now compared blood glucose levels determined by this device with those measured by SMBG in 40 individuals with type 2 diabetes mellitus. The mean absolute relative difference (MARD) for FreeStyle Libre Pro® measurements compared with SMBG measurements was calculated as an index of CGM accuracy. Overall blood glucose values measured by SMBG were 167.0 ± 60.1 mg/dL, and those determined by FreeStyle Libre Pro® were 155.0 ± 60.7 mg/dL, with this difference being statistically significant. The MARD for FreeStyle Libre Pro® relative to SMBG was 12.7 ± 9.3%. It was substantially higher in 2 of the 40 patients, at 49.2% and 47.5%, than in the other 38 individuals. MARD values did not differ significantly between before and 2 h after meals. However, the MARD was significantly higher for SMBG values of <100 mg/dL than for those of ≥250 mg/dL. Our results thus indicate that the measurement accuracy of FreeStyle Libre Pro® is relatively good, but that some cases in which values determined by the device deviate from SMBG values require caution in interpretation.

INTRODUCTION

For individuals with diabetes mellitus, monitoring of changes in blood glucose levels is important for treatment optimization. However, postprandial hyperglycemia and nocturnal hypoglycemia are often underestimated by conventional self-monitoring of blood glucose (SMBG) alone (1). Continuous glucose monitoring (CGM), which involves continuous measurement of subcutaneous interstitial fluid glucose (ISFG) concentration and provides a comprehensive view of blood glucose profile, has substantial advantages for the assessment and control of blood glucose levels in patients with diabetes (2). In Japan, the first retrospective CGM device, MiniMed CGMS Gold™ (Medtronic MiniMed, Northridge, CA, USA), was launched in 2009. The iPro™2 (Medtronic MiniMed) was introduced in Japan in 2012 and was widely adopted, but this analysis system was discontinued in 2021. Only FreeStyle Libre Pro® (Abbott Diabetes Care, Alameda, CA, USA), which was introduced in 2016, is currently available as a professional CGM device in Japan. FreeStyle Libre Pro® is easier to use than iPro™2 because it does not require calibration by SMBG. On the other hand, given that such calibration is not possible, obtaining SMBG data and other reference blood glucose data has been impossible. As a result, information about the accuracy of FreeStyle Libre Pro® has been insufficient.

FreeStyle Libre® (Abbott Diabetes Care), an intermittently scanned CGM (isCGM) that is used by patients themselves to support treatment, was launched in Japan in 2017. The manufacturer has not officially published the measurement algorithms for FreeStyle Libre® and FreeStyle Libre Pro®, and the differences between the algorithms are not apparent. Although many studies have examined the accuracy and safety of FreeStyle Libre®, which also does not require calibration during measurement, few studies have assessed FreeStyle Libre Pro® (3-5). In addition, studies conducted in Japan on the accuracy of the FreeStyle Libre Pro have been very small, so the factors affecting accuracy are not apparent. We have therefore now examined the measurement accuracy of FreeStyle Libre Pro® by comparison with blood glucose levels measured by SMBG.

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MATERIALS AND METHODS

Forty patients with type 2 diabetes mellitus who wore FreeStyle Libre Pro® while hospitalized at the Division of Diabetes and Endocrinology, Kobe University Hospital, were included in the study. The FreeStyle Libre Pro® sensor was worn on the upper arm. SMBG (Medisafe Fit Smile®; Terumo, Tokyo, Japan) was performed seven times per day: before and 2 h after each meal as well as at 10:00 p.m. The CGM data were obtained every 15 min, and the CGM measurement closest to each SMBG measurement was used for accuracy analysis. We used 4.5 ± 0.9 days of CGM data for the analysis, beginning on the second day of wear. As a measure of CGM accuracy, the mean absolute relative difference (MARD) of FreeStyle Libre Pro® measurements relative to SMBG measurements was calculated. MARD is the mean value of ARD, where ARD (%) is expressed by the following equation: $100 \times$ (FreeStyle Libre Pro® value – SMBG value)/(SMBG value). Given that the MARD is affected by SMBG measurements, MARD values for blood glucose ranges of <100 mg/dL and $\geq$250 mg/dL were also calculated (5). In addition, the MARD was calculated separately for preprandial and 2-h postprandial glucose values. Because MARD values were not normally distributed (Shapiro-Wilk test), the Mann-Whitney U test was applied to test for significant differences. The relation between MARD values and either age or body mass index (BMI) for each subject was evaluated with Pearson's correlation coefficient. A *P* value of <0.05 was considered statistically significant. All statistical analysis was performed with SPSS software version 22 (IBM SPSS Statistics). The study was approved by the ethics committee of Kobe University Hospital (approval no. B200290) and was carried out in accordance with the Declaration of Helsinki and its amendments.

RESULTS

The baseline characteristics of the 40 study subjects are shown in Table I. {The mean $\pm$ SD for the average of all blood glucose levels of each of the 40 subjects measured by SMBG was 167.0 ± 60.1 mg/dL, whereas the mean $\pm$ SD for the corresponding ISFG levels measured with FreeStyle Libre Pro® was 155.0 ± 60.7 mg/dL. The FreeStyle Libre Pro® values were significantly lower than the SMBG values ($P = 0.0005$) (Figure 1).

Table I. Baseline characteristics of the study patients ($n = 40$)

| Characteristic	
Male/female	23/17
Age (years)	61.5 ± 14.5
BMI (kg/m^2)	26.9 ± 5.2
Hemoglobin A$_{1c}$ (%)	8.7 ± 1.8
Duration of diabetes (years)	13.4 ± 10.2
Fasting CPR (ng/mL)	1.9 ± 0.9
Antidiabetic agents (DPP-4 inhibitors/biguanides/sulfonylureas/ thiazolidinediones/α-glucosidase inhibitors/ SGLT-2 inhibitors/GLP-1 receptor agonists/ insulin)	18/21/6/4/10/3/5/14

Date are n or mean $\pm$ SD values. Abbreviations not defined in text: CPR, C-peptide immunoreactivity; DPP-4, dipeptidyl peptidase–4; SGLT-2, sodium-glucose cotransporter–2; GLP-1, glucagon-like peptide–1.
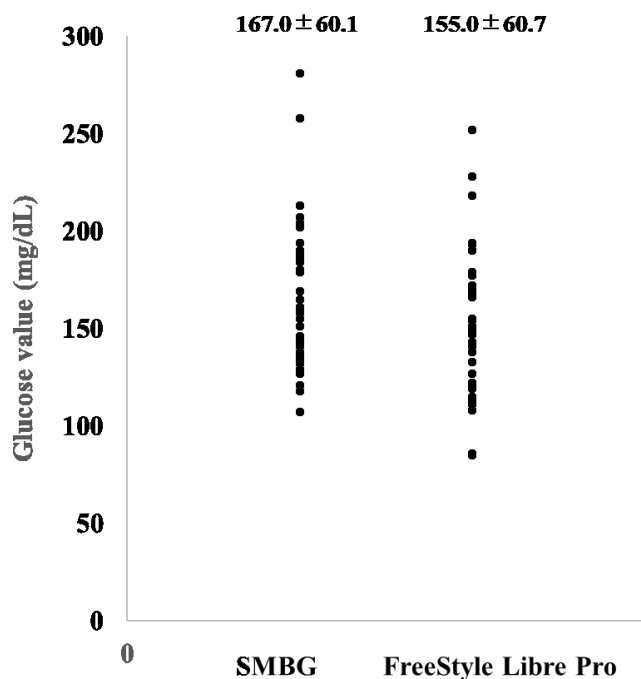
Figure 1. Glucose levels obtained by SMBG and with FreeStyle Libre Pro® for the 40 study subjects. The mean ± SD values for the two sets of measurements are also indicated. The FreeStyle Libre Pro® values were significantly lower than the SMBG values (P = 0.0005, unpaired Student's t test).

The MARD of FreeStyle Libre Pro® values relative to SMBG values for the 40 study patients was 12.7 ± 9.3% (Figure 2). It was substantially higher in 2 of the 40 patients, at 49.2% and 47.5%, than in the other 38 patients. One patient was an 80-year-old male with BMI 24.9 kg/m^2, taking DPP-4 inhibitor. The data analysis period was 19 points over three days when no special events occurred. The other patient was a 68-year-old woman who was severely obese (BMI 38.9 kg/m^2) and took GLP-1 receptor agonist, SGLT-2 inhibitor, thiazolidinedione, and biguanide. The data analysis period was 31 points over four days, during which no special events occurred. There was always a large discrepancy between SMBG values and FreeStyle Libre Pro® values during the measurement period for these two patients. There was no significant difference in the MARD between preprandial (12.5 ± 10.7%, 790 pairs) and 2-h postprandial (11.3 ± 13.4%, 476 pairs) values (Table II). In contrast, the MARD for SMBG measurements of <100 mg/dL (13.0 ± 15.8%, 95 pairs) was significantly (P = 0.008) higher than that for those of ≥250 mg/dL (9.3 ± 7.5%, 141 pairs) (Table II).
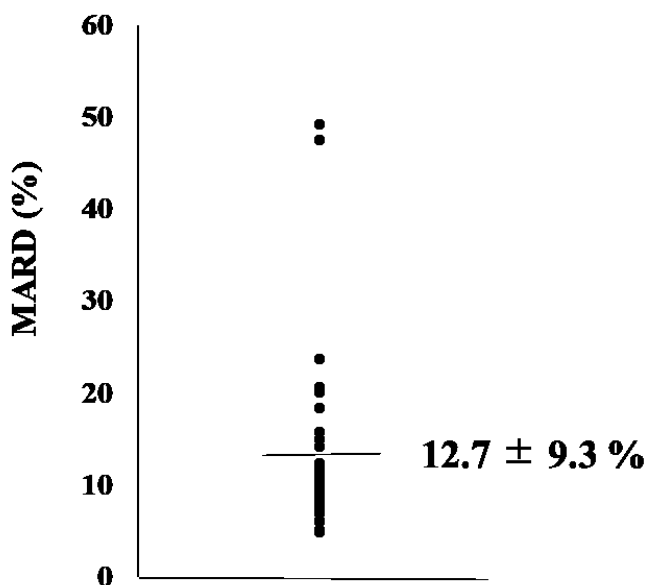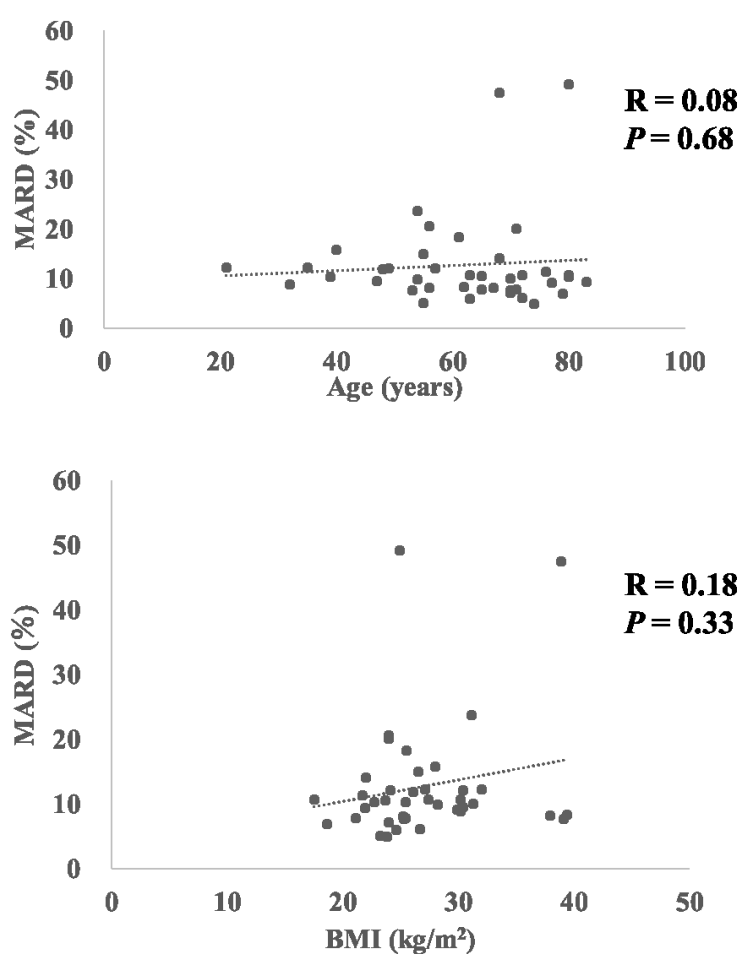

Figure 2. The MARD of FreeStyle Libre Pro® relative to SMBG for the 40 study subjects. The overall mean ± SD of the MARD values is also indicated.

Table II. Accuracy of FreeStyle Libre Pro® relative to SMBG

	n (pairs)	MARD (%)
Overall	1285	12.7 ± 9.3
SMBG of <100 mg/dL	95	13.0 ± 15.8*
SMBG of ≥250 mg/dL	141	9.3 ± 7.5
Preprandial	790	12.5 ± 10.7
2-h postprandial	476	11.3 ± 13.4

Date are mean ± SD values. *P < 0.05 versus SMBG of ≥250 mg/dL (Mann-Whitney U test).

Finally, correlation analysis of the MARD for FreeStyle Libre Pro® for each individual showed that it was not correlated with age or BMI (Figure 3).

Figure 3. Relation between the MARD of FreeStyle Libre Pro® and either age or BMI for the 40 study subjects. The MARD was not significantly correlated with age or BMI. R, Pearson's correlation coefficient.

DISCUSSION

The overall MARD of FreeStyle Libre® measurements relative to SMBG measurements was 12.7 ± 9.3%, which is similar to a previously reported value of 11.1% relative to venous blood glucose (2). The accuracy of FreeStyle Libre® was also not substantially different from the MARD for iPro[TM]2 (11.0%) (2), a conventional professional CGM device. Although the sensor values of FreeStyle Libre Pro® have previously been shown to deviate from SMBG values at 2 h after a meal (6), we found that the MARD for 2-h postprandial values was 11.3 ± 13.4%, which was similar to that for preprandial values (12.5 ± 10.7%). The accuracy of FreeStyle Libre®, an

isCGM device, was previously found not to be affected by BMI, age, type of diabetes, sensor insertion site, insulin administration, or hemoglobin A_{1c} level (3). We have now shown that the accuracy of FreeStyle Libre Pro® was also not affected by age or BMI. Our results overall thus suggest that evaluation of glycemic variability in individuals with type 2 diabetes by monitoring with FreeStyle Libre Pro® is reasonable.

A previous study found that FreeStyle Libre Pro® is inaccurate, with a MARD of 25.1%, at blood glucose levels of <100 mg/dL in individuals with type 2 diabetes (7). In our study, the accuracy was 13.0 ± 15.8% for SMBG measurements of <100 mg/dL, suggesting that the device is less accurate at such low blood glucose levels. A study that compared the accuracy of FreeStyle Libre Pro® with that of iPro™2 found that the median absolute difference between the two devices was significantly higher under conditions of hypoglycemia than under those of hyperglycemia or normoglycemia, suggesting that the accuracy of CGM for hypoglycemia may vary depending on the device (8). Given that glucose values provided by CGM may be inaccurate during hypoglycemia, with the MARD having been found to vary according to glucose values (9,10), caution should be exercised in interpreting CGM data depending on the blood glucose range.

Two of the 40 patients in the present study showed MARD values that were substantially higher at 49.2 ± 34.0% and 47.5 ± 18.9% than those in the other subjects. Although one patient was characterized as elderly and the other as severely obese, overall age and BMI were not correlated with MARD, with the reason for these unusually high values being unclear. Because of this significant discrepancy in some cases, it was considered desirable to perform SMBG measurements at least once during Freestyle Libre Pro® measurements to confirm the accuracy of the Freestyle Libre Pro® values. Given that the MARD of FreeStyle Libre® differs among studies, it is possible that such differences are due to variability among individual sensors (3,5,11-14). In addition, glucose values obtained by SMBG are less accurate than are plasma glucose values measured in a central laboratory, which also may have influenced differences among studies.

Previous studies on the accuracy of FreeStyle Libre Pro® in Japan have been small, with only 5 to 15 cases (6-8,15). In contrast, we examined a relatively large number of patients ($n = 40$), which is a strength of our study. A second strength is that we were able to determine MARD values before and after meals and for different blood glucose ranges. A limitation of our study is that 81.6% of the blood glucose levels examined for determination of the MARD were in the physiological range of 100 to 250 mg/dL, which may have led to overestimation of the accuracy of device measurement. However, the data did include 7.4% of pairs with an SMBG value of <100 mg/dL and 11.0% of pairs with an SMBG value of ≥250 mg/dL.

In conclusion, we found that FreeStyle Libre Pro®, a professional CGM device that is easy to use and does not require calibration by SMBG, has a relatively good measurement accuracy. However, some cases in which values obtained with the device deviate from SMBG values require caution in interpretation.

ACKNOWLEDGMENTS

DISCLOSURES

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