ORIGINAL ARTICLE

Flash glucose monitoring in type 1 diabetes: A comparison with self-monitoring blood glucose

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ABSTRACT

Aims/Introduction: A flash glucose monitoring (FGM) system has become available. To clarify the relationship between FGM and self-monitoring blood glucose (SMBG) values, we compared the two values after simultaneous measurement in Japanese patients with type 1 diabetes, under daily life settings.

Materials and Methods: A total of 20 outpatients with type 1 diabetes were analyzed. When FGM and SMBG were carried out simultaneously (within ±3 min), the values were adopted and each FGM value was matched and compared with the corresponding SMBG value. In addition, we analyzed other cases of simultaneity defined as "within ±2 min," "within ±1 min" and "at the exact same time."

Results: The percentage of SMBG and FGM values in the clinically acceptable zone A + B in Clarke and consensus error grid analyses were 97.9 and 99.2%, respectively. Deming regression (x-axis: FGM values, y-axis: SMBG values) determined a slope of 0.9128 (95% confidence interval 0.9008–0.9247) and an intercept of +15.94 mg/dL (95% confidence interval 14.05–17.84). FGM values were lower than SMBG values in the lower glucose range, and higher in the higher glucose range. The shorter the time lag between measurements, the higher the rate of concordance between FGM and SMBG values.

Conclusions: The results of this study provided evidence on the reliability of FGM in Japanese patients with type 1 diabetes in home conditions. Based on the results, if an abnormal glucose value is detected by FGM, SBMG should then be used to confirm the result.

INTRODUCTION

Intensive diabetes therapy has long-term beneficial effects on the risk of micro- and macrovascular complications in patients with type 1 diabetes[1]. As stringent glucose control increases the risk of hypoglycemia, glucose levels need to be closely monitored to prevent it. The self-monitoring of blood glucose (SMBG), which is usually carried out with finger-prick blood samples, is the most effective way to monitor the blood glucose in daily life. The limitation of SMBG is that the overall daily blood glucose profile is not captured, particularly the postprandial and nocturnal blood glucose levels[2]. To solve this problem, a continuous glucose monitoring (CGM) system has been developed[3]. CGM consists of a subcutaneous sensor, which measures the glucose level in the interstitial fluid, and converts it into the equivalent venous blood glucose level. Subsequent to

CGM, a flash glucose monitoring (FGM) system (Abbott Japan Diabetes Care Inc., Tokyo, Japan) has become available. It has been reported that FGM reduces the time spent in hypoglycemia for patients with well controlled type 1 diabetes[4].

When a new FGM device becomes available, it is essential to evaluate its accuracy. In September 2017, FGM was approved in Japan for use in patients who are being treated with insulin or glucagon-like peptide-1 analog. Through the daily use of the FGM device on outpatients with type 1 diabetes, we noticed that FGM values appeared to be lower in the low glucose range, and higher in the high glucose range, compared with SMBG values.

The present study aimed to clarify the relationship between glucose values measured by FGM and SMBG, in patients with type 1 diabetes, by measuring both values simultaneously in daily life settings and comparing them. This would be beneficial in enabling patients with type 1 diabetes to interpret their own

glucose levels, thereby significantly reducing the times in hypoglycemia or hyperglycemia. Furthermore, it would assist healthcare professionals to act on the results in choosing the appropriate diabetes management.

METHODS

This study took place at the Kindai University Faculty of Medicine (Osaka-sayama, Osaka, Japan). The ethics review committee of the hospital approved the protocol, and informed consent was obtained from the participants. We evaluated the stored data extracted from the FreeStyle Libre (FGM system), which were collected from patients with type 1 diabetes receiving multiple-dose insulin injection or continuous subcutaneous insulin infusion. They were all outpatients at the Kindai University Faculty of Medicine and visited once a month. The characteristics of the 20 patients investigated in this study are provided in Table 1. All patients were adults (aged 30–75 years); and all younger patients were not included. Type 1 diabetes was diagnosed according to the diagnostic criteria for acute-onset, slowly progressive and fulminant type 1 diabetes, defined by the Japan Diabetes Society[5–7].

The FreeStyle Libre has triple functions of CGM, FGM and SMBG. When using FreeStyle Libre for CGM and FGM, it serves as a receiver for a subcutaneous sensor placed on the back of the upper arm, which measures glucose in the interstitial fluid every 15 min in the case of CGM; however, in FGM, the glucose data is not constantly shown, and is available only on demand. When glucose values are required, the receiver is placed in front of the sensor. These data are automatically stored in the personal FreeStyle Libre. When using the FreeStyle Libre for SMBG, it serves as a meter of capillary blood glucose with FreeStyle Precision glucose strips (Abbott Japan Diabetes Care Inc.); the data are again automatically stored in the personal FreeStyle Libre. The accuracy of SMBG values measured with the FreeStyle Precision glucose strips (which used the same system as the FreeStyle Optium) has been clarified by the manufacturing company (https://freestylediabetes.co.uk/images/uploads/documents/White_Paper__Clinical_FreeStyle_Optium_Neo.pdf) and by Freckmann et al.[8] When the patients visited our hospital, they brought their FreeStyle Libre, and the data were extracted and stored. Patients' data were collected in the usual daily life settings. They could measure glucose levels by FGM and/or SMBG at an arbitrary time. A total of 62,301 FGM values and 9,646 SMBG values were extracted. Out of these, 5,991 paired data, which included both the FGM value and the SMBG value, measured simultaneously (within ±3 min), were selected and compared. In addition, we analyzed these data stratified by the degree of simultaneity, defined as "within ±2 min," "within ±1 min" and "at the exact same time."

Outcomes from FGM values and SMBG values were superimposed on the error grids, as described by Clarke et al.[9] and Parkes et al.[10] with R/ega program by Schmolze D (https://cran.r-project.org/web/packages/ega/vignettes/ega.html). Values in zone A and B were deemed to be clinically acceptable, whereas those in zones C, D and E were considered to be potentially unsafe. The clinical accuracy of FGM values was determined as >99% of the values that were within zones A and B compared with the SMBG results (based on International Organization for Standardization [ISO]: 15197:2013 criteria). In addition, the mean absolute differences and mean absolute relative differences (MARD) were used to evaluate the analytical accuracy. Absolute differences were calculated as follows: absolute differences (mg/dL) = |FSL − SMBG|. Absolute relative differences were calculated as follows: absolute relative differences (%) = $100 \times$ absolute differences / SMBG. Mean absolute differences and MARD were used to evaluate the accuracy at the low (<100 mg/dL) and mid-to-high (≥100 mg/dL) glucose ranges, respectively. The proportion of results within ±15 mg/dL of the SMBG value for glucose levels <100 mg/dL and within ±15% of the SMBG value for glucose levels ≥100 mg/dL was also used to evaluate the overall analytical accuracy (based on ISO: 15197:2013 criteria).

Statistical analysis was carried out by the Mann–Whitney U-test for grouped data or χ^2-test for categorical variables. Deming regression was used to evaluate the relationship between FGM and SMBG values. Bland–Altman plot analysis was carried out to compare the bias between FGM and SMBG values. Linear regression was used to characterize the relationship between FGM values and differences (FGM − SMBG), overall and for individual patients. Statistical tests were carried out using Prism software (GraphPad Prism®, La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 5,991 pairs of FGM and SMBG values were available. Figure 1a,b shows Clarke and consensus (Parkes) error grid analyses, respectively, of SMBG values (x-axis) and the coincident FGM values (y-axis). Clarke error grid analysis showed that 75.6 and 22.3% of glucose values measured using FGM fell into zone A and B, respectively, whereas consensus error grid analysis showed that 78.2 and 21.1% of glucose values measured using FGM fell into zone A and B, respectively.

Mean glucose values decreased by 2.56% in FGM compared with SMBG (141.0 vs 144.7 mg/dL, $P < 0.0001$, Mann–Whitney U-test). The overall mean absolute differences and MARD were 21.5 mg/dL and 15.9%, respectively. We evaluated the analytical accuracy of FGM values based on ISO: 15197:2013 criteria (>95% of the results were within ±15 mg/dL of the SMBG value for glucose levels <100 mg/dL, and within ±15% of the SMBG value for glucose levels ≥100 mg/dL). For paired results at lower glucose concentrations, with SMBG value <100 mg/dL ($n = 1,656$), the proportion of those <15 mg/dL was 69.4%; for those at higher glucose concentrations, with SMBG value ≥100 mg/dL ($n = 4,335$), the proportion of those <15% was 62.4%.

Deming regression (x-axis: FGM values, y-axis: SMBG values) was used to determine the slope of 0.9128 (95%

Table 1 | Characteristics of patients and the results of the linear regression analysis

Participant number	Age (years)	Sex	BMI	Classification of type 1 diabetes	Years since diagnosis	Therapy	Total unit of insulin injection per day	HbA1c (%)	Fasting serum CPR (ng/mL)	No. paired data analyzed	Deming regression (y = sensor glucose, x = flush glucose)	Linear regression (y = sensor glucose, x = flush glucose)
1	46	Female	18.1	Acute	1.1	MDI	20.0	7.2	0.277	220	y = 0.7800x + 32.74	y = 0.6853x + 45.20
2	73	Female	14.9	SP	13.1	MDI	30.0	8.2	0.093	86	y = 1.002x − 135.1	y = 0.4761x + 26.70
3	61	Male	26.8	Acute	19.6	CSII	48.2	9.2	<0.01	313	y = 1.077x + 17.55	y = 0.9828x + 36.44
4	70	Female	22.0	SP	25.6	CSII	51.2	7.6	<0.01	712	y = 0.9194x + 11.12	y = 0.8838x + 16.74
5	75	Female	25.5	SP	16.6	CSII	40.2	7.5	0.106	31	y = 0.8940x + 25.48	y = 0.8512x + 32.35
6	70	Female	20.0	Acute	30.7	MDI	32.0	6.7	<0.01	675	y = 0.8867x + 18.64	y = 0.7836x + 31.19
7	70	Female	20.7	SP	23.6	MDI	8.0	6.4	0.85	798	y = 0.8082x + 27.34	y = 0.7021x + 38.19
8	48	Female	24.5	Acute	6.6	MDI	31.0	7.7	<0.01	89	y = 1.101x − 3.128	y = 1.0745x + 0.6805
9	55	Female	19.8	SP	0.7	MDI	23.0	6.5	1.35	42	y = 0.8697x + 1453	y = 0.8366x + 18.33
10	30	Male	27.3	Acute	14.6	CSII	53.2	11.8	<0.01	125	y = 0.8840x + 1689	y = 0.8449x + 27.02
11	32	Female	22.0	Fulminant	0.8	CSII	31.3	6.5	<0.01	435	y = 0.9175x + 1049	y = 0.8457x + 21.17
12	62	Male	20.2	Acute	1.3	MDI	33.0	7.3	0.081	259	y = 1.066x + 10.71	y = 0.9607x + 24.89
13	38	Female	18.9	Acute	0.8	CSII	34.0	6.0	0.409	89	y = 0.7257x + 2126	y = 0.6375x + 2894
14	42	Male	27.8	Fulminant	8.8	MDI	55.0	6.9	<0.01	354	y = 0.8469x + 26.75	y = 0.7593x + 37.39
15	42	Male	24.3	SP	3.4	CSII	38.5	6.9	0.318	239	y = 0.9054x + 5.253	y = 0.8558x + 12.20
16	62	Female	15.9	SP	3.7	MDI	13.0	7.0	0.095	364	y = 0.9281x + 9.808	y = 0.8428x + 20.69
17	52	Male	23.2	Acute	1.8	MDI	15.0	6.5	0.449	20	y = 0.7276x + 26.70	y = 0.6533x + 35.21
18	38	Female	19.5	Acute	12.2	MDI	27.0	6.6	<0.01	133	y = 0.8405x + 1855	y = 0.8139x + 21.96
19	75	Female	18.4	Acute	4.8	MDI	17.0	8.4	0.75	186	y = 0.8647x + 13.18	y = 0.8477x + 15.52
20	43	Female	18.9	SP	6.2	CSII	26.0	7.2	0.109	821	y = 0.9847x + 14.91	y = 0.8810x + 30.03
Total or mean ± SD	54.2 ± 15.0	Female: 14, Male: 6	21.4 ± 3.7	Acute: 10, SP: 8, Fulminant: 2	9.8 ± 9.3	MDI:12, CSII:8	31.3 ± 13.5	7.4 ± 1.3	0.244 ± 0363†	5,991	y = 0.9128x + 15.94	y = 0.8191x + 29.15

The classification of type 1 diabetes includes acute-onset (Acute), slowly progressive (SP) and fulminant (Fulminant) type 1 diabetes, as defined by the Japan Diabetes Society. BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated hemoglobin; MDI, multiple dose insulin injection. †The values of serum C-peptide immunoreactivity (CPR) "<0.01" were considered as 0 and calculated.

(a)
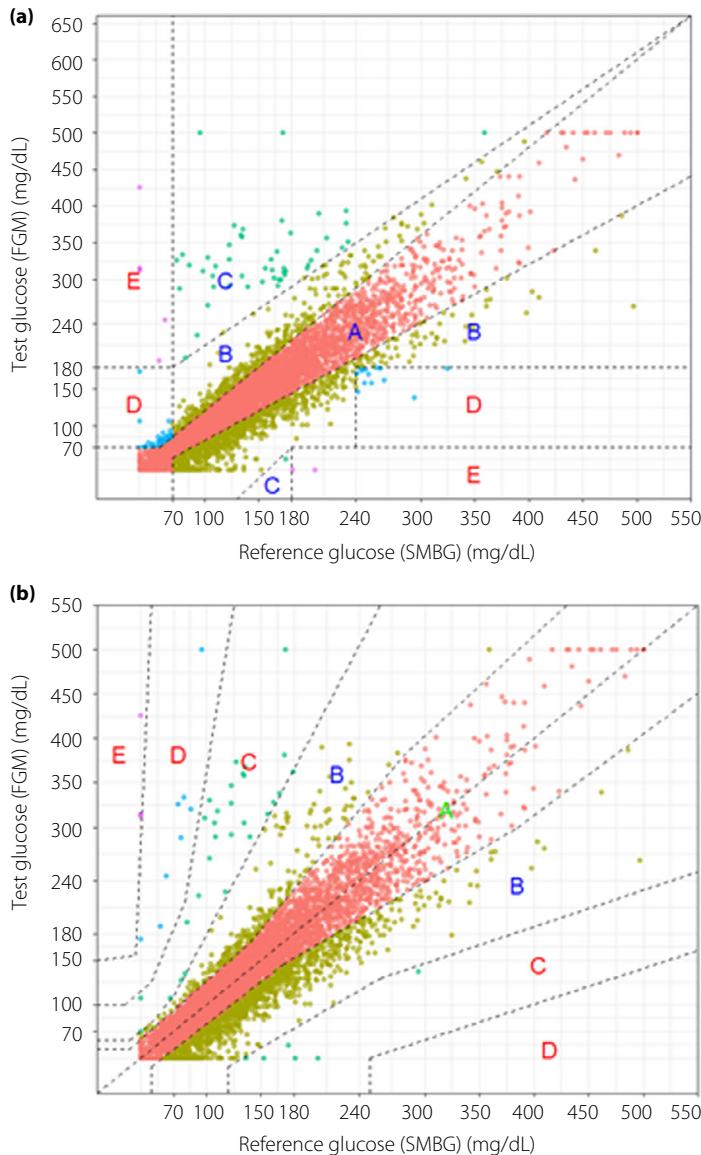
Clarke zone	*n*	%
A	4,532	75.6
B	1,336	22.3
C	50	0.8
D	65	1.1
E	8	0.1

(b)

Consensus zone	*n*	%
A	4,682	78.2
B	1,262	21.1
C	35	0.6
D	8	0.1
E	4	0.1

Figure 1 | (a) Clarke error grid and (b) consensus (Parkes) error grid. Analysis of glucose level measured in flash glucose monitoring (FGM) versus self-monitoring blood glucose(SMBG) values as the reference. Based on a total of 5,991 measurements; 4,532 and 1,336 measurements in FGM fell in zone A and B in the Clarke error grid analysis, respectively, and 4,682 and 1,262 measurements fell in zone A and B in the consensus error grid analysis, respectively.

confidence interval [CI] 0.9008–0.9247) and an intercept of +15.94 mg/dL (95% CI 14.05–17.84; Figure 2a; Table 2). Findings from the Bland–Altman analyses showed a fixed bias of −4.85% (95% CI −5.41, −4.30) with limits of agreement from −48.0 to 38.3% (Figure 2b), suggesting that FGM values were significantly less than SMBG values by −4.85% (or −3.64 mg). These results showed that bias increased linearly as the average glucose value increased ($P < 0.0001$).

In Figure 3a, we compared FGM values with the difference (FGM − SMBG) values. The reason why this figure was

constructed was to verify our speculation that FGM values were lower in the lower glucose range, and higher in the higher glucose range compared with SMBG values. As expected, linear regression was used to determine a slope of 0.1809 (95% CI 0.1702–0.1916), a *y*-intercept of −29.15 mg/dL (95% CI −30.85 to −27.46) and an *x*-intercept of 161.2 mg/dL (95% CI 156.8–165.7); suggesting that the difference in glucose values between FGM and SMBG was more pronounced in low and high glycemic conditions. Figure 3b shows the number of data pairs in different FGM value ranges. In total, FGM values were lower
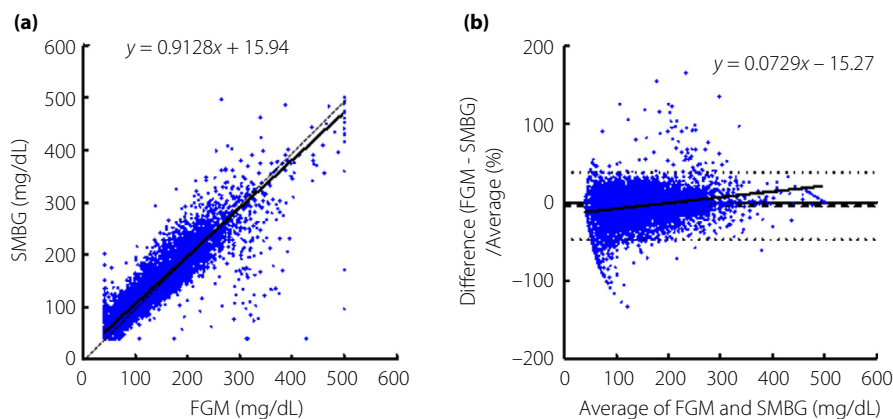
Figure 2 | (a) Scatterplot showing the relationship between flash glucose monitoring (FGM; *x*-axis) and self-monitoring blood glucose (SMBG values; *y*-axis). The dotted diagonal line is the line of identity, and the solid line is the line of best fit from Deming regression. (b) Bland–Altman plot of the difference between FGM and SMBG values against the mean glucose concentration for both methods. The long dashed horizontal line is the mean bias, and the two horizontal dotted lines represent the 95% confidence interval for agreement. The plot shows that bias increased linearly as the average value increased ($P < 0.0001$, linear regression).

Table 2 | Deming regression and Bland–Altman analysis in the difference in measurement period

Measurement period	Deming regression (y = SMBG, x = FGM)			Bland–Altman analysis	
	Best-fit line	95% CI of a slope	95% CI of a *y*-intercept when $x = 0.0$	A fixed bias % (mg)	95% CI of a fixed bias %
Within ±3 min (n = 5,991)	$y = 0.9128x + 15.94$	0.9008–0.9247	14.05–17.84	−4.85 (−3.64)	−5.41 to −4.30
Within ±2 min (n = 5,502)	$y = 0.9217x + 14.80$	0.9093–0.9340	12.84–16.76	−4.66 (−3.68)	−5.23 to −4.10
Within ±1 min (n = 4,081)	$y = 0.9541x + 10.74$	0.9412–0.9671	8.668–12.81	−4.32 (−4.16)	−4.92 to −3.71
At the exact same time (n = 1,123)	$y = 0.9705x + 5.132$	0.9461–0.9949	1.466–8.798	−1.40 (−1.08)	−0.34 to −2.47

CI, confidence interval; FGM, flash glucose monitoring; *n*, number of paired data analyzed; SMBG, self-monitoring of blood glucose.

than SMBG values in 56.2% (3,366/5,991), higher in 41.5% (2,487/5,991) and even in 2.3% (138/5,991) of all glucose values. In the lower glucose range (40–69 mg/dL in FGM), FGM values were lower than SMBG values in 78.1%, and higher in 17.6% of all the glucose values. On the contrary, in the extremely higher glucose range (251–500 mg/dL in FGM), FGM values were higher than SMBG values in 72.4%, and lower in 24.8% of all the glucose values. In the slightly higher glucose range (181–250 mg/dL in FGM), FGM values were higher than SMBG values in 54.6%, and lower in 44.7% of all the glucose values. The χ^2-test for the categorical variables showed statistical significance ($P < 0.001$).

When the FGM values and difference (FGM − SMBG) in values for each patient were compared (Figure 4), 16 out of 20 patients had a positive correlation with the *x*-intercept of approximately 70–260 mg/dL in the linear regression analysis; suggesting that 80% of the patients matched our speculation. Three out of 20 patients had a positive correlation with the no *x*-interception, one patient with higher glucose in FGM than that in SMBG, and two patients with lower glucose in FGM

than that in SMBG, in all ranges of glucose values. Only one out of 20 patients (Table 1, participant number 8) had a negative correlation in the linear regression analysis.

In addition to the simultaneity "within ±3 min" between FGM and SMBG values described above, we further studied the simultaneity defined as "within ±2 min," "within ±1 min" and "at the exact same time." Among a total of 5,991 paired data, 5,502, 4,081 and 1,123 paired data were available as "within ±2 min," "within ±1 min" and "at the exact same time," respectively; and the results obtained were essentially the same as in the case of "within ±3 min" (Table 2). However, the Deming regression lines were moved toward the line "$y = x$" compared with "within ±3 min" as the time lag decreased (Table 2).

DISCUSSION

The present study evaluated the performance of the FreeStyle Libre System in Japanese patients with type 1 diabetes in a usual daily life setting. The percentages of results in the clinically acceptable A + B zone in Clarke and consensus error grid analyses were 97.9% and 99.2%, respectively. The analytical
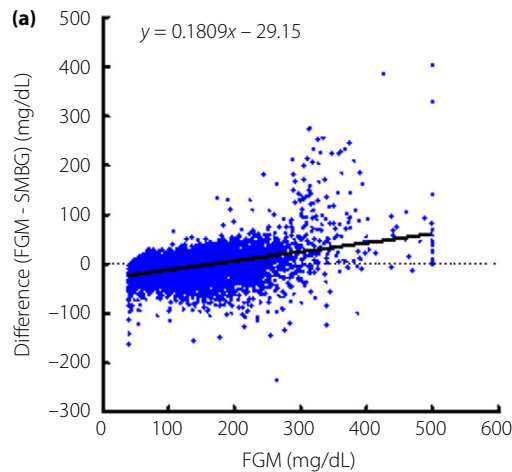
Figure 3 | (a) Scatterplot showing the relationship between flash glucose monitoring (FGM; *x*-axis) and difference (FGM − SMBG) in values (*y*-axis). The solid line is the line of best fit from the linear regression. (b) The number of data pairs in different FGM value ranges. The categorization of FGM values was made based on the target ranges of the sensor glucose, according to the international consensus report[19]. Statistical analysis was carried out by the χ^2-test ($P < 0.001$). SMBG, self-monitoring blood glucose.

accuracy, however, did not conform to ISO: 15197:2013 criteria. These results showed a good agreement between FGM and SMBG values for just clinical use.

The overall MARD was 15.9% in the present study. Although this value was higher than the value in the earliest study (11.4%)[11] that was used to introduce the product by the manufacturing company, subsequent studies showed different values; this is, 11.8%[12], 13.2%[13] 16.7%[14]. This difference might be due to differences in patients' background characteristics and study design. For example, it could have been due to differences in diabetes types (type 1, type 2, gestational and combinations thereof) and differences in measurement time (premeal, bedtime, postprandial and combinations thereof). In the report in which a high MARD value of 16.7% was reported[14], only children and adolescents with type 1 diabetes were studied. The result suggests the possibility that the rapid and frequent fluctuations in blood glucose levels is related to MARD. In fact, when the patients were stratified by serum

C-peptide levels (< or >0.1 ng/mL), MARDs values were larger in insulin-depleted patients, with 17.3 and 14.0% ($P < 0.0001$), respectively.

Accuracy in detection of hypoglycemia is clinically important. In the present study, glucose levels measured with FGM were lower than that measured with SMBG, in the lower glucose range. Although the manufacturer's effort might be required to improve the product, the lower glucose values measured with FGM, as compared with SMBG, might prevent the occurrence of hypoglycemia. If a low glucose value is detected in FGM, re-measurement of the glucose levels using SMBG is recommended, in order to detect the correct value and to prevent the occurrence of hypoglycemia in the early stages. In addition, in case hyperglycemia is detected in FGM, an early alert would be more appropriate, although, re-measurement of the glucose value by SMBG is necessary.

In accordance with the results of the present study, Fokkert *et al.*[15] reported that FGM values were lower in the lower
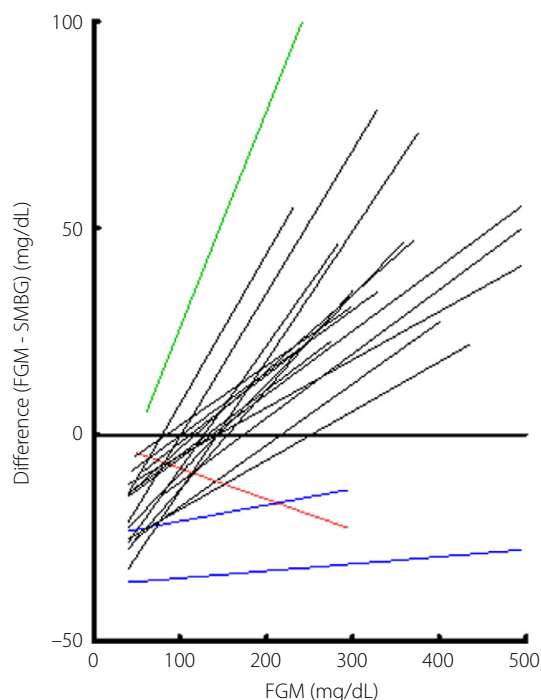
Figure 4 | The lines of best fit from the linear regression between flash glucose monitoring (FGM; *x*-axis) and difference (FGM − SMBG) in values (*y*-axis) for each patient. Black lines represent lines with a positive correlation and an *x*-intercept of approximately 70–260 mg/dL (16/20 patients). Green and blue lines represent lines with a positive correlation and no *x*-interception, as far as the line of fit could be drawn. The negative correlation in linear regression was detected in just one patient (red line). SMBG, self-monitoring blood glucose.

glucose levels measured by FGM were just 4.85% (3.64 mg) lower than the SMBG values, and this tendency was similar to the results of earlier studies[13,16,17]. However, the mean glucose value in the present study was approximately 140 mg/dL. If the average glucose level was approximately 160–180 mg/dL, the fixed bias might not have been detected, because the present data showed that FGM values were lower in the lower glucose range, and higher in the higher glucose range compared with SMBG values.

There were limitations in the present study. First, it was limited by the lack of a gold standard against which to compare the measured plasma glucose values, as our study was applied in a daily life setting. Many of the previous CGM studies[11–18] adopted the comparison with SMBG method, and achieved their goals, which might alleviate our limitation. However, the use of SMBG as a reference allowed us to evaluate the real-life accuracy of the FGM system under normal daily use. Second, there might be biases due to the habits of the patients. For example, when high or low glucose values were unexpectedly detected by FGM, patients might have preferably re-examined the value by SMBG. However, even after excluding FGM values in the range of 40–69 and 251–500 mg/dL in Figure 3b, it continued to have a statistical significance according to the χ^2-test. In addition, taking the result of Fokkert *et al.*[15] into consideration, there are few biases if any, affected by the habits of patients. Third, there might have been selection biases with the limited number of participants. Participants in the present study were adult patients with type 1 diabetes only, these included not only those with typical acute type 1 diabetes, but also those with slowly progressive and fulminant type 1 diabetes; and children with type 1 diabetes were not included. Furthermore, patients received different types of insulin therapy (multiple-dose insulin injection or continuous subcutaneous insulin infusion). However, when patients were stratified by type 1 diabetes subtypes or by different insulin therapy types, FGM values were lower in the lower glucose range and higher in the higher glucose range compared with SMBG values (data not shown). Further studies are required to clarify whether this similar tendency will be observed in children with type 1 diabetes.

In conclusion, the present study provided evidence on the reliability of FGM in patients with type 1 diabetes in a usual daily life setting. However, the finding obtained in this study was that FGM showed lower glucose values in comparison with SMBG in the low glucose range, and FGM values were higher than SMBG values in the high glucose range. Therefore, when an abnormal glucose value is detected in FGM, it should be confirmed by SMBG before actions are taken to prevent the outcomes of hypoglycemia or hyperglycemia. With advances in technology, FGM devices will further improve in accuracy. Further studies are required to establish more effective use of these devices.

glucose range, and higher in the higher glucose range compared with SMBG values. However, as described in that previous study, the foremost limitation in their study was that the number of samples analyzed was small[15]. In addition, they did not clearly describe the simultaneity of the measurements between FGM and SMBG values, and did not account for the method of regression analysis (Deming or linear). In the present study, we affirmed the findings by using much larger sample sizes, Deming regression analysis and a minimized time lag between glucose measurements. As mentioned earlier, we extracted and analyzed only those matches from our database with the simultaneity "within ±3 min," between FGM and SMBG values. In addition, we studied the simultaneity "within ±2 min," "within ±1 min" and "at the exact same time." Although the Deming regression lines were moved toward the "'*y* = *x*" line compared with that "within ±3 min" as the time lag decreased, the tendency of lower values in the lower glucose range and higher values in the higher glucose range remained even with "at the exact same time." Therefore, attention must be paid to the timings of measurement in future studies.

In the present study, we found both the fixed bias and proportional bias for the systematic bias. For the fixed bias, the

DISCLOSURE

The authors declare no conflict of interest.

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