ORIGINAL

Difference in the accuracy of the third-generation algorithm and the first-generation algorithm of FreeStyle Libre continuous glucose monitoring device

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Abstract : Background : FreeStyle Libre uses the algorithm to calculate the sensor glucose (SG) levels. The manufacturer announced that they had changed the algorithm from the first generation (Gen. 1) to the third generation (Gen. 3). To assess the difference, we conducted an observational study to analyze the characteristics of the measurements by these two algorithms compared to the capillary blood glucose (BG) levels. Methods : Participants with type 1 diabetes wore two FreeStyle Libre sensors, one on the left arm used with Gen. 3 algorithm, and another on the right arm used in combination with the FreeStyle Libre Reader with Gen. 1 algorithm. Results : Data were collected from 11 participants. The Bland-Altman analysis of the measurements by Gen. 3 algorithm showed bias of 7.4 mg/dl and no proportional bias was observed ($r = 0.130$). In contrast, the Bland-Altman analysis of the measurements by Gen. 1 algorithm showed bias of 4.4 mg/dl and proportional bias was observed ($r = 0.424$). The MARD of Gen. 3 algorithm and Gen. 1 algorithm was 11.9 ± 9.0% and 9.7 ± 8.3%, respectively ($P = 0.053$). Conclusion : No proportional bias in the measurements by Gen. 3 algorithm was observed, but in those by Gen. 1 algorithm. J. Med. Invest. 71 : 225-231, August, 2024

Keywords **:** *continuous glucose monitoring, FreeStyle Libre, accuracy, algorithm*

INTRODUCTION

The use of continuous glucose monitoring (CGM) has become very common, especially in patients with type 1 diabetes (T1D), based on accumulated evidences of its benefits (1). CGM measures glucose concentration in the interstitial tissue, and display sensor glucose (SG) levels using algorithm equipped in each model of CGM. Abbott Diabetes Care (Alameda, CA, USA), the manufacturer of the intermittent-scanning CGM (isCGM) device FreeStyle Libre (original version without alert function), had announced that they had changed the algorithm used to calculate the SG levels from the first-generation algorithm (Gen. 1) to the third-generation algorithm (Gen. 3) ; however, the technical details have not been disclosed yet. The manufacturer reported that the mean absolute relative difference (MARD) of Gen. 1 algorithm was 11.4% compared to the capillary blood glucose (BG) levels measured by the self-monitoring of BG (SMBG) (2) ; in contrast, the MARD of Gen. 3 algorithm was 9.2% compared to the venous BG levels measured at the central laboratory (3). However, the difference in the modality of reference BG levels makes it difficult to compare their accuracy directly. To directly assess the accuracy of the two algorithms using the same reference, we conducted an observational study to analyze the characteristics of the measurements by these two algorithms.

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METHODS

Study design

This study was a multicenter, single-armed, observational study. The participants continued their treatment of T1D as usual. Participants wore two FreeStyle Libre sensors, one on the left arm used in combination with the FreeStyle Libre Reader with Gen. 3 algorithm, and another on the right arm used with Gen. 1 algorithm. FreeStyle Libre sensors with a single serial number (6778572) was used. Capillary BG levels were measured by FS precision electrode. After 14 days of usage, data were downloaded from both the FreeStyle Libre Reader with Gen. 3 algorithm and that with Gen. 1 algorithm to computers for analysis.

The primary outcome was the Bland-Altman analysis of the SG levels measured by FreeStyle Libre Reader with Gen. 3 algorithm compared to the capillary BG levels. The secondary outcomes included Bland-Altman analysis of the SG levels measured by FreeStyle Libre Reader with Gen. 1 algorithm compared

to the capillary BG levels, correlation between the SG levels measured by FreeStyle Libre Reader with Gen. 1 algorithm and the capillary BG levels, between the SG levels measured by that with Gen. 3 algorithm and the capillary BG levels, between the SG levels measured by FreeStyle Libre Reader with Gen. 3 algorithm and that with Gen. 1 algorithm, MARD, mean absolute difference (MAD), median absolute relative difference (MedARD), median absolute difference (MedAD), the Clarke error grid analysis and the Parkes (Consensus) error grid analysis.

Study participants and setting

Twelve participants were recruited at the following study cites ; NHO Kyoto Medical Center (n = 4), Kobe University (n = 4) and Tokai University (n = 4). Inclusion criteria were ; being diagnosed as T1D according to the criteria by the Japan Diabetes Association (4), aged 20 years old or more, and using FreeStyle Libre. Exclusion criteria were ; having end-stage renal failure (either on hemodialysis or after kidney transplantation), being blind, having an implanted medical device such as a pacemaker or being unable to participate based on the opinion of the treating clinician.

The study was conducted in an outpatient setting and the data was collected between 1 August 2022 and 13 October 2022.

Variables

The SG levels downloaded from FreeStyle Libre Reader with Gen. 3 algorithm or FreeStyle Libre Reader with Gen. 1 algorithm, and capillary BG levels were used for the analysis. Primary outcome was the Bland-Altman analysis of the SG levels of Gen. 3 algorithm compared to capillary BG levels. Secondary outcomes included Bland-Altman analysis of the SG levels of Gen. 1 algorithm compared to capillary BG levels, MARD, MAD, MedARD, MedAD, Clarke error grid analysis and Parkes error grid analysis.

Data sources and measurements

The data of the SG levels and the capillary BG levels were downloaded from FreeStyle Libre Reader with either Gen. 3 algorithm or Gen. 1 algorithm at each study cite. The capillary BG levels were measured by FS precision electrode and FreeStyle Libre Reader ; the SMBG function did not differ between FreeStyle Libre Reader with Gen. 3 algorithm and Gen. 1 algorithm.

Bias

All the obtained SG data were used for generating measurement triplets to avoid selection bias.

Statistical analysis

Triplets of the SG levels (Gen. 3 and Gen. 1) and the capillary BG levels with a timestamp less than 3 minutes difference to each other were used for the analysis. Pearson's r correlation coefficient was used to evaluate the linear correlation between two variables, and interpreted as follows : Less than 0.3 was considered poor correlation, 0.3 to 0.5 fair, 0.6 to 0.8 moderately strong, and at least 0.8 very strong (5). Comparisons among the groups were performed by an unpaired Student's t-test or Mann-Whitney U test. Bland-Altman analysis was conducted to analyze the agreement between the two different methods, and the upper limit of agreement (ULoA) and the lower limit of agreement (LLoA) represented the 95% confidence interval (95%CI) of the bias (6). MARD, MAD, MedARD, and MedAD were calculated using the pooled triplets of the SG levels (Gen. 3 and Gen. 1) and the capillary BG levels. Clarke error grid analysis and the Parks error grid analysis for T1D were used to evaluate clinical significance of the inaccuracy in the measurements of glucose levels (7-9). Passing-Bablok regression analysis was used to estimate the agreement and possible systemic bias between two analytical methods (10). Analyses were conducted using R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Written informed consent was obtained from 12 participants. One participant voluntarily withdrew from the study before starting the observation. The characteristics of the 11 participants who completed the observation are summarized in Table 1.

To analyze the accuracy, 125 triplets of SG levels (Gen. 3 and Gen. 1) and the capillary BG levels were used ; these triplets were derived from 10 participants, as no triplet was obtained from one participant. The mean and median SG levels by Gen. 3 algorithm, SG levels by Gen. 1 algorithm and capillary BG levels are shown in Table 2. There was strong correlation between the senor glucose levels by Gen. 3 algorithm and the capillary BG levels ($r = 0.938$), between the senor glucose levels by Gen. 1 and the capillary BG levels ($r = 0.958$), and between the senor glucose levels of Gen. 3 and the senor glucose levels of Gen. 1 ($r = 0.961$).

The Bland-Altman analysis of the measurements by Gen. 3 algorithm using capillary BG levels as control showed the bias of 7.4 mg/dl, 95% CI [3.7, 11.1], with ULoA being 48.4 mg/dl, 95% CI [42.1, 54.7], LLoA -33.5 mg/dl, 95% CI [-39.8, -27.2]), and no proportional bias was observed ($r = 0.130$). However, the measurements by Gen. 1 algorithm showed the bias of 4.4 mg/dl, 95% CI [1.0, 7.9], with ULoA being 42.9 mg/dl, 95% CI [37.0, 48.9], LLoA -34.1 mg/dl, 95% CI [-40.0, -28.1], and proportional bias was observed ($r = 0.424$) (Figure 1). The MARD of Gen. 3

Table 1. The characteristics of the participants.

Variables	
Age, years	59.0 ± 9.9
Male, %	45.5
Height, cm	161.5 ± 7.1
Body weight, kg	58.3 ± 14.8
Body mass index, kg/m^2	22.2 ± 4.4
HbA1c, %	7.6 ± 0.8
Handedness, %	
Right	81.8
Left	9.1
Cross-dominance	9.1

N = 11. Numbers are percentage or Mean ± SD.

Table 2. SG levels and capillary BG levels.

	SG levels by Gen. 3	SG levels by Gen. 1	Capillary BG levels
Mean, mg/dl	161.0 ± 60.2	158.0 ± 65.8	153.6 ± 57.6
Median, mg/dl	154 [118, 197]	148 [107, 197]	145 [110, 194]

N = 10. Triplets = 125. Mean ± SD or Median [25%, 75%].

algorithm and Gen. 1 algorithm compared to capillary BG levels was 11.9 ± 9.0% and 9.7 ± 8.3%, respectively ($P = 0.053$) ; the MAD of Gen. 3 algorithm and Gen. 1 algorithm was 17.1 ± 14.0 mg/dl and14.8 ± 13.5 mg/dl, respectively ($P = 0.187$) ; the MedARD of Gen. 3 algorithm and Gen. 1 algorithm was 9.8% and 8.5%, respectively ($P = 0.040$) ; The MedAD of Gen. 3 algorithm and Gen. 1 algorithm was 14 mg/dl and 11 mg/dl, respectively ($P = 0.086$) (Table 3). The Clarke error grid analysis demonstrated that 99.2% of measurements by Gen. 3 algorithm belonged to zone A+B, and 100.0% of those by Gen. 1 algorithm belonged to zone A+B (Figure 2 a, b). The Parks error grid analysis demonstrated that 100.0% of measurements by Gen. 3 algorithm belonged to zone A+B, and 100.0% of those by Gen. 1 algorithm belonged to zone A+B (Figure 3 a, b).

The bias was shown by post-hoc Passing–Bablok regression analysis for the SG levels by Gen. 3 algorithm (vertical axis) versus the capillary BG levels as reference (horizontal axis) with the slope of 1.04, 95% CI [0.97, 1.11] and the corresponding intercept of 3.9 mg/dl, 95% CI [-5.8, 12.4] ; for the SG levels by Gen. 1 algorithm (vertical axis) versus the capillary BG levels as reference (horizontal axis) with the slope of 1.13, 95% CI [1.07, 1.19] and the corresponding intercept of -13.0 mg/dl, 95% CI [-21.8, -4.7] ; and the SG levels by Gen. 3 algorithm (vertical axis) versus the SG levels by Gen. 1 algorithm (horizontal axis) with the slope of 0.94, 95% CI [0.89, 1.00] and the corresponding intercept of 12.4 mg/dl, 95% CI [6.0, 19.8].

DISCUSSION

In this study, strong correlation was observed between measurements by Gen. 3 algorithm, measurements by Gen. 1 and capillary BG levels. The Bland-Altman analysis clarified that no proportional bias in measurements by Gen. 3 algorithm, unlike those by Gen. 1 algorithm. MARD, MAD, MedAD did not differ between measurements by Gen. 3 algorithm and measurements by Gen. 1 algorithm ; however MedARD was significantly greater in measurements by Gen. 3 algorithm compared to measurements by Gen. 1 algorithm. The Clarke error grid analysis and the Parkes error grid analysis suggested that both measurements by Gen. 3 algorithm and measurements by Gen. 1 algorithm were clinically acceptable. Passing-Bablok regression analysis revealed the absence of constant and proportional errors in the SG levels by Gen. 3 algorithm compared to capillary BG levels, but the presence of constant and proportional errors in the SG levels by Gen. 1 algorithm compared to capillary BG levels ; there was constant, but no proportional error in the SG levels by Gen. 3 algorithm compared to the SG levels by Gen. 1 algorithm.

In a previous study comparing measurements by Gen. 1 algorithm and the capillary BG levels, the MARD and the MAD were 15.6% and 23.2 mg/dl, respectively, and the bias of -13.0 mg/dl (ULoA 43.8 mg/dl, LLoA -69.7 mg/dl) was observed, but no proportional bias ($r = 0.085$) in Bland-Altman analysis (11, 12). There is the possibility that FreeStyle Libre sensor might have different measurement characteristics between products with different manufacturing lot numbers or between individual products. Actually, some FreeStyle Libre sensor with specific lot numbers (6916030 and 6916031) were recalled because they did not satisfy the required standard of quality (13, 14). There is also a case report in which marked discrepancy was observed between the SG levels and the capillary BG levels, possibly due to the failure in factory calibration, and resulted in inappropriately high readings in the SG levels (15). The reason why the median value of Gen.3 was higher than the capillary BG levels remained unclear. To address this issue, further investigation using multiple lots of FreeStyle Libre sensor with larger number of study participants will be required.

There are several limitations to be addressed in this study. This study used FreeStyle Libre sensor with single lot number, and there is the possibility other lots might present different results. The number of study participants is small. Temporal

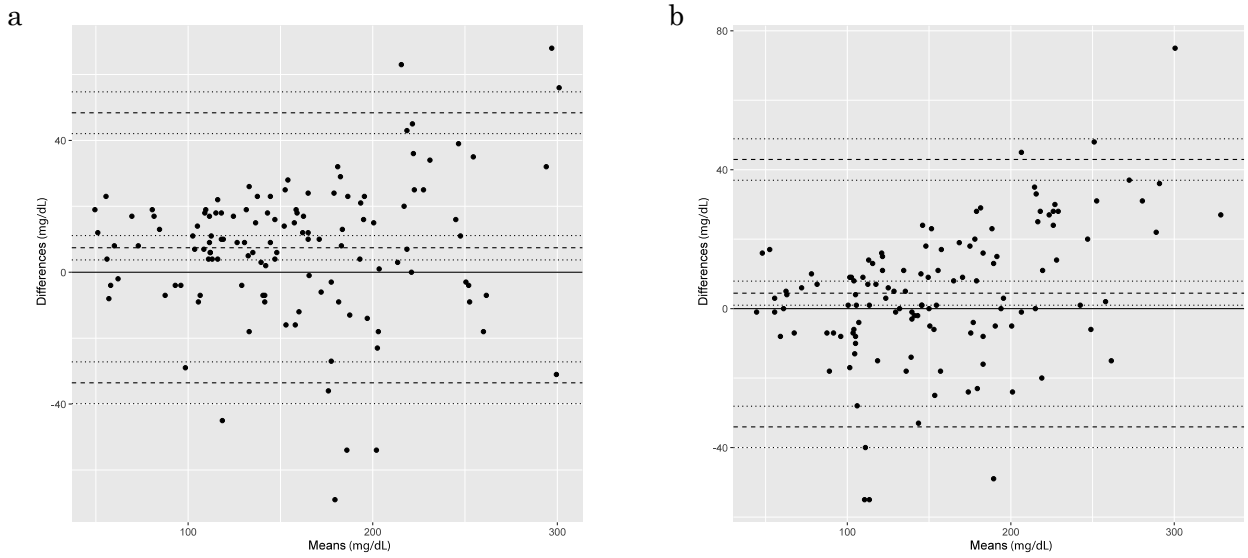

Figure 1. Bland-Altman analysis.
The horizontal axis represented the means of the two methods, and the vertical axis represented the difference of the two methods (SG - BG). Broken lines represented the bias, ULoA, or LLoA. Dotted lines represented their upper or lower limit of 95% CI, respectively. a. Gen. 3 vs. capillary BG. There was bias of 7.4 mg/dl, 95% CI [3.7, 11.1], with ULoA being 48.4 mg/dl, 95% CI [42.1, 54.7], LLoA -33.5 mg/dl, 95% CI [-39.8, -27.2]. No proportional bias was observed ($r = 0.130$). b. Gen. 1 vs. capillary BG. There was bias of 4.4 mg/dl, 95% CI [1.0, 7.9], with ULoA being 42.9 mg/dl, 95% CI [37.0, 48.9], LLoA -34.1 mg/dl , 95% CI [-40.0, -28.1]. Proportional bias was observed ($r = 0.424$).

Table 3. MARD, MAD, MedARD, MedAD in different glucose ranges.

Variables	Gen. 3	Gen. 1	*P* value
MARD, %			
Overall	11.9 ± 9.0	9.7 ± 8.3	0.053
<70 mg/dL	21.1 ± 17.2	12.5 ± 14.6	0.243
70-180 mg/dL	10.7 ± 6.7	9.2 ± 7.8	0.231
>180 mg/dL	11.8 ± 8.8	10.0 ± 7.0	0.320
MAD, mg/dl			
Overall	17.1 ± 14.0	14.8 ± 13.5	0.187
<70 mg/dL	10.5 ± 7.1	6.1 ± 6.0	0.151
70-180 mg/dL	13.5 ± 8.4	12.1 ± 11.1	0.397
>180 mg/dL	25.7 ± 19.2	22.1 ± 15.9	0.371
MedARD, %			
Overall	9.8 [5.5, 16.5]	8.5 [3.9, 13.0]	0.040*
<70 mg/dL	13.7 [8.5, 27.6]	7.5 [3.1, 11.7]	0.105
70-180 mg/dL	8.8 [5.5, 15.7]	8.0 [3.9, 12.2]	0.099
>180 mg/dL	10.3 [4.7, 17.3]	10.0 [4.9, 13.2]	0.557
MedAD, mg/dl			
Overall	14 [7, 23]	11 [5, 23]	0.086
<70 mg/dL	8.0 [5.0, 15.8]	4.5 [1.5, 7.5]	0.102
70-180 mg/dL	12 [7, 18]	9 [5, 17]	0.079
>180 mg/dL	22.0 [10.5, 36.0]	23.5 [10.3, 30.3]	0.544

N = 10. Triplets = 125. Mean ± SD or Median [25%, 75%]. * $P < 0.05$.

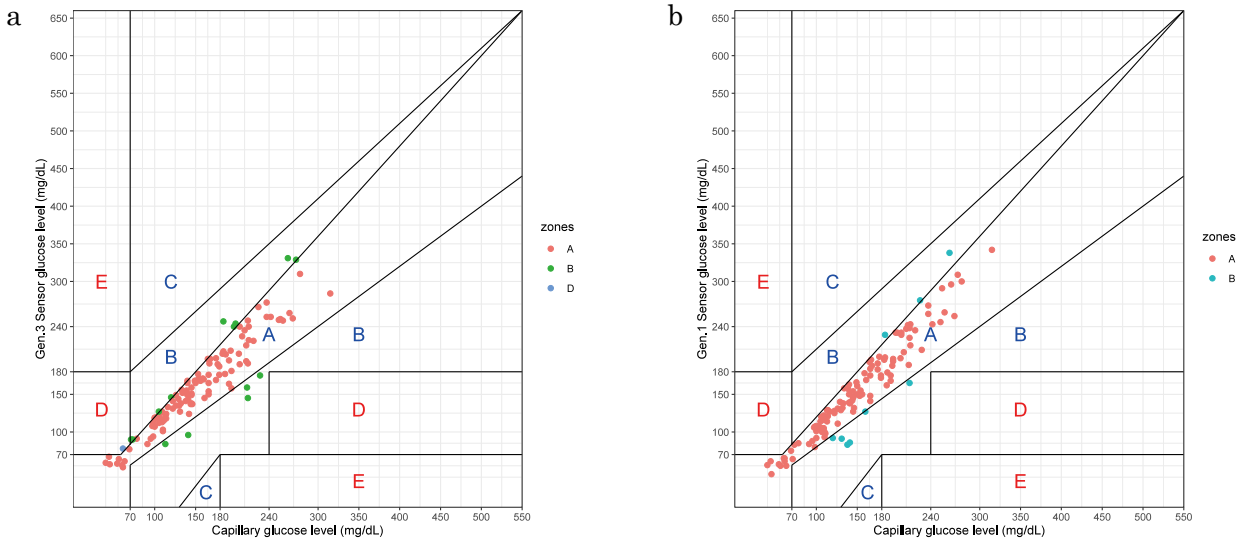

Figure 2. The Clarke error grid analysis.
a. Gen. 3 vs. capillary BG. Zone A : 88.0%, zone B : 11.2%, zone C : 0.0 %, zone D : 0.8 % and zone E : 0.0 %. b. Gen. 1 vs. capillary BG. Zone A : 92.8%, zone B : 7.2%, zone C : 0.0%, zone D : 0.0% and zone E : 0.0%.

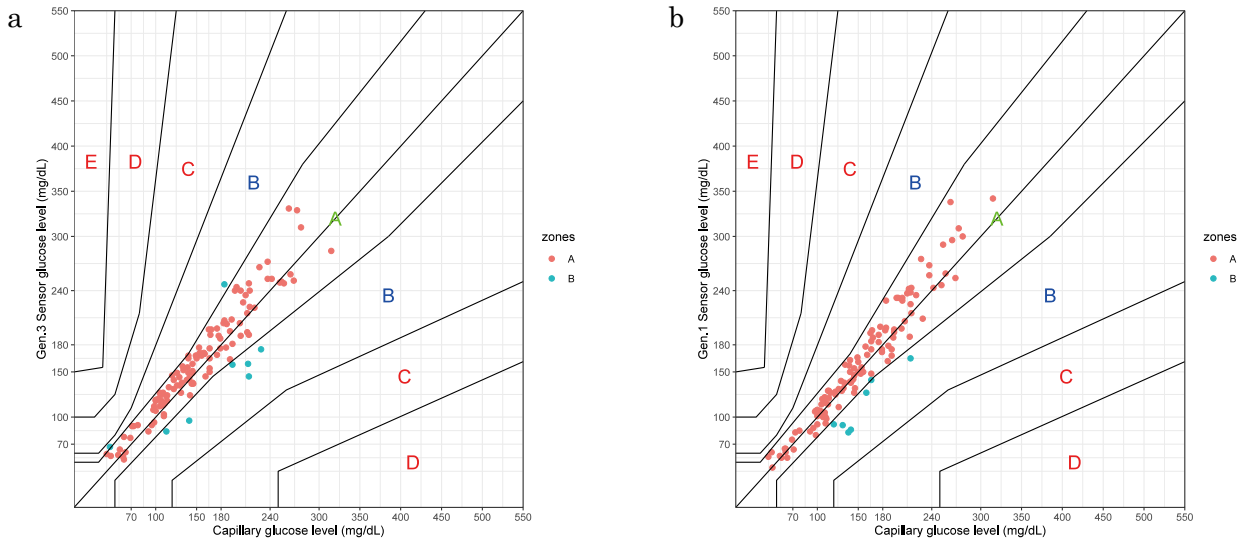

Figure 3. The Parks error grid analysis.
a. Gen. 3 vs. capillary BG. Zone A : 94.4%, zone B : 5.6%, zone C : 0.0%, zone D : 0.0% and zone E : 0.0%. b. Gen. 1 vs. capillary BG. Zone A : 93.6%, zone B : 6.4%, zone C : 0.0%, zone D : 0.0% and zone E : 0.0%.

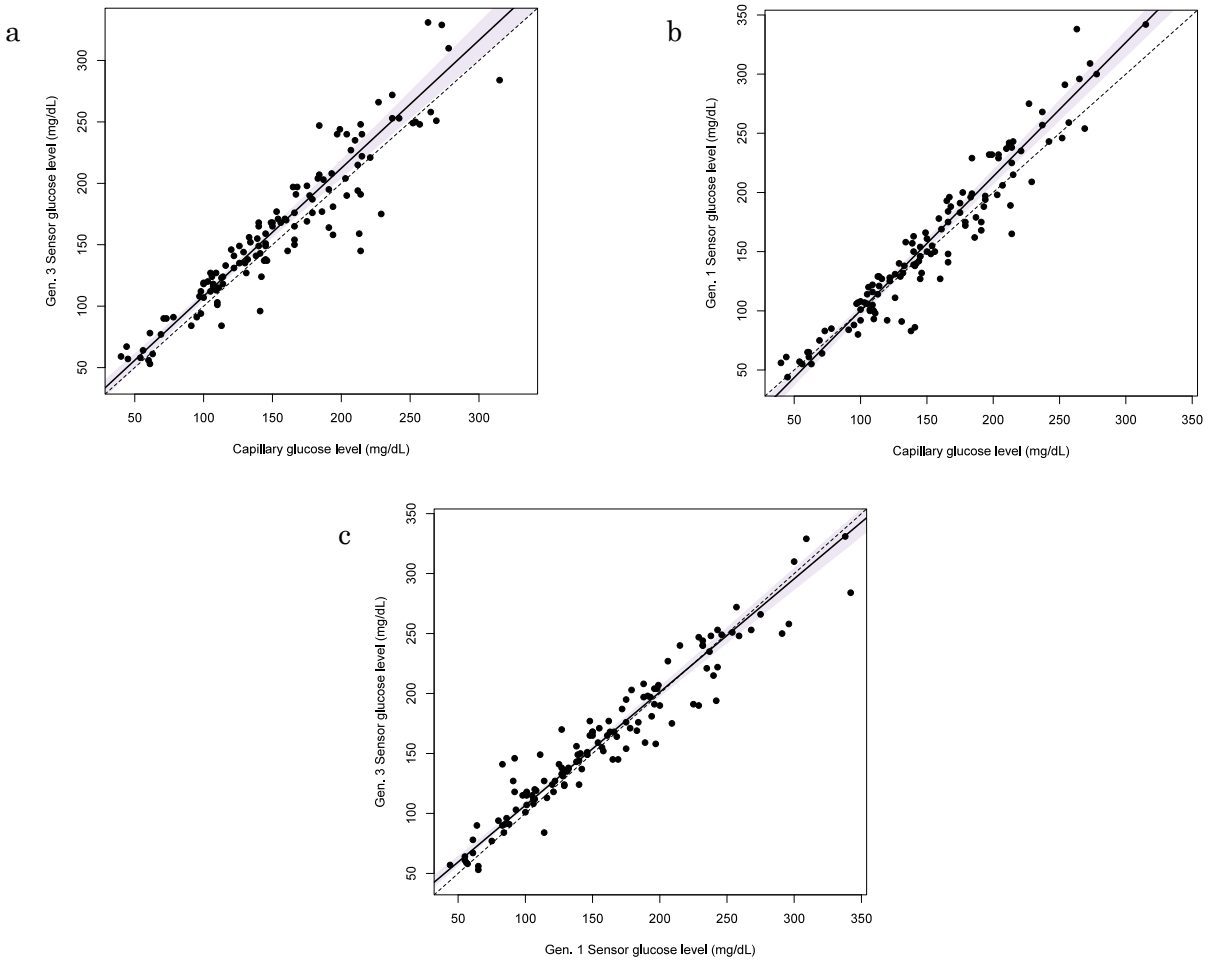

Figure 4. Relationship between the SG levels by Gen. 1 algorithm, those by Gen. 3 algorithm, and the capillary BG levels. Passing–Bablok regression analysis showed the following relationship between the variables. Solid lines represented the regression equations, shadowed areas represented the corresponding 95% CIs, and broken lines represented the evenness : a. [senor glucose levels by Gen. 3 algorithm] = 1.04* [capillary BG levels] + 3.9. Corresponding 95% CIs were [0.97, 1.11] and [-5.8, 12.4], respectively. b. [senor glucose levels by Gen. 1 algorithm] = 1.13* [capillary BG levels] - 13.0. Corresponding 95% CIs were [1.07, 1.19] and [-21.8, -4.7], respectively. c. [senor glucose levels by Gen. 3 algorithm] = 0.94* [senor glucose levels by Gen. 1 algorithm] + 12.4. Corresponding 95% CIs were [0.89, 1.00] and [6.0, 19.8], respectively.

change of the accuracy was not analyzed in this study, although studies sponsored by Abbott had reported that such change was minor (2, 3). There is the possibility that some of the SMBG measurements might not be accurate due to the contamination of the skin, however both SMBG measurements of the capillary blood and the central laboratory measurements of the venous blood had been reported to be acceptable as the reference methods for evaluating the accuracy of CGM (2). Only participants with T1D were recruited, and there was no participants with type 2 diabetes.

The current observations reported here suggested that the main difference of the Gen. 3 algorithm and the Gen. 1 algorithm of FreeStyle Libre may be the absence or the presence of the constant and proportional error, as identified by the Passing-Bablok regression analysis. Considering MARD, MAD, MedAD did not differ and MedARD was significantly greater in measurements by Gen. 3 algorithm compared to measurements by Gen. 1 algorithm, we could not conclude from this study that Gen. 3 algorithm was more accurate compared to Gen. 1 algorithm.

Historically, both the capillary BG levels and the venous BG levels have been used as the reference value to evaluate the accuracy of CGM. However it is important to note that the venous BG levels are considered to be more accurate than the capillary BG levels, because the measurement of the capillary BG levels has its own limitation in the accuracy, mainly due to the definitions in ISO15197 : 2013 for SMBG devices which accept ±15% error in the glucose levels 100 mg/dl or more and ±15 mg/dl error below 100 mg/dl in 95% of the measurements compared to the reference values of venous BG levels measured at the central laboratory. Theoretically, there is the possibility that the indices of CGM accuracy assessed by SMBG as reference could be different from those assessed by the central laboratory measurements of venous BG, due to the relative inaccuracy of the measurements tolerated in SMBG. However, in a study comparing different reference methods for the accuracy assessment of CGM, MedARD of Dexcom G5 (Dexcom [San Diego, CA, USA]), a capillary calibrated CGM system, did not differ between venous BG levels, arterialized-venous BG levels and capillary BG levels used as the reference measurements (16). Therefore, it is unclear whether the smaller MARD of Gen. 3 algorithm compared to Gen. 1 algorithm reported by the manufacture could be related with the difference in the reference measurements of the venous BG levels and capillary BG levels, respectively (2, 3).

Although this study used FreeStyle Libre sensor with a single lot number, the results of Clarke error grid analysis and the Parks error grid analysis suggested both the measurements by Gen. 3 algorithm and those by Gen. 1 algorithm are clinically acceptable. These observations support the non-adjunctive use of FreeStyle Libre to SMBG, except for the confirmation of the hypoglycemia and in occasions that the SG levels do not match the clinical symptoms or users' prediction as described in the product's labeling. Currently, the product's labeling contains a segment that reads "Users should not change the dose of oral medications, GLP-1 receptor agonists, or insulin based on the measurements : Changes of treatments need to be directed by physicians" (17). This part is different from the labeling in US and EU, and do not match the general consensus of dose adjustment of insulin according to the glucose levels, especially in patients with T1D. Abbot Japan is encouraged to apply for non-adjunct use of FreeStyle Libre to the regulatory authority, in order to promote the adequate usage of this device, otherwise dose adjustment of insulin using FreeStyle Libre remains off-label use.

CONCLUSION

In this study population, the superiority of the Gen. 3 algorithm compared to Gen. 1 algorithm was not proven. There was proportional bias in the Gen. 1 algorithm of FreeStyle Libre, but not in the Gen. 3 algorithm. The MARD, MAD, MedAD did not differ between measurements by Gen. 1 algorithm and those by Gen. 3 algorithm, but MedARD did. Error grid analyses suggested both measurements by Gen. 1 algorithm and those by Gen. 3 algorithm are clinically acceptable. There were neither constant nor proportional errors in the SG levels by Gen. 3 algorithm compared to capillary BG levels, however there were both constant and proportional errors in the SG levels by Gen. 1 algorithm compared to capillary BG levels.

CONFLICT OF INTEREST

The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article : T.M. discloses the following relationships : speaker honoraria from Kyowa Kirin, Novo Nordisk, Sanofi and ; grants from AstraZeneca, Eli Lilly, Novo Nordisk, Medtronic. N.S. discloses the following relationships : speaker honoraria from Boehringer Ingelheim, Life Scan, Novo Nordisk, Sanofi, Sumitomo Pharma, and Takeda. Y.H. discloses the following relationships : speaker honoraria from Abbott Japan, AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Kissei Pharmaceutical, Kowa, Kyowa Kirin, Medtronic, Mochida Pharmaceutical, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Otsuka Pharma, Sanofi, Sanwa Kagaku Kenkyusho, Ono, Pfizer, Roche DC Japan, Sumitomo Pharma, Taisho Pharma, Takeda, Teijin Pharma and Terumo ; grants from Abbott Japan, Kyowa Kirin, Medtronic, Sumitomo Pharma. M.T. discloses the following relationships : speaker honoraria from Abbott Japan, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Medtronic, Mitsubishi Tanabe, MSD, Nipro, Novartis, Novo Nordisk, Ono, Sanofi, Sumitomo Pharma, Takeda, Terumo, AstraZeneca, and Astellas ; grants from Abbott Japan, Life Scan, Roche DC Japan, Sumitomo Pharma and Dexcom. M.M. discloses the following relationships : speaker honoraria from Abbott Japan, Astellas, Boehringer Ingelheim, Eli Lilly Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Ono, Sanofi, Sumitomo Pharma and Terumo ; grants from Boehringer Ingelheim, Nissui, Novo Nordisk, Sanofi and Sysmex. A.K. discloses the following relationships : speaker honoraria from Eli Lilly, Life Scan, Medtronic, Novo Nordisk and Sanofi. A.I. discloses the following relationships : speaker honoraria from Abbott Japan, AstraZeneca, Daiichi Sankyo, Eli Lilly, Kowa, Medtronic, Mitsubishi Tanabe, Novo Nordisk, Sanofi, Sumitomo Pharma and Terumo. S.M. discloses the following relationships : speaker honoraria from Abbott Japan, Asahi Kasei Pharma, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, EA Pharma, Eli Lilly, Kaken Pharmaceutical, Kowa Company, Kyowa Kirin, Kowa, Life Scan, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Novo Nordisk, Ono, Otsuka Pharma, Sanofi, Sanwa Kagaku Kenkyusho, Sumitomo Pharma, Taisho Pharma, Takeda, Terumo, and Teijin Health Care. J.M. discloses the following relationships : speaker honoraria from Abbott Japan, Astellas, AstraZeneca, Eli Lilly, Kowa, Life Scan, Medtronic, Novo Nordisk, PHC, Sanofi, Sumitomo Pharma, Taisho Pharma and Terumo ; grants from Terumo. Y.M. discloses the following relationships : speaker honoraria from AstraZeneca, Daiichi Sankyo, Kowa, Kyowa Kirin, Medtronic, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono, Sumitomo Pharma and Teijin Pharma. K.K. discloses the following relationships : speaker honoraria

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AUTHOR CONTRIBUTION

T.M., Y.H., M.T. conceived the design of the study, collected data, drafted and edited the manuscript. N.S. conceived the design of the study, collected data, conducted statistical analyses, drafted and edited the manuscript. M.M., A.K., A.I., S.M., J.M., Y.M., K.K., S.S. conceived the design of the study, collected data, drafted and edited the manuscript. A.S. drafted and edited the manuscript.

ETHICAL APPROVAL

This study was approved by the Ethics Committee at NHO Kyoto Medical Center (21-055).

INFORMED CONSENT

All the participants provided written informed consent.

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REFERENCES

1. Elbalshy M, Haszard J, Smith H, Kuroko S, Galland B, Oliver N, Shah V, de Bock MI, Wheeler BJ : Effect of divergent continuous glucose monitoring technologies on glycaemic control in type 1 diabetes mellitus : A systematic review and meta-analysis of randomised controlled trials. Diabet Med 39(8) : e14854, 2022. doi : 10.1111/dme.14854.
2. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S : The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. Diabetes Technol Ther 17(11) : 787-794, 2015. doi : 10.1089/dia.2014.0378.
3. Alva S, Bailey T, Brazg R, Budiman ES, Castorino K, Christiansen MP, Forlenza G, Kipnes M, Liljenquist DR, Liu H : Accuracy of a 14-Day Factory-Calibrated Continuous Glucose Monitoring System With Advanced Algorithm in Pediatric and Adult Population With Diabetes. J Diabetes Sci Technol 16(1) : 70-77, 2022. doi : 10.1177/19322 96820958754.
4. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus : Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 1(5) : 212-228, 2010. doi : 10.1111/j.2040-1124.2010.00074.x.
5. Chan YH : Biostatistics 104 : correlational analysis. Singapore Med J 44(12) : 614-619, 2003
6. Bland JM, Altman DG : Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1(8476) : 307-310, 1986
7. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL : Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care 10(5) : 622-628, 1987. doi : 10.2337/diacare.10.5.622.
8. Parkes JL, Slatin SL, Pardo S, Ginsberg BH : A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. Diabetes Care 23(8) : 1143-1148, 2000. doi : 10.2337/diacare.23.8.1143.
9. Pfützner A, Klonoff DC, Pardo S, Parkes JL : Technical aspects of the Parkes error grid. J Diabetes Sci Technol 7(5) : 1275-1281, 2013. doi : 10.1177/193229681300700517.
10. Bilić-Zulle L : Comparison of methods : Passing and Bablok regression. Biochem Med (Zagreb) 21(1) : 49-52, 2011. doi : 10.11613/bm.2011.010.
11. ISCHIA Study Group : Prevention of hypoglycemia by intermittent-scanning continuous glucose monitoring device combined with structured education in patients with type 1 diabetes mellitus : A randomized, crossover trial. Diabetes Res Clin Pract 195 : 110147, 2023. doi : 10.1016/j.diabres.2022.110147.
12. Toyoda M, Murata T, Hirota Y, Hosoda K, Kato K, Kouyama K, Kouyama R, Kuroda A, Matoba Y, Matsuhisa M, Meguro S, Miura J, Nishimura K, Shimada A, Suzuki S, Tone A, Sakane N ; ISCHIA Study Group : Possible Relationship between the Deteriorated Accuracy of Intermittent-Scanning Continuous Glucose Monitoring Device and the Contact Dermatitis : Post-hoc analysis of the ISCHIA Study. Tokai J Exp Clin Med 48(3) : 83-90, 2023
13. Pharmaceutical and Medical Devices Agency : Summary of the recall of the medical device (Class 1). https://www.info.pmda.go.jp/rgo/MainServlet?recallno=1-2011 (Accessed 13 June 2023). (in Japanese)
14. Abbott Japan : Announcement of the recall of FreeStyle Libre glucose monitoring system with specific lot numbers. https://www.abbott.co.jp/media-center/press-releases/03-03-2023.html (Accessed 13 June 2023). (in Japanese)
15. Kato K, Masuda T, Sakane N, Nishimura E, Mukai U, Mitsui E, Yamamoto Y, Murata T : A case of isCGM sensor in which the failure of factory calibration was suspected. Journal of Association for the Study of Innovative Diabetes Treatment in Japan 15 : 1-6, 2019. https://doi.org/10.34612/asindtj.15.0_1 (in Japanese)
16. Kropff J, van Steen SC, deGraaff P, Chan MW, van Amstel RBE, DeVries JH : Venous, Arterialized-Venous, or Capillary Glucose Reference Measurements for the Accuracy Assessment of a Continuous Glucose Monitoring System. Diabetes Technol Ther 19(11) : 609-617, 2017. doi : 10.1089/dia.2017.0189.
17. Murata T, Sakane N, Kato K, Tone A, Toyoda M : The Current Intermittent-Scanning CGM Device Situation in Japan : Only Adjunctive Use to SMBG Is Approved and the Latest Health Insurance Coverage Details. J Diabetes Sci Technol 12(3) : 729-730, 2018. doi : 10.1177/1932296817749860.