Accuracy of flash glucose monitoring in insulin-treated patients with type 2 diabetes

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ABSTRACT
The present study evaluated the accuracy of interstitial glucose measurements by flash glucose monitoring (FGM) and continuous glucose monitoring (CGM). Five diabetes patients simultaneously underwent FGM (FreeStyle Libre Pro) and CGM (iPro™2), and their glucose levels were compared with venous blood and capillary blood glucose levels. The range of daily venous blood glucose levels (30 measurements) was 70–245 mg/dL, with a median of 138 mg/dL. There were good correlations of glucose levels measured by FGM ($r^2 = 0.90$, mean absolute relative difference $8.2 \pm 5.6\%$), CGM ($r^2 = 0.86$, mean absolute relative difference $9.2 \pm 9.1\%$) and capillary blood ($r^2 = 0.87$, mean absolute relative difference $7.2 \pm 7.2\%$) with venous blood glucose levels. The accuracy of FGM measurements was also shown against CGM, with 99.9% of the FGM values (1,279 measurements) being within the Parkes error grid zones A and B. The results suggest that the accuracy of FGM is similar to that of CGM, and that FGM is a useful tool for determining daily glucose profile.

INTRODUCTION
It is well known that tight glycemic control can delay the onset and progression of diabetes mellitus-related complications1. Introduction of continuous glucose monitoring (CGM) has been shown to reduce hypoglycemia and to improve glycemic control in patients with type 1 diabetes mellitus and insulin-treated type 2 diabetes mellitus2–4. However, CGM has not been widely used because of limitations of CGM devices, such as the need for self-monitoring of blood glucose for device calibration and short sensor lifetime.

Flash glucose monitoring (FGM) by FreeStyle Libre (Abbott Diabetes Care Inc., Alameda, CA, USA) is a novel glucose monitoring system to continuously monitor interstitial glucose levels for up to 14 days. What is noteworthy about this system is that self-monitoring of blood glucose is not required during the 14-day wearing period. Several studies have shown the accuracy of interstitial glucose measurements, and the usefulness and safety of FGM5–11. Furthermore, it has been shown that the use of FGM reduced hypoglycemia in patients with type 1 and type 2 diabetes mellitus, although the effects of FGM on glycemic control are controversial5,6,9,10,16. Thus, we investigated the accuracy of glucose measurements by FGM in comparison with glucose measurements by CGM, and capillary and venous blood glucose levels in patients with diabetes mellitus.

METHODS
The present study was approved by the Clinical Investigation Ethics Committee of Sapporo Medical University Hospital (No. 25-4). Written informed consent was obtained from all participants.

Five insulin-treated patients with type 2 diabetes mellitus who were admitted to Sapporo Medical University Hospital in Sapporo, Japan, for management of glycemic control agreed to participate in the present study. They received 1,400–1,600 kcal meals depending on their standard bodyweight during hospital admission. We used FreeStyle Libre Pro (FSL-pro) for FGM and iPro™2 (Medtronic Japan Co. Ltd., Tokyo, Japan) for CGM, and the devices were attached to the left upper arm region and abdominal region, respectively. FSL-pro and iPro™2 were attached at 2–5 and 4–7 days after admission, respectively (Table 1). Patients carried out at least four calibrations for iPro™2 each day. At least 24 h after attaching FSL-pro (70.8 ± 34.0 h, median 72 h) and iPro™2 (50.8 ± 24.6 h, median 66 h), daily glucose levels (before and 2 h after each meal)
were measured in both capillary blood and venous blood samples for 1 day. Capillary blood and venous blood glucose levels were measured by a Glutest mint (Sanwa Kagaku Kenkyusho Co., Nagoya, Japan) and a glucose oxidase/hydrogen peroxide electrode method using the ADAMS glucose GA-1171 system (Arkray, Kyoto, Japan), respectively. iPro™ was removed just after the daily glucose profile measurement or the next morning after the measurement. In contrast, FSL-pro was continued for the therapeutic need of each patient. Durations of simultaneous glucose measurements by FGM and CGM varied by patients, ranging 38–86 h (Table 1).

RESULTS
The clinical characteristics of the patients showing their poor glycemic control (glycated hemoglobin >8.0%) at the time of admission are shown in Table 1.

The range of daily venous blood glucose levels (total of 30 measurements) was 70–245 mg/dL (143.7 ± 39.3 mg/dL, median 138 mg/dL). Venous blood glucose level was correlated with capillary blood glucose level ($r^2 = 0.87$, mean absolute relative difference [MARD] 7.2 ± 7.2%; Figure 1a) and with levels measured by CGM ($r^2 = 0.86$, MARD 9.2 ± 9.1%; Figure 1c) and FGM ($r^2 = 0.90$, MARD 8.2 ± 5.6%; Figure 1e). The Parkes error grid method showed that percentages of values within zone A against venous blood glucose levels were 100% (capillary blood), 100% (CGM) and 90% (FGM). The mean absolute differences were 10.2 mg/dL for capillary blood, 12.1 mg/dL for CGM and 11.4 mg/dL for FGM. Interstitial glucose levels measured by FGM tended to be low compared with venous blood glucose levels (Figure 1f).

We also compared glucose measurements by FGM and CGM. As shown in Figure 2a, 1,084 of 1,279 plots (84.8%) were within zone A, and the remaining 15.1% of the plots fell within zone B. Bland–Altman analysis showed that FGM tended to underestimate glucose level compared with that estimated by CGM (~8.7%), and the 95% limits of agreement was 33.5% (Figure 2b).

DISCUSSION
Bailey et al. first reported the accuracy of interstitial glucose measurements by FGM against capillary blood glucose measurements. In their study, the accuracy was stable over a period of 14 days of wear with a MARD of 11.4%, and was not affected by patient characteristics, such as type of diabetes mellitus, age and sex, although MARD was higher on the first day of use. Several studies have also shown that there was good agreement between measurements by FGM and capillary blood glucose measurements, and that the validity for FGM was similar to that of CGM. However, to our knowledge, no study has simultaneously examined the relationships between glucose levels measured in capillary blood and venous blood, and those measured by CGM and FGM in the same study participants. The present results showed that there was a good correlation between glucose levels measured by FGM and those measured in venous blood, and that the accuracy of FGM was similar to that of capillary blood and CGM.

Table 1 | Characteristics of the patients included in the study

| Patient no. | 1   | 2   | 3   | 4   | 5   |
|-------------|-----|-----|-----|-----|-----|
| Age (years) | 41  | 57  | 54  | 47  | 67  |
| Sex         | Male| Male| Female| Male| Female|
| BMI (kg/m²) | 22.9| 23.8| 26.2| 31.7| 19.0 |
| Diabetes duration (years) | 2  | 21  | 5   | 17  | 9   |
| HbA1c (%)   | 11.6| 8.3 | 10.8| 12.4| 8.3 |
| C-peptide index | 0.43| 1.29| 1.28| 0.44| 0.69|
| eGFR (mL/min/1.73 m²) | 95.0| 58.5| 82.8| 45.5| 149.2|
| Nephropathy (stage) | 1  | 2   | 1   | 3   | 2   |
| Retinopathy | None| None| None| PPDR| None|
| Daily insulin dose (IU) | 48 | 28  | 26  | 24  | 6   |
| Other therapy | DPP-4i| Biguanide GLP-1 RA| DPP-4i| SGLT-2i GLP-1 RA| Biguanide DPP-4i SU|
| Days of FreeStyle Libre Pro use after admission | Day 4–10| Day 5–15| Day 2–12| Day 4–9| Day 5–11|
| Days of iPro™ use after admission | Day 4–7| Day 7–9| Day 4–7| Day 4–5| Day 5–8|
| Day of BG profile exam after admission | Day 7| Day 8| Day 6| Day 5| Day 8|
| Duration for continuous glucose monitoring and FGM measurement (h) | 82| 42  | 86  | 38  | 76  |

BG profile exam, examination for daily blood glucose profile; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; PPDR, preproliferative diabetic retinopathy; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea.
We found that glucose levels measured by FGM were slightly lower than those measured in venous blood (−6.5 mg/dL, 30 measurements) and those measured by CGM (−13.6 mg/dL, 1,279 measurements), and this tendency was similar to the results of earlier studies. Aberer et al. reported that glucose level measured by FGM was 7.6% lower than that measured in venous blood. Olafsdóttir et al. also reported that the glucose value measured by FGM was 9.2 mg/dL lower than...
that in capillary blood. Although the reason why FGM indicates slightly low glucose level is uncertain, we should consider the possibility of underestimation of glucose level at the time of glucose monitoring by FGM.

Considering a time lag (4–10 min) between interstitial fluid and blood glucose\(^{17,18}\) and a time interval between glucose measurements by FSL-pro (i.e., 15 min), we used data of FGM measurements at 1–15 min (6.3 ± 4.1 min) after venous sampling in the present study. In contrast, CGM measurement by the iPro\(^{TM}\)2 system was carried out every 5 min, and we therefore compared the glucose levels measured in venous blood and those measured by CGM at 0, 5 and 10 min after venous blood sampling. There was a stronger correlation between venous blood glucose and CGM measurements at 5 min after sampling than the correlations at 0 min (\(r^2 = 0.84\), MARD \(9.3 ± 8.3\%\)) and at 10 min (\(r^2 = 0.83\), MARD \(9.7 ± 9.5\%\)), although there were good correlations between venous blood glucose and CGM measurements at all three time-points.

There were limitations in the present study. First, the number of study participants and the number of blood glucose measurements per participant were small. Thus, we cannot exclude the possibility of a type II error in statistically insignificant differences between glucose level determined by FGM, venous blood glucose level and glucose level determined by CGM. Second, as the range of venous blood glucose variations in the study participants was within an almost physiological range; that is, 70–245 mg/dL, the accuracy of measurements might have been overestimated in the study. In fact, it has been reported that discrepancy between glucose levels determined by different devices was greater in patients with in hypoglycemia (<70 mg/dL)\(^{9,16}\) and in non-diabetic individuals with acute glucose loading\(^{19}\). Third, differences in the timing of measurements of daily glucose profile after admission and/or after attaching FSL-pro and iPro\(^{TM}\)2 among patients might have some influence on the results of data analysis.

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**DISCLOSURE**

The authors declare no conflict of interest.

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