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Accuracy of a Factory Calibrated Retrospective CGM Device and the Comparison to a Conventionally Calibrated Retrospective CGM Device: A Pilot Study

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Abstract: Objective: This study aimed to examine the accuracy of FreeStyle Libre Pro, a factory calibrated retrospective continuous glucose monitoring (CGM) device, and compare its measurements to those by iPro2, a conventionally calibrated retrospective CGM device. Methods: FreeStyle Libre Pro and iPro2 were simultaneously used in 15 patients with type 2 diabetes mellitus. As these devices have different sensor duration, data from the initial 168 hours period were used. Finger prick glucose tests were performed using a conventional glucose meter, OneTouch UltraVue. The mean absolute relative difference (MARD) and mean absolute difference (MAD) of FreeStyle Libre Pro compared to conventional finger prick blood glucose tests were calculated. Furthermore, the paired glucose measurements obtained by FreeStyle Libre Pro and iPro2 were compared. Results: Overall MARD of FreeStyle Libre Pro was 17.4%, and, when limited to range ≥ 100 mg/dl, MARD was 16.8%. Overall MAD of FreeStyle Libre Pro was 32.0 mg/dl, and, when limited to range < 100 mg/dl, MAD was 21.1 mg/dl. Mean glucose measurements obtained by FreeStyle Libre Pro were significantly lower than those obtained by iPro2 (151.3±60.4 mg/dl vs. 179.4±64.1 mg/dl, $P < 0.01$). Linear regression analysis revealed significant correlation between glucose measurements obtained by FreeStyle Libre Pro and those obtained by iPro2: Glucose (FreeStyle Libre Pro) (mg/dl) = 0.86 × Glucose (iPro2) - 3.31 (mg/dl), $r = 0.914$, $P < 0.01$. Conclusions: FreeStyle Libre Pro is convenient to use because it does not need calibration by finger prick glucose tests, however our results supports the importance of confirming the measurements of FreeStyle Libre Pro by conventional finger prick glucose tests or central laboratory tests.

Keywords: CGM, Accuracy, FreeStyle Libre Pro, IPro2, Type 2 Diabetes Mellitus

1. Introduction

Continuous glucose monitoring (CGM) is widely used to measure glycemic excursions in patients with diabetes mellitus [1-4]. CGM measures glucose levels of the interstitial fluid by implanting an enzyme electrode sensor in the subcutaneous tissue. CGM devices convert interstitial fluid glucose levels to blood glucose levels using computer algorithm that is proper to each device. When blood glucose levels are rapidly rising or falling, the change in the measurement by CGM is delayed compared to the actual change in the blood glucose levels [4]. There are two types of CGM according to the intended purpose to use. One is aimed for the retrospective analysis, called as retrospective CGM or professional CGM. The other type is

aimed to be used as adjunctive to or non-adjunctive to self-monitoring of blood glucose (SMBG) by conventional finger prick glucose tests, called as real-time CGM, personal CGM, intermittent-scanning CGM (isCGM), or intermittently viewed CGM (iCGM) depending on the device's functions. The term "Flash Glucose Monitoring (FGM)" is the commercial name for isCGM or iCGM by its manufacturer Abbott Diabetes. However the company sometimes includes its retrospective CGM product depending on the market, which causes confusion in the definition of FGM. For example, in the Japanese market, Abbott includes retrospective CGM product in FGM, but not in the American market.

In Japan, iPro2 (Medtronic MiniMed, Northridge, U.S.A.) has been widely used as retrospective CGM, after the first generation retrospective CGM device, MiniMed CGMS Gold (Medtronic MiniMed, Northridge, U.S.A.). iPro2 requires calibration at least four times per day by conventional finger prick blood glucose tests. In 2016, FreeStyle Libre Pro (Abbott Diabetes Care, Alameda, CA, U.S.A.), a retrospective CGM device that is factory calibrated and does not need calibration by conventional finger prick blood glucose tests, was introduced to Japan. Factory calibration depends mainly on *in vitro* tests of the sensitivity of the enzyme electrode sensor [5].

The mean absolute relative difference (MARD) is a standard benchmark of the accuracy of CGM devices. The MARD of FreeStyle Libre Pro reported by the manufacturer was 11.1% [6]. The number of publications reporting the accuracy of FreeStyle Libre Pro is quite limited [6, 7]. According to a study funded by the manufacturer, the MARD of FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, U.S.A.), an isCGM device using common technology of factory calibration with FreeStyle Libre Pro, was 11.4%, which was slightly different from that of FreeStyle Libre Pro [8]. There are several publications reporting the accuracy of FreeStyle Libre [9 - 13].

A study using FreeStyle Libre Pro on non-diabetic adults involving meal tests reported that this device may not be sufficiently accurate in normal glucose levels [6]. Another study using both FreeStyle Libre Pro and iPro2 on patients with type 2 diabetes mellitus reported that the MARD of FreeStyle Libre Pro was 8.2% compared to venous blood glucose levels measured by ADAMS glucose GA-1171 system (Arkray, Kyoto, Japan), and the measurements by FreeStyle Libre Pro was lower than those by iPro2 [7].

Therefore, the present study aimed to assess the accuracy of FreeStyle Libre Pro and compare it to the measurements by iPro2 in patients with type 2 diabetes mellitus.

2. Materials and Methods

2.1. Study Subjects

Fifteen patients were recruited for this study during the period between June 2017 and January 2018. Inclusion criteria were patients with type 2 diabetes, and hospitalized for diabetes education at the National Hospital Organization Mie Chuo Medical Center. Exclusion criteria were, aged less than 20 years, severe liver impairment, concurrent renal impairment, severe infection, malignancies, alcohol addiction, severe mental illness, severe dementia, history of diabetic ketoacidosis, in perioperative period, pregnant, breastfeeding, and those who were judged unsuitable for any reason by the attending physician.

2.2. Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Ethical Review Board at National Hospital Organization Mie Chuo Medical Center. Oral informed consent was obtained from the patients. The study was registered on the University Hospital Network Clinical Trial Registry (UMIN R000034730).

2.3. Data Collection and Measurements

This prospective observational study was conducted for a maximum 168 hours period, during which the patients simultaneously wore FreeStyle Libre Pro and iPro2. FreeStyle Libre Pro Sensor was worn on the upper arm, and Enlite Sensor for iPro2 was worn on the abdomen, according to the recommendation in the user guide of these devices. FreeStyle Libre Pro Sensor with one of the following lot numbers was used: 170410R, 170426R, 170502P, 170506R, 170508W, 170508U, 170509P, 170918P, 170822P, 170918Q, 170918U, 170918T or 171024P. Elite Sensor with one of the following lot numbers was used: F077P, H207P, I247P or K097P.

For conventional finger prick blood glucose tests, OneTouch UltraVue (Johnson & Johnson K. K., Tokyo, Japan) was used. Nurses conducted finger prick glucose tests six times per day, three times before the meals (around 8 a.m., 12 a.m. and 6 p.m.) and three times after the meals (around 10 a.m., 2 p.m. and 8 p.m.), however omitting tests due to appropriate reasons were accepted. iPro2 was calibrated following the instructions provided by the manufacturer at least four times per day.

FreeStyle Libre Pro takes measurements every 15 min over 14 days (336 hours) period, whereas iPro2 takes measurements every 5 min over 7 days (168 hours) period. Thus, this study was limited to the initial 168 hours period, in which data from the both devices were available. CGM data from FreeStyle Libre Pro or iPro2 were downloaded using FreeStyle Libre Pro Software (Abbott Diabetes Care, Alameda, U.S.A.) or CareLink iPro Software (Medtronic MiniMed, Northridge, U.S.A.) respectively, and were saved to log files as text data.

Paired measurements obtained by FreeStyle Libre Pro and iPro2 were compared, and maximum difference of 3 minutes between the two different devices was accepted to pair the data. The analysis range was limited to 40–400 mg/dl based on the range of the measurements by iPro2, and measurements $\leq$ 40 mg/dl or $\geq$ 400 mg/dl were excluded as outlier data.

2.4. Statistical Analysis

Absolute difference (AD) was determined as the absolute values of the difference between the measurements by the factory calibrated retrospective continuous glucose monitoring device (FreeStyle Libre Pro) and those by the conventional finger prick blood glucose tests (OneTouch UltraVue). Absolute relative difference (ARD) was determined as the ratio of AD to the measurements by the conventional finger prick blood glucose tests in percentage terms. For the assessment of the accuracy of FreeStyle Libre Pro, mean absolute relative difference (MARD) and mean absolute difference (MAD) were calculated [6]. As MARD and MAD are affected by the levels of measurements by the conventional finger prick blood glucose tests, MARD and MAD both in range ≥ 100 mg/dl and < 100 mg/dl were also calculated [10]. MARD and MAD of iPro2 were not calculated, as the measurements by the conventional finger prick blood glucose tests were used for the calibration of iPro2 and therefore not suitable for the assessment of the accuracy of iPro2. A paired Student's *t*-test was used to test for significant difference. Linear regression analysis was performed to clarify the relationship between the glucose measurements obtained by FreeStyle Libre Pro and those by iPro2. Analyses were performed using STATA version 12.0 (Stata Corporation LP, College Station, TX, USA). A *P* value of <0.05 was considered significant.

3. Results

The study participants included 15 patients with the average age of 65.5 ± 11.5 years, males accounted for 66.6% of the study participants, with average HbA1c of 10.3 ± 1.8% and average body mass index (BMI) of 27.1 ± 5.1 kg/m^2 (Table 1).

The overall MARD of FreeStyle Libre Pro compared to conventional finger prick blood glucose tests measured by OneTouch UltraView was 17.4%, and when limited to the range ≥100 mg/dl, MARD was 16.8% (Table 2). The overall MAD was 32.0 mg/dl, and when limited to the range <100 mg/dl, MAD was 21.1 mg/dl.

Table 1. *Characteristics of the study patients.*

Characteristics	Value
Age (years)	65.5 (11.5)
Male (%)	66.6
BMI (kg/m^2)	27.1 (5.1)
HbA1c (%)	10.3 (1.8)
Oral hypoglycemic agents (%)	86.6
GLP-1 analog (%)	6.6
Insulin (%)	66.6

Date are presented as mean (SD) or number (%). SD: standard deviation. BMI: body mass index. HbA1c: hemoglobin A1c. GLP-1: glucagon-like peptide-1.

Table 2. *Accuracy of FreeStyle Libre Pro.*

Glucose levels	MARD %	MAD mg/dl
Overall	17.4	32.0
≥100 mg/dl	16.8	32.7
≥250 mg/dl	16.2	49.1
≥100 and <250 mg/dl	17.0	28.5
<100 mg/dl	25.1	21.1

MARD: mean absolute relative difference. MAD: mean absolute difference.

Table 3. *Comparison of the measurements by FreeStyle Libre Pro and iPro2.*

Range	Glu (LP) mg/dl	Glu (iP) mg/dl	*P* value
Overall	151.3 (60.4)	179.4 (64.1)	<0.01*
≥250 mg/dl	255.9 (47.7)	299.6 (39.3)	<0.01*
≥100 and <250 mg/dl	138.4 (38.7)	164.6 (37.2)	<0.01*
<100 mg/dl	70.3 (24.0)	85.7 (11.1)	<0.01*

Date are presented as mean (SD). SD: standard deviation. Glu(LP): Glucose (FreeStyle Libre Pro). Glu(iP): Glucose (iPro2). * *P* <0.05.

After removing outlier data, 8982 pairs of the glucose measurements obtained by FreeStyle Libre Pro and iPro2 were analyzed. Mean glucose measurements obtained by FreeStyle Libre Pro were significantly lower than those obtained by iPro2 (151.3±60.4 mg/dl vs. 179.4±64.1 mg/dl, *P* <0.01) (Table 3). Similar difference was observed in range ≥250 mg/dl (1296 pairs), ≥100 mg/dl and <250 mg/dl (7155 pairs), and <100 mg/dl (531 pairs), respectively.

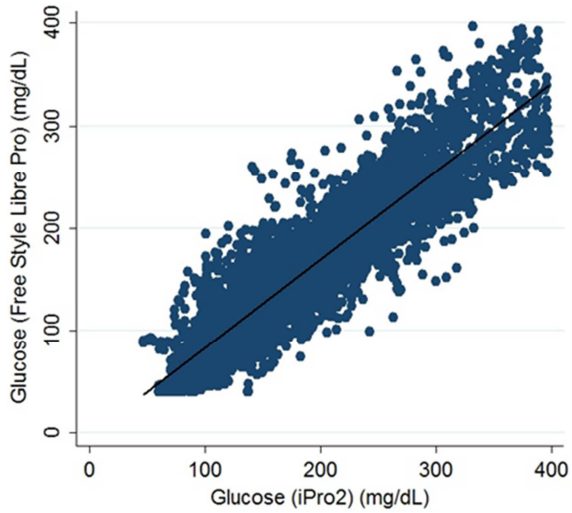

Figure 1. *Scatter plot and linear regression analysis of the measurements by FreeStyle Libre Pro and iPro2.*

Linear regression analysis revealed significant correlation between glucose measurements obtained by FreeStyle Libre Pro and those obtained by iPro2: Glucose (FreeStyle Libre Pro) (mg/dl) = 0.86 × Glucose (iPro2) - 3.31 (mg/dl), $r = 0.914$, $P < 0.01$*. * $P < 0.05$.

Linear regression analysis revealed significant correlation between glucose measurements obtained by FreeStyle Libre Pro and those obtained by iPro2: Glucose (FreeStyle Libre Pro) (mg/dl) = 0.86 × Glucose (iPro2) - 3.31 (mg/dl), r = 0.914, P <0.01 (Figure 1).

4. Discussion

The MARD of FreeStyle Libre Pro in the present study was greater than that reported by the manufacturer and by other investigators, however the reason remains unclear [6, 7]. One possibility is that the accuracy of FreeStyle Libre Pro Sensor might be different between individual sensors. In fact, MARD of FreeStyle Libre was different between previous studies, suggesting the possibility of the difference in the accuracy between individual sensors [8-13]. Another possibility is that the glucose levels obtained by the finger prick glucose tests using OneTouch UltraVue might be less accurate compared to the plasma glucose levels measured at the central laboratory. It is also known that finger prick glucose tests can be affected by the contamination of the skin by the environmental sugar, especially in case patients ate something using their hands and did not wash them after doing so.

The measurements by FreeStyle Libre Pro were significantly lower compared to those by iPro2 in this study. This observation was similar to that in other study using both FreeStyle Libre Pro and iPro2 [7]. On the other hand, a study comparing FreeStyle Libre and Dexcom G4 Platinum (Dexcom, San Diego, CA, USA) reported no significant difference between them [14]. The reason why the measurements by FreeStyle Libre Pro were lower than those by iPro2 in this study remains unclear. One possibility is the difference in the algorithm used in FreeStyle Libre Pro and iPro2. Another possibility is the difference of the recommended sites of use of these devices. According to the user guide of iPro2, the recommended sites of use are the abdomen and the hip. In contrast, for FreeStyle Libre Pro, the recommended site of use is limited to upper arm [12].

Noteworthy, reading of FreeStyle Libre Pro in hypoglycemic range was reported to be inaccurate, as 40% of the time when the device indicated that the sensor glucose values were ≤60 mg/dL, the reference glucose values were actually in the range of 81- 160 mg/d [15]. Therefore, confirmation of hypoglycemia by conventional methods such as finger prick blood glucose tests or central laboratory tests is indispensable for the appropriate interpretation of the CGM studies using FreeStyle Libre Pro.

There is ongoing discussion regarding the reliability and the limitation of the factory calibrated CGM. For example, non-adjunctive use of FreeStyle Libre to finger prick glucose tests is approved in E. U. and in U.S.A., but not in Japan [16, 17]. A real-time CGM, Dexcom G6 (Dexcom, San Diego, CA, U.S.A.), is also factory calibrated and is approved for non-adjunctive use to finger prick glucose tests in U.S.A. [18]. Interestingly, FreeStyle Libre do not accept calibration by finger prick glucose tests, but Dexcom G6 can be calibrated as option [19]. Furthermore, users of FreeStyle Libre must confirm hypoglycemia by finger prick glucose tests, but users of Dexcom G6 can confirm hypoglycemia by CGM alone on condition that both glucose levels and trend arrow are available [19, 20]. Compared to real-time CGM and isCGM that may be directly used for insulin dosing decision, the stringency of factory calibration required for retrospective CGM might not be the same. However there is little evidence regarding the relationship between the accuracy of retrospective CGM and clinical outcomes by using it.

One of the great benefits of CGM compared to conventional finger prick glucose tests is that CGM provides more information about glucose trends, such as dawn phenomenon, nocturnal hypoglycemia and postprandial hyperglycemia. Although trend arrow is not available in retrospective CGM devices, looking into not only the glucose levels but also into the glucose trends is essential for the patient education and treatment optimization.

The limitations of this pilot study were small sample size, and data after 168 hours were not included for FreeStyle Libre Pro.

5. Conclusions

The MARD of FreeStyle Libre Pro was greater than that reported by the manufacturer and by other investigators, and the measurements by FreeStyle Libre Pro were significantly lower than those by iPro2. These results support the importance of confirming the measurements of FreeStyle Libre Pro by conventional finger prick glucose tests or central laboratory tests. Further studies with larger number of patients, longer period of use, and controlled lot numbers of FreeStyle Libre Pro Sensor would address the accuracy of FreeStyle Libre Pro in the real world setting.

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