Flash glucose monitoring can accurately reflect postprandial glucose changes in healthy adults in nutrition studies

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Abstract

Objective: This study investigated the accuracy of a flash glucose monitoring system (FGMS) in a postprandial setting.
Methods: Ten fasted adults without diabetes wore the FGMS sensors then consumed a standard breakfast. Their glucose levels were subsequently recorded for two hours, both by the FGMS and by measuring capillary glucose levels using the glucose oxidase method. The accuracy of the FGMS data was assessed using the accuracy limits stated in ISO 15197:2013.
Results: FGMS measurements were mostly lower than glucose oxidase measurements (mean absolute relative difference ± SD: 25.4 ± 17.0 %, $p < 0.001$). However, the maximum difference from baseline captured by the two methods was not significantly different (mean ± SD, glucose oxidase: 58.5 ± 18.9 mg/dl; FGMS, 54.4 ± 28.9 mg/dl, $p = 0.366$).
Conclusions: FGMS could track the incremental glycaemic excursions after meals in adults without diabetes, yet further studies with greater sample sizes are needed to confirm this finding.
Keywords: adult, flash glucose monitoring system, postprandial glucose, capillary glucose, interstitial glucose
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Introduction

Regular postprandial hyperglycaemia has been implicated in the etiology of type 2 diabetes mellitus (T2DM) [1] – high glucose levels after meals in adults without diabetes led to increased oxidative stress [2] and insulin resistance [3], thus reducing the surge in glucose level after meals could favour the prevention of T2DM [4]. Therefore, in the research of diabetes prevention, postprandial glucose measurements in adults without diabetes remains a popular study outcome.

In clinical trials that involved the monitoring of postprandial glycaemia, capillary glucose levels, which is more sensitive to changes than those in venous samples [5], were measured for several times to keep track of the changes after meal consumption. Consequently, multiple finger-pricks are inevitable in order to collect capillary blood samples during the experiment, which would bring pain to study subjects. Developing a method to track postprandial glucose variations with less suffering would benefit subjects in similar studies in the future.

Flash glucose monitoring system (FGMS) is an alternative tool to monitor changes in glucose levels. It involves the insertion of a sensor into the interstitial layer of the subject, which automatically measures the glucose level of the interstitial fluid at a fixed interval. The use of this technique can greatly reduce the frequency of finger-pricks to just 1 prick at the beginning for calibration, thereby reducing the study subjects' discomfort. The glucose data could also be captured with greater frequency than the finger-prick method, which is important for periods of rapid changes in glucose levels, such as after meals.

Previous studies evaluated the accuracy of the FGMS in patients with type 1 [6] and 2 diabetes [7] during postprandial periods and the measurements were of good accuracy. However, while the FGMS could reduce the pain and nuisance when measuring postprandial glycemic excursion of experiment participants, its performance has never been assessed in those without diabetes. Hence, the aim of this study is to assess the accuracy of an FGMS against plasma glucose measurements, which is the recommended measurement in reporting glucose concentrations [8], in an acute feeding study setting involving adult subjects without diabetes.

Experimental methods

Study design

This validation study was conducted between August 2016 and September 2017 at the University of Hong Kong (HKU). The experimental protocols and the process for obtaining informed consent were approved by the Human Research Ethics Committee of the University of Hong Kong (Approval no.: EA1604004). The study was conducted according to the guidelines laid down in the Declaration of Helsinki as revised in 1983. All participants provided written consent before the commencement of the study.

Study participants

Participants were recruited from the staff and students of HKU through emails and face-to-face recruitment. The inclusion criteria were aged between 18-40 years old, having a body mass index (BMI) between 18.0-23.0 kg/m^2, able to finish the test meal in 10 minutes, have never smoked before, not on regular medication (except oral contraceptives), and not using any medical ointment regularly.

Study protocol

Each participant came to the laboratory in the morning after an overnight fast. After 10 minutes of rest, their weight, height, and body fat were measured. An FGMS sensor (FreeStyle Libre, Abbott, Berkshire, UK) was then inserted at the back of the upper arm of the participant by the research staff. After the sensor was activated, a reading was obtained using the reader of the FGMS, and a blood sample was collected, which served as the baseline measurement. The participant then consumed a standard breakfast, which was made by adding 30 g rice cereal and 10 g glucose powder into 150 ml rice milk, thereby providing 40 g carbohydrate. The breakfast was finished in 10 minutes and blood samples were taken at 15, 30, 45, 60, 90, and 120 minutes after breakfast. Immediately before collecting the blood sample at each timepoint, a reading of the FGMS was obtained using the reader. During the session, participants were advised to remain seated in the laboratory. At the end of the experiment session, the sensor was removed by the research staff and the measurement record was extracted using the designated software of the FGMS.

Two days before the experimental session, participants were required to refrain from consuming alcohol and were advised not to take part in any vigorous physical activity. Participants were instructed to consume a standard dinner package (spaghetti with bacon and mushroom in cream sauce) on the day before the session, refrain from consuming any food and drink after dinner and before the experiment, fast for at least 10 hours, and sleep for at least seven hours before the experiment. Participants were advised not to attend the session if they took any medication within two days prior to the scheduled time, except for oral contraceptives. Female participants were advised not to attend the session within a week before the commencement of the menstrual period and during that, so as to avoid variation in results due to hormonal fluctuation.

Anthropometry measurement

Height and weight were measured to the nearest 0.1 cm and 0.1 kg respectively, both using an electronic column scale (Seca 769, Seca, Hamburg, Germany). Body-mass-index (BMI) was calculated by dividing body weight (kg) by the square of height (m). Body fat was measured in a supine position using the bioimpedance measuring device (BIA 101, Akern bioresearch srl, Florence, Italy) and was presented as a percentage relative to the total body mass.

Table 1 – Characteristics of study participants

Variables	Male (n = 5) Mean	SD	Female (n = 5) Mean	SD
Age (years)	26.6	8.0	22.4	5.4
Weight (kg)	65.5	3.1	53.3	6.4
Height (m)	174.3	3.8	158.0	7.5
BMI (kg/m^2)	21.3	0.8	21.6	1.4
Fat percentage (%)	14.2	2.9	23.2	2.3
Fasting glucose (mg/dl)	96.4	8.7	88.6	3.9
Fasting insulin (μU/ml)	6.1	1.4	6.8	4.2
HOMA-IR	0.8	0.2	0.9	0.5

BMI, body mass index. HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.

Sample handling

Capillary blood samples were collected by finger-pricking using disposable, single-use lancing devices (Accu-Chek, Roche, Indianapolis, Indiana USA) and were collected into Eppendorfs coated with heparin. All samples were stored on ice and centrifuged (3000 *g*, 1.5 minutes, 4°C) within 30 minutes after collection. It was shown that glucose loss in samples was minimal within this period on ice [9, 10]. Plasma was collected and stored at -80 °C until analysis.

Capillary glucose and insulin measurement

Plasma glucose levels were measured by the glucose oxidase method (Stanbio Glucose LiquiColor®, Stanbio Laboratory, Boerne, TX, USA). Plasma insulin levels were measured by enzyme-linked immunosorbent assays (ImmunoDiagnostics Limited, Shatin, Hong Kong). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [11] was calculated for each participant to serve as an indirect measurement of insulin resistance, using the fasting glucose and insulin levels obtained during the experiment.

Statistical analysis

The primary outcome of this study is the accuracy of glucose levels measured by the FGMS. It was assessed by testing whether the FGMS measurements fell within the boundaries stated in ISO 15197:2013, which is a set of standards used to assess the performance of glucose monitoring systems for self-measurements in diabetes management. Although subjects without diabetes were involved in our study, we decided to adapt this set of accuracy limits to enable comparison with the results of previous studies [7, 12]. The boundaries were as follow: at glucose concentration < 100 mg/dl, differences between the results obtained by the test method and the reference method should be within ± 15 mg/dl, while at ≥ 100 mg/dl the differences should be within ± 15%. We also assessed the accuracy of the FGMS data by plotting the FGMS measurements on the consensus error grid (CEG) and comparing the results with the boundaries stated in ISO 15197:2013 i.e. 99% of the data points should be in zone A and zone. The CEG used for T2DM patients was used in this study and was drawn according to the article by Pfützner *et al.* [13].

The secondary outcomes were the differences between the two measurements at each time-point and between the incremental area-under-curves (iAUC). The differences were presented as absolute relative differences (MARD), which were calculated by the following formula:

$$(|\ \text{FGMS} - \text{glucose oxidase}\ |\ /\ \text{glucose oxidase}) * 100\%$$

as well as in differences from baseline. The iAUCs were calculated using the trapezoidal rule.

In the post-hoc analysis, a linear regression was carried out with glucose oxidase data as the outcome variable and FGMS data as the predictor variable. This was done on data from all participants, as well as stratified by sex. Both the correlation and the regression coefficients were presented. Regression coefficients were tested for statistical significance, with $p < 0.05$ considered statistically significant. The equations obtained were then used to adjust the original FGMS data and the accuracy of the adjusted data was assessed using the same method described above.

Since all variables were found to be normally distributed using the Shapiro-Wilk test, all measurements were presented as mean ± SD. Differences in measurements between the two methods and the iAUCs were tested for statistical significance using paired t-tests. A $p < 0.05$ was considered statistically significant. A sample size of 10 was determined *a priori* to be able to detect an effect size of 0.68 with 80% power at $p < 0.05$. This translates to 19.8 mg/dl in differences in glucose levels.

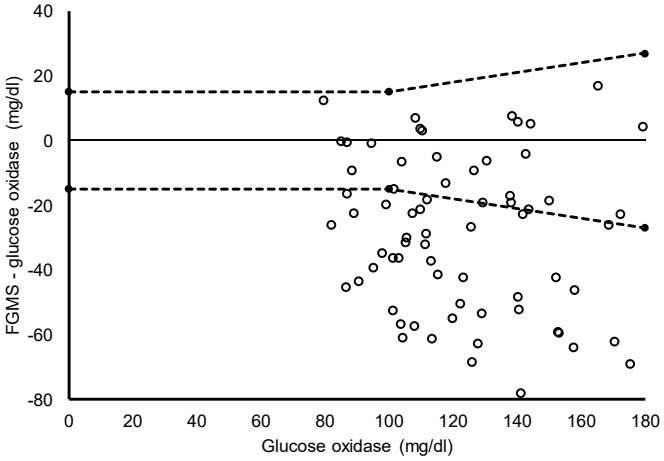

Figure 1 – Scatter plot showing the differences in measurements between the two methods against glucose oxidase data. Dashed lines depict the accuracy boundaries applied based on ISO 15197:2013. FGMS, flash glucose monitoring system.

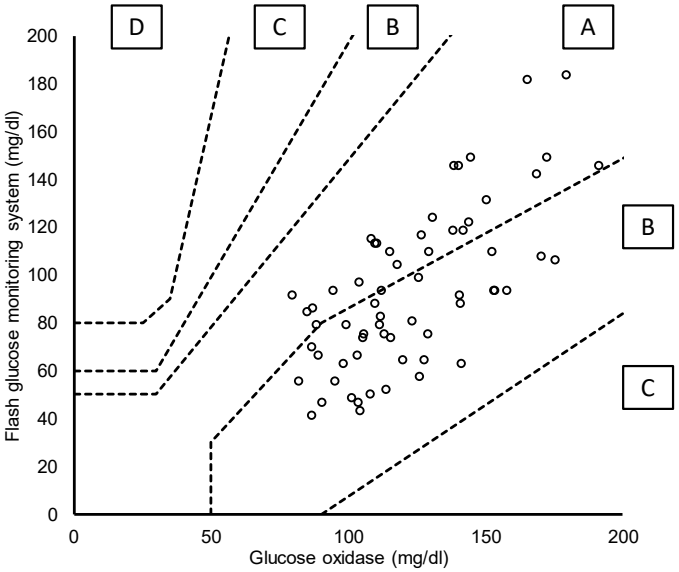

Figure 2 – Scatter plot of FGMS measurements against glucose oxidase measurements, super-imposed on the consensus error grid. Dashed lines are the boundaries of the different zones implying different degrees of risk posed by inaccurate measurement. Zone A – no effect on clinical action; zone B – altered clinical action with little or no effect on clinical outcome; zone C – altered clinical action and likely to affect clinical outcome; zone D – altered clinical action which could have significant medical risk; zone E – altered clinical action, could have dangerous consequences. Boundaries of zone E were not shown for better clarity.

Results

A total of 10 subjects were recruited and all of them completed the whole experimental protocol, providing a total of 70 data pairs for evaluation. Their characteristics are shown in **Table 1**. All participants had similar age and BMI, and half of them were male. Female participants had higher body-fat percentages than males. The fasting glucose levels of all participants were within normal range and none of them were insulin resistant.

The accuracy of the FGMS measurements is shown in **Figure 1**. Less than half of the data points (40%, n = 28) were within the acceptable range, while the rest were below the lower limit of the range. The results of the CEG analysis are shown in **Figure 2**. Around half of the data points (46%, n = 32) were in zone A, which were classified as clinically accurate measurements. The rest of the points (54%, n = 38) were in zone B (altered clinical action, little or no effect on the clinical outcome).

The differences between the glucose measurements of the two methods were shown in **Table 2**. The average glucose levels measured during the experiment by the FGMS were lower than those measured by the glucose oxidase method (mean absolute relative difference, MARD ± SD: 25.4 ± 17.0 %, $p < 0.001$). Peak glucose level of the glucose oxidase method appeared at 30 min while that of the FGMS appeared at 45 min. The glucose levels measured by the FGMS were 14.6 – 38.2 % lower than those

Table 2 – differences between the measurements of the flash glucose monitoring system and glucose oxidase method

	FGMS		Glucose oxidase		Absolute relative difference[a]		*P*[b]
	Mean	SD	Mean	SD	Mean	SD	
Average $_{0\text{-}120\ min}$ (mg/dl)[c]	93.9	32.4	122.9	26.7	25.4	17.0	<0.001
iAUC (mg/dl * min)[d]	3146.5	1794.3	3771.3	1771.8	19.9	16.5	<0.001
At different time-points (mg/dl)							
0 min	71.6	19.1	93.5	6.3	23.8	17.8	0.002
15 min	74.3	22.0	119.4	11.7	38.2	15.0	<0.001
30 min	106.2	22.4	152.0	18.3	29.7	15.2	<0.001
45 min	126.0	28.5	146.3	28.5	14.6	11.6	0.014
60 min	115.2	34.8	131.1	23.7	16.2	12.5	0.055
90 min	89.6	27.0	113.5	17.6	24.9	14.3	0.009
120 min	74.3	26.7	104.2	13.4	30.1	22.4	0.007

FGMS, flash glucose monitoring system. iAUC, incremental area-under-curve.
[a] Absolute relative difference is calculated by the following formula: (| FGMS – glucose oxidase | / glucose oxidase) * 100%
[b] Differences between FGMS and glucose oxidase data were tested for statistical significance using paired t-tests. $p < 0.05$ depicts statistical significance.
[c] Average $_{0\text{-}120\ min}$ was calculated by averaging the glucose measurements at all time-points.
[d] iAUC was calculated by the trapezoidal rule.

measured by the glucose oxidase method at all time-points, and the differences achieved statistical significance at all time-points except for T = 60 min. The mean iAUC obtained from the FGMS were also significantly lower than that from the glucose oxidase method (MARD ± SD: 19.9 ± 16.5 %).

The differences in glucose levels from baseline from the data of the two methods are shown in **Figure 3**. The glucose levels recorded by the glucose oxidase method rose earlier than those of the FGMS. The rises were significantly different between the two sets of results at 15 and 30 min. The glucose excursions measured by the glucose oxidase method peaked at 30 min, while the maximum rise in that of the FGMS appeared at 45 min. Nonetheless, the maximum rise recorded by the two methods were not significantly different (mean difference from baseline ± SD: glucose oxidase, 58.5 ± 18.9 mg/dl; FGMS, 54.4 ± 28.9 mg/dl, $p = 0.366$) and the rates of glucose decrease recorded by the two methods were similar.

Results of the linear regression between data of the two measurement methods were shown in **Supplementary Table 1**. All regression coefficients were statistically significant, although the regression coefficient obtained from males was higher than that from females. Results of the accuracy assessment of the adjusted FGMS data was shown in **Supplementary Figure 1**. After adjustments were made, around 70% of the data points were within the acceptable accuracy range for both male and female. Results of the CEG analysis using adjusted data was shown in **Supplementary Figure 2**. Most data points were in zone A, with 1 – 3 data points in zone B. Differences between the adjusted FGMS data and the glucose oxidase data was shown in Supplementary Table 2. Although the differences were still statistically significant at some time-points, the absolute relative differences were smaller than those before adjustments. Nonetheless, since the baseline measurements (i.e. T = 0 min) of the FGMS data were increased after adjustment, the iAUC of the adjusted FGMS data was significantly lower than that of the glucose oxidase data. Similarly, the incremental curve of the adjusted FGMS data was significantly lower than the glucose oxidase curve at all time points (**Supplementary Figure 3**).

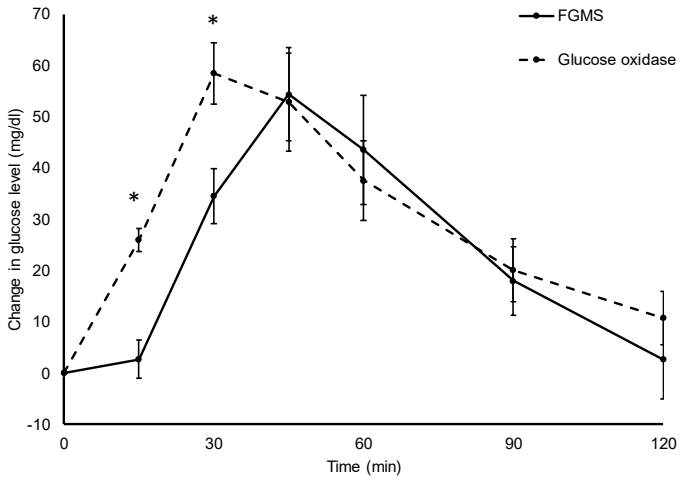

Figure 3 – mean differences from baseline of the FGMS data and the glucose oxidase data. Error bars depict SEM. Differences from baseline at each timepoint were calculated by subtracting the measurement at that timepoint with the baseline measurement (i.e. T = 0). The differences between the mean differences from baseline obtained using the two methods at each timepoint were tested for statistical significance using paired *t*-test. *, $p < 0.05$. FGMS, flash glucose monitoring system.

Discussion

Results of this study showed that the postprandial glucose measured by an FGMS in adult subjects without diabetes were generally lower than capillary glucose levels measured by the glucose oxidase method. However, both the peak differences from baseline measured and the rates of decrease in glucose levels were similar between the two methods.

The results of this study could serve as a comparison for similar investigations in the future. To the best of the authors' knowledge, only one study reported results in assessing the accuracy of the FGMS in postprandial period on subjects without diabetes [14]. The results of that study, which compared glucose data obtained by the FGMS on 26 children without diabetes with venous plasma glucose levels during an oral glucose tolerance test, indicated substantial differences during the postprandial period, which was the same as our findings. Our results further showed that the differences from pre-meal baseline, which was an outcome frequently included in nutrition studies involving human subjects [15, 16], was not significantly different between the two methods in adults. These results indicated that FGMS, which is substantially less expensive than continuous glucose monitors in general, may be used in trials involving subjects without diabetes to generate postprandial glucose data with acceptable accuracy, and there is also great potential for the FGMS to be used in studies with large sample sizes.

The differences between the FGMS and the reference method in this study were greater than those observed in previous trials. Bailey *et al.* [12] conducted a validation study using the same brand of FGMS as the current study. They recruited patients with type 1 or 2 diabetes and compared the results recorded by the FGMS sensor with capillary blood glucose measured using the blood glucose meters built in the FGMS reader. Their results showed an MARD of 11.4%, which was smaller than those found in the current work. Similarly, Fokkert *et al.* [7] carried out another validation study of an FGMS on patients with type 1 or 2 diabetes and compared the results with capillary blood glucose measurements obtained using the Statstrip Xpress monitoring system. Their results showed that the MARD ranged from 10 – 24% at different magnitudes of glucose levels. These differences were also smaller than those observed in the present study.

One reason for the difference could be the different number of non-prandial and postprandial glucose measurements made between previous trials and the current study. In previous trials, the preferred measurement timepoints were mainly non-prandial periods, such as upon waking up, before meals, and bedtime [7, 12]. In contrast, only one fasting measurement was made for each subject in this study, with the rest being postprandial glucose measurements.

A small sample was included in this study ($n = 10$), which may lead to the worry that individual variability might hinder the reproducibility of the results. However, we recruited subjects with similar baseline characteristics i.e. without glucose intolerance, non-smokers, and with similar BMIs, thereby minimizing errors due to this variation. Moreover, the user manual of the FGMS did not indicate any deviation in performance on subjects with any distinct characteristics, while this was also not reported in previous validation trials conducted by other groups [6, 7, 12]. It should also be noted that generating glycaemic index values is not an outcome we aimed to measure using the FGMS. In fact, the

creation of GI values of foods required the use of standardized protocols and standardized calculations [17], which are different from those involved in the current validation study.

Results from future trials involving more subjects without diabetes will strengthen the case of this finding, which could establish the use of FGMS for recording daily glycemic variations in apparently healthy individuals. Profiles of glucose levels during the day, as well as the time of glucose levels above or below a desirable range, are both important measures in determining the overall glucose control over a period of time [18] and are often reported in clinical trials [19, 20]. FGMS could measure both of them with ease and these measurements obtained from individuals without diabetes could serve as important control data in future diabetes research, especially in studies aiming to determine the effect of intervention regimes for glucose level management [21].

The potential difference in the performance of FGMS on subjects with and without diabetes warrants further investigation. One distinct difference between the two subject groups is that diabetic subjects had compromised ability in tissue glucose uptake due to insulin resistance [22]. According to the two-compartment model proposed by Rebrin *et al.* [23], lower cellular glucose uptake was associated with higher interstitial glucose level, which would make it more sensitive towards changes in blood glucose level. Therefore, the difference between interstitial and blood glucose levels might be smaller in subjects with diabetes, both in fasting and postprandial state. The fact that the differences observed in the present trial were greater than those of the previous studies supported this speculation. In spite of this finding, since this model was only validated in an animal study [24], more data from human trials are needed to confirm this speculation.

Results of the *post-hoc* analysis showed that the association between FGMS data and glucose oxidase data was stronger in male participants than in female participants. Although hormonal fluctuation during the mensural cycle may affect glucose tolerance in females, female subjects were advised not to attend the session during and before the onset of menstruation to minimize this effect, thus other sex-specific factors may be responsible for the observed differences. One previous study observed that women had higher insulin sensitivity than men at the same fitness level [25]. However, since muscle mass is the main contributor to tissue glucose uptake, and women generally have lower muscle mass than men, such an advantage may possibly be offset. Another study found that height was a factor that affected postprandial glucose excursions, and contributed this finding to it being an indirect measurement of muscle mass [26]. In our study, female participants had a more varied height than male participants as shown by the greater SD, which may explain the weaker association. Future validation studies will need to address the effect of sex differences, particularly in terms of anthropometric variations.

Our results showed that adjusting the FGMS data using the regression equation developed led to improved accuracy when compared with glucose oxidase data, yet the differences from baseline deviated further. This implied that adjustment could be beneficial when absolute readings were of interest, at the expense of the ability to assess the incremental glycemic excursion. The power of our regression analyses is likely limited owing to the small sample size, yet our results showed the possibility to improve the accuracy of the readings. In order to improve the adjustments in FGMS-based glucose data, future studies will need to involve more participants.

To our knowledge, this study is the first to assess the accuracy of the FGMS measurements in a postprandial setting in adults without diabetes. The FGMS data were compared against plasma glucose levels measured using the glucose oxidase method, which was the recommended analysis method according to the American Diabetes Association [27]. Moreover, the manufacturer of the FGMS was not involved in any part of this study, thus guaranteeing the results to be unbiased. On the other hand, one limitation of the current study was that the accuracy of the FGMS was usually lower on the first day of insertion due to the body's natural inflammation responses towards the sensor, which was shown to reduce the sensor's sensitivity [28]. Nonetheless, while this is inevitable in validation studies involving invasive sensors, doing the experiments on this day will better reflect the real-life use of this sensor, as it is unlikely to be logistically feasible for the subjects to come a day before the test session just to have the sensor attached. Furthermore, since only young adults participated in this study, the results may need to be validated in older adults, who were more likely to have compromised glucose tolerance and immune response.

Conclusions

When used in adults without diabetes in a postprandial setting, the FGMS measurements were lower than plasma glucose levels. Nonetheless, the incremental glycemic variation captured by the two methods were similar in magnitude. While our findings have to be confirmed by future studies with greater sample sizes, our results suggest monitoring of change in postprandial blood glucose level could be a novel and feasible application for FGMS in diabetes research.

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Data availability statement: There is no dataset associated with the paper available.

Authorship: JCYL designed research; TWHT conducted research; JCYL and TWHT analyzed data; JCYL, JMFW, and TWHT drafted and revised the manuscript. JCYL had primary responsibility for final content. All authors read and approved the final manuscript.

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Supplementary Table 1 – results of linear regression[a] between data of the two measurement methods

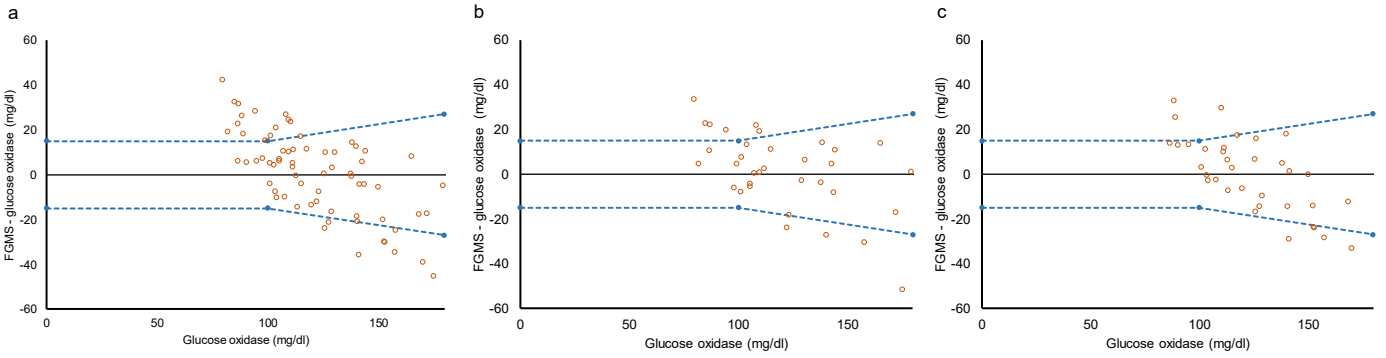
Participant groups	Correlation	Regression coefficient[b]	*P*[c]
Overall	0.70	0.57 ± 0.07	<0.001
Male	0.79	0.73 ± 0.10	<0.001
Female	0.69	0.55 ± 0.10	<0.001

[a] The dependent variable is glucose oxidase data and the predictor variable is flash glucose monitoring system data.
[b] Regression coefficients were presented with standard error.
[c] *P* values were calculated using linear regression.

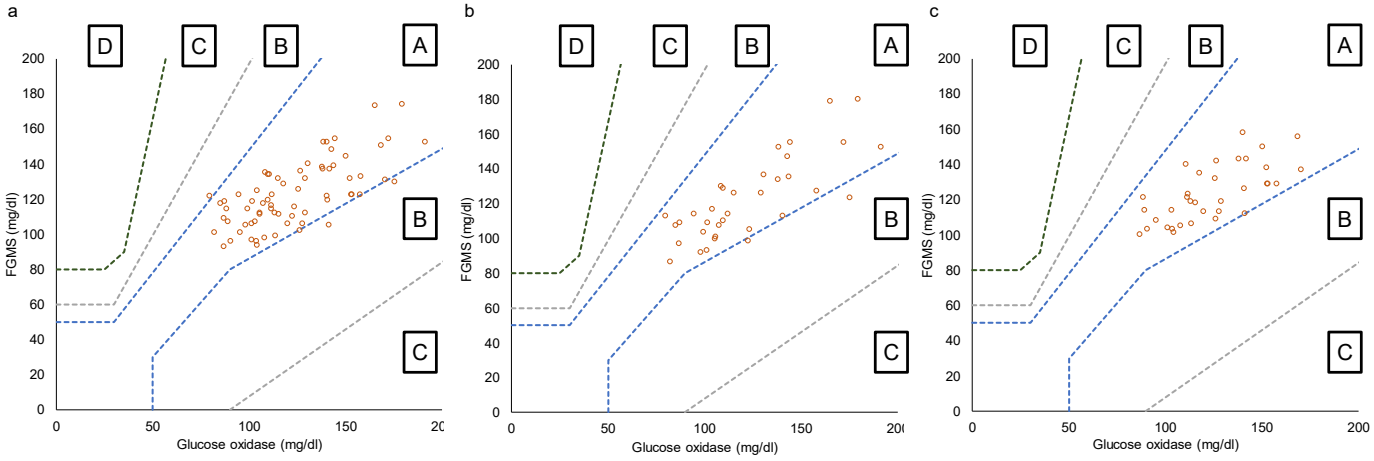
Supplementary table 2 – differences between the measurements of the adjusted[a] flash glucose monitoring system and glucose oxidase method

	Adjusted FGMS	Glucose oxidase	Absolute relative difference[b]	*P*[c]
Average $_{0\text{-}120\ min}$ (mg/dl)[d]	123.0 ± 18.6	122.9 ± 26.7	13.0 ± 10.1	0.996
iAUC (mg * 2 hr/dl)[e]	1789.7 ± 1031.8	3771.3 ± 1771.8	54.3 ± 10.1	<0.001
At different time-points (mg/dl)				
0 min	110.2 ± 10.9	93.5 ± 6.3	17.8 ± 9.2	<0.001
15 min	111.8 ± 12.6	119.4 ± 11.7	9.1 ± 5.3	0.050
30 min	130.0 ± 12.9	152.0 ± 18.3	16.6 ± 7.1	0.004
45 min	141.4 ± 16.4	146.3 ± 28.5	10.5 ± 8.3	0.444
60 min	135.2 ± 20.0	131.1 ± 23.7	9.1 ± 11.1	0.438
90 min	120.5 ± 15.5	113.5 ± 17.6	11.8 ± 15.1	0.204
120 min	111.8 ± 15.3	104.2 ± 13.4	16.2 ± 10.4	0.221

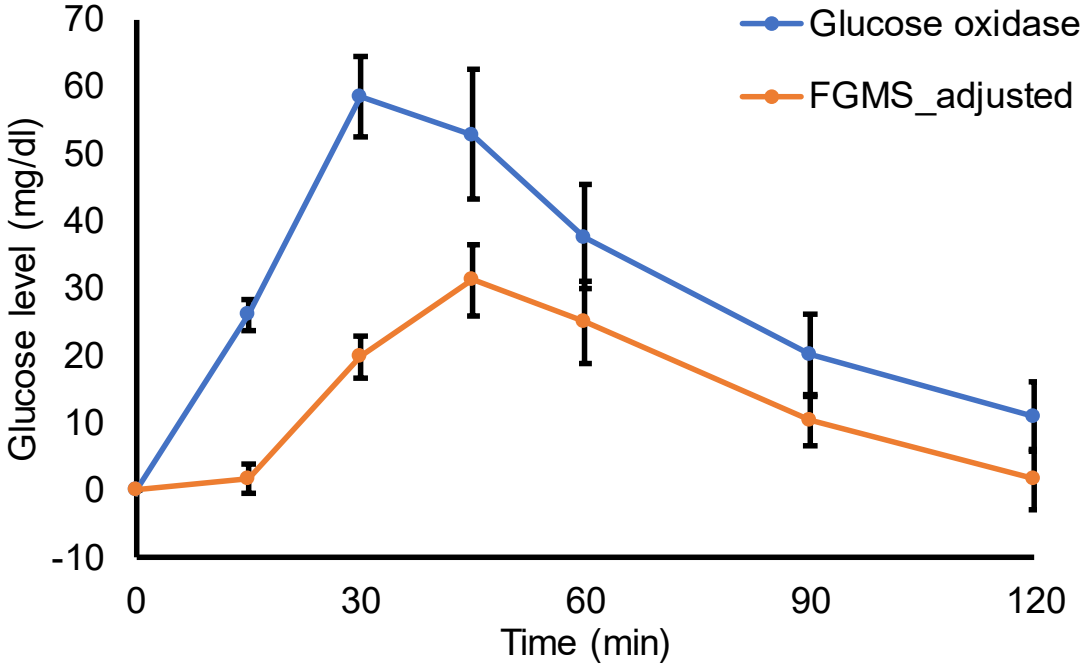
Note: data are presented as mean ± SD. FGMS, flash glucose monitoring system. iAUC, incremental area-under-curve.
[a] data adjustment was done by carrying out a linear regression with glucose oxidase data as the outcome variable and FGMS data as the predictor variable. The linear equation obtained was applied to the FGMS data to obtain the adjusted FGMS data.
[b] Absolute relative difference is calculated by the following formula: (| Adjusted FGMS – glucose oxidase | / glucose oxidase) * 100%
[c] Differences between adjusted FGMS and glucose oxidase data were tested for statistical significance using paired t-tests. $p < 0.05$ depicts statistical significance.
[d] Average $_{0\text{-}120\ min}$ was calculated by averaging the glucose measurements at all time-points.
[e] iAUC was calculated by the trapezoidal rule.



Supplementary Figure 1 – Scatter plot showing the differences between the two sets of data against the glucose oxidase data, together with the accuracy boundaries applied based on ISO 15197:2013 (depicted by dashed lines). Adjustments were done by regressing glucose oxidase data against FGMS data, then the regression equation was applied to adjust the FGMS data. (a) adjustments done to data of all participants. (b) adjustments done to data of male participants only. (c) adjustments done to data of female participants only. FGMS, flash glucose monitoring system.



Supplementary Figure 2 – Scatter plot of adjusted FGMS measurements against glucose oxidase measurement super-imposed on the consensus error grid. Dashed lines are the boundaries of the different zones implying different degrees of risk posed by inaccurate measurement. Zone A – no effect on clinical action; zone B – altered clinical action with little or no effect on clinical outcome; zone C – altered clinical action and likely to affect clinical outcome; zone D – altered clinical action which could have significant medical risk; zone E – altered clinical action, could have dangerous consequences. Boundaries of zone E were not shown for better clarity. Adjustments were done by regressing glucose oxidase data against FSL-FGM data, then the regression equation was applied to the FGMS data. (a) adjustments done to data of all participants. (b) adjustments done to data of male participants only. (c) adjustments done to data of female participants only. FGMS, flash glucose monitoring system.



Supplementary Figure 3 – time-matched mean difference from baseline of the adjusted FGMS data and the glucose oxidase data. Error bars depict SEM. Adjustments were done by regressing glucose oxidase data against FGMS data, then the regression equation was applied to the FGMS data. The difference from baseline was calculated by subtracting the glucose measurements at baseline from measurements at all subsequent timepoints. The differences between the mean differences from baseline obtained using the two methods at all timepoints were tested for statistical significance using paired *t*-test. *, $p < 0.05$. FGMS, flash glucose monitoring system.