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Disagreement between capillary blood glucose and flash glucose monitoring sensor can lead to inadequate treatment adjustments during pregnancy

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ABSTRACT

Objective. – Continuous glucose monitoring tends to replace capillary blood glucose (CBG) self-monitoring. Our aim was to determine the agreement between CBG and a flash glucose monitoring system (Flash-GMS) in treatment decision-making during pregnancy.

Research Design and Methods. – Insulin-treated women with either type 1 (n = 25), type 2 (n = 4) or gestational diabetes (n = 4) were included. A Flash-GMS sensor was applied for 14 days. Women scanned the sensor whenever they wished to monitor their CBG. The primary endpoint was the proportion of discordant therapeutic decisions they would have made based on Flash-GMS rather than CBG results. Glucose averages, mean absolute difference (MAD), mean absolute relative difference (MARD) and Flash-GMS accuracy were also estimated.

Results. – Data for 40 14-day periods were available. Preprandial Flash-GMS and CBG values were 93 ± 42 mg/dL and 105 ± 45 mg/dL, respectively ($P < 10^{-4}$), and 2-h postprandial (PP) values were 106 ± 45 mg/dL and 119 ± 47 mg/dL, respectively ($P < 10^{-4}$). MAD was 14 ± 22 mg/dL preprandial and 15 ± 24 mg/dL 2-h PP; MARD was 19%; and 99% of glucose value pairs were within the clinically acceptable A and B zones of the Parkes error grid. Concordance rate for therapeutic decision-making was 80–85% according to ADA targets and 65–75% according to a pragmatic threshold. At different time points of the day, 83–92% of discordant results were due to Flash-GMS values being lower than their corresponding CBG values.

Conclusion. – Flash-GMS tends to give lower estimates than CBG. Thus, in cases requiring therapeutic changes to treat or prevent hypo- or hyperglycaemia, 25–35% of choices would have been divergent if based on Flash-GMS rather than CBG.

Keywords: Continuous glucose monitoring; Insulin treatment; Pregnancy

INTRODUCTION

Hyperglycaemia during pregnancy is associated with adverse outcomes for both the fetus and mother [1,2], whereas tight glucose control from the prepregnancy period onwards reduces fetal and maternal risks [3]. In all women with diabetes, near-normal blood glucose targets are recommended: < 95 mg/dL (5.3 mmol/L) for preprandial and bedtime glucose; and < 120 mg/dL (6.7 mmol/L) for 2-h postprandial (PP) glucose [3,4]. Intensive capillary blood glucose (CBG) self-monitoring is mandatory for achieving and maintaining such targets. However, in women with insulin-treated diabetes, these targets are associated with an increased risk of severe hypoglycaemia [2].

Recently, devices for continuous glucose monitoring (CGM) have been made available to patients with type 1 diabetes (T1D) [5] that estimate blood glucose concentration from interstitial glucose measurements. Acceptable correlation has been shown between estimates from interstitial glucose and reference blood glucose measurements except during acute changes in blood glucose concentration [6]. However, few studies have assessed the reliability of interstitial measurements during pregnancy [7]. The controlled Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) reported a small reduction in HbA1c and improved neonatal outcomes among those in the CGM group. In that study, CGM was used as an adjunct to CBG self-monitoring, and pregnant women were asked to perform CBG self-monitoring prior to insulin dose adjustment to verify CGM accuracy [8] as CGM devices are tending to replace CBG in T1D routine care [9]. However, blood glucose targets during pregnancy were determined from CBG and not interstitial values [4].

The Flash Glucose Monitoring System (Flash-GMS; Abbott Diabetes Care, Alameda, CA, USA) is now available in many countries and, of course, leads the women using it before pregnancy to continue its use during pregnancy. Like other such devices, Flash-GMS extrapolates blood glucose concentration from measurements of interstitial subcutaneous glucose and requires no routine calibration [10]. Recently, the accuracy, safety and user acceptability of the system in pregnant women with diabetes were demonstrated [11], although no study has evaluated whether Flash-GMS without CBG assessment is acceptable for treatment adjustments during pregnancy. Thus, the aim of the present study was to determine whether therapeutic decisions taken to prevent or treat hypo- and hyperglycaemia should be based solely on Flash-GMS results in pregnant women with insulin-treated diabetes.

PATIENTS AND METHODS

This prospective two-centre observational study was conducted from May 2016 to May 2017. Consecutive insulin-treated pregnant women, aged ≥ 18 years, with T1D, type 2 diabetes (T2D) or gestational diabetes were included in the study if they performed CBG self-monitoring at least seven times per day and agreed to participate after informed consent. Women with severe renal failure [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²] before pregnancy or with coronary heart disease were excluded.

A nurse applied a glucose sensor to the back of each participant's left arm for 14 days, and each woman was then trained how to use it. The women were requested to scan the sensor with the Flash-GMS Reader to monitor their CBG both before and 2-h after each meal, and at bedtime. All sensors were from the same production batch. For the comparable CBG measurements, the women used their own glucose meters. Blood glucose targets were those recommended by the American Diabetes Association (ADA) [4]: ≤ 95 mg/dL preprandial and at bedtime; and ≤ 120 mg/dL at 2-h PP. All decisions to change insulin dosages to prevent or treat out-of-target values were based exclusively on CBG results. In addition, for pragmatic targets, the women were instructed to increase insulin dosages if fasting CBG was > 105 mg/dL or 2-h PP CBG was > 130 mg/dL, and to decrease insulin dosages if fasting CBG was < 65 mg/dL or 2-h PP CBG was < 90 mg/dL. Hypoglycaemia was defined as a CBG < 60 mg/dL.

The study protocol was approved by the ethics committee CPP Ile-de-France I (2016-fevrier-14165 ND). Written informed consent was obtained from all participants before enrolment. The study was performed in line with the latest form of good clinical practice guidelines of the Declaration of Helsinki.

Outcomes

The primary endpoint of the study was the proportion of divergent therapeutic decisions that would have been made if therapeutic decisions (to treat hypoglycaemia or to change insulin dosages) to prevent hyper- or hypoglycaemia had been decided according to glucose sensor measurements rather than CBG, whether above or below target values. Two analyses were therefore conducted. In the first, CBG and sensor values were considered concordant if both were within the same range (both below target, both at target or both above target, according to ADA guidelines). In the second analysis, the above-defined pragmatic thresholds were used (65–105 mg/dL fasting and 90–130 mg/dL 2-h PP for adjustment of insulin dosage), with hypoglycaemia corrected when CBG was < 60 mg/dL.

Glucose measurement averages before and 2-h after meals and at bedtime were also assessed, and the mean absolute difference (MAD) between CBG and sensor measurements was estimated on day 1, day 7 and day 14. Flash-GMS accuracy was also assessed by the mean absolute relative difference (MARD) [12], analysis of the Parkes error grid and Bland–Altman plots.

Statistical analysis

First, the proportion of inconsistent pairs of blood glucose results in an independent sample ($n = 264$; 18.4% of inconsistent pairs) was estimated. This proportion was then used to calculate the sample size necessary to have an upper boundary of the 95% confidence interval (CI) of the proportion of inconsistent pairs not exceed the arbitrary limit of 20% [assuming independent pairs; University of California San Francisco (USCF) Clinical and Translational Science Institute (<http://www.sample-size.net/confidence-interval-proportion/>), accessed 11/22/2018]. The sample size was 2100 pairs for a 95% CI of 0.170–0.200. Each participant measured paired glucose values seven times a day for 14 days. To allow for 20% missing data, 33 women were ultimately included.

Analyses were performed using Student's t test for paired numerical values, with analysis of variance (ANOVA) where appropriate. Categorical values were compared using the chi-squared test. Data were presented as medians [interquartile range, IQR] if $n < 35$ and as means \pm standard deviation (SD) if $n > 35$.

RESULTS

Clinical characteristics of subjects

All of the women participating in our present study met the inclusion and exclusion criteria, and all agreed to participate in the study. The main characteristics of the included 33 pregnant women are presented in [Table I](#). A total of 25 women had T1D, four had T2D and four had gestational diabetes, and all were being treated with insulin. In those with preexisting diabetes, the known median duration of diabetes was 9 [IQR: 4–20] years. Median HbA1c at inclusion was 6.05% [IQR: 5.6–6.7%; 38–50 mmol/mol]. A total of 40 14-day glucose profiles were available (three women were studied at two different trimesters of pregnancy, and two other women at each trimester).

No haematoma or cutaneous reactions to the sensor were observed when the sensor was either applied or removed.

CBG and sensor glucose values

On comparing the paired CBG and glucose sensor values (Table II) at all time points, the mean sensor values were significantly lower than CBG values. On average, mean preprandial sensor and CBG values were 93 ± 42 (n = 1510) and 105 ± 45 mg/dL (n = 1483), respectively ($P < 10^{-4}$), and 2-h PP values were 106 ± 45 (n = 1177) and 119 ± 47 mg/dL (n = 1171), respectively ($P < 10^{-4}$). MAD values were 14 ± 22 mg/dL (n = 1464) preprandial, and 15 ± 24 mg/dL (n = 1145) 2-h PP ($P = 0.27$).

The mean differences between sensor and CBG values did not significantly differ on day 1 (D1), day 7 (D7) or day 14 (D14): D1: 14 ± 19 ; D7: 10 ± 16 ; D14: 17 ± 29 mg/dL (ANOVA: $P = 0.32$) preprandial; and D1: 18 ± 21 ; D7: 12 ± 17 ; D14: 17 ± 32 mg/dL (ANOVA: $P = 0.10$) 2-h PP.

Agreement between CBG and sensor glucose values

On assessing the agreement between sensor and CBG values using the Parkes error grid (Fig. 1), of the total 2568 paired CBG and sensor glucose values, 74% (n = 1896) were in the A zone, 25% (n = 652) were in the B zone, 1% (n = 20) were in the C zone, and none were in the D and E zones. Thus, 99% of the pairs were within the clinically acceptable range. On analyzing the distribution in the A, B and C zones of the Parkes error grid according to the timing of measurements (preprandial and 2-h PP), 76% (n = 1094) of the preprandial measurements were in the A zone, 23% (n = 329) were in the B zone and 1% (n = 12) were in the C zone. At 2-h PP, the corresponding values were 71% (n = 802), 28% (n = 323) and 1% (n = 8), respectively. The relative proportion of pairs in the A, B and C zones differed significantly for preprandial vs 2-h PP (chi-squared test: 10.4, $P = 0.005$), suggesting better concordance for preprandial than for 2-h PP values.

When a Bland–Altman plot was also performed (Fig. S1; see supplementary material associated with this article online), the estimated bias was 14 ± 22 mg/dL. On considering all of the results (n = 2568 pairs), the MARD was $23 \pm 30\%$. Likewise, similar results were observed when four of the 33 women with gestational diabetes were excluded (data not shown).

Concordance rate for therapeutic decision-making

On analyzing the concordance rate between CBG and sensor glucose values according to ADA targets [4], pairs were considered concordant if both values were either below, equal to or above the CBG thresholds for the given time points (before meals, 2-h PP, bedtime). As shown in Table III, all rates of concordance were 80–85%, with no differences between preprandial and 2-h PP measurements ($P = 0.97$). In addition, nearly all discordant pairs (83–92% according to time of measurement) were due to sensor values being lower than CBG values.

On analyzing our data using the alternative pragmatic targets (thresholds indicating a need to adjust insulin dosage to prevent or treat hypoglycaemia, as defined in the Methods section above) and as summarized in Table III using those decision-making thresholds, rates of concordance were lower than observed for ADA targets (65–75%) according to time-point analysis.

DISCUSSION

Flash-GMS is now available to many patients with T1D and, of course, leads the women using it before pregnancy to continue its use during pregnancy. However, no such CGM system has yet been approved for use in pregnancy. As insulin dose adjustments rely solely on CBG self-monitoring, inaccurate glucose monitoring during pregnancy (when the blood glucose range makes for a narrow target) can lead to inappropriate decisions for the treatment and prevention of both hypo- and hyperglycaemia [13]. Indeed, thus far, there is no evidence that any glucose-monitoring technique is superior to any other in pregnant women with either T1D or T2D [7].

The present study compared CBG values and simultaneous sensor glucose estimates taken in 33 pregnant women at different trimesters of pregnancy. The main result was that, although sensor values were similar to CBG values, the former were significantly more frequently below than above CBG values, thereby suggesting a bias towards underestimation of blood glucose with the sensor. In fact, if only sensor measurements had been considered, the discordant estimations of blood glucose concentration would have had clinical consequences, such as conflicting decisions to prevent or treat hypoglycaemia, or to change insulin dosage or not, in 25–35% of cases. Moreover, the percentage of discordant pairs was higher when ‘pragmatic thresholds’ were used instead of ADA targets, as those thresholds take into

consideration not only values above target, thereby leading to increased insulin dosages, but also values below target during both fasting and 2-h PP, thereby leading to snacking and decreases in insulin dosages. Thus, these pragmatic target blood glucose values narrow the range of acceptable blood glucose concentrations.

To our knowledge, this is the first-ever study to analyze the possible conflict in therapeutic decision-making based on interstitial values using Flash-GMS techniques compared with the usual CBG monitoring in pregnant women with diabetes under real-life conditions. In fact, few studies of CGM have dealt with women during pregnancy [7,13]. The first randomized trial of intermittent real-time CGM in pregnancy involving self-monitored blood glucose showed no differences in either glycaemic control or pregnancy outcome in women with pregestational diabetes [14]. One multicentre study demonstrated good safety and acceptable reliability with Flash-GMS over 14 days vs CBG in 74 pregnant women with T1D (n = 24), T2D (n = 11) or gestational diabetes (n = 39) [11]. Another study revealed that CBG self-monitoring plus additional CGM vs CBG alone in T1D women either planning a pregnancy (30%) or during pregnancy (70%) improved time-in-range glucose levels and reduced several neonatal adverse effects, such as large-for-gestational-age infants, the number of hypoglycaemia episodes requiring intravenous (IV) glucose infusion and > 24-h hospitalization in an intensive care unit (ICU) [8]. However, in that study, therapeutic decisions were taken based only on CBG results.

In the present study, a MAD of around 15 mg/dL was observed between CBG and Flash-GMS values, which is similar to that observed in other studies with an equivalent blood glucose range. In agreement with this MAD, Bland–Altman plot analysis showed a 14 mg/dL (14%) bias between CBG and Flash-GMS. Such a small bias was not apparent on Parkes error grid analysis (there was no association with changes in grid zones). Likewise, in agreement with our results, Fokker et al. [15] found a MAD of 13 mg/dL for blood glucose values of 101–110 mg/dL in non-pregnant women with diabetes and a MAD of 19 mg/dL for blood glucose values > 151 mg/dL. However, underestimation of blood glucose by sensor vs CBG is important in the context of pregnancy, where blood glucose levels must remain within a narrow range close to low blood glucose values. Indeed, such an underestimation of blood glucose by Flash-GMS had already been observed in a previous study of 21 non-pregnant women with T1D (A. Sola-Gazagnes, unpublished data).

In the present study, the MARD was greater than in other studies [15]. In fact, MARD has been found to depend on insertion site [15,16]; in the present study, the sensor insertion site was the same for all our participants (at the back of the left upper arm). Another factor that may have influenced MARD was the

use of non-standardized CBG estimations, as our women used their own glucose meters. The MARD of the usual CGM device is considered clinically acceptable when between 10% to 17% [17], whereas our present data found a MARD of 22%, considerably greater than the 11.4% observed in non-pregnant T1D and T2D populations [6] as well as the 11.8% [11] found in pregnant women with a similar mean glycaemic level (111.1 ± 30 mg/dL). However, in the lattermost study, 39 of the 74 women had gestational diabetes compared with only four of the 33 women in our study, which included mostly women with T1D. Moreover, differences similar to those observed between Flash-GMS and CBG can be observed when two different glucose meters are used. An accuracy of around 15% is required for marketing of blood glucose meter, but such accuracy may be even lower if the meter is not used under optimal conditions, such as in a population with a high prevalence of anaemia.

A physiological time lag of about 5–10 min has been noted between capillary and interstitial values in the post-meal period [6]. In our present study, MARD did not significantly differ between preprandial and 2-h PP blood glucose levels, although the latter did include some high glucose values.

One limitation of the present study was the lack of standardization in glucose meters used for CBG, although despite the diversity of CBG devices used, the results were nonetheless consistent. In addition, CBG values were not compared against a reference method (plasma glucose concentration). On the other hand, Bland–Altman plots consider the fact that each method produces some error in their measures, and our pregnant women each used their own CBG devices, as this was a study under real-life conditions. Yet another limitation of the present study was that it covered the use of only 14 days at different times of pregnancy in only 33 women.

CONCLUSION

Therapeutic decisions taken during diabetic pregnancies would have been similar in 65–75% of cases if based on Flash-GMS rather than CBG monitoring. Blood glucose concentrations estimated by sensor were lower than CBG values with an estimated bias of 14 ± 22 mg/dL. This underestimating tendency of the Flash-GMS sensor should certainly be taken into consideration to prevent insulin underdosing, or unjustified prevention or treatment of hypoglycaemia. Indeed, the concomitant use of CBG devices should continue to be recommended with Flash-GMS during diabetic pregnancies, particularly to confirm values close to the lower threshold of acceptability.

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Conflicts of interest

A.S.-G. has received speaker honoraria from Abbott, Novo Nordisk and Johnson & Johnson, served on advisory board panels for Abbott and Eli Lilly, and is an investigator of studies sponsored by Roche and Eversense® and by Eli Lilly.

R.R. has received grants, personal fees and non-financial support from Sanofi, personal fees and non-financial support from MSD, grants from Amgen, personal fees from Physiogenex, AstraZeneca, Janssen, Eli Lilly, Abbott, Medtronic, Novo Nordisk and Servier, and grants from Novo Nordisk.

P.F., S.J., C.C. and D.D.L. have no relevant conflicts of interest to disclose.

H.M.P. has received speaker honoraria from Abbott.

E.L. has been involved in conferences for Eli Lilly, Novo Nordisk and MSD, is an investigator of a study sponsored by Eli Lilly and has been an investigator of a study sponsored by Sanofi.

Authors' contributions

A.S.-G., P.F. and E.L. interpreted the data and edited the final version of this manuscript. All authors were involved in the design of the study protocol, and were investigators for the study, collected data, and worked collaboratively to review and prepare the final manuscript.

Guarantors

A.S.-G. and E.L. are the guarantors of this study.

Appendix supplementary materials

Supplementary materials (Fig. S1) associated with this article can be found at <http://www.sciencedirect.com> at doi . . .

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Figure legend

Fig. 1. Parkes error grid analysis showing zones A–E to compare Flash Glucose Monitoring System (Flash-GMS) values with concomitant capillary blood glucose (CBG) monitoring. Preprandial values are blue; 2-h postprandial values are green.

Supplementary figure legend

Fig. S1. Bland–Altman plot analysis of 1886 paired values based on a Flash Glucose Monitoring System (Flash-GMS) and concomitant capillary blood glucose (CBG) monitoring to determine differences in values between the two systems. Mean bias was 14 ± 22 mg/dL ($14 \pm 20\%$), 95% limits of agreement (indicated by dotted lines): -30 – 58 mg/dL (-26 – 54%).

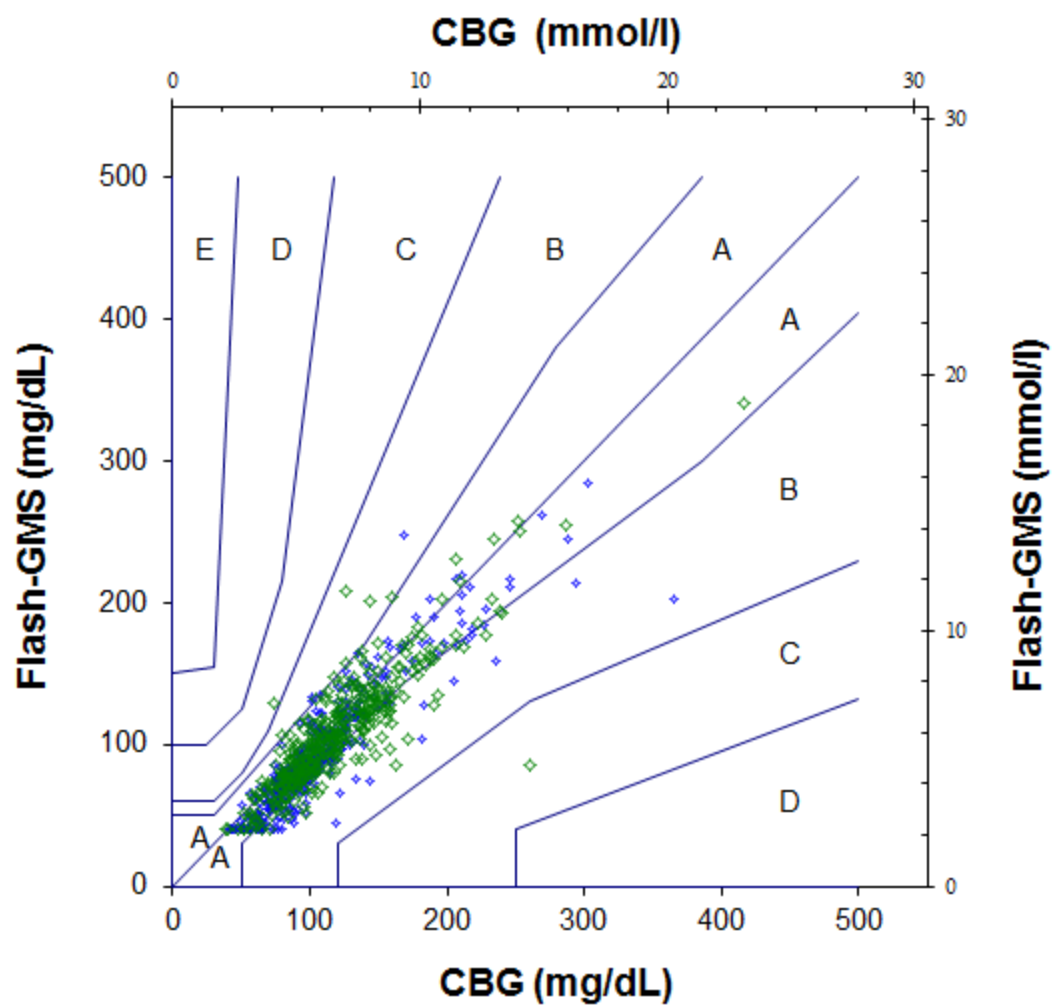


Table I
Clinical characteristics of the study participants

Number of women	33
Diabetes type (1/2/gestational)	25/4/4
Age (years)	32.3 [29.1–35.7]
Known duration of diabetes (years)	9 [4–20]
BMI before pregnancy (kg/m ²)	24.9 [21.7–29.7]
HbA1c at inclusion (%)	6.05 [5.6–6.7]
HbA1c at inclusion (mmol/mol)	43 [38–50]
Mean CBG over 7 days before inclusion (mg/dL)	111 [99–146]
Mean term of pregnancy at inclusion (weeks) ^a	10/17/30
Duration of sensor use (days)	12.2 [12–14]

Data are either numbers or medians [IQR];

^a Of amenorrhoea by diabetes type;

BMI: body mass index; CBG: capillary blood glucose

Table II

Values according to capillary blood glucose (CBG) monitoring and flash glucose monitoring sensor

	Breakfast		Lunch		Dinner		Bedtime
	Before	2-h after	Before	2-h after	Before	2-h after	
CBG							
Mean ± SD	104 ± 44	120 ± 45	97 ± 38	117 ± 51	108 ± 50	120 ± 44	122 ± 47
n	459	385	451	412	426	374	175
Flash sensor							
Mean ± SD	93 ± 42	109 ± 44	86 ± 37	102 ± 45	93 ± 42	106 ± 45	108 ± 47
n	454	384	427	415	442	378	188
MAD							
Mean ± SD	12 ± 18	12 ± 22	11 ± 20	15 ± 23	15 ± 23	15 ± 20	14 ± 19
n	408	365	394	384	376	344	167
<i>P</i> *	6.10 ⁻³	6.10 ⁻⁴	9.10 ⁻⁵	10 ⁻⁴	10 ⁻⁴	7.10 ⁻⁴	2.10 ⁻²

* By Wilcoxon signed-rank test of paired glucose values (in mg/dL; multiply by 0.055 to convert to mmol/L);

MAD: mean absolute difference (CBG value minus sensor value)

Table III

Rates of concordance between values by capillary blood glucose (CBG) monitoring and Flash Glucose Monitoring System (Flash-GMS) for decision-making according to American Diabetes Association (ADA) and pragmatic targets

	Breakfast		Lunch		Dinner		Bedtime
	Before	2-h after	Before	2-h after	Before	2-h after	
ADA targets							
Concordance (n)	370	317	333	322	349	301	152
Discordance (n)	76	55	71	76	67	62	25
CBG > Flash-GMS (n)	69	46	61	67	60	55	23
CBG < Flash-GMS (n)	7	9	10	9	7	7	2
Concordance rate (%)	83.0	85.0	82.2	80.7	83.7	82.7	85.4
Pragmatic targets							
Concordance (n)	325	249	277	278	284	234	124
Discordance (n)	106	122	125	118	128	125	50
CBG > Flash-GMS (n)	89	101	109	100	113	108	47
CBG < Flash-GMS (n)	17	21	16	18	15	17	3
Concordance rate (%)	75.4	66.9	68.7	70.0	68.7	65.0	70.8

CBG and Flash-GMS pairs considered concordant if both were ≤ 95 mg/dL or > 95 mg/dL (preprandial), or ≤ 120 mg/dL or > 120 mg/dL (2-h postprandial); considered discordant if one measure was on one side of target and the other on the other side of target; for discordant pairs, pragmatic CBG > Flash-GMS if CBG was above target and Flash-GMS was not; CBG < Flash-GMS was when the opposite was observed; Therapeutic targets were set at 65–105 mg/dL (preprandial) and at 90–130 mg/dL (2-h after)