ORIGINAL ARTICLE

Accuracy of Continuous Glucose Monitoring During Exercise in Type 1 Diabetes Pregnancy

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Abstract

Background: Performance of continuous glucose monitors (CGMs) may be lower when glucose levels are changing rapidly, such as occurs during physical activity. Our aim was to evaluate accuracy of a current-generation CGM during moderate-intensity exercise in type 1 diabetes (T1D) pregnancy.

Subjects and Methods: As part of a study of 24-h closed-loop insulin delivery in 12 women with T1D (disease duration, 17.6 years; glycosylated hemoglobin, 6.4%) during pregnancy (gestation, 21 weeks), we evaluated the Freestyle Navigator[®] sensor (Abbott Diabetes Care, Alameda, CA) during afternoon (15:00–18:00 h) and morning (09:30–12:30 h) exercise (55 min of brisk walking on a treadmill followed by a 2-h recovery), compared with sedentary conditions (18:00–09:00 h). Plasma (reference) glucose, measured at regular 15–30-min intervals with the YSI Ltd. (Fleet, United Kingdom) model YSI 2300 analyzer, was used to assess CGM performance.

Results: Sensor accuracy, as indicated by the larger relative absolute difference (RAD) between paired sensor and reference glucose values, was lower during exercise compared with rest (median RAD, 11.8% vs. 18.4%; $P < 0.001$). These differences remained significant when correcting for plasma glucose relative rate of change ($P < 0.001$). Analysis by glucose range showed lower accuracy during hypoglycemia for both sedentary (median RAD, 24.4%) and exercise (median RAD, 32.1%) conditions. Using Clarke error grid analysis, 96% of CGM values were clinically safe under resting conditions compared with only 87% during exercise.

Conclusions: Compared with sedentary conditions, accuracy of the Freestyle Navigator CGM was lower during moderate-intensity exercise in pregnant women with T1D. This difference was particularly marked in hypoglycemia and could not be solely explained by the glucose rate of change associated with physical activity.

Introduction

EXERCISE IN TYPE 1 DIABETES (T1D) is associated with a significantly increased risk of hypoglycemia.¹ Despite awareness of the benefits of exercise, fear of hypoglycemia often results in avoidance of exercise and/or overcompensatory behaviors such as excess carbohydrate consumption, which are associated with worse metabolic control.² Guidelines for T1D recommend checking capillary glucose at least twice before and every 30 min during exercise as well on recovery.³ This regimen can be difficult to adhere to, particularly if testing requires interruption of activity. Moreover, isolated glucose measurements provide only

limited information. A survey of endurance athletes with T1D found that although almost 90% monitored glucose levels before and after exercise, only 50% reported checking during exercise.⁴

Continuous glucose monitor (CGM) devices provide a much more detailed picture of glycemic control.⁵ This may be particularly useful as a tool to recognize impending hypo- or hyperglycemia during physical activity, while empowering patients to make informed decisions regarding insulin therapy and carbohydrates.⁶ Additionally, CGMs may play an important role in detecting delayed, including nocturnal, hypoglycemia that may otherwise go unnoticed when exercise is performed later in the day.⁷

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Optimal performance of currently available glucose oxidase-based CGM devices is limited by calibration errors and a physiological time lag of glucose transport between blood and interstitial fluid compartments, as well as a device-dependent delay associated with sensor signal processing and filtering out measurement noise. Performance may be lower at the extremes of the glucose range or when levels are changing rapidly, both of which are situations commonly associated with exercise. CGM device evaluation has primarily been carried out under sedentary conditions. Accuracy, as measured by the median relative absolute difference (RAD) between paired sensor and reference glucose values in time, ranges from 11% to 14% under resting conditions.^{8,9}

There is limited objective evidence on performance of CGMs during physical activity,^{10–15} in particular none using current-generation sensors. There are no studies evaluating CGM use in pregnant women during exercise. Only two prior studies have been performed during T1D pregnancy: both were carried out under sedentary conditions,^{16,17} and one used capillary glucose as reference.¹⁷ The aim of this study was to evaluate performance of a current CGM during moderate-intensity exercise in pregnant women with T1D. Preliminary results have been published elsewhere in abstract form.¹⁸

Research Design and Methods

Study protocol and subjects

As part of a study evaluating closed-loop insulin delivery in pregnant women with insulin pump-treated T1D during normal daily activities,¹⁹ performance and accuracy of a CGM during moderate-intensity exercise were measured. The study protocol was approved by the local Research Ethics Committee (Essex 2 Research Ethics Committee protocol number 09/H0302/113), and all participants gave written informed consent.

Study procedures

Women attended a clinical research facility (Cambridge, United Kingdom) for two 24-h visits, from 12:00 midday until 12:30 h the following day. On one visit, aspart insulin was delivered subcutaneously based on CGM readings and advice from a model predictive control algorithm (closed-loop). On the other visit, aspart insulin was delivered using subjects' usual insulin pump regimen with preset basal rates and boluses calculated using insulin/carbohydrate ratios (open loop). Aside from the mode of basal insulin infusion, the study protocol was identical on both visits. Women consumed standardized 50–60-g carbohydrate meals, with snacks for exercise according to finger-prick capillary glucose measurements. The physical activity included scheduled low-intensity (three postprandial 20-min walks at participants' own speed) and moderate-intensity (two 55-min treadmill sessions) exercise. In between planned activity, women undertook sedentary tasks such as working on a computer or watching television and went to sleep according to their preference.

Exercise

Women undertook two 55-min sessions of moderate-intensity exercise: in the afternoon (15:00–16:00 h) on Day 1 and morning (09:30–10:30 h) on Day 2. Each session involved two 25-min periods of brisk walking on a treadmill at pre-

determined speeds (2.6–4.8 km/h) and inclines (0–10%), with a 5-min rest interval. The Borg rating of perceived exertion (scale range of 6–20) was used every 10 min during exercise to assess women's effort level.²⁰

Study measures

Continuous glucose monitoring. The FreeStyle Navigator[®] CGM (Abbott Diabetes Care, Alameda, CA) with a 1-h run-in calibration period was used to measure interstitial glucose.²¹ A single sensor was inserted 1–2 days prior to each study visit and worn for the duration of the study. The sensor was placed in either the abdomen or upper arm according to women's preference and was calibrated with capillary glucose measurements as per the manufacturer's instructions.

Reference glucose. Blood sampling for reference glucose was carried out at 15–30-min intervals throughout study visits, via a peripheral intravenous cannula inserted on arrival. Plasma glucose was measured in duplicate in real-time on a model YSI 2300 STAT Plus analyzer (YSI Ltd., Fleet, United Kingdom). The intra-assay coefficient of variation was 1.5% at 4.1 mmol/L. During exercise, sampling was carried out prior to, halfway, and at the end of each session and at 30-min intervals during the 2-h recovery period.

Statistical analysis

Analyses were conducted using IBM SPSS version 17 (SPSS Inc., Chicago, IL). Level of statistical significance was set at $P < 0.05$. Plasma glucose was used as reference glucose and was paired with the nearest CGM value within ± 1 min. Difference (bias) and RAD were calculated for each pair. The RAD reflects the magnitude of CGM error, whereas bias also considers the direction of error. Hourly paired sensor-reference glucose values were analyzed to reduce the effect of autocorrelated errors. The relative absolute rate of change of plasma glucose was calculated as the absolute difference between consecutive plasma glucose values divided by the average plasma glucose over that hour.

Each pair was evaluated to determine whether the CGM value met the International Organization for Standardization (ISO) requirements for blood glucose monitoring systems (percentage of CGM values within ± 0.8 mmol/L when reference blood glucose was ≤ 4.2 mmol/L or within $\pm 20\%$ when reference was > 4.2 mmol/L).²² Median bias, RAD, and ISO criteria were evaluated for the overall period as well as during hypoglycemia (≤ 3.5 mmol/L), target range for pregnancy (3.5–7.8 mmol/L),²³ and hyperglycemia (> 7.8 mmol/L).

Comparisons were made between sedentary (18:00–09:00 h, including overnight) and exercise (15:00–18:00 h and 09:30–12:30 h, including a 2-h recovery period) conditions. Differences in RAD, bias, and relative absolute rate of change of plasma glucose were analyzed using analysis of variance (ANOVA). A rank normal transformation was performed for RAD and the relative absolute rate of change of plasma glucose as the data were non-normally distributed.

Individual paired sensor and reference glucose values were plotted using the Clarke error grid analysis, which uses five zones to denote errors of varying levels of clinical significance.²⁴ Values in Zones A and B are deemed clinically acceptable, resulting in either effective or no treatment, whereas those in Zones C, D, or E are considered potentially unsafe.

Results

Demographic data

Twelve pregnant women (gestation 21 weeks) with T1D (disease duration, 17.6 years; insulin pump therapy for 2.0 years; baseline glycosylated hemoglobin, 6.4%) completed the study. Median age was 32.9 years, and median body weight was 77.4 kg.

CGM wear

The Freestyle Navigator CGM was worn for 24 study visits carried out in the clinical research facility. Sensors were in situ for at least 24 h prior to each study visit. Nine women wore the sensor on the upper arm, and three wore it on the abdomen, for both visits. Compliance with CGM wear was 100%, and none of the sensors required replacing. There were no occurrences of disconnection of the sensor, even during exercise.

CGM accuracy

The period analyzed spanned from 15:00 h on Day 1 until 12:30 h on Day 2. There were 490 paired sensor and reference glucose values in total used for evaluation: 352 during sedentary periods and 138 during exercise (Table 1).

The overall median RAD between sensor and reference (plasma) glucose was 11.8% under sedentary conditions compared with 18.4% during exercise ($P < 0.001$, by ANOVA). Sensor accuracy, illustrated by the median RAD in Figure 1, was superior during the sedentary period for all glucose ranges compared with exercise. Analysis by glucose range demonstrated the largest RAD in hypoglycemia, for both sedentary (24.4%) and exercise (32.1%) conditions.

It is notable that, after adjusting for the absolute relative rate of change of plasma glucose, the difference in median RAD between the resting and exercise periods remained significant ($P < 0.001$).

The CGM overestimated the plasma glucose concentration, as measured by median bias, by 0.15 mmol/L during resting conditions compared with 0.84 mmol/L during exercise ($P < 0.001$, by ANOVA) (Table 1). The greatest bias was seen in the hypoglycemic range: 0.77 mmol/L at rest and 1.02 mmol/L during exercise. Under resting conditions, 78% of CGM values met ISO criteria, compared with only 58% during exercise (Table 1).

Using the Clarke error grid analysis, 96% of values were in Zones A and B (76% and 20%, respectively) during resting conditions, compared with 87% (61% and 26%, respectively) during exercise (Table 1). The remaining values lay in Zone D: 4% at rest and 13% during exercise. Individual paired sensor and reference glucose measurements are displayed in Figure 2.

Rate of change of glucose

The relative absolute rate of change of the plasma glucose level was significantly lower during sedentary (12.3%) compared with exercise (24.6%) conditions ($P < 0.001$, by ANOVA).

Discussion

This is the first evaluation of accuracy of CGM during physical activity in pregnancy. Using finger-prick testing as reference glucose, the CGMS® (Medtronic MiniMed, Northridge, CA) in

TABLE 1. SUMMARY OF SENSOR ACCURACY MEASURES DURING SEDENTARY AND EXERCISE PERIODS FOR OVERALL, TARGET (3.5–7.8 mmol/L), HYPOGLYCEMIA (≤ 3.5 mmol/L), AND HYPERGLYCEMIA (> 7.8 mmol/L) RANGES

	Sedentary	Exercise
Number of paired values		
Overall	352	138
Target	270	93
Hypoglycemia	23	30
Hyperglycemia	59	15
Median relative absolute difference (%)		
Overall	11.8 (5.7, 19.5)	18.4 (10.9, 32.4)
Target	10.7 (5.5, 18.4)	18.4 (11.1, 30.4)
Hypoglycemia	24.4 (13.2, 36.4)	32.1 (16.3, 60.7)
Hyperglycemia	12.6 (3.9, 18.2)	8.5 (3.8, 13.4)
Median difference (mmol/L)		
Overall	0.15 (−0.65, 0.66)	0.84 (0.11, 1.38)
Target	0.14 (−0.65, 0.58)	0.86 (0.23, 1.42)
Hypoglycemia	0.77 (0.35, 1.22)	1.02 (0.41, 1.71)
Hyperglycemia	−0.17 (−1.30, 0.67)	−0.40 (−1.36, 0.30)
Clarke error grid analysis (%) ^a		
Zone A	76	61
Zone B	20	26
Zone C	0	0
Zone D	4	13
Zone E	0	0
ISO criteria (%) ^b		
Overall	78	58
Target	79	59
Hypoglycemia	61	37
Hyperglycemia	83	93
Median plasma glucose relative absolute rate of change (% per hour)	12.3 (5.5, 23.0)	24.6 (10.1, 51.2)

Data are value or median (interquartile range).

^aClarke error grid analysis divides paired sensor and reference (plasma) glucose values into five zones (A–E) of clinical accuracy.²⁴

^bInternational Organization for Standardization (ISO) criteria represent the proportion of sensor values within ± 0.8 mmol/L when reference glucose is ≤ 4.2 mmol/L or within $\pm 20\%$ when reference glucose is > 4.2 mmol/L.²¹

15 pregnant women with T1D demonstrated a bias of 0.74 mmol/L with 93.8% of values in Zones A and B of the Clarke error grid analysis.¹⁷ Performance of the Freestyle Navigator was previously evaluated during overnight closed-loop insulin delivery in 10 women with T1D.¹⁶ Using plasma glucose as reference, median RAD was 11.4%, with 94.6% of glucose readings in the safe zones of the Clarke error grid analysis. These values are similar to that observed in our study during the sedentary period and comparable to those (median RAD, 11–14%) seen outside of pregnancy using similar glucose oxidase sensors.⁹

The higher median RAD (18.4%) during exercise suggests inferior performance of the CGM during physical activity. Similar results have been reported in children (median RAD, 17%), adolescents (mean RAD, 23%), and nonpregnant adults (mean RAD, 22%) with T1D testing glucose oxidase-based sensors during exercise.^{10,12,25} In contrast, a recent study in 12 adults found better accuracy of the CGM during both resistance and aerobic exercise compared with resting conditions.¹⁵

FIG. 1. Median relative absolute difference between paired sensor and plasma glucose values for sedentary and exercise periods, by glucose range.

In our study, 13% of values during exercise were considered clinically unsafe using the Clarke error grid analysis with the potential to lead to wrong treatment decisions, compared with only 4% when sedentary. All of these values were in Zone D, indicating that most of the inaccuracy could be attributed to lack of sensor responsiveness or sensitivity to rapid changes in glucose concentration.

In Europe, at least 95% of individual glucose results measured by self-monitoring blood glucose devices must comply with the ISO standard (ISO 15197:2003), prior to obtaining the Conformité Européenne label by the regulatory authority.²² The ISO criteria may also be applied to CGM devices. In our study, only 78% of Freestyle Navigator CGM values met the ISO standard during sedentary conditions, with an even lower proportion under exercise conditions (58%).

Inferior performance of the CGM during physical activity may be attributed to the rapid fluxes in glucose levels during exercise, which exaggerate the physiological transport delay.²⁶ During moderate-intensity exercise lag times of up to 20 min were observed with the Guardian® REAL-Time (Medtronic MiniMed),¹⁴ compared with only 8–12 min at rest for the next-generation Enlite™ sensor (Medtronic MiniMed).²⁷ The DexCom® (San Diego, CA) and FreeStyle Navigator CGM devices report similar lag times (6 and 13 min, respectively) under sedentary conditions.^{8,28} Such transport delays may result in underestimation of a decline in blood glucose with exercise. Evaluation of the Freestyle Navigator CGM in 30 children with T1D demonstrated a median RAD of 17% during 60 min of moderate-intensity exercise on a treadmill, which improved to 11% with incorporation of a 10-min sensor lag, comparable with the median RAD of 12% over the entire 24-h study period.¹⁰

Accuracy of the CGMS System Gold™ (Medtronic MiniMed), when assessed in 50 adolescents with T1D, showed a median RAD of 13% when the rate of change of glucose was <0.03 mmol/L/min and 19% when it was ≥ 0.08 mmol/L/min.²⁶ In our study, when the rate of change of plasma glucose was included in the ANOVA, there was still a significant difference in accuracy as measured by median RAD between resting and exercise periods, suggesting that rate of

FIG. 2. Clarke error grid analysis showing paired sensor and plasma (reference) glucose values, during (A) sedentary and (B) exercise periods. There were 352 data pairs during the sedentary period and 138 during exercise.

change alone does not account for the observed differences in accuracy.

Other factors that may contribute to reduced performance include changes in subcutaneous tissue circulation and increased temperature associated with physical activity. Conventional self-monitoring blood glucose devices have been shown to over- and/or underestimate results by at least 5% because of rapid shifts in ambient temperature.²⁹ The accuracy of microdialysis-based CGM devices is influenced by temperature with a 4% variation in current signal for each change in °C,³⁰ which may be overcome by application of a temperature-compensating algorithm.³¹ Decline in pH, as occurs with the development of lactic acidosis during more intense exercise, has not been shown to affect sensor performance.³² Errors due to variations in oxygen concentration of blood are less likely in the current-generation glucose

oxidase-based CGM devices.³³ Calibration of the device also has an important effect on accuracy, which may be improved by avoiding calibration at times of rapidly changing glucose or glucose extremes.⁸

Another potential source of inaccuracy is sensor dislodgement due to sweating or by direct mechanical forces on sensors sited in exercising limbs.^{11–13} The noninvasive GlucoWatch® Biographer (Cygnus, Redwood City, CA), no longer available for clinical use, measures interstitial glucose using reverse iontophoresis. It was the first CGM device to be tested during exercise, demonstrating a progressive decline in accuracy with more intense activity and a high skip rate due to perspiration.¹³ The GlucoDay® (Menarini Diagnostics, Florence, Italy) was worn during exercise of varying intensity on a cycle ergometer, showing 99.3% of values in the safe zones (A+B) of the Clarke error grid analysis.¹¹ However, 39% of the inserted microfiber sensor probes broke because of the mechanical stress exerted by exercising muscles. In a study of 58 adolescents during three sports camps, one-third of sensors (CGMS System Gold) required replacing within 48 h because of disconnection from sweating or loss of signal.¹² Accuracy was lower for high-contact activities, as observed by mean RAD of 19%, 24%, and 27% for the golf, soccer, and floorball and/or cross-country skiing camps, respectively. In our study there were no problems with loss of signal during exercise, with sensors remaining in situ for the duration of the visit in all participants, although the intensity of exercise performed may not have been high enough to result in displacement. Studies using the currently available CGM devices during physical activity of longer duration and at higher intensities are required.

The major strength of our study was the objective evaluation of a current-generation CGM, compared with previous studies that used older-generation devices.^{10–15} The study was carried out in a carefully controlled clinical research facility setting, over a 22.5-h duration, thus providing numerous paired glucose values for analysis. We used plasma glucose measured by the YSI 2300 STAT Plus analyzer as the reference standard, unlike other studies that used capillary glucose.¹⁴ It is important that the CGM was calibrated with capillary finger-prick glucose according to the manufacturer's instructions, thus providing a better indication of performance of the CGM in a real-life setting. Previous studies used blood glucose measurements for calibration.¹²

Limitations include the evaluation of only one type of glucose sensor: the Freestyle Navigator CGM. As such, our observations may not be transferable to the performance of other existing CGM devices. As pregnancy is associated with a unique and dynamic metabolic state, including increased volume of distribution, it is not possible to differentiate between the impact of pregnancy-induced physiological changes from those of physical activity on sensor performance.³⁴ However previous evaluations of sensor accuracy under resting conditions showed comparable accuracy in early and late gestation,¹⁶ suggesting that the changes demonstrated are more likely related to physical activity than to changes in gestational physiology. Additionally, as the effect of physical activity on glucose levels is complex, these observations of CGM performance cannot be extrapolated to other intensities, timing, or duration of exercise.

In conclusion, this is the first evidence of CGM performance in pregnant women with T1D during physical activity. Fur-

thermore, this is the first objective evaluation of accuracy of a current-generation sensor during moderate-intensity exercise, demonstrating feasibility of using the Freestyle Navigator sensor while maintaining reasonable performance. Sensor accuracy was lower when glucose levels were in the hypoglycemic range during both sedentary and exercise conditions. Although accuracy was reduced during exercise, this difference was only partly explained by the higher rate of change of glucose associated with physical activity. Technological advances have resulted in significant improvements in accuracy of commercially available CGM devices; however, further testing and refinements are required to improve accuracy and usability during physical activity, where CGM may be particularly useful. These improvements are also crucial in the future development of a closed-loop insulin delivery system for daytime glucose control.

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Author Disclosure Statement

H.R.M. has received honoraria for speaking engagements from Medtronic, Roche, Novo Nordisk, and the Medtronic European Advisory Panel. S.A.A. has received consultancy and lecture fees from Medtronic, Roche, Novo Nordisk, and Eli Lilly. M.E.W. has received license fees from Becton Dickinson and has received patent applications. R.H. has received honoraria for speaking engagements from Medtronic, LifeScan, Novo Nordisk, Eli Lilly, Animas, and the Medtronic Advisory Panel, has received license fees from Becton Dickinson, and has received patent applications. K.K., D.E., J.M.A., K.C., and M.N. declare no competing financial interests exist. H.R.M., R.H., K.K., and S.A.A. designed the study. J.M.A., K.K., and K.C. recruited participants. K.K., K.C., J.M.A., D.E., and H.R.M. performed studies. K.K. analyzed the data. H.R.M., K.K., and R.H. interpreted the data. K.K. drafted the manuscript. H.R.M. and R.H. reviewed/edited the manuscript. All authors approved the final version. K.K. takes overall responsibility for the work.

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