Accuracy of continuous glucose monitoring during differing exercise conditions

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Abbreviation title / Short running title:

CGM in differing exercise conditions

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Word Count:

Abstract 250 words, main text 1784 words (in addition 2 tables and 2 figures)

Key words:

continuous glucose monitoring, accuracy, type 1 diabetes, intermittent high-intensity exercise, continuous moderate intensity exercise

Clinical Trial Registration Number:

www.trialregister.nl (NTR02068638)

Abstract

Aim

Depending on intensity, exercise may induce a strong hormonal and metabolic response, including acid–base imbalances and changes in microcirculation, potentially interfering with the accuracy of continuous glucose monitoring (CGM). The present study aimed at comparing the accuracy of the Dexcom G4 Platinum (DG4P) CGM during continuous moderate and intermittent high-intensity exercise (IHE) in adults with type 1 diabetes (T1DM).

Methods

Ten male individuals with well-controlled T1DM (HbA1c $7.0 \pm 0.6\%$ [54 ± 6 mmol/mol]) inserted the DG4P sensor 2 days prior to a 90 min cycling session (50% VO_2peak) either with (IHE) or without (CONT) a 10 s all-out sprint every 10 min. Venous blood samples for reference glucose measurement were drawn every 10 min and euglycemia (target 7 mmol/l) was maintained using an oral glucose solution. Additionally, lactate and venous blood gas parameters were determined.

Results

Mean reference blood glucose was 7.6 ± 0.2 mmol/l during IHE and 6.7 ± 0.2 mmol/l during CONT ($p < 0.001$). IHE resulted in significantly higher levels of lactate (7.3 ± 0.5 mmol/l vs. 2.6 ± 0.3 mmol/l, $p < 0.001$), while pH values were significantly lower in the IHE group (7.27 vs. 7.38, $p = 0.001$). Mean absolute relative difference (MARD) was $13.3 \pm 2.2\%$ for IHE and $13.6 \pm 2.8\%$ for CONT suggesting comparable accuracy ($p = 0.90$). Using Clarke Error Grid Analysis, 100% of CGM values during both IHE and CONT were in zones A and B (IHE: 77% and 23%; CONT: 78% and 22%).

71 **Conclusions**

72 The present study revealed good and comparable accuracy of the DG4P CGM system during
73 intermittent high intensity and continuous moderate intensity exercise, despite marked
74 differences in metabolic conditions. This corroborates the clinical robustness of CGM under
75 differing exercise conditions.

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1. Introduction

Real-time use of continuous glucose monitoring (CGM) has recently emerged as a novel tool to improve glycemic control in patients with type 1 diabetes mellitus (T1DM) (1). While CGM is generally considered a reliable tool for diabetes management during resting conditions, the reliability in the setting of physical exercise remains controversial (2, 3). Of importance, recent studies support the concept that CGM accurately reflects glucose changes even during the dynamic state of exercise (4). Several studies investigated CGM during different exercise activities (e.g., spinning (5), long-distance running (6), cross-country skiing (7), and scuba diving (8)) including team sport activities (7, 9). However, so far no studies have systematically assessed the impact of exercise intensity on the accuracy of CGM.

Intermittent high-intensity exercise (IHE; i.e., moderate intensity exercise with short bouts of interspersed all-out efforts) is a well-established and modern training modality (10, 11). Metabolically, IHE differs from isoenergetic continuous activity in terms of neurohormonal and metabolic response (12). Repetitive sprinting elicits counterregulatory hormones such as catecholamines and elevates lactate levels, and recent studies have suggested that IHE may be of particular benefit to optimize exercise-associated glycemia in T1DM (9, 13–15). However, IHE with its associated metabolic changes (e.g., changes in pH, microcirculation, oxygen tension, etc.) may potentially interfere with CGM accuracy (16).

The aim of the present study was, therefore, to systematically compare the accuracy of the Dexcom G4 Platinum (DG4P) CGM during IHE and isoenergetic continuous moderate intensity exercise in young adults with T1DM.

2. Material and methods

2.1 Study design and participants

Ten male adult patients with well-controlled T1DM ($\text{HbA1C} < 7.5\%$ [58.5 mmol/mol]) and no known complications were included in this single-center randomized cross-over study. Participants were randomly assigned to a 90 min cycling session at 50% of their individual maximal O_2 consumption ($\text{VO}_{2\text{max}}$) with (IHE) or without (continuous moderate intensity exercise, CONT) interspersed 10 s all-out sprints every 10 min. Exercise intensity was monitored using breath-to-breath spirometry (Cardiovit AT-104 PC; Schiller, Baar, Switzerland) as well as continuous heart rate recording by a portable three-channel electrocardiogram (Lifecard CF, Del Mar Reynolds Medical Inc., Irvine, California, USA). Baseline examinations included assessment of anthropometric data and physical status, determination of basal metabolic rate as well as an incremental cardiopulmonary exercise test in order to determine $\text{VO}_{2\text{peak}}$. During the 48 h prior to the exercise interventions (IHE and CONT, respectively) patients were guided to standardize their food intake and insulin regime and withdraw from strenuous physical activity. The DG4P sensor was inserted 2 days prior to the study visits subcutaneously, in the left lower abdomen. Participants were instructed to perform calibrations every 12 hours according to the manufacturer's recommendations (last calibration before exercise scheduled early in the morning in fasting state). On the study day patients ingested a standardized breakfast and injected their usual insulin dose prior to 7 am. Exercise performance was scheduled in the post-absorptive phase during lunchtime. Over the entire study period glycemia was targeted at a glycemia of 7 mmol/l by oral administration of a 10% dextrose solution according to a prespecified carbohydrate intake algorithm (17) with individual adaptations.

An intravenous catheter was inserted in the patient's forearm. Plasma glucose was measured with an YSI 2300 STAT Plus glucose analyzer (YSI Life Sciences, Inc., Yellow Springs, OH). In addition, venous plasma samples were regularly drawn for lactate, insulin, and blood gas parameters (pH, bicarbonate, oxygen, and carbon dioxide tension). The study was approved by the local ethical committee and registered on www.trialregister.nl (NTR02068638). Informed consent was obtained from every individual.

2.2 Statistical analysis

For each patient and intervention, CGM readings were paired with blood glucose values measured simultaneously every 10 min. CGM accuracy was assessed using MARD (the absolute value of the difference between sensor readings and reference divided by the reference [expressed as a percentage]) averaged for each patient and intervention. In addition, Clarke Error Grid Analysis was applied to quantify the clinical accuracy of CGM (17). Values are expressed as mean $\pm$ standard error of the mean, unless specified otherwise. Continuous variables were analyzed for normal distribution using Shapiro–Wilk test and qq-plots. Parametric variables were compared using two-tailed paired *t*-test or Wilcoxon signed-rank test where appropriate. A *p*-value <0.05 was considered statistically significant. All analyses were performed using Stata 13.0 (Stata Corporation, College Station, TX, USA) and Matlab R2015a (The MathWorks, Inc., Natick, Massachusetts, USA)

3. Results

3.1 Patient characteristics

Ten male physically active and well-controlled patients with T1DM were enrolled in this study. Mean ($\pm$ SD) age was 26.3 ± 3.5 y, mean HbA1C ($\pm$ SD) was $7.0\pm 0.6\%$ (54 ± 6 mmol/mol) and diabetes duration ($\pm$ SD) was 12.9 ± 5.2 years. Eight patients were on continuous subcutaneous insulin infusion pumps, and two delivered insulin via multiple daily injections. Table 1 depicts additional characteristics of the study population.

3.2 CGM accuracy and blood parameters

Mean glycemia was 7.56 ± 0.21 mmol/l during IHE and 6.71 ± 0.23 mmol/l during CONT ($p<0.001$). Insulin levels were comparable between the interventions with 20.7 ± 1.7 mU/l for IHE versus 19.4 ± 1.5 mU/l for CONT ($p=0.73$). IHE resulted in significantly higher lactate concentrations compared with CONT (7.25 ± 0.47 vs. 2.58 ± 0.29 mmol/l). Conversely, pH (7.27 ± 0.01 vs. 7.38 ± 0.01) and bicarbonate levels (22.0 ± 0.30 vs. 25.0 ± 0.65 mmol/l) were significantly lower in IHE compared with CONT, respectively ($p<0.001$ for all comparisons). Details of blood gas analyses are summarized in Table 2.

Figure 1 illustrates blood and interstitial glucose response during the different exercise interventions. The CGM analysis included 108 readings for IHE and 100 readings for CONT, each with corresponding (matched) reference YSI glucose values. CGM readings showed a mean glucose value of 7.39 ± 0.21 mmol/l during IHE compared with 6.44 ± 0.19 mmol/l during CONT ($p<0.001$). The overall MARD was $13.3\pm 2.2\%$ for IHE and $13.6\pm 2.8\%$ for CONT ($p=0.90$). Using Clarke Error Grid Analysis, 100% of CGM values during both IHE and CONT were located in the A and B zones (IHE: 77% and 23%; CONT: 78% and 22%; Figure 2).

4. Discussion

The present study prospectively compared the accuracy of a commercially available CGM system (DG4P) under two differing exercise modalities (e.g., continuous moderate intensity exercise and IHE) in young adult individuals with T1DM. The main findings are twofold. First, CGM revealed a comparable accuracy in both exercise conditions despite fundamental differences in the metabolic responses between the two modalities. Of note, this observation was obtained while maintaining stable glucose levels throughout the exercise periods. Second, the overall accuracy during continuous moderate and IHE was good, thus corroborating the reliability of CGM in individuals with T1DM under varying exercise conditions, when glycemic levels were normal and comparably stable.

With a MARD of 13.3% during IHE and 13.6% during CONT the present study observed comparable or even higher numeric accuracy when compared to previous studies assessing CGM performance under exercise conditions. Adolfsson et al. reported an overall MARD of 23.0% during various physical activities, whereas a median ARD of 18.4% was observed in exercising pregnant women (2, 7). Accuracy assessment based on Clarke Error Grid Analysis during physical activity has so far only been used in one study, showing a lower percentage of values within clinically safe zones A and B compared with the present study (87.0 vs. 100%) (2). Such discrepancies may be due to differences in glycemic excursions during exercise (variability was kept low as per protocol in the present study). In addition, changes in technology (e.g., previous-generation CGM devices in earlier studies) and differences in pre-study sensor running time (in the present study exercise was scheduled for day 3 to minimize run-in instability) are likely to contribute to the discrepant findings.

Our findings of a comparable CGM accuracy during two different exercise conditions suggest that metabolic conditions associated with high intensity exercise do not generally interfere with CGM performance despite documented variations in pH and oxygen tension which have

been shown earlier to potentially affect glucose oxidase-based measurements (18, 19). This concept is in line with a study in healthy male individuals, where a marked transient fall in blood pH induced by a single all out 30 s sprint did not affect estimates of plasma glucose using the Minimed CGMS glucose sensor (20). In addition, results from more recent studies investigating CGM performance under intensive care unit conditions indicated that low pH and elevated lactate levels, as well as use of vasoactive drugs, did not compromise the agreement between blood and interstitial glucose measurements (21–23).

A major strength of the present study lies in the prospective setting with a standardized protocol. Physical exercise was carried out in a carefully controlled clinical research facility setting. Paired sensor and venous blood glucose values were collected applying a fixed time interval of 10 min. Plasma glucose values were measured by a laboratory standard method (YSI 2300 STAT Plus glucose analyzer), unlike other studies that used capillary glucose measurements (5). Still, the CGM was calibrated with capillary finger-prick glucose according to the manufacturer's instructions, reflecting a real-life setting and therefore extending the robustness of the results to daily practice.

We, nevertheless, acknowledge several limitations. First, the sample size was comparably small and restricted to a young male population of adults with T1DM. Conversely, the aim was explicitly to study CGM accuracy in a homogenous study group where such aspects are of clinical relevance, i.e., a well-defined physically active group of individuals with T1DM. Second, the majority of exercise-associated blood glucose levels were in the normal range, since the study concept aimed at maintaining euglycemia during the exercise period. Although we realize that this may not always reflect clinical reality, CGM technology, on the other hand, empowers patients to target and maintain euglycemia during exercise performance (24). On average, glycemic levels in IHE were slightly higher, most likely due to the well-known glucose-raising effect of counter-regulatory hormones induced by higher exercise intensities (25), but glycemia was still well in the normal range in both IHE and CONT.

Statements regarding exercise-associated accuracy of CGM have, therefore, to be restricted to the normal glycemic range and extensions towards hypo- and hyperglycemic ranges have to be made with caution. Still, the focus of the present study was not an analysis of CGM accuracy in differing glucose ranges, but to compare CGM in two different exercise conditions. As a consequence, the classical Clarke Error Grid was not expanded to the Continuous Glucose Error Grid Analysis, which considers accuracy according to direction and rate of blood glucose fluctuations and within different glycemic ranges (26). Third, our reference glucose measurement method was not based on pH-insensitive spectrophotometric technology. However, the YSI 2300 STAT Plus glucose analyzer provides a phosphate buffer system in order to normalize pH within the measurement chamber, rendering measurement interference in the setting of only mildly decreased pH unlikely. Fourth, in the present study only one type of glucose sensor (DG4P) was evaluated, thereby limiting the applicability of our findings to other CGM devices.

In conclusion, the present study revealed good and comparable accuracy of the DG4P CGM system during IHE and continuous moderate intensity exercise despite marked differences in metabolic conditions in these two exercise modalities. These findings corroborate the clinical robustness of CGM in differing exercise conditions and support the usefulness of CGM for physically active T1DM patients engaging in sports activities of variable intensities.

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239 **Acknowledgments**

240 The authors would like to thank all the volunteers for their participation and enthusiasm.

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244 **Figure legends**

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246 **Figure 1:** Blood glucose and continuous glucose monitoring response during (A) IHE;
247 intermittent high-intensity exercise and (B) CONT; continuous moderate intensity exercise.

248 Values represent mean $\pm$ SEM.

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250 **Figure 2:** Clarke Error Grid Analysis showing paired sensor and plasma (reference) glucose
251 values, during (A) IHE; intermittent high-intensity exercise and (B) CONT; continuous
252 moderate intensity exercise.

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References

1. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care*. 2005;28(5):1231–1239.
2. Kumareswaran K, Elleri D, Allen JM, Caldwell K, Nodale M, Wilinska ME, et al. Accuracy of continuous glucose monitoring during exercise in type 1 diabetes pregnancy. *Diabetes technology & therapeutics*. 2013;15(3):223–229.
3. Herrington SJ, Gee DL, Dow SD, Monosky KA, Davis E, Pritchett KL. Comparison of glucose monitoring methods during steady-state exercise in women. *Nutrients*. 2012;4(9):1282–1292.
4. Yardley JE, Sigal RJ, Kenny GP, Riddell MC, Lovblom LE, Perkins BA. Point accuracy of interstitial continuous glucose monitoring during exercise in type 1 diabetes. *Diabetes Technology & Therapeutics*. 2013;15(1):46–49.
5. Iscoe KE, Campbell JE, Jamnik V, Perkins BA, Riddell MC. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technology & Therapeutics*. 2006;8(6):627–635.
6. Cauza E, Hanusch-Enserer U, Strasser B, Ludvik B, Kostner K, Dunky A, et al. Continuous glucose monitoring in diabetic long distance runners. *International Journal of Sports Medicine*. 2005;26(9):774–780.
7. Adolfsson P, Nilsson S, Lindblad B. Continuous glucose monitoring system during physical exercise in adolescents with type 1 diabetes. *Acta Paediatrica (Oslo, Norway : 1992)*. 2011;100(12):1603–1609.
8. Bonomo M, Cairoli R, Verde G, Morelli L, Moreo A, Grottaglie MD, et al. Safety of recreational scuba diving in type 1 diabetic patients: the Deep Monitoring programme. *Diabetes & Metabolism*. 2009;35(2):101–107.
9. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabetic medicine : A Journal of the British Diabetic Association*. 2011;28(7):824–832.
10. Esteve-Lanao J, San Juan AF, Earnest CP, Foster C, Lucia A. How do endurance runners actually train? Relationship with competition performance. *Medicine and Science in Sports and Exercise*. 2005;37(3):496–504.
11. Gillen JB, Gibala MJ. Is high-intensity interval training a time-efficient exercise strategy to improve health and fitness? *Applied physiology, nutrition, and metabolism = Physiologie Appliquee, Nutrition et Metabolisme*. 2014;39(3):409–412.
12. Peake JM, Tan SJ, Markworth JF, Broadbent JA, Skinner TL, Cameron-Smith D. Metabolic and hormonal responses to isoenergetic high-intensity interval exercise and continuous moderate-intensity exercise. *American Journal of Physiology Endocrinology and Metabolism*. 2014;307(7):E539–552.
13. Guelfi KJ, Ratnam N, Smythe GA, Jones TW, Fournier PA. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *American Journal of Physiology Endocrinology and Metabolism*. 2007;292(3):E865–870.
14. Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care*. 2005;28(6):1289–1294.
15. Campbell MD, West DJ, Bain SC, Kingsley MI, Foley P, Kilduff L, et al. Simulated games activity vs continuous running exercise: A novel comparison of the glycemic and

metabolic responses in T1DM patients. *Scandinavian Journal of Medicine & Science in Sports*. 2014.

16. Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. *Journal of Diabetes Science and Technology*. 2012;6(2):396–411.

17. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care*. 1987;10(5):622–628.

18. Weibel MK, Bright HJ. The glucose oxidase mechanism. Interpretation of the pH dependence. *The Journal of Biological Chemistry*. 1971;246(9):2734–2744.

19. Kilpatrick ES, Rumley AG, Smith EA. Variations in sample pH and pO₂ affect ExacTech meter glucose measurements. *Diabetic Medicine : A Journal of the British Diabetic Association*. 1994;11(5):506–509.

20. Davey RJ, Ferreira LD, Jones TW, Fournier PA. Effect of exercise-mediated acidosis on determination of glycemia using CGMS. *Diabetes Technology & Therapeutics*. 2006;8(4):516–518.

21. Marics G, Koncz L, Eitler K, Vatai B, Szenasi B, Zakarias D, et al. Effects of pH, lactate, hematocrit and potassium level on the accuracy of continuous glucose monitoring (CGM) in pediatric intensive care unit. *Italian Journal of Pediatrics*. 2015;41(1):17.

22. van Hooijdonk RT, Leopold JH, Winters T, Binnekade JM, Juffermans NP, Horn J, et al. Point accuracy and reliability of an interstitial continuous glucose-monitoring device in critically ill patients: a prospective study. *Critical Care (London, England)*. 2015;19(1):34.

23. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PG, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. *Intensive Care Medicine*. 2009;35(8):1383–1389.

24. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study. *Diabetes Technology & Therapeutics*. 2011;13(8):819–825.

25. Marliss EB, Simantirakis E, Miles PD, Purdon C, Gougeon R, Field CJ, et al. Glucoregulatory and hormonal responses to repeated bouts of intense exercise in normal male subjects. *J Appl Physiol (1985)*. 1991;71(3):924–233.

26. Clarke WL, Anderson S, Kovatchev B. Evaluating clinical accuracy of continuous glucose monitoring systems: Continuous Glucose-Error Grid Analysis (CG-EGA). *Current Diabetes Reviews*. 2008;4(3):193–199.

Figure1

Figure2

Table1

Table 1. Baseline characteristics of study patients	
Characteristics	n=10
Age (years)	26.3 ± 3.5
Weight (kg)	82.0 ± 11.9
Height (m)	1.81 ± 0.04
BMI (kg/m2)	25.2 ± 3.8
Fat-free mass (%)	76.7 ± 7.3
BMR (kcal/day)	2039 ± 214
VO2 peak (ml [kg body weight]-1 min-1)	48.0 ± 11.2
Diabetes duration (years)	12.9 ± 5.2
Hemoglobin A1c (%)	7.0 ± 0.6
Hemoglobin A1c (mmol/mol)	54 ± 6
Total average daily insulin (U kg-1 d-1)	0.72 ± 0.10

Data are expressed as mean ± standard deviation.
BMI, body mass index; BMR, basal metabolic rate. CHO, carbohydrate. VO2 peak, peak oxygen uptake

Table 2. Venous blood gas analysis during exercise

	IHE	CONT	p-value*
glucose (mmol/l)	7.56 ± 0.21	6.71 ± 0.23	0.0001
lactate (mmol/l)	7.25 ± 0.47	2.58 ± 0.29	<0.001
pH (bpm)	7.27 ± 0.01	7.38 ± 0.01	<0.001
HCO ₃ (mmol/l)	22.0 ± 0.65	25.0 ± 0.30	<0.001
PvO ₂ (mmHg)	43.1 ± 3.26	53.0 ± 2.63	0.012
PvCO ₂ (mmHg)	49.5 ± 1.61	43.9 ± 0.84	0.001

Data are expressed as mean ± standard deviation. IHE, intermittent high intensity exercise; CONT; continuous moderate intensity exercise; HCO₃, bicarbonate; PvO₂, venous oxygen tension; PvCO₂, carbon dioxide tension. *Significance based on paired t-test to compare between interventions.