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Performance of intermittently scanned continuous glucose monitoring systems in people with type 1 diabetes: A pooled analysis

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Abstract

Aims: To conduct a pooled analysis to assess the performance of intermittently scanned continuous glucose monitoring (isCGM) in association with the rate of change in sensor glucose in a cohort of children, adolescents, and adults with type 1 diabetes.

Material and Methods: In this pooled analysis, isCGM system accuracy was assessed depending on the rate of change in sensor glucose. Clinical studies that have been investigating isCGM accuracy against blood glucose, accompanied with collection time points were included in this analysis. isCGM performance was assessed by means of median absolute relative difference (MedARD), Parkes error grid (PEG) and Bland-Altman plot analyses.

Results: Twelve studies comprising 311 participants were included, with a total of 15 837 paired measurements. The overall MedARD (interquartile range) was 12.7% (5.9-23.5) and MedARD differed significantly based on the rate of change in glucose ($P < 0.001$). An absolute difference of −22 mg/dL (−1.2 mmol/L) (95% limits of agreement [LoA] 60 mg/dL (3.3 mmol/L), −103 mg/dL (−5.7 mmol/L)) was found when glucose was rapidly increasing (isCGM glucose minus reference blood glucose), while a −32 mg/dL (1.8 mmol/L) (95% LoA 116 mg/dL (6.4 mmol/L), −51 mg/dL (−2.8 mmol/L)) absolute difference was observed in periods of rapidly decreasing glucose.

Conclusions: The performance of isCGM was good when compared to reference blood glucose measurements. The rate of change in glucose for both increasing and

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decreasing glucose levels diminished isCGM performance, showing lower accuracy during high rates of glucose change.

KEYWORDS
continuous glucose monitoring (CGM), type 1 diabetes

1 | INTRODUCTION

The accessibility and use of continuous glucose monitoring (CGM) systems have facilitated the management of type 1 and type 2 diabetes, leading to sustained improvements in hypoglycaemia management, decreased fear of hypoglycaemia, and fewer acute hypoglycaemic events and disease-associated days absent from work.[1]

Currently, two different types of personal CGM systems are available: real-time CGM and intermittently scanned CGM (isCGM). Both systems measure the glucose concentration in the interstitial fluid via a subcutaneous sensor and transfer the value via a transmitter to a reader/scanner device. Real-time CGM systems automatically transfer the current sensor glucose level to a contactless reader device via Bluetooth (every 1-5 minutes), while isCGM systems require proactively conducted swipes with a scanning device via near-field communication.

Various studies have assessed the performance of all these technologies for sensor accuracy, detailing a substantial variety of median absolute relative differences (MedARDs), ranging from ~9% to 45%.[2-5] Elevated MedARDs are often observed during phases of high glucose swings[6] that are attributed to the physiological lag time for the glucose to diffuse from the bloodstream into the interstitial fluid.[7]

The performance of isCGM systems was often assessed during routine environmental conditions,[8] exercise[5] and glycaemic challenges.[9] Due to methodical differences in study designs, for example, different reference blood glucose measurements methods used, different cohorts and rates of glucose change, generalizable and large-scale accuracy data are currently not available for isCGM systems. Furthermore, as the isCGM system is approved as a non-adjunctive glucose-sensing device, people with type 1 diabetes using multiple daily injections or continuous subcutaneous insulin infusion therapy need to know if the displayed glucose level is reliable during episodes of stable and rapidly changing glucose.

Although most studies have shown that isCGM systems are within a safe clinical range[10-12] conclusive large-scale assessments of isCGM performance and the impact of the rate of change in glucose are currently lacking. Therefore, the aim of this pooled analysis was to assess isCGM (FreeStyle Libre 1; Abbott Diabetes Care, Alameda, California) performance and the rate of change in sensor glucose in a cohort of children, adolescents, and adults with type 1 diabetes.

2 | MATERIALS AND METHODS

This study was conducted as a retrospective pooled analysis, in which isCGM accuracy was assessed against reference blood glucose levels derived from following standardized systems: the Contour Plus One glucometer (Ascensia Diabetes Care, Leverkusen, Germany), YSI 2300 STAT (Yellow Springs Instrument Inc., Yellow Springs, Ohio), Super GL Glucose Analyser (Dr. Müller Gerätebau GmBH, Freital, Germany), Freestyle Freedom Lite (Abbott Diabetes Care, Chicago, USA), Contour Next USB (Ascensia Diabetes Care, Leverkusen, Germany), EKF Biosen C-Line (EKF Diagnostic GmbH, Barleben, Germany), COBAS 8000 (Hoffmann-La-Roche Ltd, Basel, Switzerland) with respect to the rate of change in glucose in individuals with type 1 diabetes (Supplementary Appendix S1). The study protocol was approved by the Ethics Committee of the Medical University of Graz, Austria (32-372 ex 19/20) and registered with German Clinical Trials (DRKS00024682). Additionally, the study was conducted in full conformity with the 1964 Declaration of Helsinki and all its subsequent revisions and in accordance with the guidelines provided by the International Conference on Harmonization for Good Clinical Practice (E6 guidelines).

2.1 | Study selection

A nonsystematic database search was performed in PubMed, selecting publications that investigated isCGM (FreeStyle Libre 1) accuracy in people with type 1 diabetes until March 2020. The following search terms were used: type 1 diabetes AND intermittently scanned glucose monitoring OR Freestyle Libre OR flash glucose monitoring AND performance OR accuracy. In total, 23 studies were preselected, and authors were requested to provide their data for this pooled analysis. Eleven studies were excluded; one study did not meet the selection requirements and data for 10 studies could not be shared for analyses for various reasons, including not having an allowance for data transfer, ethical reasons, or timeline issues. In total, 12 studies were included that met the following inclusion criteria for participants: clinical diagnosis of type 1 diabetes; use of an isCGM system against reference blood glucose measurements; and time points of measurements recorded to assess the rate of change.

Prior to quality assessment, we received in total 54 830 points of comparison from 311 participants with type 1 diabetes. In total, for the general assessment of isCGM accuracy independent of the rate of change, 15 837 paired datapoints were available (reference blood glucose and sensor glucose). For the assessment of glucose sensor accuracy in relation to the rate of change, 4041 datapoints were excluded as the maximum time between two reference blood glucose points exceeded 120 minutes. This maximum time was defined to ensure that the real rate of change in glucose was captured. In total, 11 796 points of comparison, accompanied by the associated rate of change in sensor glucose, were available (Figure 1).

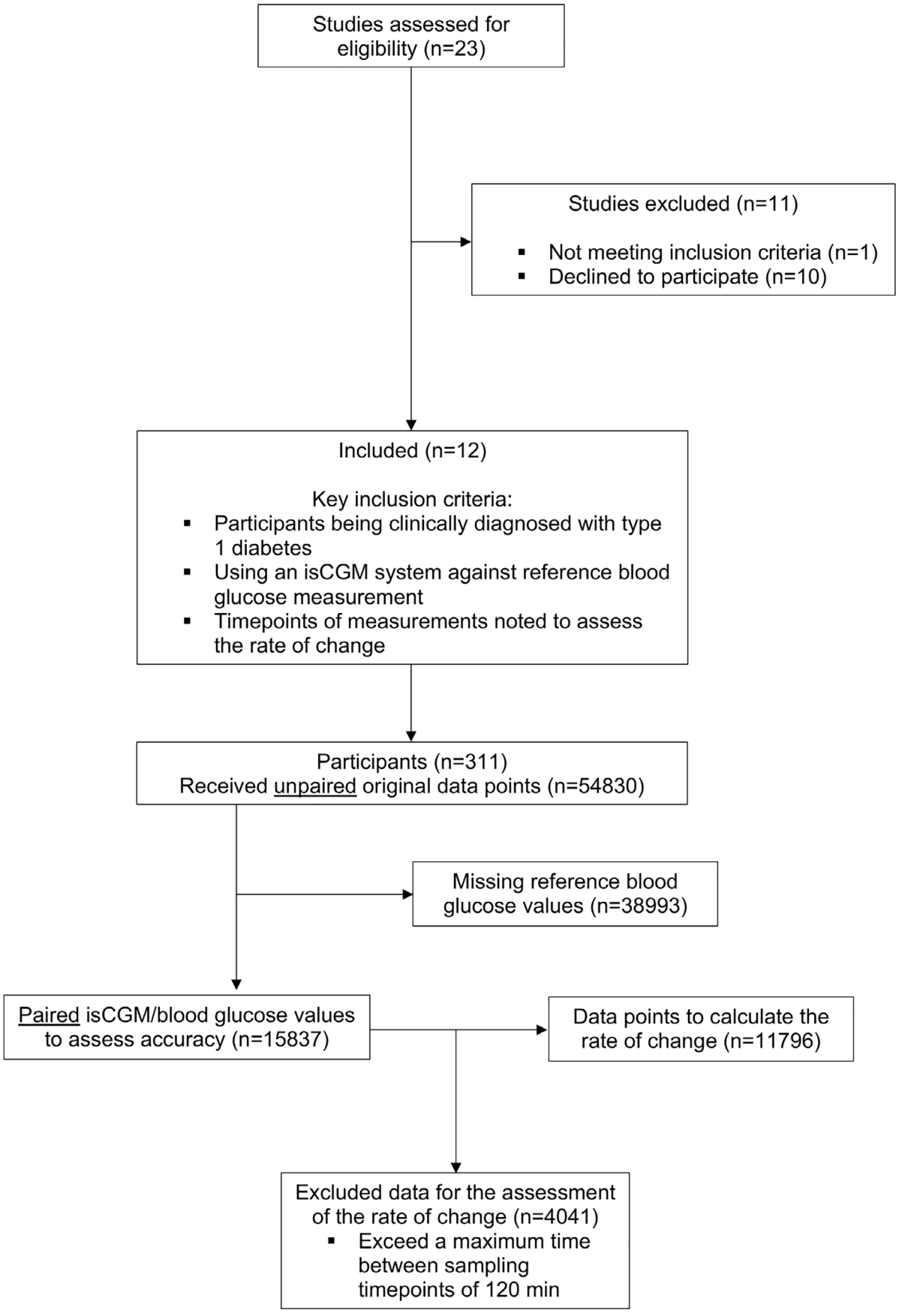

FIGURE 1 Flow chart of included and excluded participants and study data

In this pooled analysis, the accuracy of the isCGM system (FreeStyle Libre 1) was assessed depending on the rate of change in sensor glucose. Data from various studies that investigated isCGM accuracy against blood glucose (all types), accompanied by collection time points (in order to assess the rate of change in glucose), were obtained. For the assessment of the rate of change, a maximum time between sampling time points of 2 hours was allowed. Both sexes, all age groups, and all types of insulin treatments were included. All conditions were included: laboratory conditions, real-life data, resting, and physical activity/exercise data.

2.2 | Statistical analyses

Data were tested for normal distribution by means of a Shapiro-Wilk normality test. Based on the distribution, sensor accuracy was measured according to MedARD, with interquartile ranges, between isCGM sensor glucose and reference blood glucose.

Absolute difference between sensor glucose levels and reference blood glucose levels was analysed via the Bland-Altman method. The clinical safety of isCGM accuracy was assessed by means of Parkes error grid (PEG) analysis, dividing isCGM performance into five grids, defined as follows: zone A: clinically accurate measurements, no effect on clinical action; zone B: altered clinical action, little or no effect on clinical outcomes; zone C: altered clinical action, likely to affect clinical outcomes; zone D: altered clinical action, could have significant clinical risks; and zone E: altered clinical action, could have dangerous consequences.[13]

Participants' characteristics including age, body mass index, diabetes duration and glycated haemoglobin (HbA1c) level were given as mean ± standard deviation. Analyses were also separated for nighttime and daytime (06.00 AM to 12.00 AM), laboratory (YSI Inc., United States/EKF Diagnostics, Germany)[14] and glucometer assessments, age groups (<18 years and ≥18 years), physical activity/exercise and non-physical activity/exercise. Furthermore, isCGM accuracy was also investigated for the following glycaemic ranges: hypoglycaemia level 2 (<54 mg/dL (<3.0 mmol/L)), hypoglycaemia level 1 (54-69 mg/dL (3.0-3.9 mmol/L)), euglycaemia (70-180 mg/dL (3.9-10.0 mmol/L)), hyperglycaemia level 1 (181-250 mg/dL (10.0-13.9 mmol/L)) and hyperglycaemia level 2 (>250 mg/d 13.9 mmol/L)).[15] The collected glucose levels were divided based on their associated rates of change into four quantiles: low (0 to 25th percentile, 26th quartile to 50th percentile, 51st to 75th percentile and above the 75th percentile); additionally, the rate of change was assessed based on the providers' trend arrows: increasing/decreasing >2 mg/dL/min, increasing 1 to 2 mg/dL and not increasing/decreasing >1 mg/dL/min at the time of glucose measurement. Group comparisons were performed by means of one-way analysis of variance with Tukey's post hoc testing ($P < 0.05$).

3 | RESULTS

Of the 12 studies included, 10 were performed in adults and two in children and adolescents with type 1 diabetes[8,9,16-24] (Supplementary Appendix S1). In one adult study, isCGM accuracy was assessed in pregnant women with type 1 diabetes. Five studies were performed in a clinical research facility setting, four studies in a real-world setting, and three studies in a combined clinical research facility and real-world setting. In four studies isCGM performance was investigated around exercise and in two studies during a glycaemic challenge. The two studies performed in children and adolescents assessed isCGM accuracy during a summer camp. Participants' characteristics are shown in Table 1.

TABLE 1 Participants' characteristics assessed at screening for each specific study

Participants' characteristics (n = 311)	
Sex: female/male, %	**53/47**
Age, years	27 ± 15
BMI, kg/m^2	23.4 ± 4.3
Type of therapy: CSII/ MDI, %	64/36
HbA1c, % (mmol/mol)	7.3 ± 1.0 (56.3 ± 9.3 mmol/mol)
Diabetes duration, years	13 ± 10

Note: Data are given as mean ± standard deviation, unless otherwise stated.
Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycated haemoglobin; MDI, multiple daily injections.

TABLE 2 Median absolute relative differences based on glycaemic thresholds, time of day, exercise and age

	Glycaemia	isCGM accuracy, %; Median (IQR)
MedARD (IQR)	Overall	12.7 (5.9-23.5) n = 15 837
	Hypoglycaemia level 2 (<54 mg/dL; < 3.0 mmol/L)	17.8 (8.0-29.6) n = 350
	Hypoglycaemia level 1 (54-69 mg/dL; 3.0-3.9 mmol/L)	20.5 (9.4-37) n = 1153
	Euglycaemia (70-180 mg/dL; 3.9-10.0 mmol/L)	13.7 (6.5-24.7) n = 10 253
	Hyperglycaemia level 1 (181-250 mg/dL; 10.0-13.9 mmol/L)	9.6 (4.2-17.9) n = 2809
	Hyperglycaemia level 2 (>250 mg/dL; >13.9 mmol/L)	8.9 (4.6-15.4) n = 1272
	Daytime (06.00 AM to 12.00 AM)	13.1 (6.0-24.0) n = 14 782
	Night-time (12.01 AM to 05.59 AM)	9.3 (4.1-16.1) n = 1055
	During exercise adults	23.6 (14.9-33.4) N = 1481
	Adults; no exercise	12.9 (5.9-24.0) N = 11 199
	Children/adolescents overall	9.1 (4.2-15.9) N = 3157

Abbreviation: IQR, interquartile range.

3.1 | Median absolute relative difference

In this retrospective pooled analysis, the overall MedARD was 12.7% (IQR 5.9-23.5). When isCGM accuracy was assessed by means of glucometer, the MedARD was 10.8% (IQR 5.1-19.8), and was 15.6% (IQR 7.2-28.5) when assessed against a laboratory measurement device. When comparing these two MedARDs based on the assessment tool, the MedARD was significantly lower for glucometer assessment ($P < 0.001$). MedARDs based on glycaemic thresholds, time of day, exercise and age are given in Table 2.

3.2 | Rate of change in glucose and MedARD

The rates of change quartiles in glucose based on the instruction leaflet and based on the quartiles are shown in Figure 2. The rate of change in glucose based on the instruction leaflet significantly altered the MedARD ($P < 0.001$), displaying a U-shaped relationship. When accuracy was assessed based on the quartiles in rate of change in glucose, the MedARD was elevated for those in the highest quartile of glucose change, for both decreasing and increasing glucose levels (both $P < 0.001$).

When assessing the rate of change in glucose within the different glycaemic ranges, the specific glycaemic range had a significant impact on the MedARD over all rates of changes in glucose (Table 3).

3.3 | Clinical assessment of isCGM accuracy

Overall, clinical performance assessed by means of PEG analysis was as follows: 75.1% in zone A, 22.1% in zone B, 2.6% in zone C, 0.3% in zone D, and no values in zone E. When data were separated for age groups and resting and exercise conditions, the following clinical accuracy rates were found: adults, rest: 75.4% in zone A, 21.9% in zone B, 2.3% in zone C, 0.4% in zone D, and no values in zone E; adults, exercise: 43.2% in zone A, 46.7% in zone B, 9.9% in zone C, 0.3% in zone D, and no values in zone E; children and adolescents: 88.9% in zone A, 10.7% in zone B, 0.4% in zone C and no values in zones D or E. PEG analysis based on the rate of change (trend arrows) showed the following clinical performance results: stable glucose: 77.47% in zone A, 20.17% in zone B, 2.15% in zone C, 0.22% in zone D, and no values in zone D; slightly decreasing glucose: 73.48% in zone A, 22.09% in zone B, 4.03% in zone C, 0.40% in zone D, and no values in zone E; slightly increasing glucose: 73.66% in zone A, 23.75% in zone B, 1.76 in zone C, 0.83% in zone D, and no values in zone E; rapidly decreasing glucose: 50.17% in zone A, 40.22% in zone B, 9.09% in zone C, 0.43% in zone D, 0.09% in zone E; rapidly increasing glucose: 56.63% in zone A, 40.81% in zone B, 2.18% in zone C, 0.38% in zone D, and no values in zone E (Supplementary Appendix S2).

3.4 | Assessment of isCGM based on Bland-Altman method

Assessment of isCGM accuracy showed an overall bias of 3 mg/dL (95% limits of agreement [LoA] 74 mg/dL (4.1 mmol/L), −68 mg/dL (-3.8 mmol/L)), for adults during resting conditions of −3 mg/dL (95% LoA 61 mg/dL 3.4 mmol/L)), −67 mg/dL(−3.7 mmol/L), for adults during exercise of 39 mg/dL (2.2 mmol/L) (95% LoA 110 mg/dL (6.1 mmol/L), −32 mg/dL (−1.8 mmol/L)) and for children and adolescents of 7 mg/dL (95% LoA 56 mg/dL, −42 mg/dL (−2.4 mmol/L)). Bland-Altman analysis based on the instruction leaflets' rate of change in glucose is given in Supplementary Appendix S3.

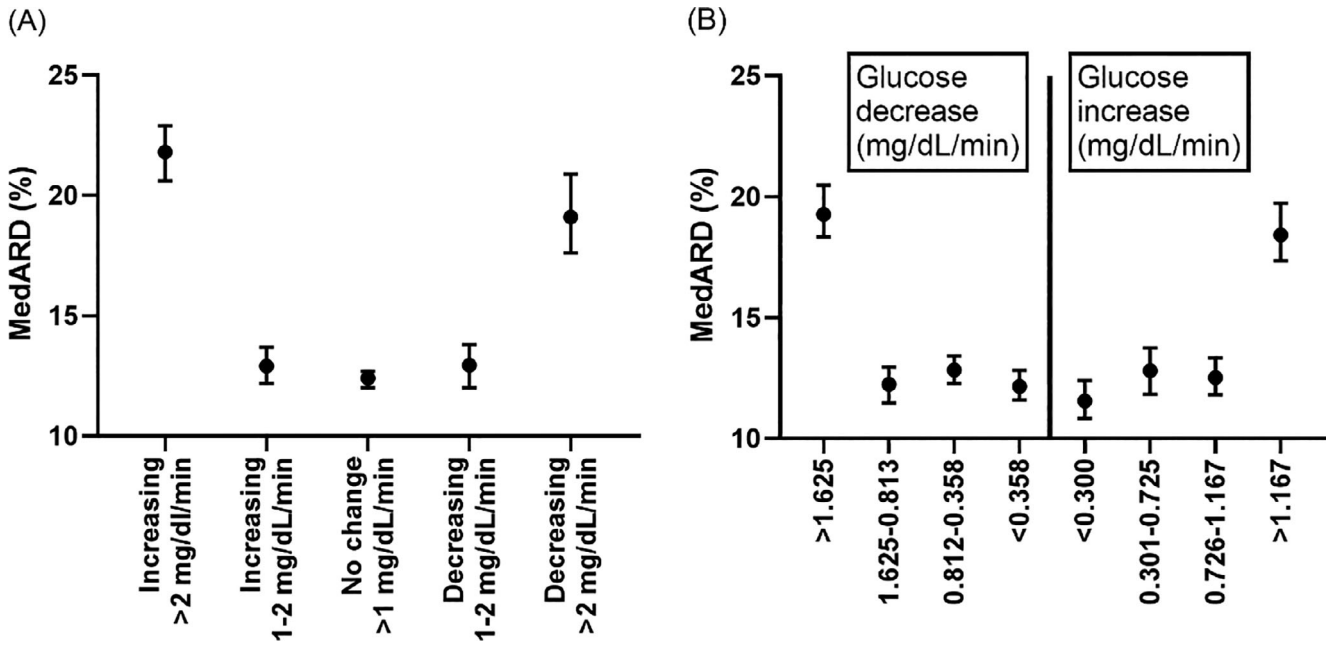

FIGURE 2 Median absolute relative difference (MedARD; %) based on the rate of change in glucose (instruction leaflet; [A]) and based on quartiles (B)

TABLE 3 Median absolute relative differences based rate of change in glucose

Rate of change in glucose	Glycaemic range					*P* value
	<54 mg/dL (<3.0 mmol/L) MedARD (IQR), %	54-69 mg/dL (3.0-3.9 mmol/L) MedARD (IQR), %	70-180 (3.9-10 mmol/L) mg/dL MedARD (IQR), %	181-250 mg/dL (10.0-13.9 mmol/L) MedARD (IQR), %	>250 mg/dL (>13.9 mmol/L) MedARD (IQR), %	
↓	37 (28-52) n = 17	30 (19-46) n = 69	24 (13-36) n = 817	14 (6-22) n = 208	9 (5-15) n = 55	<0.0001
↘	21 (10-30) n = 47	24 (12-37) n = 171	14 (7-25) n = 1124	8 (3-16) n = 288	9 (4-16) n = 108	<0.0001
→	16 (8-28) n = 161	19 (9-35) n = 569	13 (6-23) n = 4495	9 (4-16) n = 1092	9 (4-16) n = 437	<0.0001
↗	30 (24-50) n = 7	26 (13-45) n = 41	15 (8-28) n = 578	10 (4-19) n = 286	10 (6-17) n = 170	<0.0001
↗	4 (34-46) n = 2	20 (7-35) n = 8	24 (11-47) n = 562	18 (10-31) n = 293	8 (4-12) n = 191	<0.0001

arr. ↓, rapidly decreasing; ↘, slightly decreasing; →, stable; ↗, slightly increasing; ↗, rapidly increasing.
Abbreviations: IQR, interquartile range; MedARD, median absolute relative difference.

4 | DISCUSSION

4.1 | Sensor accuracy and glycaemia

In line with different CGM systems, isCGM performance slightly deteriorated during hypoglycaemia.[25] Over the course of CGM advancement, the performance during hypoglycaemia clearly improved, with MedARDs similar to those found in our study: up to 21.7% (Senseonics Eversense)[26] and up to 26.9% (Medtronic Guardian Sensor 3),[8] which was also seen for Dexcom G6.[27] Several factors influence CGM performance during hypoglycaemia; however, hypoglycaemia is induced by a mismatch of insulin to blood glucose ratio, and hence is associated with a drop in glucose levels. Considering this, our data clearly showed that when separating the rate of change in glucose within different glycaemic ranges, isCGM has a higher MedARD during hypoglycaemia compared to the other glycaemic ranges (Table 3).

Nevertheless, a MedARD of 17.8% during hypoglycaemia level 2 and 20.5% during hypoglycaemia level 1 is still acceptable, especially for those with normal awareness of hypoglycaemia.[28] The MedARD during euglycaemia was lower than observed during hypoglycaemia but was higher than observed during hyperglycaemia. Additionally, in line with previous studies comparing different CGM systems,[8] isCGM sensor performance was more accurate during the nighttime period when compared to the daytime period. This difference in the MedARD might underline the lower rate of change in glucose during phases when no or fewer carbohydrates are ingested and no bolus insulin injections are performed.

4.2 | Sensor accuracy and exercise

In line with the results of a large number of studies performed during physical activity and exercise for different CGM systems,[7,29-31] isCGM sensor accuracy decreased, leading to a MedARD of 23.6% in adults with type 1 diabetes. In exercise with more rapidly changing glucose values, achieving an agreement between sensor glucose and blood glucose is even more challenging, hence current CGM systems help to overcome this challenge by providing regularly updated algorithms.

As shown by Zaharieva et al,[7] the lag time for the Dexcom G4 device was 12 ± 11 minutes during aerobic exercise when compared with reference blood glucose. However, as isCGM and CGM systems display trend arrows accompanied by the actual sensor glucose levels, therapy actions should be performed based on consideration of both.[32]

4.3 | Rate of change in glucose and sensor performance

The rate of change in glucose might be the strongest predictor for isCGM sensor performance, showing the highest MedARD during rapidly increasing and decreasing glucose levels (Figure 2 and Supplementary Appendix S2). isCGM tended to overestimate reference blood glucose levels during rapidly decreasing glucose levels (bias 32 mg/dL (1.8 mmol/L)) and tended to underestimate reference blood glucose levels during rapidly increasing glucose levels (−22 mg/dL (−1.2 mmol/L); Supplementary Appendix S3), which reflected the expected lag time as observed during exercise,[7] and which was confirmed in another study.[6] Furthermore, due to the absolute difference of 32 mg/dL during decreasing glucose values, assessing both the trend arrow and the actual sensor glucose level might also lower the risk of wrong therapeutic decisions.[33] From our point of view and based on our findings, diabetes education needs to highlight the fact that the physiological lag time for glucose to diffuse from the blood stream into the interstitial space can be assessed via trend arrows. This means that, for example, for downwards trend arrows (rapidly decreasing glucose) the actual sensor glucose level can be assumed to be subtracted by approximately −32 mg/dL.

This study has some limitations. Firstly, as we received data from different studies, we could not assess the actual software version (algorithm) of the isCGM systems; updated algorithms incorporated into isCGM systems improve sensor performance and lower physiological lag time. As we were not able to retrieve data from all identified studies, our study analysis is not fully representative of all data published for isCGM. Additionally, from a statistical point of view, datapoints from each person were not weighted; however, due to the large number of points of comparison, we do not suspect that this statistical limitation would mitigate our findings. Furthermore, we decided to assess isCGM sensor accuracy by means of MedARD, PEG and Bland-Altman analysis instead of ISO 15197:2013 due to the density of our data. Additionally, as our data analyses were based on testing for normal distribution, we decided to show our data only as MedARD and not as MARD. Notwithstanding, this study was well powered and showed clearly that glycaemia and, in particular, its rate of change, alter isCGM sensor accuracy.

This analysis showed that isCGM measures the interstitial glucose accurately when compared to reference blood glucose, with a MedARD of 12.7% in a total of 15.837 points of comparison. The rate of change in glucose altered isCGM performance, with lower accuracy during high rates of change, for both increasing and decreasing glucose levels.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Othmar Moser and Christoph Sternad wrote the manuscript. Max L. Eckstein, Agnieszka Szadkowska, Arkadiusz Michalak, Julia K Mader, Othmar Moser, Haris Ziko, Hesham Elsayed, Felix Aberer, Agnes Sola-Gazagnes, Etienne Larger, Gian Poalo Fadini, Benedetta Maria Bonora, Daniela Bruttomesso, Federico Boscari, Guido Freckmann, Stefan Pleus, Sverre C. Christiansen and Harald Sourij reviewed and edited the manuscript and contributed to the discussion. Othmar Moser, Christoph Sternad and Harald Sourij collected the data. Haris Ziko and Christoph Sternad performed the statistical analysis. Othmar Moser and Harald Sourij are the coordinators of this initiative. Harald Sourij is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14609.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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