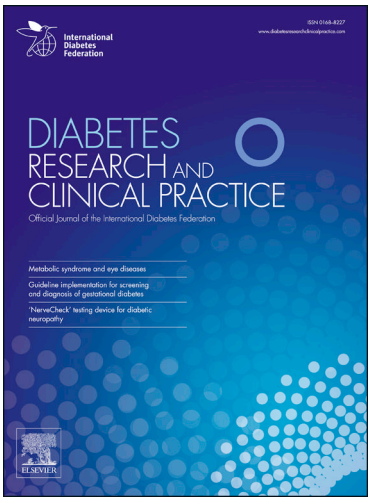

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Continuous Glucose Monitoring Use and Glucose Variability in Pre-school Children with Type 1 Diabetes

CGM use and GV in Pre-schoolers with Type 1 Diabetes

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Aims

The objective of this nationwide population-based cohort study was to evaluate the correlation between continuous glucose monitoring (CGM) use and glucose variability in pre-schoolers with type 1 diabetes.

Methods

We analysed data from the Slovenian National Registry. The primary endpoint was the difference in glucose variability between periods, during which participants were using CGM and periods, during which CGM was not used, over 5 years.

Results

A total of 40 children <8 years old were followed for an estimated observational period of 116 patient/years. Mean age at CGM initiation was 3.5 (±1.7) years. Both standard deviation of mean glucose [3.6 mmol/L (3.2–3.9) with CGM and 4.3 mmol/L (3.8–4.7) without CGM, p<0.001] and coefficient of variation [44.0% (40.4–47.0) with CGM and 46.1% (42.3–49.4) without CGM, p=0.021] were lower during the periods, when CGM was used. Frequent Continuous Glucose Monitoring use (>5 days/week) was associated with a 0.4% [4.4 mmol/mol] reduction in glycated haemoglobin level (7.6% compared to 7.2%, p=0.047).

Conclusions

Our results indicate that the use of CGM was associated with reduced glucose variability during a 5-year follow-up period among pre-schoolers with type 1 diabetes.

Key words

Continuous Glucose Monitoring, Type 1 Diabetes, Children, Insulin therapy

Trial Registration

Clinicaltrials.gov: NCT-03293082

Introduction

Continuous glucose monitoring (CGM) has been repeatedly demonstrated to improve glycaemic control, both in adult and paediatric populations [1], and is recommended as part of routine diabetes management [2]. However, in the youngest children, the benefit of CGM on glycated haemoglobin (HbA1c) has not been demonstrated [3]. Glycaemic variability (GV) is associated with a negative impact on brain volume and growth [4], and markers of cardiovascular morbidity [5] in children with type 1 diabetes, despite short disease duration. The use of CGM can reduce GV in adults and youth with type 1 diabetes [6,7], however, this has not yet been proven in pre-school children. To explore the impact of CGM use on GV in pre-school children with type 1 diabetes, we analysed data from a prospective national type 1 diabetes registry [8] during a 5-year follow-up.

Subjects

Data on pre-school children with type 1 diabetes using continuous subcutaneous insulin infusion (CSII) therapy, who started using CGM before the age of seven (inclusive) years from 2012 until 2017 were searched from the Slovenian National Type 1 Diabetes Registry. To be included in the analysis, children had to have type 1 diabetes for at least 6 months prior to the observation start date, more than 3 months of CSII use, and at least one follow-up period with and one without CGM use. Only reports after the introduction of CGM therapy were included.

The study protocol was approved by the Slovene Medical Ethics Committee and conducted in line with the last revision of Declaration of Helsinki with amendments. Patients gave their written informed consent for the anonymous use of data.

Materials and Methods

All participants used the same real-time CGM brand (Enlite II sensor with MiniLinkREAL-Time transmitter; Medtronic Diabetes, Northridge, CA, USA) and CSII – either Minimed 640G system or Paradigm Veo (both Medtronic Diabetes, Northridge, CA, USA). CSII device infuses a rapid-acting human insulin analog to the subcutaneous tissue at programmed basal rates to mimic the individual's needs, with additional bolus doses to cover meals and correct hyperglycemia. This form of therapy is, based on international recommendations, becoming the insulin regimen of choice in many countries, particularly for young children with type 1 diabetes and for better comparability, we have included only children with type 1 diabetes using CSII [9, 10].

The primary endpoint was the difference in GV, measured as standard deviation (SD) of mean glucose coefficient of variation (CV) [11], between periods during which participants were using CGM, and periods during which CGM was not used (self-monitoring of blood glucose (SMBG) periods). When a participant had multiple CGM and/or multiple SMBG periods, median values of investigated variables during the CGM or SMBG periods were calculated.

The parameters between CGM and SMBG periods were compared using Wilcoxon signed-rank test. To further elucidate the impact of CGM usage, participants were divided into frequent sensor users and non-frequent sensor users based on the threshold of using CGM for more than 5 days per week during the sensor period. These variables between frequent and non-frequent CGM users were compared with Mann–Whitney U test. To balance the effect of the outliers, we have used non-parametric statistical methods and we report the full range of values for each section. Statistical analysis was performed using R statistical language.

To account for the possible effect of a different number of times the glucose value was measured (glucose value in people with diabetes is non-normally distributed) with a sensor device and with SMBG on the standard deviation of glucose values, we simulated daily

glucose variability of a person with type 1 diabetes, sampled from this simulation 10.000-times two samples with either 10 or 200 measurements, calculated standard deviation for each sample, and compared the standard deviations to each other. The mean standard deviation of samples with 10 measurements was significantly lower (t-test) from the mean standard deviation of samples with 200 measurements (data not shown).

Results

We identified 43 pre-school children (age < 8 years) with type 1 diabetes using CGM (mean (SD) age at diabetes onset 2.6 (±1.3) years, at CSII initiation 2.8 (±1.6) years, age at CGM initiation 3.5 (±1.7) years, and mean duration of type 1 diabetes of 3.7 (±1.8) years. Three participants were excluded due to lack of non-CGM periods data. Data from 40 participants were analysed. CGM data were available for 214 reports, and SMBG only (control) data for 250 reports, with an estimated observational period of 116 patient/years. On average, participants had 5.4 (±4.4) CGM reports and 6,3 (±4.6) non-CGM (SMBG only) reports, with a median (IQR) number of SMBG measurements of 7.1 (2.1) in CGM and 7.7 (1.8) in non-CGM (p = 0.15) per day.

Data representing glucose variability and glycaemic control are shown in Table 1 (median (IQR)) and Figure 1. Both glucose SD and CV decreased with CGM use: SD was 3.6 mmol/L (3.2-3.9) with CGM, compared to 4.3 mmol/L (3.8-4.7) without CGM, p<0.001; and CV was 44.0% (40.4 – 47.0) with CGM, compared to 46.1% (42.3-49.4) without CGM, p=0.021.

There was no difference in CGM-measured mean glucose level (9.4 mmol/L) compared to SMBG mean glucose (9.3 mmol/L, p=0.189), or HbA1c (7.6 % (59.6 mmol/mol) with CGM and 7.7% (60.7 mmol/mol) with SMBG use, p=0.867). The numerical difference in total daily insulin failed to reach statistical significance: 9.7 units per day (7.3-12.9) with CGM and 8.9 units per day (6.2-12.2, p=0.057) with SMBG.

Frequent (>5 days/week, 12 participants) CGM use was associated with a reduction in HbA1c by 0.4% [4.4 mmol/mol]: 7.2% (6.8–7.6) [55.2 mmol/mol (50.8–59.6)] with frequent CGM use and 7.6% (7.4–8.0) [59.6 mmol/l (57.4–63.9)] with non-frequent CGM use, p=0.047.

Overall, there were no severe hypoglycaemic events in either group. Five participants (one in CGM group and four in SMBG group, estimated admission rate 4.3/100 patient-years) required hospitalization due to diabetic ketoacidosis that resolved with parenteral hydration and iv insulin infusion.

Discussion

Increased availability and reimbursement of real-time CGM devices among paediatric patients has the potential to improve glycaemic control beyond HbA1c in this vulnerable population [12,13]. This study in pre-school children with type 1 diabetes demonstrated that CGM use can reduce glucose fluctuations compared to SMBG alone, hence improving glycaemic control beyond HbA1c in a real-life setting. Possible explanations include more frequent real-time insulin adjustments based on sensor glucose trends in this group of children, where parents are usually responsible for diabetes management. Similarly, data from the JDRF study of CGM use in type 1 diabetes, which included 142 children aged between 8 and 14 years, showed that after 26 weeks of CGM use almost all indices of GV declined compared to baseline [14].

The role of GV as a risk factor for developing complications of diabetes remains controversial, however, several reports associate GV with oxidative stress and damage to susceptible organs [15,16] and chromosomes [17]. Consequently, preventing excessive glucose fluctuations early in the disease course could provide long-term benefit for children. A recent call to action emphasized than not only diabetologists but also

regulatory bodies should acknowledge therapies that improve time in range, glycaemic variability, and other parameters beyond HbA1c [18,19].

An appropriate incorporation of CGM data into clinical practice, both for day-to-day decision making and retrospective analysis, remains a challenge for children, their families, and professional health-care providers. Particularly as the CGM efficacy is associated with the frequency of its use: those who used near-daily CGM have a greater reduction in HbA1c and a greater percentage of blood glucose values in target range compared with those who use it less frequently [20]. Our data showed that frequent use of CGM for at least five days per week was associated with a significant decrease in HbA1c by 0.4% [4.4 mmol/mol].

Limitations of this analysis include the observational design and retrospective analysis, therefore, we could not control for confounding factors and observed associations cannot prove causality. Also, some of the recommended CGM and glycemic variability metrics (such as low and high blood glucose index, mean amplitude of glycemic excursions and others) could not be calculated. Reasons for CGM use discontinuation were not evaluated in this analysis. As some participants use CGM intermittently between non-CGM periods, there might be possible carry-over effect with the lack of any wash-out period. The difference in the number of glucose measurements per day with the CGM compared to SMBG can influence the standard deviation of mean glucose, however, in the direction opposite to the result in this study, as demonstrated by our *in silico* sampling. Because of these limitations, our reported observations should be interpreted with caution.

In summary, long-term CGM use reduced GV in pre-school children with type 1 diabetes. Our data support the use of CGM early in disease course in pre-school children, for whom we currently lack evidence-based treatment guidelines. Prospective studies investigating potential benefits of CGM use in this subgroup of patients, particularly related to the developing brain, and implementing outcomes beyond HbA1c, are warranted.

Article Information

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Duality of Interest. NB received honoraria for participation on the speaker's bureau of Medtronic and Roche. TB served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic and Bayer Health Care. TB's Institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. KD, KC, JS and AS declare that there is no duality of interest associated with their contribution to this manuscript. No commercial company was involved in the planning, conduct, statistical analysis, results reporting and drafting of the manuscript.

Author Contributions. KD, KC, JS, AS, NB, and TB contributed to the study concept and design. NB and TB supervised the study. KD, KC, JS, and AS collected data. All authors participated in data analysis and interpretation. The manuscript was drafted by KD, NB and TB, and reviewed by KD, KC, JS, AS, NB, TB. All authors read and approved the final submitted version of the manuscript.

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Figure 1. A. Glycaemic control comparing **A.** CGM (purple) to non-CGM (green) periods and **B**. CGM frequent (>5 days/week) CGM (purple) to non-frequent CGM (green) periods. CGM – Continuous Glucose Monitoring. CV – Coefficient of variation of mean glucose. HbA1c – glycated Hemoglobin. SD – Standard deviation of mean glucose

Table 1. Glycaemic control comparing sensor-based glucose metrics to SMBG and frequent (>5 days/week) CGM to non-frequent CGM

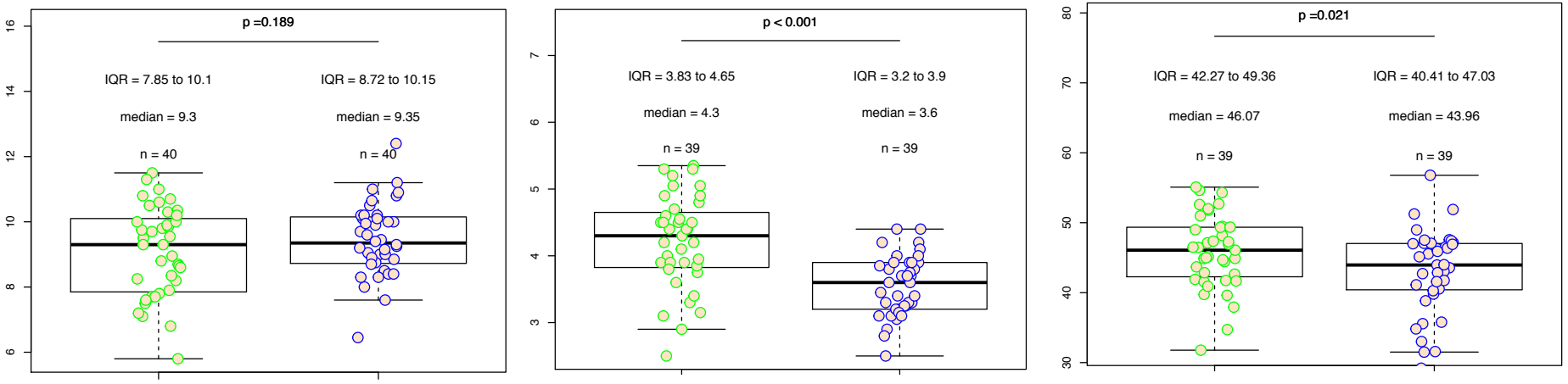
			p value
	CGM	*SMBG only*	
CV (%)	44.0 (40.4–47.0)	46.1 (42.3–49.4)	0.021
SD (mmol/L)	3.6 (3.2–3.9)	4.3 (3.8–4.7)	< 0.001

SD (mg/dL)	64.8 (57.6–70.2)	77.4 (68.4–84.6)	< 0.001
Mean glucose (mmol/L)	9.4 (8.7–10.2)	9.3 (7.9–10.1)	0.189
Mean glucose (mg/dl)	169.2 (156.6–183.6)	167.3 (142.2–181.8)	0.189
TDD (units/day)	9.7 (7.3−12.9)	8.9(6.2−12.2)	0.057
HbA1c (%)	7.6 (7.2–8.0)	7.7 (7.2–8.0)	0.867
HbA1c (mmol/mol)	59.6 (55.2–63.9)	60.7 (55.2–63.9)	0.867
	Frequent CGM	*Non-Frequent CGM*	
CV (%)	36.0 (34.0–37.0)	37 (35.0–39.0)	0.152
SD (mmol/L)	3.3 (3.1–3.7)	3.6 (3.3–3.9)	0.144
SD (mg/dL)	59.4 (55.8–66.6)	64.8 (59.4–70.2)	0.144
Mean glucose (mmol/L)	9.1 (8.6–9.8)	9.7 (8.9–10.1)	0.286
Mean glucose (mg/dL)	163.8 (154.8–176.4)	174.6 (160.2–181.8)	0.286
HbA1c (%)	7.2 (6.8–7.6)	7.6 (7.4–8.0)	0.047
HbA1c (mmol/mol)	55.2 (50.8–59.6)	59.6 (57.4–63.9)	0.047

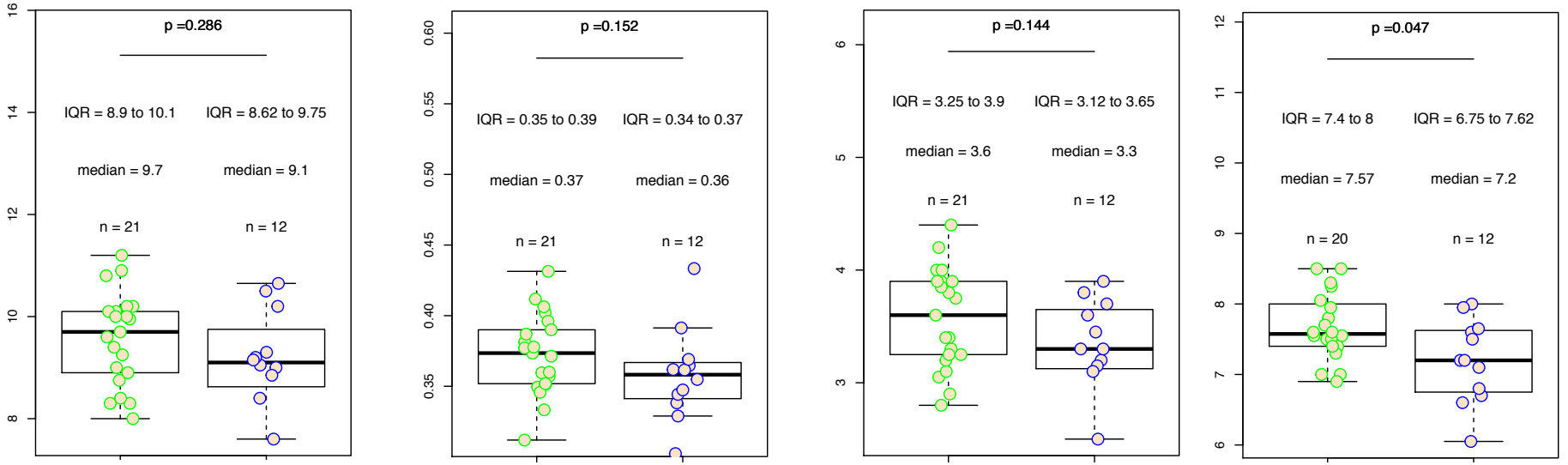
Nonparametric analyses for data on glucose control (paired nonparametric Wilcoxon signed rank test), frequent/non-frequent CGM use (Mann–Whitney U test), and outcome data are presented as median (IQR), although variables for the analyses were mean (glucose, glucose concentration SD).

CGM – Continuous glucose monitoring, SMBG – Self-monitoring of blood glucose, TDD – Total daily dose

A


Average glucose (mmol/l)
p =0.189
IQR = 7.85 to 10.1
median = 9.3
n = 40
IQR = 8.72 to 10.15
median = 9.35
n = 40
SD (mmol/l)
p < 0.001
IQR = 3.83 to 4.65
median = 4.3
n = 39
IQR = 3.2 to 3.9
median = 3.6
n = 39
CV (%)
p =0.021
IQR = 42.27 to 49.36
median = 46.07
n = 39
IQR = 40.41 to 47.03
median = 43.96
n = 39

B


Average glucose (mmol/l)
p =0.286
IQR = 8.9 to 10.1
median = 9.7
n = 21
IQR = 8.62 to 9.75
median = 9.1
n = 12
CV (%)
p =0.152
IQR = 0.35 to 0.39
median = 0.37
n = 21
IQR = 0.34 to 0.37
median = 0.36
n = 12
SD (mmol/l)
p =0.144
IQR = 3.25 to 3.9
median = 3.6
n = 21
IQR = 3.12 to 3.65
median = 3.3
n = 12
HbA1c (%)
p =0.047
IQR = 7.4 to 8
median = 7.57
n = 20
IQR = 6.75 to 7.62
median = 7.2
n = 12