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The use of CGM to identify hypoglycemia and glycemic patterns in congenital hyperinsulinism

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Abstract

Objectives: Unrecognized hypoglycemia, especially in the neonatal population, is a significant cause of morbidity and poor neurologic outcomes. Children with congenital hyperinsulinism (HI) are at risk of hypoglycemia and point of care testing (POCT) is the standard of care. Studies have shown that continuous glucose monitoring (CGM) improves glycemic control and reduces the frequency of hypoglycemia among children with type 1 diabetes. There is limited experience with the use of CGM in children with HI. To assess the glycemic pattern of children with HI on stable therapy and evaluate the frequency of undetected hypoglycemia using Dexcom G6® CGM.
Methods: A cross-sectional, observational pilot study was done in 10 children, ages 3 months to 17 years. Each child had a clinical or genetic diagnosis of HI on stable medical therapy. Participants were asked to continue their usual POCT blood glucose monitoring, as well as wear a blinded Dexcom G6® CGM during a 20-day study period with the potential of unblinding if there was severe hypoglycemia detected during the study trial.
Results: During the study period, 26 hypoglycemic events were noted by CGM in 60 % of the participants with 45 % occurring between 0600 and 0800.
Conclusions: CGM can help detect hypoglycemia and blood glucose trends during a time when there is usually no POCT, which can guide medical management. 30 % of our population had a dose adjustment in their medications. This study was limited by population size.

Keywords: congenital hyperinsulinism; continuous glucose monitoring; hypoglycemia; absolute relative difference (MARD)

Introduction

Patients with congenital hyperinsulinism (HI) can experience significant morbidity, mainly secondary to hypoglycemia. In patients with HI, inappropriately elevated insulin concentration leads to hypoglycemia. Insulin suppresses ketogenesis, hence depriving the body and brain of other sources of energy. This can have profound consequences for the neonate and infant's brain development, whether the disease is transient or permanent. Studies have shown neurological impairment with associated MRI findings as high as 50 % in children with HI [1, 2].

Prompt diagnosis of hypoglycemia should be the primary focus in management of infants with HI, and treatment should be tailored to each patient's glycemic patterns. Typically, hypoglycemia in children and adolescents with HI is treated with carbohydrate supplementation and/or medications that inhibit insulin secretion such as diazoxide, which works to keep the K+ ATP channels open, or octreotide, a somatostain analogue. Point-of-care testing (POCT) using capillary glucose meters is the standard of care for blood glucose monitoring in patients with HI. The frequency varies from one to more than eight measurements per day according to the perceived severity of the disease, number of symptomatic episodes, and the age of the patient. At our tertiary academic care center, most patients with HI are seen every 3–6 months.

Intermittent POCT only provides a snapshot information of a patient's glycemic trends. Even if measurements are performed multiple times per day, they do not accurately reflect glycemic patterns and may fail to detect hypoglycemia, particularly when they occur overnight or in patients that are asymptomatic. In addition, POCT can be inconvenient and add significant distress and burden for patients and their caregivers. In newborns and infants, heel lance, the routine method of drawing blood, is recognized as a painful procedure, and is usually done without analgesia or sedation [3].

Continuous glucose monitoring (CGM) may provide a solution to some of these challenges. These sensors provide

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continuous interstitial glucose readings. For Dexcom G6®, glucose readings are reported every 5 min, for a total of 288 values/day. Most studies assessing the accuracy of these devices have been conducted in people living with diabetes. Whereas older device generations such as Dexcom G5® had a high false positive rate of hypoglycemia [4] and needed calibration with POCT by the user, Dexcom G6® has shown more precise and accurate results during hypoglycemia, specifically with a mean absolute difference (MAD) of 0.43 mmol/L when blood glucose is between 3.0 and 3.9 mmol/L, and a MAD of 0.6 mmol/L, when blood glucose is less than 3.0 mmol/L [5]. In patients with diabetes, CGM has been shown to improve glycemic control and reduce the frequency of hypoglycemia, and is now considered standard of care [6].

Recent studies have evaluated the use of CGM in pediatric patients with HI. Braune et al. [7] used Dexcom G6® in a newborn with transient hyperinsulinism to decrease the frequency of POCT. A randomized, controlled, multicenter study in preterm neonates showed that CGM could help decrease exposure to prolonged or severe hyperglycemia and hypoglycemia in this at-risk group [8]. Worth et al. [9] evaluated a large dataset of pediatric patients with HI using either Dexcom G4® or G6® and found that patients experienced a mean of 1.3 hypoglycemic events per day (and 2.6 hypoglycemic events when not on therapy). Despite its use in this patient population, CGM has not been approved since there remain challenges with the use of CGM, particularly related to accuracy [10–12].

To better understand the frequency of hypoglycemia and glycemic patterns in patients with HI on stable medical therapy, we performed a pilot study and hypothesized that children and adolescents with HI on stable medical therapy can still experience asymptomatic hypoglycemia not recognized by routine POCT, which can be detected using CGM.

Objectives

(1) To assess the glycemic patterns in patients medically treated for HI using Dexcom G6®.
(2) To compare the number of hypoglycemic episodes detected by standard POCT vs. Dexcom G6® in children and adolescents treated for HI.

Materials and methods

Study design and participants

This is a prospective, pilot observational study in children 0–18 years old with HI followed by the endocrinology division at British Columbia Children's Hospital (BCCH), a tertiary pediatric academic center located in Vancouver, Canada.

All children under the age of 18 years with a genetic or clinical diagnosis of HI under medical treatment with diazoxide or octreotide were eligible to be enrolled in the study, and were identified from the endocrinology database at BCCH. Exclusion criteria included the use of CGM 60 days prior to the start of the study, and changes in medical therapy or a hospital admission 15 days prior to the start of the study.

After identification, each chart was manually reviewed to determine eligibility. A letter of study introduction was sent to all potential participants and/or their caregivers. They were then contacted by the research coordinator who presented the research project. Participants were enrolled after informed consent and assent (as applicable) were obtained.

The duration of the study was 20 days. The study timeline is shown in Figure 1. At their first visit to the study site, participants had a blinded Dexcom G6® sensor inserted. They were also given a new glucometer, Contour Next®, and asked to monitor their blood glucose, as advised by their primary endocrinologist, and to continue the same medical therapy. The blinded use of Dexcom G6® was mandatory for the first 10 days of the study. At the second visit (after 10 days), data was uploaded to the Dexcom software, Clarity, and reviewed by the investigators. If prolonged or severe hypoglycemia episodes were detected by CGM (BG <2.8 mmol/L for 60 min or BG <2.0 mmol/L for 30 min), families were offered to use an unblinded CGM for the remaining 10 days. If there was no prolonged or severe hypoglycemia detected, participants continued using the blinded CGM. At the third visit (end of the 20-day study period), CGM data was uploaded and reviewed again on Clarity. Contour Next® POCT data was also obtained from all participants. The participants and their primary endocrinologists were provided with a copy of the CGM data to guide dose adjustments if necessary.

Measurements

Demographic data for participants included age, gender, etiology of hyperinsulinism, and their current medical therapy. As per the Canadian Pediatric Society statement [13], hypoglycemia in patients with known HI is defined by a blood glucose value below 3.3 mmol/L. Hence, in this study, hypoglycemia was defined by one punctual POCT BG value below 3.3 mmol/L or by a CGM value below 3.3 mmol/L sustained for a minimum of 10 min. To pair the CGM and POCT BG values for analysis, CGM sensor data up to 10 min after a POCT BG was collected, as the

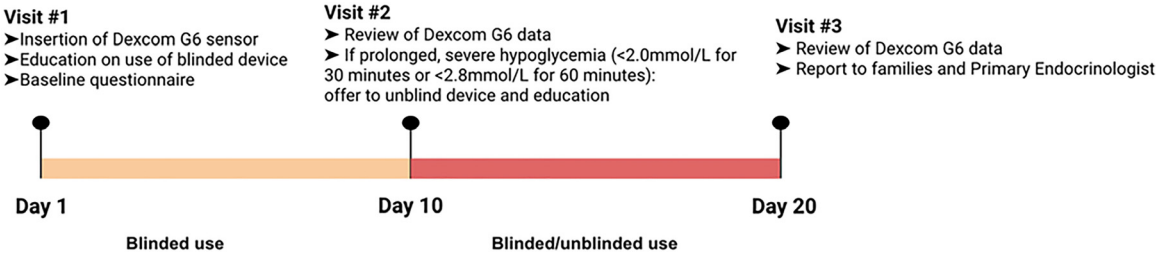

Figure 1: Study timeline.

average physiological delay between interstitial and plasma glucose can be up to 10 min. The POCT BG was paired to the nearest, 5 min, and 10 min CGM value. The absolute difference between these paired values was calculated, and the minimum absolute difference was used. The MAD and mean absolute relative difference (MARD) between the POCT and the CGM BG values was calculated using the minimum absolute differences.

Data analysis

Data from Clarity was downloaded into an Excel® spreadsheet. Verification was done between the participant ID and the sensor serial number to ensure data matched accurately. Data from the Contour Next® glucometer was manually entered into the Excel® spreadsheet in the same format as the CGM data. A double verification was performed to ensure accuracy of the transcription. Data was processed in Matlab® R2022a, a programming numeric computing platform used to analyze data. Glycemic pattern graphics were created using the Dexcom Clarity software functionality. The lower end of the target range, defined as 3.9 mmol/L for people with diabetes, was modified to 3.3 mmol/L. The upper end of the target range, defined as 10.0 mmol/L for people with diabetes, was not modified.

Results

Forty patients with HI were identified. A total of 10 participants ages 3 months to 17 years were enrolled, and nine completed the 20-day study. The study flow chart is illustrated in Figure 2. One withdrew from the study after four days, as the caregiver believed the child's increased fussiness was secondary to the sensor. The demographic data is reported in Table 1. The median age was 5.6 years (Q1: 2.8, Q3: 14.1), and half of the participants were male (n=5). The individual daily average glycemic profile of each participant is available in the Supplemental Material, Appendix 1. Analysis of these profiles showed that overall, participants remained in range more than 99 % of the time, aside from two participants who were in range 90 % and 95 % of the time.

On average, POCT was performed 1.2 (SD 0.80) times a day. No participant had their CGM unblinded after 10 days, since there was no prolonged or severe hypoglycemia detected. During the study period, a total of 26 hypoglycemia episodes were recorded by CGM in six participants, for a median of two episodes per participant (Q1: 0, Q3: 3). Four of these participants (66.7 %) were under 6 years old. One participant had nine episodes (34.5 %, AE), and another had seven episodes (26.9 %, AG). The average duration of total hypoglycemia episodes was 26.5 min, with a median of 15 min (Q1: 10.0, Q3: 28.8.). The distribution of hypoglycemia is reported in Table 2. The average blood glucose value of all hypoglycemia events was 2.9 mmol/L (Q1: 2.8, Q2: 2.9), equal to the median. The lowest blood glucose measured via CGM was 2.3 mmol/L. Only one episode of hypoglycemia was detected by POCT (2.7 mmol/L). 50 paired values between CGM and POCT BG data were collected. The MARD was 11.63 % (SD: 7.9, 95 % CI: [6.2, 17.1]) and the MAD was 0.56 mmol/L (SD: 0.43, 95 % CI: [0.26, 0.86]).

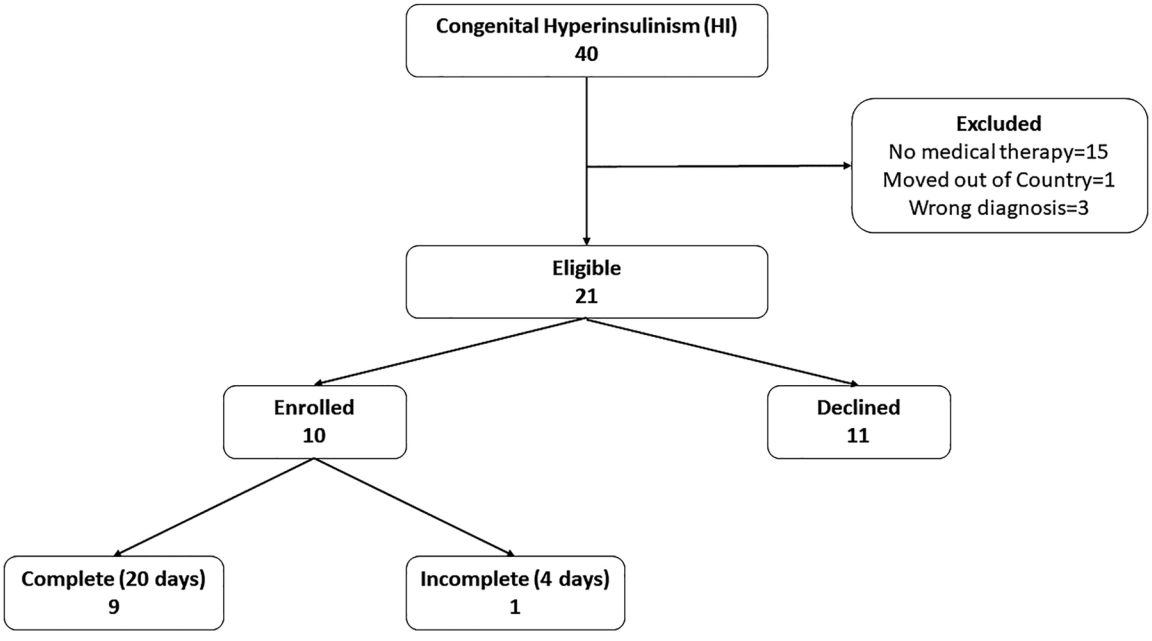

Figure 2: Flow chart diagram.

Table 1: Demographic data.

ID	Gender	Age, years	Diagnosis	Medical therapy	Dose
AI	M	0.9	Hyperinsulinism secondary to Beckwith–Wiedemann syndrome	Diazoxide	5.4 mg/kg/day
AA	M	1.1	Hyperinsulinism likely secondary to prematurity	Diazoxide	2.0 mg/kg/day
AH	M	2.5	Hyperinsulinism secondary to Kabuki syndrome	Diazoxide	2.2 mg/kg/day
AE	F	3.7	Congenital HI secondary to compound heterozygous paternally-inherited recessively-acting p.(Arg1494Trp) and a maternally-inherited recessively-acting variant p.(Glu1456Ly) in the ABCC8 gene	Diazoxide	6.2 mg/kg/day
AG	M	4.2	Congenital HI secondary to p.A447T mutation in GLUD1 gene	Diazoxide	4.4 mg/kg/day
AD	F	7.0	Congenital HI (genetic etiology unknown)	Diazoxide	9.7 mg/kg/day
AF	F	10.7	Congenital HI secondary to heterozygous variant of uncertain significance in the GLUD1 gene	Diazoxide	3.9 mg/kg/day
AC	F	15.3	Congenital HI secondary to maternally inherited heterozygous (c.946G>A or p.Gly316Arg) ABCC8 mutation	Diazoxide	5.8 mg/kg/day
AB	M	16.9	Congenital HI likely secondary to heterozygous mutation for a variant of unknown significance (val66met) of HNF4A; heterozygous variant for PCK2 and PYGL	Diazoxide	2.6 mg/kg/day
AJ	F	17.5	Congenital HI, genetic etiology unknown	Octreotide	0.94 µg/kg/day

Table 2: Results

Number of hypoglycemia detected by CGM	26
Median duration in minutes (Q1, Q3)	15.0 (10.0, 28.8)
Average duration in minutes (SD)	26.5 (40.9)
Onset between	
00h00–08h00 (%)	11 (42.3)
08h00–16h00 (%)	10 (38.5)
16h00–00h00 (%)	5 (19.2 %)
Mean absolute relative difference	
% (SD)	11.63 (7.89)
mmol/L (SD)	0.56 (0.43)

CGM results demonstrated a common glycemic pattern of a mild decrease in BGs after midnight followed by an increase in the morning around 0800, with 45 % of the hypoglycemia episodes occurring in the early morning hours between 0600 and 0800. Some specific individual analysis of glycemic patterns in our participants are described below the Supplemental Material, Appendix 1.

(1) A 3-year-old female (AE) had three hypoglycemic events all happening between 0600 and 0900 over the duration of the study, but was otherwise close to the lower threshold of 3.3 mmol/L overnight. After reviewing the CGM data and discussing with the family, the primary endocrinologist increased their diazoxide dose.
(2) A 1-year-old male (AA) showed a stable glycemic pattern overnight with consistently higher BGs ranging between 9.0 and 11.0 mmol/L throughout the day. No blood glucose measurements were below 5.0 mmol/L. This participant withdrew from the study after four days and was lost to follow-up.
(3) A 17-year-old male (AJ) showed a consistent pattern of one or two hyperglycemic events with a sharp increase above 10 mmol/L daily. At visit 2, it was noted that the morning (close to 9 am) peak in BG corresponded to the participant taking their medication along with a morning snack. The late-night peak (close to midnight) in BG corresponded to their late-night snacking habits. This participant was the only one on octreotide (0.94 mcg/kg/day), which was taken in the morning, after a discussion with their primary endocrinologist, the octreotide dose was reduced.

Discussion

The results of this pilot study revealed a total of 26 hypoglycemia episodes (less than 3.3 mmol/L for a minimum of 10 min) detected by CGM in a total of six participants (60 %), ranging from two to nine episodes per participant during the 20-day study. Four of these participants (66.7 %) were under 6 years old. Forty-five percent of the hypoglycemia episodes detected by CGM occurred in the early morning hours between 0600 and 0800. This finding agrees with Worth et al. [14], who studied the glycemic patterns in children with HI (n=23) and idiopathic ketotic hypoglycemia (n=24) using both Dexcom G4® and G6®. They identified the early morning

period (0300–0700) as being the most conducive to hypoglycemic events, when the risk is usually 2–3 times higher than other times of the day [14].

In our study, younger children with HI seem to be more prone to hypoglycemia episodes. This is likely because their medications require frequent dose adjustments as they grow. POCT BG was not systematically measured at the time of the undetected hypoglycemia episodes noted on CGM; hence, it is difficult to conclude how many of these episodes were true hypoglycemic events or compression lows that can occur when a child is laying on their sensor site when asleep. However, the glycemic patterns detected by CGM did lead to medication dose adjustments in our study: one patient had their octreotide dose reduced by 40 %, one was weaned off diazoxide completely, and another had their diazoxide dose increased by 25 %.

Worth et al. [14] showed that in children with HI, hypoglycemia episodes detected by Dexcom G6® were sustained for an average of 35 min. This agrees with our results, which showed a positively skewed distribution of time spent in hypoglycemia with an average of 26.5 min (SD 40.9) and a median of 15 min (Q1: 10.0, Q3: 28.8). This is because 33 % (2/6) of our participants had majority of the hypoglycemia episodes (16/26, 62 %).

CGM accuracy in HI is limited. The use of Dexcom G4® and G5® in patients with HI has shown MARD values ranging between 11.0 and 17.5 % [4, 10, 15, 16]. However, these analyses have also included normoglycemic values, overestimating the accuracy of CGM specifically in hypoglycemia. Worth et al. [11] showed a MARD of 19.3 % using Dexcom G6® in patients with HI; however, when the true negative values defined as sensor BG and POCT BG >4.0 mmol/L were removed, the MARD increased to 23.2 %, demonstrating a further reduction in CGM accuracy. In our study, the MARD was 11.63 % and the MAD was 0.56 mmol/L. Though the calculated MARD is low compared to what has been reported in the literature, this was because the MARD was calculated almost exclusively with euglycemic values, as only one of all POCT BG measurements was below 3.3 mmol/L. We did not have enough POCT BG measurements during hypoglycemia detected via CGM, which could be attributed to the use of a blinded CGM.

With the use of Dexcom G6®, there can still be false positives, often associated with compression lows overnight, which can result in increased parental anxiety. Further, Worth et al. [11] showed a high false negative rate of 7.2 % in patients with HI using Dexcom G6®, though this number could be higher since the incentive to check a POCT BG during normoglycemia on CGM is low. Our study highlights that the goal of using CGM is not to replace POCT in patients with HI, but rather to have a clinical adjunct method to detect asymptomatic hypoglycemia, as shown in other studies [11, 15, 17], and to identify blood glucose trends to guide medication dose adjustments. This would be helpful, especially in younger children with transient hyperinsulinism or those who need frequent medication dose adjustments as they grow, as also concluded by Ranannavar et al. [4].

CGM is not a licensed device and has not been validated for patients with hyperinsulinism. Risks regarding the accuracy of CGM needs to be considered such as the suboptimal sensitivity to detect hypoglycemia, which provides a false reassurance to patients with HI. There is also an increased incidence of false positives with compression lows. However, this should not deter clinicians from using CGM to identify blood glucose trends. Despite the limited size of our study, the use of CGM helped guide dose adjustments in 30 % of our population. It is worth considering CGM trials periodically to detect glycemic patterns and frequency of hypoglycemia episodes in patients with HI to better guide medication dose adjustments.

Limitations

Although we identified 40 potential participants, a relatively small number (n=10) showed interest in the study. We do not have a definite explanation for this modest uptake, but we postulate that patients and families may feel overly confident that no additional monitoring is needed if the POCT BG is within the target range. Our clinical experience is that unless these patients have symptoms of hypoglycemia, many of these children and adolescents only check their POCT BG the week before and after a clinic appointment to guide medication dose adjustments as requested by their endocrinologist. Overnight POCT is seldom done unless advised to specifically do so by the clinician. Thus, this could lead to a selection bias as participants in this study could potentially be families that are more anxious about the diagnosis of hyperinsulinism or those that have experienced previous episodes of symptomatic hypoglycemia.

Our study by design is in contrast to a real life situation (used in most published literature) where patients first get the information about a potential hypoglycemic episode from their CGM and then verify the sensor BG with a POCT BG. Since we used a blinded CGM, we only analyzed the CGM BG after the patient measured a POCT BG, to account for the physiologic time lag between CGM and POCT BG values. We decided to use a blinded Dexcom G6® CGM protocol to avoid bias secondary to knowledge of glycemic patterns by the participant and/or their caregivers, which could have led to more normoglycemic trends if there was treatment

intervention for the asymptomatic hypoglycemia episodes. However, there was no POCT BG measurements at the time of the hypoglycemia episodes detected by CGM; hence, it is difficult to accurately conclude which events were true hypoglycemia episodes or events related to compression lows. Thus, the MAD and MARD that we computed solely reflect the mean differences during normoglycemia. It is possible that the MAD and MARD could be higher during hypoglycemia [18]. Finally, the MAD and MARD were calculated on a relatively small number of samples (n=50) which may account for the relatively wide CI.

Though intervention for use of an unblinded CGM was outlined in our study design, there were no participants with severe or prolonged hypoglycemia. The use of an unblinded CGM could have been offered to participants for half of the study with guidance on obtaining POCT BG measurements during episodes of hypoglycemia (<3.3 mmol/L for 10 min) detected by CGM. This would have allowed us to accurately compare the frequency of hypoglycemia detected by CGM as well as calculate a MAD or MARD during hypoglycemia.

Conclusions

The results of our pilot study identified undetected hypoglycemia episodes in patients with HI with the use of Dexcom G6®, of which most of these episodes occurred in the early morning hours. It also helped us identify blood glucose trends that led to medication dose adjustments in our study. POCT BG monitoring along with the periodic use of an unblinded CGM could better guide the frequency of hypoglycemia episodes and aid in identifying blood glucose trends for medication dose adjustments, especially in the pediatric population with hyperinsulinism.

Research ethics: The study protocol was approved by the University of British Columbia Research ethics board (H21-01860). Written informed consent and assent was obtained to participate in this study from each patient and or caregiver. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Informed consent: Written informed consent and assent was obtained to participate in this study from each patient and or caregiver.

Author contributions: M.G. was involved in analyzing and interpreting the data and led the manuscript preparation. N.Y. was involved in recruiting participants, collecting the data, and assisted in manuscript preparation. C.S. was involved in designing the study and assisted in manuscript preparation. J.P.C was involved in designing the study, analyzing and interpreting the data and assisted in manuscript preparation. F.S.A was involved in analyzing and interpreting the data, assisted in manuscript preparation, and supervised the project.

Competing interests: None.

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Data availability: The raw data can be obtained upon request from the corresponding author.

References

1. Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L, et al. Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. Front Endocrinol 2013;4:60.
2. Roeper M, Salimi Dagsari R, Hoermann H, Mayatepek E, Kummer S, Meissner T. Risk factors for adverse neurodevelopment in transient or persistent congenital hyperinsulinism. Front Endocrinol 2020;11: 580642.
3. Friedrichsdorf SJ, Goubert L. Pediatric pain treatment and prevention for hospitalized children. Pain Rep 2019;5:e804.
4. Rayannavar A, Elci OU, Mitteer L, De León DD. Continuous glucose monitoring systems: are they useful for evaluating glycemic control in children with hyperinsulinism? Horm Res Paediatr 2019;92:319–27.
5. Wadwa RP, Laffel LM, Shah VN, Garg SK. Accuracy of a factory-calibrated, real-time continuous glucose monitoring system during 10 days of use in youth and adults with diabetes. Diabetes Technol Ther 2018;20:395–402.
6. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care 2010;33:17–22.
7. Braune K, Wäldchen M, Raile K, Hahn S, Ubben T, Römer S, et al. Open-source technology for ereal-time continuous glucose monitoring in the neonatal intensive care unit: case study in a neonate with transient congenital hyperinsulinism. J Med Internet Res 2020;22: e21770.
8. Beardsall K, Thomson L, Guy C, Iglesias-Platas I, van Weissenbruch MM, Bond S, et al. Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. Lancet Child Adolesc Health 2021;5:265.
9. Worth C, Tropeano Y, Gokul PR, Cosgrove KE, Salomon-Estebanez M, Senniappan S, et al. Insight into hypoglycemia frequency in congenital hyperinsulinism: evaluation of a large UK CGM dataset. BMJ Open Diabetes Res Care 2022;10:e002849.
10. Worth C, Dunne MJ, Salomon-Estebanez M, Harper S, Nutter PW, Dastamani A, et al. The hypoglycaemia error grid: a UK-wide consensus on CGM accuracy assessment in hyperinsulinism. Front Endocrinol 2022;13:1016072.

11. Worth C, Nutter PW, Dunne MJ, Salomon-Estebanez M, Banerjee I, Harper S. HYPO-CHEAT's aggregated weekly visualizations of risk reduce real world hypoglycaemia. Digit Health 2022;8: 20552076221129712.
12. Worth C, Hoskyns L, Salomon-Estebanez M, Nutter PW, Harper S, Derks TGJ, et al. Continuous glucose monitoring for children with hypoglycaemia: evidence in 2023. Front Endocrinol 2023;14: 1116864.
13. Narvey MR, Marks SD. The screening and management of newborns at risk for low blood glucose. Paediatr Child Health 2019; 24:534–44.
14. Worth C, Harper S, Salomon-Estebanez M, O'Shea E, Nutter PW, Dunne MJ, et al. Clustering of hypoglycemia events in patients with hyperinsulinism: extension of the digital phenotype through retrospective data analysis. J Med Internet Res 2021;23:e26957.
15. Win M, Beckett R, Thomson L, Thankamony A, Beardsall K. Continuous glucose monitoring in the management of neonates with persistent hypoglycemia and congenital hyperinsulinism. J Clin Endocrinol Metab 2022;107:e246–53.
16. Vijayanand S, Stevenson PG, Grant M, Choong CS, Davis EA, Abraham MB. The utility of continuous glucose monitoring systems in the management of children with persistent hypoglycaemia. J Pediatr Endocrinol Metab 2021;34:1567–72.
17. Conrad SC, Mastrototaro JJ, Gitelman SE. The use of a continuous glucose monitoring system in hypoglycemic disorders. J Pediatr Endocrinol Metab 2004;17:281–8.
18. Heinemann L, Schoemaker M, Schmelziesen-Redecker G, Hinzmann R, Kassab A, Freckmann G, et al. Benefits and limitations of MARD as a performance parameter for continuous glucose monitoring in the interstitial space. J Diabetes Sci Tech 2020;14:135–50.

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