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ORIGINAL ARTICLE

Clinical Use of Continuous Glucose Monitoring in Pediatrics

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Introduction

THE FIRST REPORTED clinical use of a continuous glucose monitoring (CGM) system in children was by Coss-Buet al. in 1999.[1] They investigated a bedside VIA 1-01G Blood Chemistry monitor for measuring glucose in the pediatric intensive care unit (PICU). The monitor was programmed to draw venous blood, analyze, and record blood glucose samples automatically at predetermined intervals. This system was large, difficult to move, required intravenous access, and took 20 min to set up. Nonetheless, the data provided were comparable to measures by a laboratory glucose analyzer and bedside glucometer and could be used to inform clinical decision-making.

Many advances have occurred since that time to benefit pediatric patients with diabetes. Most recently, the FDA has approved the Dexcom G5 CGM system for use in insulin dosing decisions (nonadjunctive use),[2] the MiniMed 670G hybrid closed-loop system which alters insulin delivery based on CGM data for children ≥14 years of age,[3] and the Abbott FreeStyle Libre Pro for use by healthcare providers in tracking glucose data for those 18 years and over.[4]

In this chapter, published Pediatric data on CGM use will be reviewed in the following areas: type 1 and 2 diabetes mellitus, prediabetes, cystic fibrosis, neonatology, adrenal insufficiency, glycogen storage disease, and critical illness. Data were obtained through review of published works from a PubMed search of ''pediatric continuous glucose monitor.'' We also review pediatric CGM data from artificial pancreas studies, a rapidly evolving field with great promise to reduce burden and improve glucose control in pediatric patients.

Type 1 Diabetes

The latest position statements by the American Diabetes Association and the International Society of Pediatric and Adolescent Diabetes recommend a Hemoglobin A1c (HbA1c) goal <7.5% across all pediatric age groups.[5,6] This goal challenges even the most motivated, knowledgeable, and socioeconomically privileged patient.

Children with diabetes, in particular, face unique challenges. For example, total daily doses of insulin are proportional to weight, so in children small dose changes can have tremendous impact on glycemic control. Moreover, younger children are by definition hypoglycemic unaware as they are unable to communicate or self-treat low blood sugars. They are completely dependent on different caretakers for disease management. Therefore, CGM has a unique role and distinct challenges and opportunities in the Pediatric population. Modern CGM provides patients and families with accurate and timely glycemic data that may assist in meeting the daily challenges of diabetes and the HbA1c goals measured quarterly.

In 2014 the T1D Exchange conducted a survey on CGM use in the last 30 days. They found CGM was used by 6% of children <13 years old ($n=5027$), 4% of adolescents aged 13–18 ($n=4855$), and 6% of young adults aged 18–25 ($n=2769$). Use was associated with higher education, higher household income, private insurance, longer duration of diabetes, pump use, and lower HbA1c in children.[7] While it may seem intuitive that providing more glucose data should improve glucose control, a causative relationship has been difficult to establish particularly in children. It should also be noted that this 2014 article and other historic data summarized in this study report use of older generation CGM systems that have been significantly improved in current versions as far as accuracy, comfort, and usability.

Kaufman et al.[8] performed the first study addressing whether CGM influenced glycemic control in 2001. CGM data from 47 pediatric patients at Children's Hospital of Los Angeles were used by physicians to make insulin dose adjustments. The group found a statistically significant, although clinically small difference in HbA1c from 8.6% ± 1.5% at

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baseline to 8.4% ± 1.3%.[8] In 2003 Ludvigsson and Hanas performed a controlled crossover study with 27 patients with diabetes age 5–19 in which an open and masked study arm wore CGM for 3 days every 2 weeks. The open study arm received insulin dose adjustment based on the glycemic profiles obtained from the CGM. There was a statistically significant HbA1c reduction in the open arm from 7.7% to 7.3%, which was not observed in the masked arm.[9] A single-blind randomized controlled trial of participants 7–17 years old with CGM also demonstrated a statistically significant decrease in HbA1c for the intervention group from 8.4% ± 0.98% to 7.8% ± 0.88%. Of note, the difference in HbA1c between the intervention and control groups did not reach statistical significance (0.61% ± 0.68% in the intervention group of $n = 18$ vs. 0.28% ± 0.78% in control group of $n = 9$; $P = 0.18$).[10]

While these initial studies were conducted with early Medtronic CGMs, similar results were reported with a pilot study of the FreeStyle Navigator in 27 children and adolescents (age 4–17 years) on multiple daily injections. Mean HbA1c level fell from 7.9% ± 1.0% at baseline to 7.3% ± 0.9% at 13 weeks.[11] Meta-analysis in 2012 of seven randomized controlled trials with these previous generation CGM systems did provide evidence of HbA1c reduction, but the studies included adults and it is difficult to know if the conclusions generalize to the pediatric population or to current CGM systems.[12]

Unfortunately, not all historic studies support the assertion that CGM use improves HbA1c in pediatric age patients. Interpretation of these data requires an understanding of how CGM technology has evolved in the past decade to be more accurate and user friendly. Deiss et al.[13] performed a double-blind crossover study in 30 children with diabetes age 2–16 years in 2006. Subjects were randomized to open or masked study arms and had CGM placed for 3 days at the beginning of the study, 3 months, and 6 months. The open group received insulin dose changes based on the CGM data, while the masked group did not. There was no significant change in HbA1c within each group with this limited sensor use.[13]

The JDRF randomized clinical trial from 2008 also failed to show a significant difference in HbA1c between CGM and control for subjects 8–24 years old.[14] A 2009 secondary analysis of the JDRF cohort revealed that age was strongly positively associated with ≥6 days/week CGM use. In all three age groups (8–14, 15–24, and ≥25 years old), near-daily use of CGM was associated with similar improvements in HbA1c. The authors concluded that additional work is needed to overcome barriers to daily CGM use in children and adolescents.[15]

Another 2010 study showed that the frequency of CGM use among those aged 8–17 years decreases over time, but those using CGM for more than 6 days per week had significant decrease in HbA1c and greater satisfaction with CGM.[16] A randomized controlled trial of CGM in those aged 4–9 years for 26 weeks showed a high degree of parental satisfaction, an important metric in this patient population, but no significant change in HbA1c or incidence of severe hypoglycemia. In this group heavy use of CGM (>6 days per week) did not correlate with improved HbA1c. The authors suggested this may have been due to parental fear of hypoglycemia impeding more aggressive insulin changes.[17] Among individuals <4 years there was no difference in HbA1c after 6 months of use; there was, however, a high degree of parental satisfaction.[18]

Another purported benefit of CGM is avoidance of nocturnal hypoglycemia and increased time in target blood sugar range. Indeed, among the first observations of home CGM use in 2001 was asymptomatic nocturnal hypoglycemia.[19] Another study conducted by Kaufman revealed that among 47 youths with type 1 diabetes wearing CGM for 167 nights, 27% had blood glucose ≤40 mg/dL and 35% ≤ 50 mg/dL. Most of these episodes occurred between 9 PM and 1 AM.[20] In 2003 Amin et al. evaluated 28 prepubertal children (<12 years old) on injection regimens who wore sensors for 3 consecutive days and nights and found hypoglycemic prevalence of 10.1% (mean 2.6 h/subject/day) particularly between 4 and 7:30 AM. Risk factors included younger age, greater daily insulin dose, and increased weight.[21] In a JDRF 2010 masked CGM study 33% of subjects age 8–14 ($n = 64$) and 49% of subjects age 15–24 ($n = 42$) had one or more episodes of nocturnal hypoglycemia in a week.[22] Ly et al. investigated hypoglycemic unawareness among adolescents with diabetes and found that CGM with a low alarm set at 108 mg/dL improved counter regulatory hormone response under hypoglycemic clamp compared to standard glucose monitoring.[23] Data strictly pertaining to CGM intervention in pediatric age patients are more limited and often amalgamated with older populations. A trial in 2011 demonstrated that among 120 patients ages 10–65 years old with well-controlled type 1 diabetes (HbA1c < 7.5%), there was a statistically significant decrease in hypoglycemia and HbA1c among CGM users.[24]

With respect to postprandial hyperglycemia, a 2007 study suggested that excursion and rate of glycemic change following breakfast were greater than with lunch or dinner. They also reported no significant difference in postprandial hyperglycemia with multiple daily injections versus pump.[25] Multiple professional organizations have attempted to provide recommendations based on these numerous studies with data spanning well over a decade (Table 1).[26–28]

One goal of accurate CGM is to inform control systems that modulate insulin delivery using a mechanical pump. The 2010 Sensor Augmented Pump Therapy for A1c Reduction (STAR3) study involved a 1-year, multicenter randomized controlled trial among 156 children (age 7–18 years) and 329 adults with type 1 diabetes and suboptimal control (HbA1c 7.4%–9.5%). The study compared multiple daily injections and glucometer use with Medtronic insulin pump and CGM. Among children, there was an absolute reduction in HbA1c of 0.4% ± 0.9% in the pump-therapy group and an increase of 0.2% ± 1.0% in the injection-therapy group, for a between-group difference favoring the pump-therapy group by –0.5% (95% confidence interval: –0.8 to –0.2; $P < 0.001$).[29] The system simply provided sensor data that could be viewed on a pump, insulin delivery was fully controlled by the user.

Since that time effort has been focused on sensor augmented pump or closed-loop systems that take advantage of modern, more accurate, and user-friendly CGM. CGM systems from Abbott, Dexcom, and Medtronic have been investigated in conjunction with a variety of pumps and internal or external control systems. On September 28, 2016 the FDA approved the Medtronic 670G pump and Guardian Sensor 3 for those aged 14 and above with type 1 diabetes.[30] This represents the first hybrid closed-loop insulin delivery device on the market. In 2017, Garg et al. published an in-home study of the 670G system, including 30 participants of age 14–21 years. They report that HbA1c levels decreased from

Table 1. Professional Society Guidelines on Continuous Glucose Monitoring in Pediatrics

Organization	*Pediatric recommendations for CGM*
American Associate of Clinical Endocrinologists (AACE) and American College of Endocrinology[26]	• CGM recommended particularly for patients with history of severe hypoglycemia, hypoglycemia unawareness, and to assist in correction of hyperglycemia in patients not at goal. • CGM users must know basics of sensor insertion, calibration, and real-time data interpretation. • Both prevalence and persistent use of CGM are lower in children than adults. More in-depth training, as well as more frequent follow-up, is recommended to enable children to adopt the technology more successfully.
American Diabetes Association (ADA)[27]	• Although the evidence for HbA1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. • CGM may be a supplemental tool in those with hypoglycemia unawareness or frequent hypoglycemia. • Given variable adherence to CGM, assess individual readiness for continuing CGM use before prescribing. • When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use.
Endocrine Society[28]	• Recommend CGM in those with type 1 diabetes and HbA1c <7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia. • Recommend CGM in those with HbA1c ≥7.0% who are able to use these devices on a nearly daily basis. • No recommendations for or against CGM in children with type 1 diabetes <8 years old. • Recommend treatment guidelines for patients to allow them to take advantage of CGM data. Suggest intermittent use of CGM for short-term retrospective analysis in pediatric patients with diabetes and nocturnal hypoglycemia, dawn phenomenon, postprandial hyperglycemia, hypoglycemic unawareness, and important changes to their regimen.

CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c.

7.7% ± 0.8% to 7.1% ± 0.6% and in-target CGM values increased from 60.4% ± 10.9% to 67.2% ± 8.2%.[31] We fully expect that these closed-loop innovations will make CGM an integral component of diabetes care.

Type 2 Diabetes

The first reported use of CGM in pediatric patients with type 2 diabetes was by Boland and Tamborlane in 2000.[32] They reported on two patients with insulin resistance and demonstrated significant postprandial excursions, but also stability of overnight glucose due to endogenous insulin production. The additional information regarding prandial insulin needs helped the clinician increase meal coverage with insulin. The authors also suggested the use of CGM as an educational and motivational tool to encourage lifestyle modification.

A 2008 study demonstrated frequent hyperglycemia during the day, which correlates with HbA1c, and hypoglycemia during the night for seventeen adolescents with poorly controlled type 2 diabetes.[33] There is a paucity of data on CGM use in pediatric patients with type 2 diabetes. It remains to be seen whether CGM data can encourage users to make lifestyle modifications to decrease insulin resistance and improve glycemic control.

Prediabetes

Although no definitive intervention has been established, early identification of hyperglycemia may eventually prove helpful in those at high risk of diabetes, especially as CGM systems become more accurate, less expensive, and burdensome for patient use. In 2014 Steck et al. reported that among 14 asymptomatic children with positive islet autoantibodies, ≥18%–20% CGM time spent above 140 mg/dL predicted progression to diabetes within 6 months.[34] Helminen et al. compared CGM, HbA1c, and oral glucose tolerance testing (OGTT) for 10 asymptomatic children with genetic predisposition for type 1 diabetes and 2 or more islet autoantibodies against 10 age- and sex-matched controls with genetic predisposition who were antibody negative. Interestingly, no difference was observed in glucose or C-peptide levels during OGTT. However, both HbA1c and CGM values differed significantly between groups. Those with positive autoantibodies had greater mean glucose and greater variation in glucose. The authors concluded that CGM may be a useful early indicator of dysglycemia during prediabetes versus OGTT.[35]

In 2015 Chan et al. collected CGM data on 98 subjects aged 10–18 years with body mass index (BMI) ≥85 percentile with A1c ≤7.5%. They utilized CGM to help differentiate the predictive power of HbA1c and OGTT for dysglycemia. HbA1c had a greater magnitude of correlation to CGM average glucose, total area under CGM curve (by trapezoidal method), and minimum glucose. OGTT had a greater magnitude of correlation to CGM standard deviation, peak glucose, and time spent in hyperglycemia. They conclude that both HbA1c and OGTT outperform fasting glucose in predicting CGM outcomes, but that they may reflect different underlying pathologic mechanisms for progression to type 2 diabetes.[36]

Cystic Fibrosis

Cystic Fibrosis-Related Diabetes (CFRD) is a complication that usually develops with age, but can present in

pediatric age patients. The onset of the disease is insidious, which has prompted annual OGTT screening. In 2008 Franzese et al. compared OGTT and CGM for cystic fibrosis patients 5–20 years old with borderline high glucose during OGTT. CGM and OGTT were in agreement in 43.7% of the patients.[37] Schiaffini et al. suggested that CGM excursions >200 mg/dL can be a useful tool to predict future impaired glucose tolerance and CFRD. An insidious clinical decline can occur even during the prediabetic state in people with cystic fibrosis, so early detection and treatment can improve long-term health outcomes.[38]

Neonatal Use

Blood loss from diagnostic sampling is the most frequent cause of anemia in hospitalized infants. Neonates in the neonatal intensive care unit (NICU) frequently have risk factors for hypoglycemia, prompting frequent capillary and venous glucose checks. As early as 2001 Baumeister et al. reported the use of long-term subcutaneous glucose monitoring by microdialysis catheter. They report the safe application of microdialysis catheters in neonates born between gestational age of 30 and 45 weeks for 4–16 days. The method demonstrated 92.3% sensitivity and 88.1% specificity for detection of hypoglycemia.[39] These are especially impressive performance characteristics given CGM accuracy (particularly for hypoglycemia) at the time and results should be confirmed with modern CGM systems.

Although the physiologic significance is unknown, Harris et al. identified many more episodes of low blood glucose using a glucose oxidase sensor than with traditional interstitial glucose monitoring.[40] In 2013 Beardsall et al. performed a multicenter randomized controlled trial that validated the use of Medtronic CGM from 188 very low birth weight premature infants (<1000 g). The CGM data correlated well with point of care devices, with minimal bias and accuracy that did not deteriorate over a 7-day period.[41]

Prompted by the safety and validation data in neonates, a group in Japan utilized CGM to detect severe postprandial hypoglycemia associated with dumping syndrome in infants undergoing Nissen fundoplication. They suggest that postsurgical dumping syndrome may be underdiagnosed in infants and that CGM may provide the most sensitive diagnostic tool.[42]

Adrenal Insufficiency

In 2012 Meyer et al. screened 13 patients with primary adrenal insufficiency due to Addison's disease for hypoglycemia through use of CGM for 3–5 days. They detected a single subject with overnight blood sugar of 46 mg/dL, which prompted an increase in hydrocortisone dosing. The authors conclude that CGM can be used to help detect occult nocturnal hypoglycemia and prevent impaired quality of life and possibly serious adverse events.[43]

Another study by Cambiaso et al. in 2013 evaluated 11 pediatric patients (age 1–16 years) with adrenocorticotropic hormone and growth hormone (GH) deficiency. Subjects utilized CGM for 36 h and were evaluated for hypoglycemia. There was no relationship between growth hormone dose in GH deficient subjects with and without hypoglycemia (defined as two consecutive glucose values <50 mg/dL). Conversely, there was a statistically significant difference in hydrocortisone dose in patients with secondary adrenal insufficiency who experienced hypoglycemia (5.9 mg/m^2/day) and those who did not (8.5 mg/m^2/day). As in the first study the authors infer that CGM can be used to detect asymptomatic nocturnal hypoglycemia, which may prompt physicians to increase hydrocortisone dosing.[44]

Glycogen Storage Disorders

Glycogen storage disease type I (GSD I) is an autosomal recessive metabolic disease effecting the enzyme glucose-6-phosphatase. Clinically, it is characterized by fasting hypoglycemia within 3–4 h after a meal. Kasapkara et al. placed 16 children with GSD I on CGM for 72 h and then used the data to inform dietary changes. Following the intervention there was a significant reduction in CGM recorded hypoglycemia and liver size and improvement in lactic acidemia and hyperlipidemia. The authors conclude that even this time-limited intervention can have meaningful impact for long-term management of patients with GSD I.[45]

Critical Illness

In the PICU there are many fluctuating physiologic parameters which can adversely affect the performance of glucose oxidase based sensors. In addition, awareness of acetaminophen interference with these systems is particularly important in an ICU setting.[46,47] Branco et al. explored physiologic aberrations in the use of CGM in the PICU. Specifically, they examined the correlation between glucose measured from arterial blood, point of care glucometer, and CGM in 14 children ages 1 month to 16 years requiring mechanical ventilation with at least two organ system failures. Measures of mean absolute relative difference (MARD) appeared to correlate with significant acidosis and therapeutic hypothermia, which the authors felt may limit the use of CGM.[48] Using statistical definitions (Bland–Altman and Clarke error grid analysis) both this study and another demonstrated clinically acceptable correlation despite the aforementioned limitations.[49] There is sufficient trust in the technology that the 2017 HALF-PINT study investigating tight glycemic control in critically ill children used CGM to signal impending hypoglycemia.[50]

Special Considerations in Pediatrics

A multicenter observational study performed on 149 children and adolescents with type 1 diabetes in 2015 revealed that the majority of subjects discontinued CGM use, even when financial considerations were not an issue. Only 38% used CGM regularly more than 75% of the time, despite the finding that those using CGM consistently had better glycemic control during the year compared to intermittent users. Consistent use correlated with younger age and more frequent finger-stick glucose checks at baseline. The authors conclude that providers should be aware that CGM is most useful in compliant patients.[51]

Naranjo et al. reported in 2016 that those using pumps, CGMs, or sensor augmented pumps had more positive attitudes about diabetes technology than those on multiple daily injections and conventional glucose monitoring.[52] Among all participants in the JDRF CGM study group common barriers to continued use include insertion pain, system alarms, and body issues related to the need to wear the device,[53] although this was with early generation systems.

Certain concerns are more specific to the pediatric age patient. Children with diabetes spend 4–7 h in school per day during which time they have decreased diabetes supervision. Based on one survey, 75% of students, 70% of parents, and 51% of teachers found CGM useful at school. More students felt the devices to be disruptive than parents or teachers. The authors suggest educational materials be provided to teachers to increase their comfort.[54] With the recent FDA approval of insulin dosing based on Dexcom CGM and the Medtronic 670G system, advocacy and education for use of these systems in school will be required.

Pediatric use of CGM can be limited by body surface area in smaller children, ambient temperature/humidity, and physical activity. Sensor adhesion appears significant for improving long-term adherence. Englert et al. suggest adhesive wipes, liquid adhesive, transparent dressings, tape, and wraps to combat the physical factors that impair good CGM placement.[55] During hybrid closed-loop studies it was felt that calibrating CGM to interstitial glucose obtained from a second drop of blood (rather than the first) reduced errors with MARD of 10.8% versus laboratory standard and 12.6% versus glucometer.[56]

CGMs generate a tremendous, at times overwhelming, quantity of data. The information must be processed and analyzed to have meaningful impact. Parents report high levels of satisfaction when they have the ability to monitor their children's blood sugars remotely.[57] Frequently, this provides reassurance regarding hypoglycemia. In addition, the rate of glucose change, in the form of arrows, can allow one to act reflexively in anticipation of high or low blood sugars. While these techniques do assist in the short term, assessing prior data to make long-term insulin dose changes can obviate the need for these reflexive behaviors by increasing time in target range. Automated insulin dosing systems that integrate CGM data will also address this need.

There are many ways of retrospectively visualizing glucose data, for example, the ambulatory glucose profile (AGP). A recent analysis by Forlenza revealed differences in the average AGP glycemic patterns for the JDRF-CGM dataset when stratified by age group (8–14, 15–24, and ≥25 years) and HbA1c. They report that for a given HbA1c level, all age groups were significantly different, with older patients having lower averages and less variability than younger patients.[58]

We encourage patients and families to actively download CGM statistics, evaluate the data, and send it to their diabetes care team. Passively moving CGM data to physicians for analysis is another active area of research. Dexcom's CGM can send glycemic data to an iOS app through Bluetooth which can then be exported to the electronic medical record system without patient intervention.[59] As data accumulate we can now analyze trends on large patient populations.

Relative Performance

In 2014 Damiano et al. published a head-to-head comparison of the Abbott FreeStyle Navigator (Navigator), Dexcom G4 Platinum (G4P), and Medtronic Enlite (Enlite) CGM in participants over the age of 12.[60] Previously, the G4P received a software update which has been shown to improve MARD from 17% to 10% over a 7-day period in children aged 2–17 years.[61] The G4P had an aggregate MARD of 10.8% ± 9.9%, which was not significantly different from the Navigator at 12.3% ± 12.1%. The Enlite had significantly less accurate performance with an aggregate MARD of 17.9% ± 15.8%. The average MARD for experiments in adolescent subjects was lower than in adult subjects for the Navigator and G4P, while there was no difference for Enlite.

Sensor technology and accuracy continue to improve with time. CGM accuracy is a requirement for closed-loop insulin delivery. Prepublication online data from Medtronic for children and adults suggest that the Guardian Sensor 3 has a MARD of 9.64% when calibrating 3–4 times/day and 10.55% when calibrating 1–2 times/day.[62] Abbott's FreeStyle Libre system, recently approved in the United States for professional use, has a reported MARD of 11.4% (all ages) versus glucometer and does not require finger-stick calibration.[63] Rather than providing continuous glucose reading to a receiver, the Libre system provides on-demand glucose data. Another innovation of the Libre system is that no user calibration is required, removing an often cited burden of CGM use by patients and families. Abbott and Dexcom devices are approved to dose insulin based on CGM readings, a tremendous step forward which illustrates the significant improvements in CGM accuracy.

Future Directions

As described CGM has already been explored in a variety of pediatric clinical settings. The technology improves parental satisfaction, reduces hypoglycemia, and has a positive impact on overall glycemic control when used consistently. The newest iterations of CGM products have improved interfaces and are now accurate enough to be used in closed-loop insulin delivery systems. We expect that as technology improves, CGM will become less invasive, less burdensome, and more beneficial. Alternately, long-term implantable CGMs may also have a role in pediatrics in the future, although more research is required.[64,65] As the burden of wearing CGM decreases and accuracy increases, we anticipate CGM becoming an indispensable tool that succeeds the finger stick in a multitude of pediatric clinical settings.

Author Disclosure Statement

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