

Consensus Statement

Use of continuous glucose monitoring in children and adolescents*

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Children and adolescents with diabetes, their families and their care providers face the challenge of maintaining blood glucose levels in the near to normal range over years, day in and day out. Self-monitoring of blood glucose (SMBG) is an important component of therapy in patients with diabetes. SMBG provides only intermittent glimpses of blood glucose levels, without giving the 'big picture' of glucose variability over 24 h (1), especially during the night, when blood glucose is seldom measured (2, 3). Therefore, the use of real-time continuous glucose monitoring (RT-CGM) that provides continuous glucose measurements offers the potential to help patients optimize glycemic control and reduce the risk of hypoglycemia. RT-CGM provides patients with a stream of interstitial glucose

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measurements at 1–5 min intervals that can be used for adjustments of the treatment regimen. A recently published meta-analysis of randomized controlled trials (RCTs) that aimed to determine the clinical effectiveness of RT-CGM compared with SMBG in young adults with type 1 diabetes (T1D), demonstrated that CGM was associated with a significant reduction in HbA1C, especially in those with the highest HbA1C at baseline and in those who used the sensors most frequently. Exposure to hypoglycemia was also reduced during CGM. Thus, it was concluded that the most cost-effective or appropriate use of CGM is likely to be when targeted at people with T1D who have continued poor control during intensified insulin therapy and who frequently use CGM (4).

RT-CGM can be considered as one step further in achieving a safe way to target near normoglycemia, and the device can serve as another step toward closing the loop for an ‘artificial pancreas’.

While it may seem intuitively obvious that a perfect, non-intrusive, accurate and easy-to-use device would be of great benefit to patients, the benefits of the current, imperfect RT-CGM systems have been more challenging to demonstrate, especially in pediatric patients. Thus, there is still a debate as to whether RT-CGM can improve glycemic control, reduce occurrence of severe hypoglycemic events, and improve quality of life (QOL) in young patients with diabetes. Furthermore, no clear criteria have been established to help the physician choose the appropriate patient for RT-CGM use.

To address these issues, the European Society for Pediatric Endocrinology (ESPE), the Pediatric Endocrine Society (PES), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) convened a panel of expert physicians for a consensus conference.

For each major topic area, clinical experts were chosen to review the literature and provide evidence-based recommendations according to criteria used by the American Diabetes Association (ADA). Key citations identified for each topic were assigned a level of evidence (indicated in the reference list) and verified by the expert panel (Table 1). This article summarizes the consensus recommendations of the expert panel and represents the current state of knowledge about use of CGM in pediatric and adolescent patients.

Types of sensors

All designed prototypes or commercially available systems can be divided into three groups based on the way glucose measurement is carried out: non-invasive, minimally invasive, and invasive systems. Non-invasive devices measure glucose with light or electromagnetic waves without penetrating the skin. Minimally invasive sensors are inserted through the skin and measure the glucose concentration in the interstitial fluid of the skin or subcutaneous tissue. Invasive sensors use intravenous access for measurement of blood glucose levels. Currently, non-invasive systems are not available and invasive systems are only available for research or inpatient use (Biostator and Edwards Lifesciences, Elkhart, Indiana; DexCom, San-Diego, CA). Thus, this consensus statement focuses on pediatric use of minimally invasive RT-CGM systems that use glucose oxidase-based, electrochemical methods to measure interstitial glucose concentrations. Minimally invasive RT-CGM devices have been approved by the US Food and Drug Administration (FDA) for use in USA or carry Conformité Européenne (CE) marking for use in Europe. The currently available RT-CGM devices can be distinguished between blinded and unblinded systems, as defined below.

Blinded technology – Holter-type retrospective sensors

The MiniMed CGMS, its newer version the iPro™ CGM, and the GlucoDay (Menarini) system have

Table 1. ADA evidence-grading system for clinical recommendations

Level of evidence	Criteria
A	Clear evidence from well-conducted, generalizable, randomized controlled trials (RCTs) that are adequately powered, including: <ul style="list-style-type: none"> • Multicenter trial • Meta-analysis incorporating quality ratings • Compelling non-experimental evidence (i.e., ‘all or none’ rule) developed by the Centre for Evidence-Based Medicine at Oxford • Supportive evidence from well-conducted RCTs that are adequately powered, including well-conducted trials at one or more institutions
B	Supportive evidence from well-conducted cohort studies, including: <ul style="list-style-type: none"> • Prospective cohort studies or registry • Meta-analysis of cohort studies
C	Supportive evidence from a well-conducted case-control study Supportive evidence from poorly controlled or uncontrolled studies including: <ul style="list-style-type: none"> • RCTs with one or more major or three or more minor methodological flaws that could invalidate the results • Observational studies with high potential for bias • Case series or case reports
E	Conflicting evidence with the weight of evidence supporting the recommendation Expert consensus or clinical experience

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been reported to serve as tools to reveal daily glucose trends missed by SMBG, serve as educational tools to improve metabolic control, and retrospectively detect hypoglycemia in young patients with T1D. They provide a means to uncover glucose patterns and potential problems that might go undetected with standard glucose measurements. After blinded data are collected over a few days, the devices are returned to the clinicians' office and data are downloaded to a computer; standard reports are generated which are used by the clinicians to interpret results for their patients.

Unblinded technology – RT-CGM

In contrast to the physician-based analysis of retrospective data of the Holter-type sensors, RT-CGM shifts the focus to the patient and the family, enabling them to react to subcutaneous glucose readings in a 'biofeedback' open-loop fashion. Like the blinded systems, these devices require calibration using fingerstick blood glucose monitoring results. Systems are approved by the FDA for children in the age-group above 7, whereas the European Union (EU) has no age limit. They have also been used in young children who participated in clinical studies evaluating the RT-CGM devices (5, 6).

Accuracy and reliability of CGM

CGM was first available in 1999 for retrospective analysis (MiniMed CGMS; 7), and RT-CGM was first available in 2001 (Cygnus GlucoWatch that is no longer in use; 8). Since their introduction, each subsequent generation of glucose sensors has brought increased accuracy and an improved user interface for the patient. Accuracy needs to be assessed in terms of the intended use of the sensor. A sensor used for trend analysis does not need to be as accurate as a sensor used to make insulin dose decisions.

The accuracy of current sensors is presented in Table 2 (9–13). In this table, we have also included accuracy data on currently available blood glucose meters for comparison (14). A common measure of reported accuracy is the mean or median absolute relative difference (ARD) between sensor and reference blood glucose levels. Using this measure, it is common to report sensor accuracy in the hypoglycemic [<70 mg/dL (<3.89 mmol/L)], target [70–180 mg/dL (3.89–10 mmol/L)], and hyperglycemic ranges [>180 mg/dL (>10 mmol/L)].

Over the years, there has been a progressive improvement in sensors as measured by their length of wear and the percent functioning. Approved sensors available in USA and/or Europe are currently

Table 2. Accuracy of CGM sensors compared with reference standards and home glucose meters

		Meters*	Sensors†
N (paired reference to meter or CGM values)		1103	1927–20 362
Reference number		13	8–12
Measurement device for reference glucose		DCCT laboratory‡	YSI
<i>Overall</i>	Median ARD%	5%	9–13%
	Mean ARD%	6%	13–16%
	% within ISO criteria	98–99%	76–82%§
<i>Target range</i>			
70–180 mg/dL (3.9–10.0 mmol/L)	Median ARD%	5%	11–13%¶
	Mean ARD%		14–15%§
	% within ISO criteria	97–99%	73–76%
<i>Hypoglycemic</i>			
<70 mg/dL (< 3.9 mmol/L)	Median ARD%	8–9%	15–20%
	Mean ARD%		20–25%
	% within ISO criteria	96–99%	55%
<80 mg/dL (<4.4 mmol/L)	% within 20 mg/dL		57–66%
<i>Hyperglycemic</i>			
>180 mg/dL (>10.0 mmol/L)	Median ARD%	4–5%	8–11%
	Mean ARD%		10–13%
	% within ISO criteria	99–100%	80–91%**

*Ultra and FreeStyle meters.

†DexCom 7+, Navigator, Veo.

‡Hitachi hexokinase, University of Minnesota, DCCT central laboratory.

§Data reported as values within 20 mg/dL if <80 mg/dL and within 20% if >80 mg/dL, so the hypoglycemia criteria is less rigid than ISO standard which assesses the percentage of sensor glucose values within ± 15 mg/dL of the reference glucose for values ≤ 75 mg/dL and within $\pm 20\%$ for glucose values >75 mg/dL.

¶For one sensor, the cutoffs were at 81–180 mg/dL and for another 80–240 mg/dL.

||For one sensor, the cutoffs were at 8 mg/dL.

**For one sensor, the cutoffs were at 240 mg/dL.

functioning 74 to 89% of the time after 3–7 d of wear.

Current practice of CGM therapy in children and adolescents

When used with current open-loop basal/bolus insulin replacement, RT-CGM systems should provide:

- (i) **Improved overnight control** with hypoglycemia alarms and retrospective data to optimize overnight basal insulin needs. In patients using an integrated sensor-augmented pump system, the low glucose suspend (LGS) feature may help to prevent severe nocturnal hypoglycemic events.
- (ii) **Improved daytime bolus dosing** with trend arrows and hyper- and hypoglycemia alarms for real-time adjustments, and retrospective data to optimize carbohydrate ratios and correction doses.
- (iii) **Enhanced understanding of diabetes management teaching** to understand effects of different foods, exercise, stress, and menstrual cycles on glucose excursions.
- (iv) Improved management of acute illnesses.

Over the past few years, a number of RCTs have been undertaken to evaluate the impact of these devices in the treatment of T1D and several important observations have emerged regarding the indications for RT-CGM in youth with T1D. Evidence from recent clinical trials that have evaluated the efficacy of RT-CGM is presented below and detailed in the following sections.

Efficacy of RT-CGM: advantages and disadvantages

Impact on metabolic control

Most of the RCTs that evaluated RT-CGM in patients with T1D included children and adolescents, but only some of them reported data for pediatric patients separately. The GuardControl Study was one of the first RCTs that evaluated RT-CGM; it included 54 adolescents (27 in the RT-CGM group and 27 in the control group; 15). A *post hoc* intention to treat analysis of this pediatric subpopulation demonstrated a statistically significant difference in the reduction of HbA1c levels after 3 months between the RT-CGM group ($-0.72 \pm 1.13\%$) and the control group ($-0.05 \pm 0.78\%$), adjusted $p = 0.0447$. The first treat-to-target study of sensor-augmented pump (SAP) therapy for HbA1c Reduction (Star 1) was an RCT comparing the use of SAP therapy ($n = 17$) with the use of an insulin-pump and SMBG ($n = 23$) in adolescents that also showed a decrease of 0.42% in HbA1c at 6 months that favored the SAP group, but

this difference was not statistically significant (16). In another RCT of patient-led use of RT-CGM, 16 adolescent patients in the RT-CGM and 16 adolescent patients in the control group (standard pump therapy) were analyzed separately, and a statistically significant between-group difference in HbA1c of 0.6% was found in favor of the RT-CGM group ($p = 0.025$) (17). The Juvenile Diabetes Research Foundation (JDRF) trial on the use of RT-CGM included 27 children and 29 adolescents in the RT-CGM group and 29 children and 38 adolescents in the control group. There was no statistically significant difference in the change in HbA1c between the two study groups. However, the number of children reaching HbA1c levels $< 7\%$ was significantly greater in the RT-CGM as compared with the control group (15 vs. 7, respectively; $p = 0.01$) (18). The JDRF trial in well-controlled patients with T1D (HbA1c $\leq 7\%$) included 18 children and 15 adolescents in the RT-CGM group and 11 children and 18 adolescents in the control group (19). Subjects randomized to RT-CGM were able to maintain target HbA1c levels more effectively than subjects randomized to the control group in that study but the data for the pediatric subjects were not reported separately.

The study of SAP therapy from the onset of childhood T1D (ONSET study) was a pediatric trial that compared the use of SAP with insulin-pump alone from the disease onset in 80 children in the SAP group and 80 children in the control group. It showed no significant difference between the two groups in HbA1c after 12 months, but the mean amplitude of glycemic excursion (MAGE) was significantly diminished in the SAP group (-0.66 , $p < 0.04$) (5). An RCT in well-controlled patients (HbA1c $< 7.5\%$) that focused on time spent in hypoglycemia and included children and adolescents in the RT-CGM group ($n = 27$) and the control group ($n = 26$), found that the between-group difference in HbA1c at 6 months (adjusted for baseline HbA1c, center, and age group) was significantly different for the whole study population (mean 6.69 vs. 6.95%, difference in means -0.27 , 95% confidence interval (CI) -0.47 to -0.07 , $p = 0.008$) (20).

The third study of SAP therapy for HbA1c Reduction (Star 3) was a large RCT comparing SAP with the use of multiple daily injections (MDI) with insulin analogues and included 78 children and adolescents in the SAP group and 78 children and adolescents in the MDI group (21, 22). At 12 months, the pediatric between-group difference in HbA1c of 0.5%, in favor of the SAP group was statistically significant ($p < 0.001$) along with significantly more children and adolescents in the SAP group reaching the age-specific target HbA1c (between-group difference 25%, $p < 0.005$). Rates of severe hypoglycemia and diabetic ketoacidosis (DKA) were low and did not

differ between the two treatment groups. The study was not, however, designed to differentiate the effect of RT-CGM from the effect of the use of insulin pumps.

The Diabetes Research in Children Network (DirecNet) conducted several non-randomized cohort studies that demonstrated the efficacy of RT-CGM in improving metabolic control in the pediatric population. One DirecNet study reported 13 wk of use of RT-CGM in 30 children and adolescents aged 3–18 yr using insulin pumps (23). Mean HbA1c improved by 0.3% ($7.1 \pm 0.6\%$ at baseline to $6.8 \pm 0.7\%$ at the end; $p = 0.02$), with an 8% increase of glucose values within a 71- to 180-mg/dL interval (from 52 to 60%; $p = 0.01$) and without any severe hypoglycemic events. HbA1c levels did not increase in the three patients with baseline values $\leq 7.0\%$ (mean $6.6 \pm 0.4\%$), whereas in the 15 patients with baseline HbA1c levels $>7.0\%$, HbA1c levels decreased from $7.6 \pm 0.4\%$ to $7.0 \pm 0.7\%$, with no significant change in time spent in hypoglycemia. Another DirecNet study assessed the 13-wk use of RT-CGM in 27 children aged 4–17 yr using MDI with insulin glargine (24). Mean HbA1c decreased by 0.6% (from $7.9 \pm 1.0\%$ at baseline to $7.3 \pm 0.9\%$ at the end, $p = 0.004$), with a bigger drop in patients with baseline HbA1c levels $>7.5\%$. Additionally, MAGE also decreased significantly by 20 mg/dL (from 147 to 127 mg/dL, $p = 0.001$). Both DirecNet trials were extended for an additional 13 wk of follow-up; HbA1c increased close to the baseline levels, whereas MAGE remained lower throughout the 26-wk observational period (25).

A recently published large retrospective observational study reporting on 129 pediatric patients using SAP compared to 493 patients treated with CSII with no CGM, demonstrated that in ‘real-life’ setting the CGM permits a greater decrease in HbA1c after a mean follow-up of 1.6 yr (26).

Impact on hypoglycemia

Only one RCT reported significantly more severe hypoglycemia in the RT-CGM group as compared with the SMBG group (11 vs. 3 events, respectively)

(16); however, the ages of the eight patients who had 11 events of severe hypoglycemia in the RT-CGM group was not indicated. All other RCTs reported no increase in severe hypoglycemia with or without a concomitant decrease in HbA1c (15, 17–21, 27).

The rates of severe hypoglycemia in pediatric patients in the JDRF (18) and Star 3 (21) studies are shown in Table 3. In both of these studies, the rates of severe hypoglycemia did not differ by treatment group and were lower than expected. For comparison, the rate of severe hypoglycemia in intensively treated adolescents in the Diabetes Control and Complications Trial was 86 events per 100 patient years (28).

Notably, one RCT in pediatric patients reported a significant decrease in severe hypoglycemia in the group using SAP compared with the group using insulin-pump therapy with SMBG (0 vs. 4, respectively) (5). The JDRF trial in well-controlled patients demonstrated a significant decrease in time spent at <60 mg/dL (median, control vs. RT-CGM at 26 wk: 35 vs. 18 min/d, respectively) in the RT-CGM group in the total study population without results for the pediatric subpopulation being reported separately (19). Another trial in well-controlled patients demonstrated a significant decrease in time spent at <70 mg/dL (mean \pm SD, control vs. RT-CGM at 26 wk: 1.60 ± 2.02 vs. 0.91 ± 0.81 h/d, $p < 0.01$, <63 mg/dL (0.97 ± 1.55 vs. 0.48 ± 0.57 h/d, $p < 0.03$) and <55 mg/dL (0.41 ± 0.48 vs. 0.22 ± 0.34 h/d, $p < 0.05$), along with a significant decrease in the number of hypoglycemic excursions <63 mg/dL and <55 mg/dL during the night (0.21 ± 0.32 vs. 0.30 ± 0.31 , $p = 0.009$ and 0.13 ± 0.30 vs. 0.19 ± 0.19 , $p = 0.01$, respectively) for the whole study population, and a 64% statistically significant reduction in the time spent at <63 mg/dL during the night for the pediatric subpopulation (10–17 yr of age) according to a *post hoc* per-protocol analysis ($p < 0.001$) (21).

Sensor use and efficacy

In a large retrospective observational study (26), the median glucose sensor usage of 13.4 d/month was

Table 3. HbA1c (at study end) and rates of severe hypoglycemia (events/100 patient years) in major RCTs of pediatric patients

Study (reference)	Experimental group		Control group		p-Value for hypoglycemia
	HbA1c (%)	Hypoglycemia rate	Hb1Ac (%)	Hypoglycemia rate	
Star 1 (15)	8.0	12.5	8.2	16.7	NS
JDRF (8– 14 yr) (17)	7.6	17.9	7.7	24.4	0.64
JDRF (15– 24 yr) (17)	7.8	17.9	7.7	23.9	0.64
JDRF (8– 17 yr)* (17)	7.9	11.2	NA	NA	NA
Star 3 (20)	7.9	9.0	8.5	5	0.35

NA, not applicable; NS, not significant.
*RT-CGM group only over 12 months of use.

sufficient for a significant improvement in HbA1c of 0.9%.

However, most RCTs reported an association between the amount of sensor use and its efficacy in improving metabolic control (15–19, 21, 27, 29). In a separate analysis of the 80 pediatric patients aged 8–17 yr in the JDRF RCT (30), 42% of subjects were able to use CGM 6 or more days per week during the 6-month randomized trial; they lowered HbA1c levels by 0.8% vs. no change in the subjects who used the sensor less frequently. Moreover, the 0.8% improvement in HbA1c was maintained during the 6-month extension phase of the study in only the 21% of subjects who continued to use the sensor on an almost daily basis; whereas HbA1c levels reverted to baseline levels in the 21% of subjects who stopped wearing the sensor daily. *Such a decline in sensor use has proved to be the limiting factor for the efficacy in the pediatric age group in other studies (25, 27).*

Intermittent use of real-time or retrospective CGM

When the MiniMed CGMS device was first introduced for 3-d retrospective analysis of plasma glucose profiles, investigators quickly showed that this method of glucose monitoring revealed patterns of postmeal hyperglycemia and nocturnal hypoglycemia that were not evident during standard SMBG testing in children with T1D (1). Several small clinical trials suggested that even one or two uses of the MiniMed CGMS device could lead to treatment adjustments that had long-lasting improvements in metabolic control of T1D (31–33). The validity of these findings has been cast in doubt by the results of RT-CGM studies that indicate the need for near-daily use of the devices to obtain and maintain lowering in HbA1c levels. Indeed, a recent meta-analysis (34) of five RCTs in pediatric patients (6, 33, 35–37) indicated that technology which does not allow for real-time assessment of glycemia by the patient but only allows for a retrospective analysis by the doctor does not lead to a significant improvement in HbA1c levels. Although the trials with retrospective sensors have already led to considerable practical experience with this technology, they should be reserved for special indications (38).

Recommendations

- (i) RT-CGM can be used effectively for lowering HbA1c (15, 17, 21, 23, 24), reaching target HbA1c (18), and reducing the MAGE (5, 25) in the pediatric population with T1D without increasing the frequency of severe hypoglycemia;
- (ii) RT-CGM can be used effectively for reducing severe hypoglycemia (5) and shortening the time

spent in hypoglycemia (20) in the pediatric population with T1D;

- (iii) The effectiveness of RT-CGM in the pediatric population with T1D is significantly related to the amount of sensor use (17, 21, 30, 39). Therefore, efforts for increased adherence with sensor use are paramount in this age group;
- (iv) SAP is an effective means to treat youth of all ages at the onset of the disease (5);
- (v) SAP treatment is effective in lowering HbA1c levels in children and adolescents with T1D who have elevated HbA1c values on MDI therapy using standard blood glucose monitoring (19, 20);
- (vi) Intermittent, retrospective or real-time CGM may be of use in children and adolescents with T1D to detect the dawn phenomenon, postprandial hyperglycemia, asymptomatic, and nocturnal hypoglycemia and in evaluating the effects of major changes in treatment regimens (31–33);
- (vii) The development of more pediatric-oriented devices for RT-CGM is warranted along with additional well-designed RCTs in the whole pediatric age-group spectrum.

Safety of CGM in children and adolescents

Inaccurate sensor glucose readings due to errors in calibration or general sensor malfunctioning should not lead to errors in insulin dosing as patients/families are instructed in the need to use data from standard SMBG before insulin administration. Unnecessary treatment of hypoglycemia from RT-CGM glucose results is also unlikely owing to routine instructions to patients/families to check blood glucose levels before treating presumed low glucose values noted by RT-CGM (unless clinical symptoms dictate the need to treat before blood glucose confirmation).

Severe hypoglycemia or severe hyperglycemia with DKA rates should not be any greater than in routine care and may be reduced with the aid of RT-CGM data and CGM alarms for high and low glucose readings.

Data from RCTs indicated very low rates of DKA and severe symptomatic (not biochemical) hypoglycemia, and there were no differences between RT-CGM and SMBG control groups.

In Star 1, there were 11 severe hypoglycemic events in the RT-CGM group vs. 3 in the SMBG group ($p = 0.04$). This was thought to be due to lack of patient response to low glucose alarms and/or possible ‘insulin stacking’ from overzealous insulin treatment by patients (30).

Routine rates of severe hypoglycemia in the modern era of pediatric diabetes management are 20–30 events/100 patient-years (40–42) and appear to be lower with CGM use at 8 events/100 patient-years in the 15- to 24-year-old group and 13 events/100

patient-years in the 8- to 14-year-old group (43). Rates of severe hypoglycemia and DKA were low and did not differ between CGM and SMBG groups in all three age groups in the JDRF RT-CGM study (9–15, 16–21, 23–25, 30, 43) during the 6-month RCT (18).

Rates of severe hypoglycemia and DKA were similar in Star 3 in the SAP group and MDI/SMBG group (21).

Rates of sensor site infections appear to be low; only two reported events of cellulitis at the sensor site in the 8- to 14-year-old age group in the JDRF-CGM RCT (18).

However, it should be noted that there are some safety issues relating to skin irritation from sensor adhesives, sensor site infections, and broken-off or retained sensor tips in the subcutaneous space.

Recommendations: level **E**

- (i) Initial and ongoing education regarding the lag time and need to confirm CGM glucose results with standard SMBG before insulin administration and when it is possible and clinically safe, before treatment of hypoglycemia;
- (ii) Initial and ongoing education regarding the optimal approach and timing of sensor calibration should help ensure optimal sensor performance;
- (iii) Initial and ongoing education regarding sensor site care with attention to using sensors according to manufacturers' recommendations, including the need for fingerstick blood sugars for all treatment decisions.

Considerations of patient selection for use of CGM in children and adolescents

As mentioned previously, observational and RCT studies in the pediatric age group found improvement in metabolic control with the use of CGM (1, 15–18, 21, 23, 31–33). Most of the RCT studies including pediatric T1D patients (17, 21, 24, 39) have demonstrated that the frequency of the CGM use was significantly associated with the effect of lowering HbA1C levels. In the JDRF-CGM trial, the only baseline characteristic that predicted near daily CGM use in pediatric patients was frequent daily SBGM before entering the trial (39).

Alarms on the CGM for pending low glucose levels, as well as for reaching a specific low glucose threshold, are both helpful in preventing severe hypoglycemia, especially during the night. Unfortunately, data suggest that youth do not respond to approximately 71% of alarms during sleep (42). The JDRF-CGM study group reported that in patients with T1D aged 8–18 yr who have achieved HbA1c levels <7%, the RT-CGM use reduced the frequency of hypoglycemia and helped

maintain HbA1c levels <7% compared with standard SBGM over a 6-month study period (19).

Limited data from small observational studies indicate that the CGM can be used successfully in patients <8yr old (3, 44). Physically, patients must have enough subcutaneous tissue to incorporate sensor wear.

Studies of CGM use in pediatrics have shown that youth can maintain adherence to wearing the device for 3 months, and outcomes of CGM use with both continuous subcutaneous insulin infusion (CSII) and MDI have been similar (23–25).

Currently, not enough direct evidence is available to propose the specific features to identify patients likely to experience the best outcomes with CGM.

The decision to use CGM should be made jointly by the child, parents, and diabetes team. Most pediatric patients with T1D are potential candidates for use of CGM, without a lower age limit for initiating it, and CGM should be available for any pediatric patient with T1D who wants to try it. CGM can be used with either MDI or CSII (23, 24).

On the basis of the evidence presented previously, CGM should be considered in children and adolescents with T1D and in the following conditions:

Therapeutic use (continuous use)

- (i) Patients who are doing frequent blood glucose testing (39);
- (ii) Patients who have severe hypoglycemic episodes (5);
- (iii) Patients who have hypoglycemic unawareness especially in young children (45);
- (iv) Patients who have nocturnal hypoglycemia (2, 46, 47);
- (v) Wide glucose excursions regardless of HbA1c levels (48–50);
- (vi) Young children with diabetes with large blood glucose variability and difficulty in identifying hypoglycemic episodes (3, 44);
- (vii) Patients who have suboptimal glycemic control with HbA1c exceeding target range (15–17, 21, 32, 33, 36, 51);
- (viii) Patients with T1D and HbA1c levels <7% (with the aim to maintain target glycemic control, while limiting the risk of hypoglycemia) (19).

Other circumstances in which CGM may be beneficial are described below.

Diagnostic/intermittent use

CGM may also be beneficial with diagnostic/intermittent use. However, at this time, there are not enough evidence-based data, and more data have to

be acquired. Nonetheless, it has been suggested that intermittent use of CGM may be of benefit in:

- (i) Detection of nocturnal hypoglycemia or hyperglycemia (e.g. dawn phenomenon);
- (ii) Individuals in whom the causes of persistently high HbA1c levels are unclear for detection of hyperglycemic peaks not identified by SMBG;
- (iii) Making changes to patients' diabetes treatment regimen (e.g., changing of insulin type or switching from MDI to CSII or vice versa) (27, 52, 53);
- (iv) Special situations, such as: sport, eating outside the home, trying new foods; traveling or driving; or patients with severe fear of hypoglycemia;
- (v) Infants with neonatal hypoglycemia (54);
- (vi) Intensive care unit for glucose monitoring;
- (vii) Cystic fibrosis-related diabetes (55–58);
- (viii) Detection of hypoglycemia in metabolic diseases (59);
- (ix) Monitoring glycemia in research settings;
- (x) Motivated families of young children, especially if the patient suffers from recurrent hypoglycemia.

Patient perception of the benefits and hassles of CGM

Consistent usage of CGM has been difficult to achieve in clinical trials and in routine care, especially among children and adolescents. To identify ways to reduce barriers to more consistent CGM use, it is important to understand how patients perceive the benefits and hassles of CGM and how these perceptions are associated with frequency of use. To evaluate this question, youth with T1D in the JDRF RT-CGM trials and their parents completed the CGM Satisfaction Scale (CGM-SAT) developed by DirecNet (60) after 6 months of sensor use. CGM-SAT assesses impact of RT-CGM on diabetes management, family relationships, and emotional and behavioral characteristics. The psychometric properties cover two subdomains: benefits and hassles; a higher score reflects greater benefits or fewer hassles with RT-CGM use.

An important finding of the study was the relationship between perceived satisfaction and frequency of RT-CGM use (61). Youth who were frequent RT-CGM users and their parents reported greater satisfaction and had higher scores on the two subscales compared with infrequent users. Of particular note, the greatest differences between the two groups involved the hassle items. This suggests that patients using RT-CGM who perceive it to be beneficial and wear the device frequently are less bothered by the hassles, while those patients who wear the device infrequently focus more on the hassles than the benefits. In response

to open-ended questions, many participants appreciated that RT-CGM provided previously unavailable data on glucose trends/graphs, as well as the ability to self-correct out-of-range glucose levels in real-time. Conversely, between a quarter and a third of youth reported challenges with CGM alarms, insertion, and site/body issues related to the need to wear the device.

Recommendations

- (i) A pediatric multidisciplinary diabetes team experienced in RT-CGM use should focus on how to adequately select, train, manage, and motivate the child/adolescent with diabetes and parents/guardians to optimize benefits from RT-CGM. Overall, an educator support system and device trainer are crucial for success in wearing the RT-CGM device;
- (ii) The youth with diabetes must have a personal interest in wearing the RT-CGM and not be a passive accomplice to a parental decision;
- (iii) Youth with RT-CGM need help from parents/guardians with changing the sensor, responding alarms, making dose changes, and troubleshooting problems;
- (iv) The RT-CGM data have to be reviewed with the patients and parents to make conclusions regarding diabetes management and to make the proper changes.

Skills that need to be taught for RT-CGM use

To ensure the success of patients on RT-CGM, treatment guidelines have to be provided to patients to allow them to safely and effectively take advantage of the information provided by the RT-CGM (62).

Proper training is necessary for patients to use RT-CGM correctly, and maintaining a high level of contact with the families during the first months of wear (62, 63).

QOL with RT-CGM

QOL assesses the physical and mental health of individuals and is often considered in terms of how life is negatively affected by chronic illness or by treatment. QOL measures extend beyond traditional morbidity and mortality and include consideration of physical and emotional function as well as general life satisfaction. Assessment of QOL includes generic measures and disease-specific measures. In pediatric settings, QOL can include self-reported measures from older children and teenage pediatric patients and proxy reports of youth QOL as reported by parents/guardians (64–66). Generic measures of QOL allow for comparisons

across populations with health and disease as well as across cultures/regions. These measures are often insensitive to particular aspects of disease and its treatment. Disease-related QOL measures tend to be more sensitive and specific to the disease and its management. A combination of generic and disease-specific QOL measures allows for monitoring of a patient's health status over time in response to management or interventions.

Dimensions of QOL include positive well-being, negative well-being, worries, and social burden. Generic measures of health-related QOL for pediatric patients, in general, include physical and psychosocial domains with school, emotional, and social arenas included in the psychosocial domains. Disease-related measures include assessment of treatment convenience, interference, and satisfaction. Another dimension of QOL can include assessment of disease burden on the youth and on the parents/guardians. Finally, in the management of T1D, fear of hypoglycemia is another area that warrants assessment regarding a patient's perception of QOL.

Does RT-CGM confer additional psychosocial stress to the child and family?

Generic QOL measures obtained from youth with T1D and from parent proxy reports appear to be similar to reports from normative samples of youth from a US study (67), while parent proxy report from an Australian sample reported lower QOL in youth with T1D compared with a normative, age matched sample (14). However, the QOL reported by the adolescents with T1D was similar to the normative population of adolescent youth in that sample (68). Thus, reports of generic QOL in youth with T1D may be similar to reports of non-diabetic youth and may be age-dependent.

Overall, general QOL in youth with T1D appears to be associated with glycemic control in cross-sectional studies. Higher QOL was associated with lower HbA1c (69–72), although one report found no association between QOL and HbA1c (68).

A cross-sectional survey of 457 families of youth with T1D indicated that families are likely to elect RT-CGM for youth who use an insulin pump, check blood glucose levels more than six times daily, and have parental worry about either high or low blood glucose levels. Age of the child and HbA1c were not related to parental interest in RT-CGM (73).

RT-CGM use in pediatric patients could impact QOL in many ways; the wealth of glucose data resulting from RT-CGM could add distress after observing out-of-range data or could reduce concerns by providing real-time results. Nevertheless, RT-CGM use does not appear to negatively impact QOL according to youth self-reports and parent proxy

reports, using both generic and diabetes-specific measures (5, 21, 74). Specifically:

- (i) There was no change in reported fear of hypoglycemia among youth or their parents with RT-CGM use compared with SMBG (74). Adults with T1D have reported reduced fear of hypoglycemia with RT-CGM use (74);
- (ii) There was no increase in parent reports of diabetes burden with RT-CGM use compared with parent reports of diabetes burden with SMBG (74);
- (iii) Satisfaction with RT-CGM has been assessed with a validated questionnaire created specifically to assess RT-CGM technology satisfaction (75). In general, satisfaction with RT-CGM has been relatively high, with mean scores about 4 (on a 1- to 5-point scale) (76). RT-CGM satisfaction was related to RT-CGM use, with mean RT-CGM satisfaction scores being higher with greater RT-CGM use (or with lower HbA1c) (74);
- (iv) Barriers to RT-CGM use were reported by youth with T1D and their parents. Youth and their parents reported barriers related to RT-CGM alarms, body issues, and pain at insertion (77);
- (v) Benefits to RT-CGM use were reported by youth with T1D and their parents. Youth and parents reported benefits related to glucose trend graphs, detection of low blood glucose levels, availability of RT-CGM data, and ability to self-correct out-of-range glucose levels (77).

Quality and frequency of pediatric diabetes care—what is required for RT-CGM implementation and ongoing use with respect to pediatric diabetes team visits, education for RT-CGM use (i.e., extra education visits), etc.?

- (i) Quality of education: RT-CGM education is best provided by clinicians experienced in pediatric diabetes management;
- (ii) Frequency of education and follow-up visits during RCTs of RT-CGM vs. SMBG alone, not RCTs of SAP vs. SMBG:
 - (a) Randomized phase of the JDRF-CGM trial: The study groups had *four extra visits and six extra phone calls initiated by the diabetes team* during the 6-month RCT at times 0, 1, 4, 8, 13, 19, and 26 wk for the implementation of CGM. There was one phone call between each visit (18). During the 6-month extension phase of the CGM group in the JDRF trial there were visits every 3 months, as would be expected for routine follow-up diabetes care. During the 6 months cross over from SMBG to RT-CGM in the JDRF trial

there were *two extra visits and two calls by the diabetes team* at the start of RT-CGM followed by visits at 3 and 6 months (18);

- (b) GuardControl: During the 3-month study, there were two extra visits. Visits occurred at baseline, 10 d, 1 month, and 3 months (15);
- (c) RealTrend: During the 6-month study, there were visits at baseline, 3 d, 12 d, 1 month, 3 months, and 6 months, amounting to *three extra visits* (27);
- (d) O'Connell: In this 3-month multicenter RCT comparing SAP with standard pump therapy, there were *no additional visits after a baseline, standardize education visit in the use of RT-CGM* (17);
- (e) Star 1: In the 6-month study, there was training in intensive diabetes management, RT-CGM use, and data interpretation, *with increased interactions between subjects and clinicians throughout the study period* (16).

Recommendations

- (i) There should be an initial informational session about RT-CGM before prescription for general RT-CGM education, provision of realistic expectations, and device selection. This session could be in a group or as an individual visit;
- (ii) There should be a minimum of one extra visit for RT-CGM start-up (insertion, site care, alarm setting, dose adjustments, trend analysis, data analysis, nutritional changes, etc.) by RT-CGM educator specialists;
- (iii) Following RT-CGM implementation, there should be an additional follow-up visit within 1–2 wk of RT-CGM initiation to download data and review RT-CGM settings (alarms), use, and insulin regimen;
- (iv) There should be consideration for extra contact(s) to encourage ongoing RT-CGM use and to address potential barriers to RT-CGM use in the pediatric population.

Cost-effectiveness of CGM therapy

There are no published cost-effectiveness analyses or cost-benefit studies analyzing intermittent or continuous CGM in children or adolescents with T1D and such analyses are needed. The published cost-effectiveness analysis that was done based on the JDRF trial by means of the internet-based, interactive computer simulation model to determine the long-term health outcomes and economic consequences of type 1 and type 2 diabetes (CORE model) was restricted to adults with T1D who had baseline HbA1c levels

$\geq 7.0\%$. Patients in the 8–14 and 15–24-year-old age groups in that study were excluded from these cost-effectiveness analyses because the RT-CGM groups did not achieve a significant lowering of HbA1c levels compared with controls. It concluded that *'Long-term projections indicate that CGM is cost-effective among type 1 diabetic patients at the \$100 000/ quality-adjusted life-year (QALY) threshold, although considerable uncertainty surrounds these estimates'* (78). Comparable calculations from presently unpublished analyses have found an even better cost-effectiveness ratio compared with SMBG in Sweden (36 000–52 000 €/QALY) based on the RealTrend study data and in the Netherlands (21 000 €/QALY) based on the GuardControl trial. Both countries decided to reimburse RT-CGM based on these data.

Conclusions

- (i) Real-time sensors are proven to be cost-effective in well-controlled children and adults (HbA1c levels $< 7.0\%$);
- (ii) Real-time sensors have positive effects on glycemic control with evidence of cost-effectiveness vs. SMBG in adults with HbA1c levels $> 7.0\%$, and likely in children with frequent use;
- (iii) Improving RT-CGM technology and semi-automated hybrid or full-closed loop systems are rapidly emerging and make a constant re-evaluation of the cost-effectiveness of the most recent technology mandatory.

RT-CGM as part of the closed-loop system and future research opportunities

Treating T1D in children is challenging for patients, their family members, and medical staff, and keeping the blood glucose levels constant within the desired (target) range day and night is almost an impossible mission. Thus, the development of an automatic system that will decrease patient burden and improve glucose control is an unmet medical need. The typical closed-loop system has to be based on a continuous glucose sensor, insulin pump, and a computerized algorithm; technologies that are already available.

The first step toward closing the loop which is already commercially available outside the USA is an automatic suspension of the insulin delivery when the patient is in the hypoglycemic range and does not respond to the system alarm. It has been found that there is often a prolonged period of hypoglycemia preceding nocturnal hypoglycemia-associated seizures (79) which might be prevented by suspending basal insulin infusion. In addition, it has been shown that suspension of subcutaneous insulin delivery for up

to 2 h is not associated with ketosis or rebound hyperglycemia (79, 80). In a preliminary user trial conducted in the UK and Germany, using the LGS feature was shown to be safe and effective at reducing duration of hypoglycemia and was well accepted by the users (81).

Recommendation

An automatic system that will safely control blood glucose levels in children with diabetes within the desired range is currently an unmet medical need. The technology and algorithms necessary to reach this goal are currently evolving. While the ultimate goal is a fully automated system, a step-wise approach could provide clinically meaningful solutions. Insulin suspension during hypoglycemia has shown promising preliminary results in children and should be further studied for its safety and efficacy as it is the first step toward closing the loop.

Conclusions

The unifying theme of trials investigating the usefulness of CGM technology is that in order to reap benefits, the device must be worn on a near-daily basis. Education is a critical component to ensure that patients and their families are able to realize the full potential of this therapeutic tool. Families first need to be educated on what information a sensor can, and cannot provide them. Once the decision is made to pursue sensor therapy, the discussion turns to which device is right for a particular patient and family. Ensuring adequate education for the patients, and their family, on the use of the device is critical for success. It may be possible to encourage more frequent RT-CGM usage by focusing on the benefits of the technology and in preemptive counseling that provides realistic expectations and effective strategies to overcome the difficulties in using these devices. Moreover, as industry introduces improved RT-CGM systems that make them less painful and easier to use, and adds features like the LGS, it is reasonable to expect that patients will use RT-CGM more consistently, which, in turn, should result in a greater improvement in metabolic control of T1D.

The vast majority of the studies cited on RT-CGM use in children and adolescents use a multidisciplinary trained team that usually is not available to the non-academic pediatric endocrinologist. This may be a caveat to prescribing RT-CGM.

In summary, based on the available evidence and the experience of the expert panel, the use of RT-CGM may be appropriate for motivated children and youth of all ages provided that appropriate support personnel are available.

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Appendix

M. P. is a member of the board of CGM3, hold stocks in D-Medical and CGM3, consultant to D-Medical, Bristol Myers Squibb, AstraZeneca, and Physical Logic; M. P.'s institution received grants or support from Medtronic, DexCom, Roche, Abbott, Insulet, Animas, Novo Nordisk, Sanofi-Aventis, and Eli Lilly; and received honoraria and travel expenses from Sanofi-Aventis, Novo Nordisk, Bayer, and AstraZeneca.

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L. L. received grant support from Bayer Diabetes Care and is a consultant for Lilly, Sanofi-Aventis, Bristol Myers Squibb, AstraZeneca, Johnson & Johnson, and Menarini.

W. T. is a consultant and speaker for Medtronic.

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S. S. has nothing to declare.

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