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Advances in Glucose Monitoring and Automated Insulin Delivery: Supplement to Endocrine Society Clinical Practice Guidelines

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Endocrine Society guideline recommendations on diabetes technology in adults originate from the 2016 guideline titled "Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline." Society recommendations on diabetes technology in children are contained in the 2011 guideline titled "Continuous Glucose Monitoring: An Endocrine Society Clinical Practice Guideline." The field of diabetes technology is a rapidly advancing one, with new devices released annually and data from clinical trials published frequently. This report describes the most recent findings since the 2011 and 2016 guidelines were written, combining summaries of new literature with the authors' clinical experience of new devices. Although we describe what we believe to be important scientific and technological updates since these guidelines were published, we are not advancing formal additions or amendments to previously offered recommendations.

Freeform/Key Words: diabetes devices, technology

The field of diabetes technology is a rapidly advancing one, with new devices released annually and data from clinical trials published frequently. The 2016 Endocrine Society guideline on diabetes devices [1] was produced through a standard process of guideline creation: experts reviewing and summarizing the literature, meeting to reach consensus on key points, sending the manuscript out for public review, and then going through a process of internal and external review until it was published and presented at the 2016 Endocrine Society annual meeting. This 2016 guideline serves as the framework for this current report, which describes the most recent findings since that guideline was written. As with the previous guideline, some of the information presented is from the literature and some from clinical experience with these newer devices.

Abbreviations: ADA, American Diabetes Association; AID, automated insulin delivery; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DIAMOND, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes; FDA, Food and Drug Administration; HCL, hybrid closed loop; ISPAD, International Society of Pediatric and Adolescent Diabetes; MDI, multiple daily injection; SMBG, self-monitoring of blood glucose; STAR, Sensor-Augmented Pump Therapy for A1C Reduction; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range.

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1. Overview

Endocrine Society recommendations on diabetes technology in adults originate from the 2016 guideline [1]. Society recommendations on diabetes technology in children are contained in the 2011 guideline [2]. Table 1 lists these recommendations and provides summary information on the technological developments and new published data in these areas since these guidelines were published. Additional details on these developments are provided in this article. Although we describe what we believe to be important scientific and technological updates relevant to these clinical practice guidelines, we are not advancing formal additions or amendments to previously offered recommendations.

2. Insulin Delivery

A. Pediatrics

A-1 Pumps

It has been well established that insulin pump therapy is safe and effective in children, particularly those <7 years old. No recent data have been published on insulin pump therapy in children, to our knowledge, in the past 2 years, but the American Diabetes Association (ADA) and the International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines support its use. The 2014 ISPAD Clinical Practice Consensus Guidelines recommend continuous subcutaneous insulin infusion (CSII) as an option in pediatric patients but do not favor its use over that of multiple daily injection (MDI), because of concerns about patient selection and bias in observational studies. However, they do review the positive impact CSII can have on patient satisfaction, even without improvement in HbA1c [3]. Conversely, the ISPAD recommendations for management of diabetes in preschool children do specifically recommend insulin pump therapy for children <7 years old [4]. They cite data reporting improved flexibility and freedom, as well as less stress and anxiety related to disease management with the use of CSII in preschool children with diabetes [5]. As with adult users of CSII therapy, the need for adequate user education and follow-up is stressed. The 2018 ADA standards of care encourage intensification of insulin regimens in pediatric patients but only specifically comment on automated insulin delivery (AID) systems [6].

A-2. AID systems

There are more data on the use of AID systems in pediatric patients. However, current AID systems are not approved by the Food and Drug Administration (FDA) for all pediatric patients, and this must be considered when recommending or initiating treatment. In addition, device availability varies by country.

AID systems use subcutaneous glucose sensor values and dosing algorithms to deliver insulin with CSII. In a study of 15 adolescents using the Medtronic hybrid closed-loop (HCL) controller in a supervised hotel-based study, Ly *et al.* [7] found the overall percentage of time in the glucose target range of 70 to 180 mg/dL (3.9 to 10 mmol/L) was 69.8% in the adolescent cohort. The time spent at <70 mg/dL (3.9 mmol/L) was 2.5%, and the mean glucose value was 153 mg/dL (8.5 mmol/L). The system requires glucose calibrations, premeal insulin blousing, and treatment modifications with exercise, but the findings indicated safety and efficacy of AID in adolescents with type 1 diabetes (T1D).

Garg *et al.* [8] completed further investigation of AID systems in adolescents with the use of the Medtronic MiniMed 670G system in 30 individuals (14 to 21 years of age) over 3 months. Adolescents used the system 75.8% of the time, and their mean HbA1c value decreased from 7.7% to 7.1%, a statistically significant increase in their time spent in target and a decrease in their time spent hypoglycemic, but the hypoglycemia data did not reach statistical significance.

Table 1. Previous Guideline Recommendations and Recent Technology Developments

Guideline Recommendations	Technology Developments
Adults (2016 guideline)[1]	
1. Insulin pump therapy without sensor augmentation	
1.1 We recommend continuous subcutaneous insulin infusion (CSII) over analog-based basal-bolus multiple daily injections (MDI) in patients with type 1 diabetes mellitus (T1DM) who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device. (1 | ⊕⊕⊕◯)	Most updates on CSII therapy involve use of sensor augmentation; however, few studies have been reviewed on CSII use in adults. Pediatric patient use of CSII was not discussed in the 2016 Diabetes Technology guideline.
1.2 We recommend CSII over analog-based basal-bolus MDI in patients with T1DM who have achieved their HbA1c goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device. (1 | ⊕⊕◯◯)	However, the authors of the current study believe the ISPAD recommendations for CSII use in pediatric patients are reasonable and helpful in this regard. The use of CGM in a pediatric population was discussed in the 2011 Endocrine Society CGM guidelines, and relevant developments since that time are reviewed in this table.
1.3 We suggest CSII in patients with T1DM who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device. (2 | ⊕⊕◯◯)	The closing paragraph in our prior publication pointed toward the development of sensor-augmented pump therapy and since that time, the first HCL system was released in the US market: the Medtronic 670G system [1]. Available published data about this system are provided in this article, as well as clinical information regarding its use.
2. Insulin pump therapy in type 2 diabetes	
2.1 We suggest CSII with good adherence to monitoring and dosing in patients with type 2 diabetes mellitus (T2DM) who have poor glycemic control in spite of intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications. (2 | ⊕⊕◯◯)	No important new published data or technological developments
3. Insulin pump use in the hospital	
3.1 We suggest that clinicians continue CSII in patients admitted to the hospital with either type of diabetes if the institution has clear protocols for evaluating patients as suitable candidates and appropriate monitoring and safety procedures. (2 | ⊕⊕◯◯)	No important new published data or technological developments
4. Selection of candidates for insulin pump therapy/education and training	
4.1 We recommend that before prescribing CSII, clinicians perform a structured assessment of a patient's mental and psychological status, prior adherence with diabetes self-care measures, willingness and interest in trying the device, and availability for the required follow-up visits. (1 | ⊕⊕◯◯)	No important new published data or technological developments
4.2 We suggest that adults with T1DM and T2DM who use CSII and continuous glucose monitoring (CGM) receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals. (Ungraded Good Practice Statement)	No important new published data or technological developments
5. Use of bolus calculators in insulin pump therapy	
5.1 We suggest encouraging patients to use appropriately adjusted embedded bolus calculators in CSII and have appropriate education regarding their use and limitations. (2 | ⊕⊕◯◯)	Use of bolus calculators is a rapidly evolving area of technology, although clinical trials are largely lacking. We have provided in this article a discussion on insulin dose calculators for people using MDI therapy.

(*Continued*)

Table 1. Previous Guideline Recommendations and Recent Technology Developments (Continued)

Guideline Recommendations	Technology Developments
6. Real-time continuous glucose monitors in adult outpatients	
6.1 We recommend real-time CGM (RT-CGM) devices for adult patients with T1DM who have A1c levels above target and who are willing to use these devices on a nearly daily basis. (1|⊕⊕⊕◯)	There is new evidence on the use of CGM in adults with both T1D and T2D and it is summarized in this update. New, factory-calibrated CGM systems have been released (*i.e.*, Dexcom G6 and the Libre professional and personal versions). In addition, the Guardian Connect CGM has become available. All are briefly discussed in this article.
6.2 We suggest RT-CGM devices for adult patients with well-controlled T1DM who are willing to use these devices on a nearly daily basis. (2|⊕⊕⊕◯)	
6.3 We suggest short-term, intermittent RT-CGM use in adult patients with T2DM (not on prandial insulin) who have A1c levels >7% and are willing and able to use the device. (2|⊕⊕◯◯)	
Children and Adolescents (2011 guideline)[3]	
2.1 We recommend that RT-CGM with currently approved devices be used by children and adolescents with T1DM who have achieved glycosylated hemoglobin (HbA1c) levels below 7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia (1|⊕⊕⊕⊕).	There is new evidence on the use of CGM in pediatric patients with T1D, which is reviewed in this document. We also state that no specific guidance can be offered for or against the use of RT-CGM in patients <8 years old.
2.2 We recommend RT-CGM devices be used with children and adolescents with T1DM who have HbA1c levels ≥7.0% who are able to use these devices on a nearly daily basis (1|⊕⊕⊕◯).	
2.3 We make no recommendations for or against the use of RT-CGM by children with T1DM who are less than 8 years of age	
2.4 We suggest that treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM (2|⊕◯◯◯).	
2.5 We suggest the intermittent use of CGM systems designed for short-term retrospective analysis in pediatric patients with diabetes in whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness; and in patients experimenting with important changes to their diabetes regimens [such as instituting new insulin or switching from multiple daily injections (MDI) to pump therapy] (2|⊕◯◯◯).	

Abbreviations: HCL, hybrid closed loop; ISPAD, International Society of Pediatric and Adolescent Diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

In an open-label, randomized, two-arm, crossover, in-hospital clinical trial, 20 adolescents in Slovenia completed a study examining glucose control during unannounced physical activity while using an AID system (Paradigm Veo and Enlite II sensor; Medtronic). Use of the AID system increased the proportion of time spent within the target glucose range of 70 to 180 mg/dL (3.9 to 10 mmol/L) when compared with use of the insulin pump without AID. The authors concluded the AID system was safe during and after unannounced exercise protocols in an in-hospital environment [9].

The ISPAD 2014 pediatric Clinical Practice Consensus Guidelines do not comment on AID systems [3]. However, the 2018 ADA standards of care [6] do provide a B level

recommendation for consideration of AID systems to improve glycemic control and reduce hypoglycemia in adolescents.

Understanding the patient experience with chronic disease management is crucial for medical teams, but in the face of new technologies, health care providers have even more to learn. Iturralde *et al.* [10] studied 15 adolescents and 17 adults to specifically understand patient expectations and attitudes related to AID systems. They found "users are willing to accept some hassles and limitations if they also perceive health and quality of life benefits beyond current self-management" [10]. Additional work by this group found context-, system-, and person-level factors influenced trust in the AID system. When this trust was lacking, patients engaged in behaviors to override the system. However, when they trusted the system, they experienced decreased management burdens and lower levels of stress [11]. These findings are critical for providers' consideration, because the willingness to accept challenges related to new technologies and also trust the AID system will vary by patient and family, and both factors will need constant attention.

B. Adults

B-1. Continuous subcutaneous insulin infusion and AID therapy

Recent changes in intensive insulin therapy have come with incremental advances in pairing continuous glucose monitoring (CGM) with pump therapy. The Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 trial demonstrated that sensor-augmented pump therapy (*i.e.*, CGM communicating with a pump) improved glucose control without increasing hypoglycemia, compared with multiple daily doses of insulin with self-monitoring of blood glucose (SMBG) [12]. That frequency of CGM use was a strong predictor of success in STAR 3 leads to the question of whether the CGM or the pump is more important in gaining good glucose control. The independent benefit of insulin pump use in a group of patients with reasonably well-controlled T1D was questioned in the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) study [13]. In this 2-year study of the benefit of insulin pump therapy vs MDIs in patients who were all exposed to comprehensive education on intensive insulin therapy and all used a dose calculator, the insulin pump group did not have significantly greater reduction in the adjusted HbA1c level. Phase 2 of the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial found that patients with T1D who first used CGM with MDI attained a higher time in range (TIR) and less glucose variability when an insulin pump was substituted for MDI, though the HbA1c did not decrease significantly over 6 months of use [14].

Although these studies raise interesting questions, artificial pancreas development will require an insulin pump for insulin delivery. After the benefit of sensor-augmented pump therapy was demonstrated, the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial confirmed that integrating CGM with an insulin pump and adding appropriate, computerized, automated decision support could reduce time spent in hypoglycemia with the threshold suspend feature [15]. The next step, not independently marketed in the United States, was the predictive suspend feature that, again, showed further reductions in hypoglycemia and, to some degree, hyperglycemia [16, 17]. The Tandem t:slim X2 pump (Tandem Diabetes Care) is now marketed with a predictive suspend feature in an integrated system that incorporates the Dexcom G6 as the CGM component.

At this time, the most advanced FDA-approved form of the HCL uses the integrated CGM to inform the automated pump decisions between meals and overnight. In this case, the standard dose calculator continues to be used to determine each meal dose, implementing the insulin-to-carbohydrate ratio and the correction ratio. Such insulin calculators have been a key feature of "smart pumps," but the new feature of continuous adjustments of the basal rate to better reach and maintain target glucose levels has been an advancement in insulin therapeutics. A recent HCL prospective trial in adults found the HCL by Medtronic significantly decreased HbA1c by about 0.5% in adults with a baseline mean HbA1c of 7.4% [18].

The HCL also led to increased TIR, decreased time in hyperglycemia, decreased variability, and reduced hypoglycemia. Similar results were seen in adolescents [8]. The results were promising, but the study design lacked a control arm and the study group was in moderate control at baseline.

There are limitations that need to be recognized in the presently available HCL system. The CGM must be calibrated three to four times daily to ensure a mean absolute relative difference (a measure of the accuracy of a CGM device) of ~10%, the level of accuracy that has been proposed as necessary for dosing decisions. Patients must continue to enter their carbohydrates and dose before eating, because the system works less well when trying to catch up from postmeal hyperglycemia. Also, the patient must be attentive to the fact that the pump can default to a manual mode in several circumstances, including prolonged hypoglycemia, prolonged hyperglycemia, lost sensor signal, or atypically high insulin infusion rates. It can be difficult (and possibly dangerous) to silence alarms at night and patients have complained of disrupted sleep. Some patients enter "ghost carbohydrates" so the system will give more bolus insulin, but entry of incorrect data may impair the performance of system algorithms. It can be difficult for the system to function in "auto mode" for some patients during exercise, particularly intense training and competition, despite the ability to set a temporary target of 150 mg/dL for 2 hours before exercise (as is recommended by the manufacturer).

Finally, the system does not facilitate attainment of HbA1c levels much below 6.6% in most patients, because the target glucose level is set at 120 mg/dL and the target level cannot be changed other than for exercise. Therefore, mean CGM glucose values are usually near 150 mg/dL in adults and 160 mg/dL in adolescents. We note that these fixed targets of currently available HCL systems are not appropriate for use in patients for whom lower glycemic targets are recommended (*e.g.,* pregnant patients). Some patients with an HbA1c level <6.5% at baseline will see an elevation of their HbA1c level on the HCL system. This has led some concerned patients with lower HbA1c levels while using standard pump therapy to pursue the use of do-it-yourself hybrid AID systems, finding components, algorithms, and instructions for assembly online. They then can set lower targets and attain lower HbA1c and mean glucose levels. However, the safety of the do-it-yourself system is not scientifically proven and those patients who choose this approach must recognize the risks of using a non-FDA approved integrated device system for care.

In summary, the commercially available closed-loop systems represent a step forward in AID. It will often improve HbA1c level and reduce hypoglycemia, and is generally considered an improvement by most patients who are properly selected. With provider guidance, the patient must be attentive to adjustments in insulin-to-carbohydrate ratios, correction ratios, and insulin action time. An important benefit is that patients with a fear of nocturnal hypoglycemia can trust having more normal overnight blood glucose levels due to the automated adjustments by the HCL system. It is also important to note that Medtronic has produced the first commercially available HCL system, but multiple other AID systems are likely to become available in the next several years from Bigfoot, Insulet, Tandem, Eli Lilly, and Beta Bionics. For example, the Tandem Basal-IQ predictive low glucose suspend (PLGS) product using the Dexcom G5 sensor was reported to decrease time in hypoglycemia by 31% [19]. The Control-IQ that advances the Tandem system to an HCL system, similar to the Medtronic system, is now completing clinical studies.

B-2. Smart pens and dosing calculators

Although recent discussions on advances in insulin delivery often have been centered on pumps and sensors for more automated and safe insulin delivery, many of the benefits of the pump come from the application of insulin dose calculators in smart pumps and the software that downloads meaningful reports from pumps. These benefits are potentially attainable with MDI therapy as well. If a receiver (*e.g.,* a cell phone) is able to capture and process information such as glucose levels, dose amount, dose timing, and carbohydrate intake, the

information can be used to assist in dose adjustments, documentation of adherence, and better recognition of patterns.

The FDA approved the InPen system (Companion Medical), a wireless-enabled insulin pen with a proprietary mobile application in July 2016. The InPen is only now becoming available in limited markets. The device is able to calculate doses based on the same principles as dose calculators in pumps; the information is transmitted to the receiver or application via Bluetooth from the pen [20]. This also allows for tracking of the doses and timing, and that information can be shared with the provider. There is also a dose reminder and indicator of "insulin on board" (*i.e.*, how much insulin is still active in the patient's body). One would expect this technology to be valuable for both patients and providers and will clarify adherence with dosing that has not been available with MDI. Up to this time, however, no important clinical studies have been completed to show the system's performance and benefit in clinical practice. There is a growing number of insulin titration applications being approved by the FDA, and Eli Lilly and Bigfoot, among others, are aiming to further develop the potential of smart pens.

3. Continuous Glucose Monitoring

A. Pediatrics

Previous guidelines by the Endocrine Society recommended CGM for pediatric patients with HbA1c levels $<7\%$ to help limit the risk of hypoglycemia and for patients with HbA1c levels $\geq 7\%$ who can use the device almost daily. However, the guidelines were not stated to be applicable to those <8 years old. The 2011 Endocrine Society guidelines did recommend intermittent use of CGM to assist understanding glucose excursions and/or changes in insulin regimen [2].

Recently published recommendations by Laffel *et al.* [21] provide an overview of when to use CGM (*i.e.,* patient >2 years old, intensive insulin regimen, frequent hypoglycemia, hypoglycemia unawareness, excessive glucose variability, varying and/or intensive activity, desire to improve glycemic control, understanding of behavior influencing glycemic control, willingness to use CGM on a near daily basis, willingness to learn how to use device and receive ongoing education, and pregnant or wants to get pregnant). The authors present a practical approach to using trend arrows on the Dexcom G5 CGM in children and adolescents with diabetes. The approach suggested by Laffel *et al.* [21] combines recommendations from DirecNet [22], Scheiner [23], and Pettus and Edelman [24]. The Libre intermittently scanned ("flash") CGM device (Abbott Diabetes Care) was not approved for use in children at its launch, but this is likely to change. As for adult patients, an individualized approach to choosing which device is appropriate for an individual patient should be used with an understanding of the strengths and weaknesses of each system.

There are additional points to consider regarding CGM use in pediatric patients. The school setting can make CGM and remote monitoring challenging because parents may have expectations and desires beyond what is considered feasible in the school system. Erie *et al.* [25] examined responses from 33 parents and 17 daytime caregivers of pediatric patients who wore a continuous glucose monitor with remote monitoring. Parents and caregivers reported decreased worry and stress with the use of CGM in addition to overall positive feelings about the device and comfort with use.

B. Adults

B-1. Type 1 diabetes

Real-time- CGM + MDI. Since our guidelines were published in 2016, multiple studies have been done to further define the benefits of real-time CGM (RT-CGM) in a variety of settings. Two recent studies, the Glycemic Control and Optimization of Life Quality in Type 1 Diabetes

(GOLD) [26] and the DIAMOND trials [27, 28], assessed the value of RT-CMG in people with T1D treated with MDI. The GOLD study was an open-labeled, crossover, randomized controlled trial done in Sweden and included 161 participants who had an HbA1c level of ≥7.5%. Complete follow-up data were available on 142 individuals. The mean HbA1c level was 7.92% during CGM treatment and 8.35% for those who only used SMBG (treatment difference, −0.43%; $P < 0.001$). There was one episode of severe hypoglycemia in the CGM group and five episodes in the conventional treatment group. Statistically significant differences were seen in the amplitude of glycemic excursions, SD of glucose levels, and quality of life and distress measures on a variety of scales.

The DIAMOND 1 Trial was a randomized clinical trial including 158 adults with T1D who used MDI. The initial HbA1c levels ranged from 7.5% to 9.9%. There was a 2:1 randomization with 105 patients using CGM and 53 patients in the control group. The reduction in baseline HbA1c level was 1.0% at 24 weeks in the CGM group compared with 0.4% in the control group, with an adjusted treatment-group difference of −0.6% ($P < 0.001$). Median daily duration of blood glucose levels <70 mg/dL was 43 minutes in the CGM group vs 80 minutes in the control group ($P = 0.002$). CGM showed equal benefit for those older than age 60 years regardless of level of education or performance on numeracy testing. There were episodes of severe hypoglycemia in two participants in each group. In a smaller study of patients with better-controlled T1D (n = 11; HbA1c level, 7.2%), CGM improved awareness and reduced the burden of hypoglycemia, with a modest improvement of endogenous glucose production after 18 months [29].

These studies show the benefits of RT-CGM in people with T1D who are treated with MDI and support the recommendation that RT-CGM should be available to individuals with T1D. However, in these and other studies, the greatest benefits are seen in those who wear the devices more frequently, which highlight the need to encourage nearly continuous use to optimize benefit.

CGM as fingerstick replacement. The Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Type 1 Diabetes (REPLACE-BG) was done to determine whether RT-CGM values could be used safely and effectively to replace fingerstick blood glucose monitoring (BGM) in people with well-controlled T1D [30]. In this study, 226 individuals using CSII were randomly assigned 2:1 to CGM dosing only (n = 149) vs CGM plus BGM (n = 77). The average baseline HbA1c level was 7.0% and the primary outcome was TIR (70 to 180 mg/dL) over the 26-week trial. Patients in the CGM-only group measured their blood glucose level 2.8 (SD, 0.9) times daily (mostly for calibration) compared with 5.4 (SD, 1.4) tests per day in the CGM plus BGM group. The results confirmed there was no difference in TIR or hypoglycemia when people dosed insulin based on their CGM vs SMBG data when wearing a CGM. This helped lead to FDA approval for several CGM systems to be classified as nonadjunctive.

B-2 Type 2 diabetes

RT-CGM + MDI. The DIAMOND 2 Study assessed the role of RT-CGM in 158 people with type 2 diabetes (T2D) who were using MDI. As with the DIAMOND 1 Study, DIAMOND 2 was a randomized controlled trial with a 2:1 randomization scheme. The data showed there was less improvement in patients with T2D compared with those with T1D. After 24 weeks, CGM resulted in a 0.3% HbA1c reduction ($P = 0.022$) [31]. CGM is a positive motivational factor in T2D regardless of insulin use [32, 33].

C. Intermittently Scanned RT-CGM: Adults With T1D and T2D

Another form of RT-CGM, known as “flash” glucose monitoring, is essentially a continuous glucose monitor without alarms or alerts. It reveals a glucose level only when scanned by a reader. It stores the data so that retrospective analysis is possible. The currently available

flash device, the Libre, does not require calibration. There are two forms of the Libre—a professional version and a personal version. The professional version captures 2 weeks of blinded data for retrospective analysis. The personal version is scanned by the individual user in real time and glucose data are available as often as the user wishes to see them.

In patients with well-controlled (HbA1c level, 6.7%) T1D, there was a significant 38% reduction in hypoglycemic exposure after 6 months of the Freestyle Libre system compared with a control group[34]. Severe hypoglycemia was rare and not different between the two groups, and there was no difference in HbA1c levels. In a 6-month study of patients with T2D (HbA1c level, 8.7%) who were receiving multiple insulin injections, hypoglycemic exposure was again reduced with CGM and there was no difference in HbA1c level [35]. The hypoglycemia-reduction benefit remained after a 6-month follow-up [36].

In a randomized 8-week study comparing the Abbott Libre with the Dexcom CGM in a population of individuals with T1D and hypoglycemia unawareness, the Dexcom was more effective at reducing hypoglycemia burden [37]. A recent consensus statement provides information on how to use Dexcom trend arrows for adjusting insulin doses [38]; however, the recommended approach has not been tested in a clinical trial.

D. CGM for T1DM in Pregnancy

In a randomized trial with 325 women (n = 215 pregnant; n = 110 planning pregnancy), CGM during pregnancy was associated with improved neonatal outcomes most likely attributed to less hyperglycemic exposure [39]. Time above range was reduced (P = 0.03), and TIR was higher (P = 0.003) with CGM. Time spent in hypoglycemic and severe hypoglycemic episodes were not different between the two groups. Improved neonatal outcomes included babies large for gestational age, neonatal intensive care unit admissions lasting longer than 1 day, and 1-day shorter length of hospital stay. There was no apparent benefit of CGM on neonatal outcomes when it was used in women planning pregnancy [39].

E. Newest CGM Updates

In late March 2018, Dexcom received approval of the G6 CGM, which features a 10-day wear, factory calibration, a smaller transmitter, and a predictive hypoglycemia alarm. With this device, the FDA created a lower-risk 510 (k) pathway for integrated CGM. These integrated continuous glucose monitors will need to exceed stricter accuracy standards than earlier generations of devices. With this device, systems like the Dexcom G6 can be used as a stand-alone CGM or integrated in an AID system.

In the summer of 2018, the FDA approved the Sensionics Eversense CGM. This is an implantable, 90-day CGM sensor with an on-body transmitter with data transmitted to a smartphone displayed on a mobile application. Twice-daily glucose calibrations are required and this initial version is “adjunctive,” because fingerstick glucose testing is required for insulin dosing despite excellent accuracy data. For example, in the Prospective, Multicenter Evaluation of the Accuracy of a Novel Continuous Implanted Glucose Sensor (PRECISE) II trial, the overall mean absolute relative difference was 8.8% [40].

Finally, the Medtronic Guardian Connect was approved, which is an adjunctive RT-CGM device that requires twice-daily calibrations. It uses the Guardian Sensor 3 and is approved for individuals 14 to 75 years old. The system alerts the user if the glucose level is 10 to 60 minutes away from a high or a low level (as programmed by the user).

Table 2 provides a comparison of the characteristics of CGMs currently available [41].

4. Conclusion

Diabetes technology continues to evolve rapidly. In particular, the FDA creation of a new Class II pathway for continuous glucose monitors that have interconnectivity with other devices opens the door to intraoperability and accelerated development of new functionality.

Table 2. Comparison of Clinical Characteristics of Available CGMs

Attribute	Libre CGM	Dexcom G5	Dexcom G6	Medtronic Guardian G3	Eversense[a]
Calibration required?	No	Yes	No	Yes	Yes
Warm-up time, h	1	2	2	2	24
Alarms and alerts for changing and absolute BG values?	No	Yes	Yes	Yes	Yes
Duration of wear	14 d	7 d	10 d	7 d	3–6 mo
Transmits to a smartphone or smartwatch	No	Yes	Yes	No	Yes
Acetaminophen interference	No	Yes	No	No	No
Approved for pediatric use?	Not at the time of publication	Yes, ≤2 y	Yes, ≤2 y	Yes, ≤7 y	No

See [41].
Abbreviation: BG, blood glucose.
[a]Needs insertion via small surgical procedure.

This means that more tools will be available to help our patients with diabetes. However, clinical trials data will always lag behind technology development and many providers, particularly those in primary care, are not yet familiar with their use. Therefore, those familiar with the use of these devices need to be leaders in terms of educating and guiding providers and patients who have not yet been introduced to these tools. These devices have great potential to help our patients live better with diabetes, as long as they are provided in the context of health care settings with the resources to train, educate, and follow patients using this technology.

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