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ROLE OF CONTINUOUS GLUCOSE MONITORING IN DIABETES TREATMENT

CONTRIBUTING AUTHORS

IRL B. HIRSCH, MD
Professor of Medicine
University of Washington
Seattle, WA

TADEJ BATTELINO, MD, PHD
Professor of Pediatrics
University of Ljubljana
Ljubljana, Slovenia

ANNE L. PETERS, MD
Professor of Medicine
Keck School of Medicine of the
University of Southern California
Los Angeles, CA

JAMES J. CHAMBERLAIN, MD
Medical Director for
Diabetes Services
St. Mark's Hospital and
St. Mark's Diabetes Center
Salt Lake City, UT

GRAZIA ALEPPO, MD, FACE, FACP
Associate Professor of Medicine
Feinberg School of Medicine,
Northwestern University
Chicago, IL

RICHARD M. BERGENSTAL, MD
Executive Director
International Diabetes Center,
Park Nicollet and HealthPartners
Minneapolis, MN

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INTRODUCTION

History of Glucose Monitoring

Irl B. Hirsch, MD, *University of Washington, Seattle, WA*

Attempts to quantify glucose in the urine date back to the mid-1800s and laid the foundation for modern diabetes care. The most important development in the commercialization of urine glucose testing came in 1908, when Benedict developed a copper reagent for urine glucose, which was used, with some modifications, for more than 50 years (1). The cumbersome methodology of heating became more convenient in 1945 with the development of Clinitest (Ames, Elkhart, IN), which featured a modified copper reagent tablet. Glucose was oxidized, and the amount of glycosuria was proportional to the color of the heated solution.

In 1965, Ames developed the first blood glucose test strip, the Dextrostix, using glucose oxidase. A large drop of blood was placed on the strip and, after 60 seconds, was washed away. The generated color was then compared to a chart on the bottle for a semi-quantitative assessment of blood glucose. This early strip was for physicians' offices, not for home use.

The first glucose meter was used in the 1970s with the Dextrostix, but its precision and accuracy were poor. By the mid-1970s, the concept of patients using blood glucose data at home was contemplated, and by 1980, the Dextrometer was launched; this meter used the Dextrostix along with a digital display. During the 1980s, meters and strips requiring less blood became available, all at a cheaper price. Self-monitoring of blood glucose (SMBG) became the standard of care, especially for patients with type 1 diabetes. This advance, along with A1C testing and insulin pump therapy, made possible the Diabetes Control and Complications Trial, which positively answered the long debate about the relationship between glucose control and diabetes complications (2).

Through the late 1980s, 1990s, and early 2000s, SMBG technology continued to improve. The blood removal step was eliminated, smaller amounts of blood were required, electrochemical strips were developed, wider ranges of hematocrit were permitted, and new enzymatic tests were used. Lancets also improved. By 2010, SMBG was virtually painless and recommended for all patients receiving insulin and most who were not.

The evolution of home glucose monitoring was further revolutionized with the introduction of continuous glucose monitoring (CGM). In 1999, the U.S. Food and Drug Administration approved the first "professional" CGM, with which the patient was blinded to glucose data collected for 3 days, and then the information was downloaded in the health care provider's office for review. Until recently, all CGM devices required calibration with fingerstick blood glucose measurements. The first "real-time" CGM was the Glucowatch Biographer (Cygnus, Redwood, CA). This device was worn as a wristwatch using "reverse iontophoresis" to stimulate the secretion of subcutaneous fluid, from which glucose was measured using an electrode. The Glucowatch was not a commercial success, owing in large part to site irritation despite the fact that the sensor was technically noninvasive.

In 2004, Medtronic (Northridge, CA) introduced the Guardian REAL-Time CGM system, which could notify users of potentially dangerous hyperglycemia or hypoglycemia, and by 2006, the same company released the first integrated pump and sensor. That same year, Dexcom (San Diego, CA) introduced its first real-time CGM, called the STS (Short-Term Sensor). In 2008, the FreeStyle Navigator by Abbott (Alameda, CA) was released in the United States. All of the initial CGM devices required blood glucose confirmation for insulin decisions to be made.

Dexcom introduced the G4 Platinum in 2012. In 2015, the G5 Mobile was launched, now allowing data to be transmitted to a user's cell phone (similar to the G6, which was launched in 2018). Medtronic also had improvements in technology, with the next-generation professional CGM, the iPro, released in 2008. Medtronic's second-generation integrated pump-sensor device became available in 2009, and in 2013, the loop came closer to being closed with the introduction of the MiniMed 530G Enlite sensor, the first pump with "threshold suspend" for hypoglycemia. Medtronic's first hybrid closed-loop device was available in 2017 using the Guardian Sensor 3. Over time, the accuracy of all of these sensors improved.

Abbott introduced the FreeStyle Libre Pro in 2016. This professional CGM is the first that requires no fingerstick testing during wear. It also is unique in that the sensor can be worn for 14 days. As with earlier professional CGM systems, data are blinded to the user until they are downloaded and reviewed with the health care provider. The FreeStyle Libre, for direct use by patients, became available in the United States in late 2017 but earlier in other countries. In the United States, it has a 12-hour warm-up time and can be worn for 10 days. Like the Pro, it is factory-calibrated; unlike Dexcom or Medtronic CGM devices, it does not sound alarms for out-of-range glucose levels. The system includes a reader that patients can swipe or "flash" to obtain a glucose reading and trend data (or communicates with a phone in some countries). Statistical data can be seen directly on the reader, but more detailed information is available with the download.

In less than 20 years, CGM has revolutionized the way diabetes is managed, especially type 1 diabetes. Evidence supporting the use of CGM is now vast and unequivocal. In this compendium, we review the critical aspects of CGM to assist providers in their daily practice.

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Continuous Glucose Monitoring Comes of Age

Tadej Battelino, MD, PhD, *University of Ljubljana, Ljubljana, Slovenia*

Current iterations of continuous glucose monitoring (CGM) evolved from enzyme-based electrochemical glucose sensors developed in the 1960s at Cincinnati Children's Hospital in Ohio, USA. Glucose oxidase (GOx) placed on a platinum electrode catalyzed the oxidation of glucose to gluconolactone in the presence of oxygen, producing hydrogen peroxide and water as by-products. In the 1980s, oxygen was replaced with a synthetic redox electron acceptor, improving the accuracy of second-generation biosensors. Proprietary technical improvements resulted in an array of GOx CGM systems obtaining regulatory approval for routine use.

Despite considerable initial reluctance from many leading diabetologists to include CGM in diabetes management, clinical evidence has accumulated from research encompassing adult and pediatric populations with diabetes (1,2), hypoglycemia (3), use with sensor-augmented pumps (4,5), stand-alone use with multiple daily injections (6), outcomes during pregnancy (7), utility in type 1 and type 2 diabetes (8,9), and effects in real-life clinical settings (10). The article on p. 3 of this compendium offers a detailed discussion of published randomized clinical trials to date.

A recently introduced factory-calibrated intermittently scanned interstitial glucose monitoring system, also known as flash CGM (FCGM), is also based on GOx CGM technology and represents a new option with clinical benefit comparable to real-time CGM (11). FCGM received regulatory approval as a substitute for blood glucose testing and could conceivably replace traditional self-monitoring of blood glucose in diabetes management for people with diabetes who test multiple times per day (Figure 1).

The maturation of CGM technology and research is not only facilitating imminent development of closed-loop insulin delivery (12), but also substantiating the collection and analysis of continuous data as a routine treatment modality in major clinical guidelines (13,14). CGM-derived metrics such as time in range and coefficient of variation are now regarded as viable parameters for everyday diabetes management, as well as for clinical research (15).

FIGURE 1
Sample display of continuous data provided by FCGM.

As newer CGM systems with patient-centered features (see the article on p. 8 of this compendium) become a clinical reality for individuals with type 1 or type 2 diabetes, appropriate educational and technical support for both people with diabetes and health care providers will be needed to solidify the emerging status of continuous glucose data as a standard of care for daily diabetes management.

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The Evidence Base for Continuous Glucose Monitoring

Anne L. Peters, MD, *Keck School of Medicine of the University of Southern California, Los Angeles, CA*

Twenty-seven published randomized controlled trials (RCTs) assessing outcomes of continuous glucose monitoring (CGM), involving a total of 3,826 patients, have been published to date. Although the number of patients in each study has been small compared to drug trials, cumulative evidence indicates a benefit of CGM for patients treated with either continuous subcutaneous insulin infusion (CSII) or a multiple daily injection (MDI) insulin regimen. Additionally, some data suggest that CGM may benefit people with type 2 diabetes who do not use insulin therapy.

Overall, RCTs have shown improved glucose control in patients with higher initial A1Cs (often in the range of 7.8–8.8%) using CGM compared to self-monitoring of blood glucose (SMBG). People who wear their CGM device most consistently derive the most benefit. Time spent in the designated hypoglycemia range (usually <70 mg/dL) was reduced in some studies, particularly in those with patients selected for having a higher risk of hypoglycemia. These patients tended to have lower baseline A1Cs (in the range of 6.5–7.5%). Rates of severe hypoglycemia generally have not differed between CGM and non-CGM groups, and these rates have been low across all studies.

Studies fall into a few basic categories: adults with type 1 diabetes (8 trials, 698 patients), adults with type 2 diabetes (4 trials, 547 patients), children with type 1 diabetes (2 trials, 227 patients), adults plus children with type 1 diabetes (7 trials, 1,084 patients), adults with type 1 or type 2 diabetes (3 trials, 655 patients), and women during pregnancy with either type 1 diabetes or gestational diabetes mellitus (GDM) (3 trials, 585 patients). Table 1 lists general findings from all of these trials. It is important to note that some trials used A1C or time in range as the primary endpoint, whereas others used time in a hypoglycemic range as the primary outcome. Readers should also be aware that Table 1 is not a meta-analysis per se, but rather includes studies identified through a literature search of PubMed and Ovid MEDLINE, as well as all prior reviews and studies in their reference lists. Only RCT data are included; observational studies and extension phases of RCTs also have been performed but are not represented here.

The first trials, from the early 2000s, used intermittent CGM. Some used "professional" CGM, in which patients were blinded to the CGM data (see the article on p. 8 of this compendium), and others followed an intermittent use schedule. As time progressed, the trials reflected evolving use of CGM to the current day. That is, earlier studies began to suggest that CGM could improve outcomes, but lack of access to real-time data limited benefit. More recent studies of real-time CGM, in which around-the-clock data are available, have shown more benefit in terms of reduction in both A1C and time spent in a hypoglycemic range.

A major impediment to interpreting CGM studies is that no uniform standard has been employed for teaching people with diabetes how to use continuous data, and no standard follow-up is provided to ensure that dose adjustments are made. In some trials, written instructions were provided to patients regarding insulin dose adjustments, but in many others, targeted education was not provided beyond how to use the device. Additionally, rapid advances in technology are not well represented in the literature, although data from newer systems, such as the Dexcom G5 Mobile (Dexcom, San Diego, CA) and the FreeStyle Libre (Abbott, Alameda, CA), are becoming available.

TABLE 1 Summary of CGM Research Studies

Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
ADULTS WITH T1D: A1C PRIMARY OUTCOME				
Beck et al. (1,2)	▸ Adults with T1D on MDI ▸ *n* = 158 ▸ Baseline A1C: ~8.6% ▸ Parallel arms, 24 weeks	A1C reduction / Dexcom G4 Platinum	–0.6%, *P* <0.001	▸ Time <70 mg/dL was 43 vs. 80 min/day, *P* = 0.002 ▸ No difference in severe lows
Lind et al. (3)	▸ Adults with T1D on MDI ▸ *n* = 161 ▸ Baseline A1C: 8.6% ▸ Crossover, 26-week arms	A1C reduction / Dexcom G4 Platinum	–0.43, *P* <0.001	▸ Numerically less time in a hypoglycemic range with CGM
Sequeira et al. (4)	▸ Underserved adults with T1D MDI ▸ *n* = 25 ▸ Baseline A1C: 8.5% ▸ Crossover, 28-week arms	A1C reduction / Dexcom SEVEN	No significant difference between groups	▸ No change in rates of hypoglycemia

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Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Tumminia et al. (5)	▸ Adults with T1D on MDI or CSII ▸ *n* = 20 ▸ Baseline A1C: ~8.65% ▸ Crossover, 24-week arms	A1C reduction / Medtronic Guardian REAL-Time	Only analyzed 14 patients who used CGM ≥40% of the time; in these patients, there was a significant reduction in A1C (*P* <0.05)	Risk for hypoglycemia was reduced (time spent <70 mg/dL/day), *P* <0.05
ADULTS WITH T1D: HYPOGLYCEMIA PRIMARY OUTCOME				
Bolinder et al. (6)	▸ Adults with T1D on MDI or CSII ▸ *n* = 241 ▸ Baseline A1C: 6.7% ▸ Parallel arms, 6 months	Change in time in hypoglycemic range (<70 mg/dL) / Abbott FreeStyle Libre	NS	▸ Overall, 38% reduction in time in hypoglycemia (–1.24 hours/day, *P* <0.0001) ▸ Time in range (3.9–10.0 mmol/L [70–180 mg/dL]; mean difference) improved by 1.0 ± 0.30 hour, *P* = 0.0006
Hermanns et al. (7)	▸ Adults with T1D, most on MDI ▸ *n* = 41 ▸ Baseline A1C: 8.2% ▸ Crossover design, 5-day arms; patients were free-living within inpatient research setting	Proportion of time spent hypoglycemic / Dexcom SEVEN PLUS	N/A	Reduction in time in hypoglycemic range: 125 ± 89 vs. 181 ± 125 min/day, *P* = 0.005
van Beers et al. (8)	▸ Adults with T1D on MDI or CSII with a Gold score ≥4 ▸ *n* = 52 ▸ Baseline A1C: 7.5% ▸ Crossover, 16-week arms	Mean difference in time in range (4–10 mmol/L [72–180 mg/dL]) / Medtronic Enlite with a MiniMed Paradigm Veo system (used as a monitor)	NS	▸ Reductions in hypoglycemia (≤3.9 mmol/L [70.2 mg/dL]) –4.7%, *P* <0.0001 ▸ Severe hypoglycemia: 14 events with CGM vs. 34 events with SMBG, *P* = 0.033 ▸ Time in range (mean difference) improved by 9.6%, *P* = 0.0001
ADULTS AND CHILDREN WITH T1D: A1C/TIME IN RANGE PRIMARY OUTCOME				
Battelino et al. (9)	▸ Adults and children with T1D on CSII ▸ *n* = 153 ▸ Baseline A1C: 8.1% for adults, 8.6% for children ▸ Crossover, 6-month arms	A1C reduction / Medtronic Guardian REAL-Time	A1C difference –0.43% in favor of sensor on, *P* <0.001	▸ Time spent <3.9 mmol/L (70.2 mg/dL) was 19 vs. 31 min/day, *P* = 0.009 ▸ Four severe hypoglycemic episodes in sensor on mode, two in sensor off mode
Deiss et al. (10)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 156 ▸ Baseline A1C: 9.5% in arm 1, 9.7% in arm 2 ▸ Three parallel arms: continuous CGM (arm 1) vs. biweekly 3-day CGM (arm 2) vs. control for 3 months	A1C reduction / Medtronic Guardian REAL-Time	Arm 1: –0.6%, *P* = 0.003; Arm 2: no difference in A1C	One episode of severe hypoglycemia in each arm
JDRF CGM Study Group (11)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 322 ▸ Three age-groups: ≥25 years (*n* = 98), 15–24 years (*n* = 110), and 8–14 years (*n* = 98) ▸ Baseline A1C: ≥25 years, 7.6%; 15–24 years, 7.9–8.0%; and 8–14 years, 7.9–8.0% ▸ Parallel arms, 26 weeks	A1C reduction / DexCom SEVEN, Medtronic MiniMed Paradigm REAL-Time insulin pump and CGMS, and Abbott FreeStyle Navigator	▸ A1C difference: in those ≥25 years of age, –0.53%, *P* <0.001; in those <25 years of age, no difference ▸ A1C response related to use of CGM	No difference in time spent in a hypoglycemic range or in number of severe hypoglycemic episodes

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Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
O'Connell et al. (12)	▸ Adults and adolescents with T1D on CSII ▸ *n* = 55 ▸ Baseline A1C 7.3% for intervention group, 7.5% for control group ▸ Parallel arms, 3 months	Time in range during the 3-month study period / Medtronic MiniMed Paradigm REAL-Time insulin pump and CGMS	▸ No difference in primary outcome ▸ A1C was –0.43% lower in the CGM group, *P* = 0.009 ▸ Greater reduction in group with more use	No difference in time in range, variability, or hypoglycemia
ADULTS AND CHILDREN WITH T1D: HYPOGLYCEMIA PRIMARY OUTCOME				
JDRF CGM Study Group (13)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 129 ▸ Baseline A1C: 6.4% for CGM group, 6.5% for control group ▸ Parallel arms, 26 weeks	Change in time ≤70 mg/dL / DexCom SEVEN, MiniMed Paradigm REAL-Time insulin pump and CGMS, and Abbott FreeStyle Navigator	A1C treatment difference favoring CGM, *P* <0.001	▸ Time ≤70 mg/dL numerically less frequent (54 vs. 91 min/day) but not significant, *P* = 0.16 ▸ Median time with blood glucose ≤60 mg/dL was 18 vs. 35 min/day, *P* = 0.05 ▸ Severe hypoglycemia 10 and 11% for CGM and control groups, respectively, *P* = 1.0
Battelino et al. (14)	▸ Adults and children with T1D on MDI or CSII ▸ *n* = 120 ▸ Baseline A1C: 6.9% ▸ Parallel arms, 26 weeks	Time spent in hypoglycemic range / Abbott FreeStyle Navigator	A1C treatment difference favoring CGM: –0.27%, *P* = 0.008	▸ Time spent <63 mg/dL shorter in CGM group; ratio of means 0.49, *P* = 0.03 ▸ No severe hypoglycemia
Heinemann et al. (15)	▸ Adults and children with T1D on MDI with a history of impaired hypoglycemia awareness or severe hypoglycemia ▸ *n* = 149 ▸ Baseline A1C: 7.3% for control group, 7.6% for CGM group ▸ Parallel arms, 26 weeks	Baseline-adjusted hypoglycemia events (glucose ≤3.0 mmol/L [54 mg/dL] for ≥20 minutes) / Dexcom G5 Mobile	No difference in A1C	Adjusted between-group difference in low glucose events: 0.28, *P* <0.0001
CHILDREN WITH T1D				
Ludvigsson et al. (16)	▸ Children with T1D on MDI or CSII ▸ *n* = 27 ▸ Baseline A1C: ~7.7% ▸ Cross-over, 12-week arms; wore CGM for 3 days every 2 weeks	A1C reduction/ Medtronic CGMS	A1C difference at 12 weeks during open vs. blind CGM: ~–0.39%, *P* = 0.011	No significant differences in hypoglycemia
Chase et al. (17)	▸ Children with T1D ▸ *n* = 200 ▸ Baseline A1C: 8.0% ▸ Parallel arms, 6 months	A1C reduction / GlucoWatch G2 Biographer	No significant change in A1C	Sensor use declined from 2.1 to 1.5 times/week because of skin irritation and other issues
ADULTS WITH T2D				
Beck et al. (18)	▸ Adults with T2D on MDI ▸ *n* = 158 ▸ Baseline A1C: 8.5% ▸ Parallel arms, 24 weeks	A1C reduction / Dexcom G4 Platinum with an enhanced algorithm	Adjusted mean A1C difference: –0.3%, *P* = 0.022	No change in hypoglycemia
Ehrhardt et al. (19)	▸ Adults with T2D not on prandial insulin (half on oral medication alone) ▸ *n* = 100 ▸ Baseline A1C: 8.2% for SMBG group, 8.4% for CGM group ▸ Parallel arms, 2 weeks on/1 week off, 4 cycles over 12 weeks	A1C reduction / Dexcom SEVEN	Difference in A1C: –0.6%, *P* = 0.002	▸ Hypoglycemia data NA ▸ Most improvement in people who used CGM per protocol

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Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Haak et al. (20)	▸ Adults with T2D on prandial-only insulin on MDI or CSII ▸ *n* = 224 ▸ Baseline A1C: 8.74% in intervention group, 8.88% in control group ▸ Parallel arms, 2:1 randomization, 6 months	A1C reduction / Abbott FreeStyle Libre	No difference in A1C overall; difference in A1C if <65 years of age, *P* = 0.03	Time in hypoglycemia (<70 mg/dL) was reduced by 43%, *P* = 0.0006
Yoo et al. (21)	▸ Adults with T2D on oral agents or insulin ▸ *n* = 65 ▸ Baseline A1C: 8.7% in SMBG group, 9.1% in CGM group ▸ Parallel arms, real-time CGM for 3 days once per month for 12 weeks	A1C reduction / Medtronic Guardian REAL-Time	Improvement in A1C greater in CGM group, ~0.5%, *P* = 0.004 (CGM: from 9.1 ± 1.0 to 8.0 ± 1.2%, *P* <0.001; SMBG: from 8.7 ± 0.7 to 8.3 ± 1.1%, *P* = 0.01)	▸ No significant changes in hypoglycemia ▸ In real-time CGM, reduced caloric intake, weight, BMI, and postprandial glucose level; increased physical activity
ADULTS WITH T1D OR T2D				
Garg et al. (22)	▸ Adults with T1D or T2D on insulin ▸ *n* = 91 ▸ Baseline A1C: 7.6% in control group, 8.0% in CGM group ▸ Parallel arms, 3-day CGM for three consecutive 72-hour periods	Time spent in high, low, and target glucose zones / Dexcom STS sensor	▸ 23% less time in hyperglycemia (≥240 mg/dL) ▸ 26% increase in time in range (81–140 mg/dL) ▸ *P* <0.001 for each comparison	CGM group spent 21% less time in hypoglycemia (<55 mg/dL), *P* <0.0001
New et al. (23)	▸ Adults with T1D or T2D on MDI or CSII ▸ *n* = 160 ▸ Baseline A1C: 8.2% ▸ Parallel arms, 100 days	Time spent outside of target range / Abbott FreeStyle Navigator; 1/3 CGM with no alarm, 1/3 CGM with alarm, 1/3 SMBG	No difference in A1C or time spent outside of target range	Less time in hypoglycemia range in group with alarms compared to SMBG group, *P* = 0.03
Cooke et al. (24)	▸ Adults with T1D or T2D treated with at least twice-daily insulin injections ▸ *n* = 404 ▸ Baseline A1C: 9.1% ▸ Parallel arms, 18 months; GlucoWatch group wore device at least four times in the first 3 months and then as needed; Medtronic group wore device for 72 hours three times during first 3 months and on three more occasions thereafter	A1C reduction / GlucoWatch G2 Biographer vs. Medtronic MiniMed CGMS (blinded)	No significant difference in A1C reduction	No reduction in hypoglycemia; possibly an increase
PREGNANT PATIENTS WITH T1D, T2D, OR GDM				
Feig et al. (25)	▸ Adult women with T1D on MDI or CSII who were pregnant or planning pregnancy ▸ *n* = 325 (215 pregnant, 110 planning pregnancy) ▸ Baseline A1C: 6.83% in CGM group and 6.95% in control group (pregnant) and 7.57% in both CGM and control group (planning pregnancy) ▸ Parallel arms, to 34 weeks in pregnant women; for 24 weeks in those planning pregnancy	A1C reduction / Medtronic Guardian REAL-Time or MiniMed MiniLink	A1C difference –0.19%, *P* = 0.0207 in pregnant women; no A1C difference in women planning pregnancy	▸ Comparable severe hypoglycemia events (18 vs. 21) and time spent hypoglycemic (3 vs. 4%) ▸ Neonatal health outcomes: fewer LGA babies, fewer neonatal ICU stays for >24 hours, and fewer neonatal hypoglycemia events
Secher et al. (26)	▸ Adult women with T1D or T2D who were pregnant ▸ *n* = 154 ▸ Baseline A1C: 6.6% in CGM group, 6.8% in control group ▸ Parallel arms, 6 days of CGM at 8, 12, 21, 27, and 33 weeks vs. routine care	LGA babies / Medtronic Guardian REAL-time CGM with Sof-Sensor	No difference in A1C	▸ No difference in number of LGA babies ▸ No difference in hypoglycemia

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Study	Design	Primary Outcome / Type of CGM	A1C Outcomes	Hypoglycemia Change/Other
Wei et al. (27)	▸ Adult women with GDM at 24–28 weeks of pregnancy ▸ *n* = 106 ▸ Baseline A1C: 5.8% in SMBG group, 5.7% in CGM group ▸ Parallel arms; women were asked to wear CGM intermittently early (second trimester) or late (third trimester) or perform SMBG	Prenatal or obstetrical outcomes / Medtronic Gold CGMS	No significant reduction in A1C	▸ No difference in obstetrical outcomes ▸ Some reduction in maternal weight gain

JDRF, Juvenile Diabetes Research Foundation; LGA, large-for-gestational-age; NA, not applicable; NS, non-significant; T1D, type 1 diabetes; T2D, type 2 diabetes.

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Continuous Glucose Monitoring Systems: Categories and Features

James J. Chamberlain, MD, *St. Mark's Hospital and St. Mark's Diabetes Center, Salt Lake City, UT*

Continuous glucose monitoring (CGM) systems fall into two categories: *1*) "professional" (masked) CGM devices that patients wear without being able to see glucose values until their provider downloads and reviews the data retrospectively during an office visit and *2*) personal systems affording both real-time observation of continuous data by patients and retrospective review of complete profiles by patients at home, providers in clinic, or remotely. Table 1 presents key features of the commonly used systems described below.

Professional CGM

The FreeStyle Libre Pro system (Abbott, Alameda, CA) was approved by the U.S. Food and Drug Administration (FDA) in September 2016. This system consists of the FreeStyle Libre Pro sensor and a single reader device that is kept in the health care provider's office. The sensor is applied to the back of a patient's upper arm in the provider's office and requires a 2-minute activation period. The system then records glucose levels every 15 minutes for up to 14 days. The patient has no interaction with the sensor and cannot see the glucose data. At the end of the wear period, the sensor is scanned in the health care provider's office with the reader device, and the data are uploaded to the FreeStyle LibreView software. The system has a mean absolute relative difference (MARD) accuracy of 12.3% (1). Reported as a percentage, MARD is the average of the absolute error between all CGM values and matched reference values. Lower MARD values indicate greater device accuracy.

The Medtronic iPro2 system (Medtronic, Northridge, CA) features the Enlite glucose sensor, which is wearable for up to 6 days, and the iPro2 digital recorder. Glucose readings are blinded to the patient and recorded every 5 minutes. Fingerstick blood glucose measurements are not required for calibration, but at least one blood glucose entry every 12 hours is required for system uploading. While wearing the iPro2 system, patients can document events on their smartphones via the iPro2 myLog app and simultaneously send them to the Medtronic CareLink iPro website. The information from the recorder is then uploaded to the Medtronic CareLink iPro website in the health care professional's office for analysis and therapy adjustment. With a MARD of 13.6%, the Enlite sensor is 31% more accurate than the Medtronic Sof-Sensor, which was discontinued in September 2015 (2,3).

Personal CGM

Several personal CGM systems are available in the United States for daily use by people with diabetes. The Abbott FreeStyle Libre flash CGM system received FDA approval in September 2017 for stand-alone use (i.e., not requiring use of an insulin pump) with intermittent scanning. The system consists of the FreeStyle Libre sensor, which is wearable for up to 10 days, and the FreeStyle Libre reader. The system measures glucose levels every minute and records readings every 15 minutes. The user holds the reader over the sensor to scan the current glucose level to the reader. Both a glucose level and a trend arrow indicating direction and rate of change are displayed with each scan of the sensor. This system has a MARD of 9.7%. The sensor comes factory-calibrated, requiring no calibration by the user, and displays the most recent 8 hours of glucose data for patient review with each scan. Data history of up to 90 days can be uploaded from the reader to the FreeStyle LibreView software for evaluation by the user at home or by the health care provider with the patient during a clinic visit.

The Medtronic Enlite sensor is used with Medtronic MiniMed 530G and 630G insulin pumps. Real-time glucose data and rate-of-change trend arrows are available every 5 minutes on the pump screen, and both pumps use Medtronic SmartGuard technology, which will suspend insulin delivery for up to 2 hours when glucose levels fall below a preset threshold. The Enlite sensor requires calibration every 12 hours. The newer Guardian Sensor 3 glucose sensor and the Guardian Link transmitter are used with the Medtronic MiniMed 670G insulin pump system. Approved by the FDA in September 2016, the 670G is the first hybrid closed-loop insulin pump-CGM system to become available in the United States. The Guardian Sensor 3 may be worn for up to 7 days and is Medtronic's most accurate glucose sensor, with a MARD of 9.6% with abdominal insertion and 8.7% with arm insertion, based on three to four calibrations per day. The three Medtronic MiniMed pumps can all be downloaded to the Medtronic CareLink website for CGM data review.

Stand-alone real-time CGM systems approved for use in the United States include the Dexcom G4 Platinum, Dexcom G5 Mobile, and Dexcom G6 systems (Dexcom, San Diego, CA). The G4 Platinum and G5 Mobile systems feature the Dexcom Platinum G4/G5 sensor, which is placed by the user and can be worn for up to 7 days. Users must calibrate these systems twice daily with fingerstick blood glucose measurements. The G4 Platinum transmitter uses radio wave technology, and glucose data and trend arrows may be viewed continuously on a Dexcom G4 receiver, as well as on the Tandem t:slim (Tandem Diabetes Care, San Diego, CA) and Animas Vibe (Animas Corporation, West Chester, PA) insulin pumps. The G5 transmitter uses Bluetooth technology, and glucose data

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may be viewed on the Dexcom G5 receiver, the Tandem t:slim X2 insulin pump, the Dexcom G5 Mobile App on most Apple and Android devices. The G4/G5 sensor has a MARD of 9.0% when used with devices that include the most current Dexcom software (4). The Dexcom G6 CGM system received FDA approval in March 2018. This newest sensor and transmitter system will require no calibrations or fingerstick blood glucose confirmations to make diabetes treatment decisions. The sensor may be worn for up to 10 days. A previous issue with acetaminophen interference has been resolved, and the overall MARD is 9.0% (5).

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TABLE 1 Features of Selected CGM Systems Available in the United States

System Type	Device	Sensor Wear Duration (days)	Start-up Time (hours)	Calibration Requirements and Related Information	Frequency of Glucose Readings	MARD (%)	Software and/or Device Compatibility	Arrows
Professional CGM systems	Abbott FreeStyle Libre Pro sensor	Up to 14	1	None	Every 15 minutes	12.3	Data scanned from sensor using FreeStyle Libre Pro reader in provider's office	NA
	Medtronic iPro2 Enlite sensor and digital recorder	Up to 6	1	None, but at least one blood glucose entry every 12 hours is required for system uploads	Every 5 minutes	13.6	Data uploaded from sensor recorder using Medtronic CareLink iPro website	NA
Personal CGM systems	Abbott FreeStyle Libre sensor and reader	Up to 10	12	None, but patients are encouraged to check their glucose with a meter if the readings do not reflect how they feel	Available every minute; automatically records every 15 minutes	9.7	Stand-alone; data may be uploaded from the reader in provider's office using FreeStyle LibreView software	Glucose is rising quickly (>2 mg/dL per minute) ↑ Glucose is rising (1–2 mg/dL per minute) ↗ Glucose is changing slowly (<1 mg/dL per minute) → Glucose is falling (1–2 mg/dL per minute) ↘ Glucose is falling quickly (>2 mg/dL per minute) ↓
	Dexcom Platinum G4/G5 sensor with G4 Platinum transmitter	Up to 7	2	Every 12 hours	Every 5 minutes	9.0 when used with most current Dexcom software	Stand-alone with Dexcom G4 receiver and compatible with Animas Vibe and Tandem t:slim insulin pumps	Glucose is rapidly rising (>3 mg/dL per minute) ↑↑ Glucose is rising (2–3 mg/dL per minute) ↑ Glucose is slowly rising (1–2 mg/dL per minute) ↗ Glucose is steady (not increasing or decreasing >1 mg/dL per minute) → Glucose is slowly falling (1–2 mg/dL per minute) ↘ Glucose is falling (2–3 mg/dL per minute) ↓ Glucose is rapidly falling (>3 mg/dL per minute) ↓↓

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System Type	Device	Sensor Wear Duration (days)	Start-up Time (hours)	Calibration Requirements and Related Information	Frequency of Glucose Readings	MARD (%)	Software and/or Device Compatibility	Arrows
Personal CGM systems (*cont.*)	Dexcom Platinum G4/G5 sensor with G5 Mobile transmitter	Up to 7	2	Every 12 hours	Every 5 minutes	9.0 when used with most current Dexcom software	Stand-alone with Dexcom G5 receiver, most Apple and Android products, and compatible with Tandem t:slim X2 insulin pump	Same as above
	Dexcom G6 sensor and trans-mitter	Up to 10	2	None	Every 5 minutes	9.0	Stand-alone with Dexcom G5 receiver and most Apple and Android products	Same as above
	Medtronic Enlite sensor and MiniLink or Guardian Link trans-mitter	Up to 6	2	Every 12 hours	Every 5 minutes	13.6	Compatible with Medtronic 530G and 630G insulin pumps	Glucose is rising at a rate of ≥3 mg/dL per minute ↑↑↑ Glucose is rising at a rate of ≥2 but <3 mg/dL per minute ↑↑ Glucose is rising at a rate of ≥1 but <2 mg/dL per minute ↑ Glucose is falling at a rate of ≥1 but <2 mg/dL per minute ↓ Glucose is falling at a rate of ≥2 but <3 mg/dL per minute ↓↓ Glucose is falling at a rate of ≥3 mg/dL per minute ↓↓↓
	Medtronic Guardian Sensor 3 sensor and Guardian Link 3 transmitter	Up to 7	2	Every 12 hours	Every 5 minutes	Abdominal insertion: 9.6 with 3–4 calibra-tions/day; 10.6 with 2 calibrations/ day; Arm insertion: 8.7 with 3–4 calibrations/ day; 9.1 with 2 calibra-tions/day	Compatible with Medtron-ic 670G hybrid closed-loop insulin pump system	Same as above

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Patient Selection for Continuous Glucose Monitoring

James J. Chamberlain, MD, *St. Mark's Hospital and St. Mark's Diabetes Center, Salt Lake City, UT*

Identifying appropriate patients for continuous glucose monitoring (CGM) use is a vital component of therapy success. Potential candidates come from a diverse group of individuals with diabetes.

Many people with type 1 diabetes may be excellent candidates for CGM therapy. Studies of the Juvenile Diabetes Research Foundation (JDRF) showed improvement in A1C levels in children, adolescents, and adults with type 1 diabetes with the use of three different CGM systems (1,2). However, the improvement in glycemic control was significant only in the adult age-group because of relatively poor sustained adherence to CGM therapy in children and adolescents. With improved adherence, all groups showed improved A1C. Benefits were also greater for people with higher baseline A1C levels. A recent re-analysis of JDRF study data showed statistically significant improvements in the important measures of time spent in hypoglycemia, hyperglycemia, and glycemic variability (3). People with type 1 diabetes on either continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI) therapy have been shown to benefit from CGM therapy (4–6).

People with type 2 diabetes, particularly those using insulin, also may be candidates for CGM. In 2017, the U.S. Centers for Medicare & Medicaid Services (CMS) began covering the Dexcom G5 Mobile system for people with type 1 or type 2 diabetes on intensive insulin therapy, defined as three or more daily injections of insulin or CSII therapy. A recent trial involving 158 people with type 2 diabetes on MDI insulin therapy randomized patients to usual care versus Dexcom G4 Platinum CGM-guided therapy. After 6 months, mean A1C levels improved from 8.5 to 7.7% in the CGM-treated group versus 8.0% in the usual care group ($P = 0.022$) (7). CMS also covers the FreeStyle Libre (Abbott, Alameda, CA) flash CGM (FCGM) system in the same populations. Use of FCGM for 6 months in people with type 2 diabetes on intensive insulin therapy resulted in statistically significant reductions in rates of hypoglycemia below blood glucose levels of 70, 55, and 45 mg/dL by 55, 68, and 75%, respectively (8). People using FCGM also reduced test strip use by 90% and scanned the CGM sensor an average of 8.3 times per day.

Pregnant women with diabetes are strong candidates for CGM. The American Diabetes Association recommends an A1C target of <6% during pregnancy for women with preexisting type 1 or type 2 diabetes if this goal can be achieved without excessive hypoglycemia (9), an often-difficult accomplishment. Studies have demonstrated improvement in neonatal outcomes and significantly more time spent in target range during pregnancy with the use of CGM therapy (10,11). Women with gestational diabetes mellitus (GDM) may benefit from CGM use as well. In a study of 340 Chinese women with GDM randomized to intermittent prospective CGM use versus SMBG testing seven times per day throughout pregnancy, those using CGM showed superior glycemic variability, had infants with a lower mean birth weight, and had a lower risk of preeclampsia and a lower rate of cesarean delivery (12).

Another group of people who are excellent candidates for CGM therapy are those with hypoglycemia unawareness or a significant fear of hypoglycemia. Hypoglycemia unawareness increases the risk of severe hypoglycemia sixfold in patients with type 1 diabetes and ninefold in patients with type 2 diabetes (13,14). The IMPACT study using the FreeStyle Libre system in 239 people with type 1 diabetes for 6 months demonstrated reductions of 40% in nocturnal hypoglycemia, 50% in serious hypoglycemia (<55 mg/dL), and 91% in routine fingerstick blood glucose measurements (15). A retrospective study of 35 people with type 1 diabetes and established hypoglycemia unawareness showed a significant reduction in episodes of severe hypoglycemia from a mean rate of 8.1 to 0.6 episodes/patient-year ($P = 0.005$) over 1 year with multiple CGM systems (16). A subsequent retrospective study demonstrated an 86% reduction in risk for severe hypoglycemia requiring medical assistance in the first year of real-time CGM therapy ($P = 0.0013$) in people with type 1 diabetes who reported wearing their CGM system on an "almost daily" basis (17). There was also a strong trend toward a reduction in fear of hypoglycemia. More recently, a significant reduction in fear of hypoglycemia was shown in 20 people with type 1 diabetes after only 8 weeks of real-time CGM therapy ($P = 0.01$) (18).

It is important not to assess a person's eligibility for CGM based on superficial observation. In particular, those with dexterity problems or visual disability may be appropriate candidates for CGM therapy, as evidenced by a case report of a person with type 1 diabetes, complete blindness, frequent hypoglycemia, and hypoglycemia unawareness who was able to rapidly and dramatically improve glycemic control with real-time CGM by learning to respond more appropriately to high and low blood glucose alerts (19). This patient's average blood glucose decreased from 162 mg/dL during the first 4 days of CGM use to 138 mg/dL during the next 4 days, and there was also improvement in glycemic variability. The percentage of time spent in the high glucose range (>180 mg/dL) improved from 35 to 18%, and the percentage of time spent in the low glucose range (<80 mg/dL) improved from 9 to 3% with no episodes of severe hypoglycemia. People

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with dexterity or visual loss may need the help of a family member or caregiver to assist with CGM sensor insertion and calibrations.

Obviously, there are individuals for whom CGM therapy may not be beneficial or appropriate. It is important for people with diabetes to understand the strengths and limitations of CGM systems as related to their individual needs. (See the article on p. 8 of this compendium for a description of available systems.) Some people have misconceptions about CGM therapy, believing incorrectly, for example, that they may never have to perform fingerstick blood glucose testing for systems requiring calibration, that the CGM system is going to automatically adjust all aspects of CSII therapy, or that they may be able to take a completely hands-off approach to managing their diabetes. Others experience emotional distress due to "information overload" from the amount of data available through CGM. Also, people with type 2 diabetes who are stable on oral medications have not been shown to benefit from CGM. Appropriately selected individuals will have the best chance of improving their glucose control and outcomes when they consult the device frequently and are taught to use continuous data to make informed and timely treatment decisions.

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Approaches for Successful Outcomes with Continuous Glucose Monitoring

Grazia Aleppo, MD, FACE, FACP, *Feinberg School of Medicine, Northwestern University, Chicago, IL*

Successful management of diabetes requires regular monitoring of glucose levels for all patients (1), with greater frequency recommended for those with type 1 or insulin-treated type 2 diabetes (2). However, daily self-monitoring of blood glucose (SMBG) may be painful, inconvenient, costly, and difficult to maintain. In 2017, a study using Cloud-based analysis software revealed that rates of glucose monitoring in Europe and North America ranged between 2.7 and 4.4 times/day in people with any type of diabetes (3). Individuals who perform SMBG typically focus on pre-meal or bedtime glucose levels, obtaining only a static snapshot of points in time. In the past two decades, continuous glucose monitoring (CGM), using subcutaneous sensors to measure interstitial glucose levels, has emerged to provide a better understanding of glucose trends and patterns.

Real-time CGM devices, alone or integrated into insulin pump systems, display data continuously and provide alerts and alarms for current and impending hypoglycemia and hyperglycemia (4,5). In 2017, a novel factory-calibrated, sensor-based system for daily use by people with diabetes, the FreeStyle Libre (Abbott, Alameda, CA), became available in the United States (6). The Libre's technology has been alternately referred to as flash CGM (FCGM) and intermittently scanned CGM because continuous data are viewable to the user only when a dedicated reader is scanned (or "flashed") over the sensor (7). The FreeStyle Libre has no alarms, but a distinct audible tone is provided when alerts to perform fingerstick testing are displayed. This may occur during scanning when glucose is <70 or >240 mg/dL, projected to be <70 or >240 mg/dL, "hi" or "lo," projected to be "hi" or "lo," or when glucose is rapidly changing or no trend arrow displays. A built-in glucose meter and individually foil-packed glucose strips facilitate measurement of glucose levels in these situations (8). The FreeStyle Libre does not require fingerstick testing for calibration.

The accuracy of CGM systems has improved over time, and presently, several available systems are approved as tools for making treatment decisions. All have similar accuracy at glucose levels >80–200 mg/dL. However, in the hypoglycemic range, the FreeStyle Libre system is not as accurate as in the euglycemic range (9), and sensor readings should be confirmed with blood glucose measurements. All personal CGM systems provide current glucose trend arrows. Because the meaning of the arrows is system-specific (see the article on p. 8 of this compendium), health care providers must learn the differences among the devices and guide patients based on each one's ecosystem for therapy adjustment. In the United States, the Dexcom G5 Mobile and FreeStyle Libre systems are approved by Medicare for beneficiaries with diabetes who use intensive insulin therapy (three or more injections per day), perform fingerstick glucose testing four times per day, and require frequent adjustment in therapy (10–13).

Outcomes of CGM in people with type 1 and insulin-treated type 2 diabetes are reviewed in the article on p. 3 of this compendium (14–18). Results in more heterogeneous groups with type 2 diabetes show variable effectiveness and acceptability (19). With high adherence to CGM, increased physical activity, reduced calorie intake, and decreased body weight were observed. This is consistent with findings that increased frequency of SMBG and CGM correlate with positive outcomes in type 1 diabetes (14–18,20). Benefits of FCGM have also been demonstrated in the IMPACT and REPLACE studies for type 1 and type 2 diabetes, respectively, with overall time spent in hypoglycemia reduced by 38% (type 1 diabetes) and 43% (type 2 diabetes) (21,22). Previously, improved glycemic control for up to 1 year was observed in patients not on prandial insulin using intermittent real-time CGM (23).

For some people, fatigue from alerts and alarms may thwart improved glucose outcomes with real-time CGM (24,25). FCGM, which has no alarms and sounds a distinct audible tone during scanning when alerts to perform fingerstick testing are displayed, offers a viable alternative; in studies of FCGM to date, patient satisfaction and adherence have been high (21,22).

Frequency of Looking at Receiver/Reader Data

It is difficult to quantify how often users check real-time CGM data during the day and night, either actively before insulin dosing or passively when alerted to hypoglycemia or hyperglycemia; however, a reasonable estimate is at least 4–12 times/day, including before meals, at bedtime, for physical activity, and in response to alerts and alarms. Quantification of FCGM is easier, as the number of scans per day is provided on the reader and available when uploading data to the LibreView software. In two recent studies using FCGM, the average number of scans per day was reported to be 15 for type 1 diabetes and 8 for type 2 diabetes patients (21,22). A recent analysis of FCGM in >50,000 users worldwide provided additional insight into real-world experience. In this report, the number of scans per day positively correlated with glycemic outcomes, with less time spent in hypoglycemia and hyperglycemia and more time spent in range with increasing number of scans per day. The number of scans per day ranged from 4.4 (every 5.4 hours) to 48 (every 30 minutes) (26). Health care

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providers should address the ideal frequency of scanning on an individual basis and modify recommendations based on each patient's treatment regimen and needs.

Patient Selection

Careful patient selection is important when recommending CGM therapy. The article on p. 11 of this compendium provides more details about appropriate candidates. Successful outcomes will depend in large part on a person's trust in the system, willingness to calibrate the system per product specifications, the number of times the person scans or looks at the system, and the type of intervention plan set up with the health care provider. Guidelines for CGM patient selection have been developed by professional societies and other expert forums (27–29).

Regardless of baseline A1C or the degree of glucose variability at CGM initiation, users should be willing to check or scan their device on a near-daily basis to realize the greatest benefit (14–18,21,22). Users should also understand the concept of interstitial fluid versus capillary blood glucose measurements and calibration procedures for systems that require calibration. Of note, for real-time CGM systems, setting alerts and alarms with realistic expectations is essential to avoid alarm fatigue (24). Establishing a plan for sick-day or illness management with CGM is greatly encouraged. Dexcom CGM users should also consider taking advantage of the Share feature, which allows a "follower" (person chosen by the user, such as a parent, family member, or friend) to receive CGM information on a smartphone. Such data, including alerts and alarms, would allow the recipient to potentially assist the user if necessary, such as in the event of hypoglycemia. Educating family members or other caretakers about the CGM system and, for older adults, ensuring that they can see or hear the alerts and alarms, are also fundamental to successful outcomes.

Patient and Provider Education

The importance of patient and provider education cannot be overemphasized. People with diabetes should receive training on the meaning of the messages displayed on their system reader. Additionally, setting procedures for alerts and alarms, individualizing trend arrow-based treatment decisions, and reinforcing the dangers of insulin stacking (administering insulin while the previous dose is still active) are crucial to promoting adherence to CGM and improving glycemic outcomes. Although training videos are provided by manufacturers, they should not be seen as a substitute for in-depth patient education, especially when initiating CGM. Without appropriate training, CGM users may not be able to take full advantage of the information provided. Additionally, because most health care providers lack training in the interpretation of CGM data, including retrospective analysis during office visits, the availability of educational resources for health care providers is essential to achieving positive outcomes.

Hypoglycemia

Hypoglycemia is a serious concern for people with diabetes and the major limiting factor in achieving glycemic targets with intensive management. Hypoglycemia risks and frequency are well established in people with type 1 diabetes (30,31), and even self-reported severe hypoglycemia is associated with a 3.4-fold increased risk of death (32). However, hypoglycemia frequency may be underestimated in people with type 2 diabetes; whether on insulin or other antihyperglycemic regimens, these individuals can also have hypoglycemia unawareness (33). CGM technology has been demonstrated to reduce hypoglycemia frequency and hypoglycemia unawareness in people with diabetes (14–18,21,22,34–37).

When recommending CGM to patients, the presence of hypoglycemia unawareness should be evaluated and discussed to aid in selecting the most appropriate system.

Interpretation of Data

Interpretation of data for users and providers still lacks a cohesive approach. When reviewing data, time spent in the various ranges (<54, <70, 70–180, >180, and >250 mg/dL) as well as coefficient of variation should be addressed. This can be accomplished with Ambulatory Glucose Profile reports available in various software platforms (Dexcom Clarity, Glooko-Diasend, Tidepool, Medtronic CareLink, and LibreView) (38–42). Nocturnal hypoglycemia should be addressed first, with intervention to reduce its severity and frequency. Subsequently, fasting glucose levels should be evaluated, and modifications to basal insulin doses or insulin-pump basal rate settings should be implemented. CGM systems offer great advantage in identifying prandial glycemic excursions; in such cases, mealtime insulin doses and the timing of the boluses should be addressed by instructing patients to monitor glucose before and 2–4 hours after meals to better understand glucose fluctuations and make appropriate regimen adjustments. Recently, use of FCGM was associated with a significant increase in delivering bolus insulin 15–20 minutes in advance of meals (compared to immediately before or after meals) (36). People using insulin should be cautioned against making frequent dose changes in response to above-target post-meal CGM readings on their display tools because insulin stacking is a well-known and avoidable cause of hypoglycemia.

Trend Arrows

As mentioned previously, CGM systems feature trend arrows that provide information on the predicted change of glucose levels over a specific time period. It is important to be aware that the arrows correspond to different rates of glucose change depending on the brand of CGM system. Training users on the meaning of arrows displayed on their particular device will ensure that they take appropriate actions guided by the specific system they use. (See the table on p. 9 of this compendium for details about each available system.) Although approaches to adjusting insulin

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doses on the basis of trend arrows are frequently discussed and constitute an important aspect of therapeutic CGM, proposed methods have yet to be validated in randomized controlled trials (43–47). The most recently published method is specific to the Dexcom G5 Mobile (47). With this in mind, it is imperative that health care providers take an individualized approach when applying trend arrows to treatment decisions (Table 1).

In view of the aforementioned caveats, the published recommendations made with respect to the Dexcom G5 arrows cannot be extrapolated to the FreeStyle Libre system. However, using a correction factor for trend arrow–guided insulin dose adjustments in combination with mealtime dose calculations based on an insulin-to-carbohydrate ratio offers an advantage over other published methods in that it allows for personalized dose calculations based on insulin sensitivity. A proposed working algorithm for the FreeStyle Libre incorporating this concept is shown in Table 2, and sample dose adjustments are provided in Box 1. The rationale for this non-validated method is to be more aggressive when the reader displays one up-trending arrow because the predicted glucose change over time with the FreeStyle Libre in reality could be much higher than 2 mg/dL per minute. Moreover, readings in the hypoglycemic range must be confirmed with fingerstick glucose testing because of potential sensor inaccuracy; when glucose is rapidly falling and sensor glucose levels are <100 mg/dL, additional rapid-acting carbohydrate intake (15–30 g) should be considered in the pre-meal period. In the postprandial period, insulin dosing based on trend arrows should be calculated 4 hours after an insulin dose, although this recommendation may change with the recent introduction of insulin analogs with a faster onset of action (48).

Before using trend arrows for insulin dose adjustments, patients should first become familiar with their CGM systems. Because users will work within their own CGM ecosystem, education should be targeted toward patients' specific device. Although there are no head-to-head trials, all available CGM systems have decreased accuracy in the hypoglycemic range (9,49,50), but in the United States, only the FreeStyle Libre label requires confirmation with fingerstick testing in this range. Thus, individualized guidance may be needed on using trend arrows for insulin dose adjustments when glucose levels are <70 mg/dL. This is especially true in older adults with diabetes, who are at highest risk for severe hypoglycemia and hypoglycemia unawareness (51). For certain high-risk geriatric patients, use of trend arrows for insulin dose changes with the FreeStyle Libre should be assessed on a case-by-case basis, and it may be prudent to confirm glucose levels via fingerstick glucose testing when adjusting insulin per instructions from the reader display; in the setting of rapid glucose changes toward hypoglycemia, fingerstick glucose checks should be strongly recommended for safety, especially when the "check blood glucose" symbol appears on the reader display. Of note, in a small cohort of nursing home residents with type 2 diabetes, FCGM overestimated hypoglycemia, with 51.4% of the interstitial glucose readings <70 mg/dL being falsely low compared to capillary blood glucose levels (52). More studies of FCGM in geriatric populations are needed.

Non-Insulin-Using Patients

Formal studies of CGM in non-insulin-using patients on antihyperglycemic regimens are scant. For such people, the main goal of CGM should be to achieve target fasting glucose levels and decrease postprandial glycemic excursions with appropriate regimen adjustments, meal quality modifications, and lifestyle interventions (2,53). For people with type 2 diabetes, especially those on sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists, CGM therapy could have significant

TABLE 1 Published Trend Arrow Methods for Insulin Dose Adjustment

Trend Arrow	DirecNet (43)	Scheiner (44)	Pettus and Edelman (45)	Klonoff and Kerr (46)	Endocrine Society (Dexcom G5 only) (47)
↑↑	20% increase	+60 mg/dL	+100 mg/dL	+2 units	+1.5–4.5 based on correction factor
↑	20% increase	+30 mg/dL	+75 mg/dL	+1.5 units	+1–3.5 based on correction factor
↗	10% increase	0	+50 mg/dL	+1 units	+0.5–2.5 based on correction factor
→	No changes	No changes	No changes	No changes	No changes
↘	10% decrease	0	−50 mg/dL	−1 units	−0.5–2.5 based on correction factor
↓	20% decrease	−30 mg/dL	−75 mg/dL	−1.5 units	−1–3.5 based on correction factor
↓↓	20% decrease	−60 mg/dL	−100 mg/dL	−2 units	−1.5–4.5 based on correction factor

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TABLE 2 Suggested Insulin Dose-Adjustment Algorithm for FreeStyle Libre Trend Arrows

Trend Arrow	FreeStyle Libre Trend Definition	Correction Factor (mg/dL)*	Insulin Dose Adjustment (Units)†
↑	Glucose is rising quickly (>2 mg/dL per minute)	<25 25–50 50–75 >75	+4 +3 +2 +1
↗	Glucose is rising (1–2 mg/dL per minute)	<25 25–50 50–75 >75	+3 +2 +1 No changes
→	Glucose is changing slowly (<1 mg/dL per minute)	<25 25–50 50–75 >75	No changes No changes No changes No changes
↘	Glucose is falling (1–2 mg/dL per minute)	<25 25–50 50–75 >75	−3 −2 −1 No changes
↓	Glucose is falling quickly (>2 mg/dL per minute)	<25 25–50 50–75 >75	−4‡ −3‡ −1‡§ No changes‡§

*Amount of blood glucose-lowering expected from 1 unit of rapid-acting insulin.

†For pre-meal sensor glucose levels <100 or >300 mg/dL, individualized plans with the health care provider are strongly recommended. Target glucose levels should be established with the health care team. For falling glucose trends or when FCGM glucose levels are approaching 70 mg/dL, users should measure glucose levels if prompted by the reader to confirm the presence of hypoglycemia in pre-meal situations; doing so will help prevent unnecessary reduction of pre-meal insulin doses if the glucose value measured by fingerstick testing is not in the hypoglycemic range. Older adults with a history of hypoglycemia unawareness or severe hypoglycemia episodes should be counseled on a case-by-case basis.

‡Consider fingerstick glucose testing if instructed by the reader.

§Consider additional rapid-acting carbohydrate intake (15–30 g).

educational and therapeutic benefits, with the additional advantage of obtaining data relatively painlessly. Developing a plan to review CGM trends in the postprandial period, whether by setting up alerts or by instructing users to scan their FCGM at specific times after meals, can convey the dynamics of post-meal glucose fluctuations to patients and guide providers in personalizing diabetes regimen adjustments based on data accumulated between visits. More studies are needed to address the potential value of FCGM in this clinical setting.

Ideally, all systems should display glucose data on a mobile app so that users do not have to carry multiple tools; this strategy would potentially contribute to acceptance and increase uptake of CGM use in non-insulin-using people with diabetes.

Best Practice for Exercise

Standards of care recommend that most adults with type 1 or type 2 diabetes engage in daily physical activity, allowing no more than two consecutive days without activity (2,53).

BOX 1 Examples of Trend Arrow–Guided Insulin Dose Adjustments with FreeStyle Libre

PATIENT 1 is a 35-year-old man with type 1 diabetes who is planning to eat 50 g of carbohydrate. His insulin-to-carbohydrate ratio is 1:10, his correction factor is 30, and his glucose target is 120 mg/dL. His pre-meal FCGM glucose level is 180 mg/dL with one up-trending arrow. His dose will be adjusted by adding 3 units to his calculated insulin dose.

Calculation: (meal) 5 units + (correction) 2 units = 7 units. Insulin dose adjustment for trend arrow: +3 units. Total dose: 7 + 3 = 10 units

PATIENT 2 is a 60-year-old woman with type 2 diabetes who is planning to eat 50 g of carbohydrate. Her insulin-to-carbohydrate ratio is 1:5, her correction factor is 20, and her glucose target is 100 mg/dL. Her pre-meal FCGM glucose level is 280 mg/dL with one down-trending arrow. Her dose will be adjusted by subtracting 4 units from her calculated insulin dose.

Calculation: (meal) 10 units + (correction) 9 units = 19 units. Insulin dose adjustment for trend arrow: −4 units. Total dose: 19 − 4 = 15 units

PATIENT 3 is a 73-year-old man with type 2 diabetes complicated by renal insufficiency and a creatinine of 2.1 mg/dL. At 11:30 a.m., his FCGM glucose reads 65 mg/dL. He follows the FCGM reader prompt to "check blood glucose." His blood glucose level is 63 mg/dL. He ingests 15 g of rapid-acting carbohydrate in the form of apple juice. Thirty minutes later, he is ready to eat a lunch, which will include 45 g of carbohydrate. He notices an FCGM glucose level of 105 mg/dL with one up-trending arrow. Per the algorithm, he should increase his dose of insulin by 3 units. His insulin-to-carbohydrate ratio is 1:15, his correction factor is 50, and his glucose target 120 mg/dL.

Calculation: (meal) 3 units + (correction) 0 units = 3 units. Total dose should be 6 units (3 units for the meal + 3 units for algorithm). However, he feels uncomfortable with this dose and decides to take only 1 additional unit of insulin to compensate for the rapidly increasing glucose level. When he scans the FCGM reader 2.5 hours after lunch, he notices an FCGM glucose level of 155 mg/dL, which is acceptable to him. The patient discusses this episode with his health care provider, and together, they modify the algorithm to better suit the specific needs of this geriatric patient with increased risk for hypoglycemia due to decreased renal function.

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However, blood glucose responses to physical activity, especially in individuals with type 1 diabetes, can be highly variable depending on many factors, including the type and timing of activity, previous food ingestion, and level of insulin on board. Adjustments in medication doses and carbohydrate intake are often required to maintain adequate glucose levels during and after physical activity (54,55).

CGM can be of benefit by providing users with glucose-trend data at any time, thereby decreasing fear of exercise-induced hypoglycemia. This is especially relevant when sensor glucose levels are trending toward hypoglycemia. However, very few studies have addressed this issue, and the accuracy of CGM has not been fully validated with different types of exercise. For example, intermittent high-intensity interval exercise is associated with metabolic changes (e.g., changes in pH, microcirculation, and oxygen tension) that may potentially interfere with CGM accuracy. In a small study using the Dexcom G4 Platinum system, the accuracy was comparable during continuous moderate and intermittent high-intensity exercise during a cycling session (56). Similarly, the accuracy of real-time CGM (Medtronic Guardian REAL-Time) measured at various prescribed workloads was acceptable for all types of exercises with the exception of continuous high-intensity exercise, where lower accuracy was detected (57). A recent survey of 502 adults from the T1D Exchange's online patient community, 276 of whom were using CGM either alone or in combination with CSII, showed that, although most respondents adjusted carbohydrate intake and insulin doses around exercise, the majority still reported experiencing hypoglycemia after exercise and having significant difficulties with blood glucose control around exercise (58).

Using CGM trend arrows adds another level of complexity. Although trend arrows are helpful in determining the direction of glucose during exercise and guiding users in the consumption of additional carbohydrate to prevent or reduce hypoglycemia, using them to adjust insulin doses during and after exercise is more challenging. As previously suggested (47), users should be conservative when adjusting their insulin doses before exercise and should refrain from increasing their insulin dose in the presence of up-trending arrows during the active period. In the post-exercise period, as previously recommended by Riddell et al. (55), close glucose monitoring is essential. In particular, attention should be paid to the direction of trend arrows in the immediate or even late-post-exercise period to correct impending hypoglycemia with rapid-acting carbohydrate intake, if indicated. Trend arrows may also signal the need for additional carbohydrate or an insulin dose reduction at bedtime to avoid nocturnal hypoglycemia, especially when exercise takes place in the late afternoon or evening (55). It is hoped that additional studies of newer CGM systems and their accuracy in response to various exercise protocols will better define best practice for the use of CGM trend arrows during physical activity.

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Continuous Glucose Monitoring Data as an Adjunct to A1C

Richard M. Bergenstal, MD, *International Diabetes Center, Park Nicollet and HealthPartners, Minneapolis, MN*

A1C remains an established risk marker for population health and is used extensively in clinical research and regulatory trials. However, factors such as hemoglobinopathies and heritable differences in glycation dynamics can render A1C less useful as a guide to glycemic control for some patients (1). The health care improvement goal of excellent quality and patient experience at reasonable cost is further shifting emphasis away from A1C as the reigning standard of care toward minimizing the daily burdens of living with diabetes. Indeed, many experts contend that it is time to formalize a definition of optimal control that includes A1C being at target (personalized for each individual, but usually ~7% for most adults) without occurrence of severe hypoglycemia and with only a minimal number of very low or clinically significant low glucose values (2).

Yet A1C, even in combination with the rate of hypoglycemia, still has some inherent barriers to being an ideal personal management guide. First, A1C represents an average glucose level over 2–3 months and, as such, is unable to reveal potentially dangerous episodes of hypoglycemia or hyperglycemia. Second, individuals with the same mean glucose (derived through continuous glucose monitoring [CGM]) may have a clinically significant variation in their laboratory-measured A1C. In practice, this means that a laboratory-measured A1C of 8% may have a CGM-derived mean glucose ranging from 155 to 218 mg/dL, obviously with different clinical management implications. Variation in the relationship between A1C and mean glucose has been observed between races and to an even greater extent between individuals of the same race (3,4). Although the mechanisms for individual variation in the relationship of A1C to mean glucose are still being investigated, inherent differences in the rate of hemoglobin glycation and red blood cell life span remain the leading hypothesis (5).

With several excellent approved CGM systems available, including many that are factory-calibrated, and given the fact that current CGM metrics and glucose profile visualizations are mostly standardized (see the article on p. 20 of this compendium), it is now feasible to define glucose control and management decisions based on CGM data and reports. A key patient-centered metric is to have as many glucose values as possible fall within the individualized target range, referred to as time in target range or simply time in range (TIR), with the common default range of 70–180 mg/dL. The more TIR the better the A1C is likely to be because these two variables are highly correlated. For optimal management, patients should have a TIR level as high as possible with a very low level of time in hypoglycemia (TIHypo). Maximal TIR with minimal TIHypo is a reasonable overarching glycemic target (6).

Below are two ways to assess the correlation of CGM-derived TIR data and A1C laboratory data.

1. Consider the mean TIR, achieved using the most advanced currently approved technology (hybrid closed-loop therapy), of 124 individuals with type 1 diabetes who had a mean A1C of 6.9% (secondary analysis of data from Bergenstal et al. [7]).
   - TIR (70–180 mg/dL) ~72% or 17.3 hours/day
   - TIHypo (<70 mg/dL) ~3% or 43 min/day (<1% or ~14 min/day of this <54 mg/dL)
   - TIHyper (time in hyperglycemia; >180 mg/dL) ~25% or 6 hours/day (<6% or ~86 min/day of this >250 mg/dL)
2. Consider the correlations of TIR and A1C achieved from an analysis of several hundred people with type 1 or type 2 diabetes in a series of clinical trials (Table 1) (secondary analysis of data from Beck et al. [4]; R. Beck, personal communication).

TABLE 1 Correlations of TIR and A1C Achieved from an Analysis of Several Hundred People with Type 1 or Type 2 diabetes (4)

Measured TIR (70–180 mg/dL)	A1C	95% CI
40%	8.1%	7.1–9.1%
50%	7.7%	6.7–8.7%
60%	7.3%	6.3–8.3%
70%	6.9%	5.9–7.9%
80%	6.5%	5.5–7.5%

In summary, laboratory-derived A1C is a measure of population health and of long-term risk for diabetes complications but is not an individualized management tool. An elevated A1C implies that action is needed but does not help tailor treatment because neither hypoglycemia, glucose variability, nor timing of hyperglycemia are revealed by this average glucose measure. In contrast, a standardized Ambulatory Glucose Profile (AGP) report clearly shows dangerous high or low patterns that need immediate attention. The timing and magnitude of hyperglycemia, hypoglycemia, and glucose variability are clearly visualized in the AGP and quantitated by CGM metrics (TIR, TIHypo, TIHyper, and coefficient of variation/standard

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deviation). As more fully explained in the article below, with the AGP in front of them, patients and clinicians can agree on a personalized treatment plan aimed at improving the glucose profile while avoiding significant hypoglycemia.

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Understanding Continuous Glucose Monitoring Data

Richard M. Bergenstal, MD, *International Diabetes Center, Park Nicollet and HealthPartners, Minneapolis, MN*

Continuous glucose monitoring (CGM) systems are able to transmit glucose readings every 1–15 minutes to a receiver, insulin pump, phone(s), or watch, and eventually the glucose data may be uploaded to a computer, electronic medical record (EMR) system, and/or the Cloud.

After about a decade of many different, innovative CGM data reports being generated, often running to 20 or more printed pages, the Helmsley Charitable Trust supported a CGM data standardization consensus conference (1). The experts who convened modified an existing Ambulatory Glucose Profile (AGP) report (2) to arrive at a summary one-page report having three main elements: CGM metrics, an AGP modal day visualization, and a set of daily glucose profiles. In December 2017, two comprehensive consensus statements were published that agreed on definitions for core CGM metrics, priorities for routine display, and use of the AGP as the default glucose profile visualization (3,4).

Figure 1 is a sample AGP report that incorporates CGM metrics and a visual depiction that meet the consensus recommendations. There are many additional important CGM metrics and visualizations that can be helpful in clinical practice or research for a given patient or study.

CGM Metrics

Data Sufficiency. A recent study confirmed that 14 days of CGM data correlate well with 3 months of CGM data, particularly for mean glucose, time in range, and hyperglycemia measures (5). Within those 14 days, having at least 70% or ~10 days of CGM wear adds confidence that the data are a reliable indicator of usual patterns.

Average Glucose. The average glucose is highly correlated with A1C and measures of hyperglycemia but not with glycemic variability or hypoglycemia. Used in isolation, it provides no insight into glucose patterns.

Glucose Management Index (GMI). This is the proposed term to replace "estimated A1C" (eA1C). For some time, the mean glucose value obtained from self-monitoring of blood glucose or, more reliably, CGM data has been used to estimate what an individual's laboratory-measured A1C would be (and vice versa). Many clinicians and patients have found this a helpful metric to follow. Yet, there can be confusion for patients and clinicians when the laboratory A1C and the eA1C do not closely match. (See the article on p. 19 of this compendium for reasons they may not always match.) In the United States, there is now a requirement to replace "eA1C" with a new term that does not imply that the value is directly linked to the laboratory A1C value. The value is calculated from the mean CGM glucose similarly and reported in the same units. GMI is the name proposed to replace eA1C and is also intended to convey that this metric can be a helpful indicator of the need to address glucose management.

Time in Range (TIR). This is the CGM metric most commonly used as a guide to diabetes management. Collectively, there are now five agreed-upon, CGM-defined categories to quantitate the time a patient is spending with glucose values that are above, below, or in the target range. The time spent in each of these categories can be described as either the percentage of CGM glucose values or the number of minutes or hours per day spent in that category during the measurement period. For example, if half of all the CGM glucose readings over the 14 days are in the target range, TIR = 50% or 12 hours/day. The agreed-upon default TIR is 70–180 mg/dL, with the understanding that there may be circumstances in which the clinician or patient

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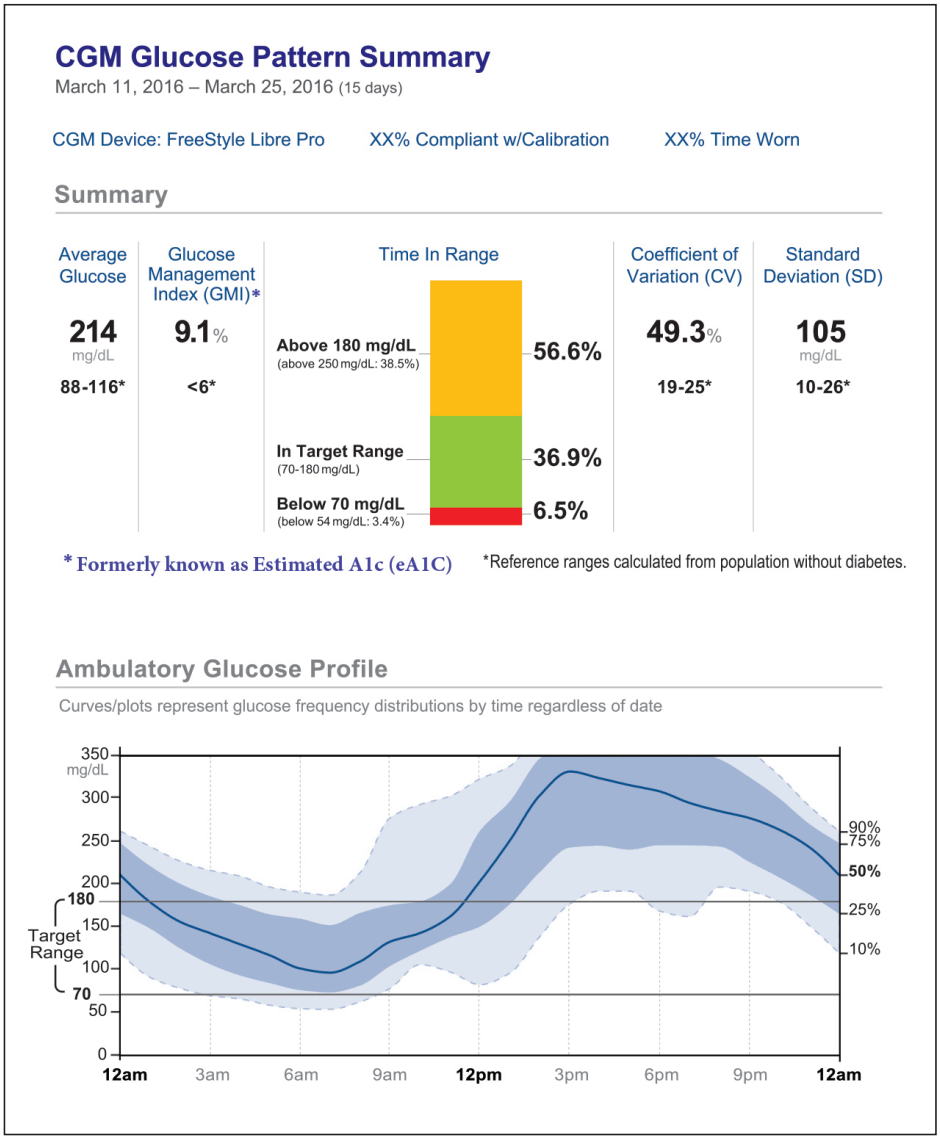
FIGURE 1 Sample AGP report and interpretation notes



- There are adequate data to make an interpretation and action plan.
- Review of CGM metrics: note that average glucose, GMI (formerly known as eA1C), and measures of GV (CV and SD) are all very high and need attention. In addition, the TIR is low, and TIHyper and TIHypo are high enough to require action.
- The AGP alerts one to immediately address the hypoglycemia pattern between 6:00 and 9:00 a.m.
  - Note that the glucose level drops steadily all night.
  - Check the daily profiles to see if these patterns of hypoglycemia occur on any specific nights.
  - Note the glucose is actually dropping from 3:00 p.m., with a rapid decline after dinner and likely at bedtime. Check on proper insulin dosing at dinner and bedtime and on evening events such as exercise that may lead to a drop in glucose.
- Once the hypoglycemia is minimized, address the rising glucose from 10:00 a.m. to 3:00 p.m.
  - Mark waking and breakfast time to help determine whether the hyperglycemia is due to a rebound from hypoglycemia or related to waking or to eating breakfast or a snack without adequate insulin coverage.

Adapted from Fonseca V, Grunberger G. Standard glucose reporting: follow-up to the February 2016 AACE CGM consensus conference. Endocr Pract 2017;23:629–632.

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wants to set an alternative target TIR (e.g., 70–140 mg/dL during the night for patients on hybrid closed-loop therapy).

Time in Hypoglycemia (TIHypo). There are two CGM-defined cut points to define TIHypo and one clinically defined hypoglycemia level.

- Level 1: Glucose <70 mg/dL and ≥54 mg/dL, or 54–69 mg/dL
  - › Hypoglycemia alert level/low/need to monitor the situation
- Level 2: Glucose <54 mg/dL
  - › Clinically significant/very low/immediate action required
- Level 3. Severe hypoglycemia
  - › Altered mental and/or physical status requiring assistance

Levels <70 mg/dL are referred to as an alert for hypoglycemia and those <54 mg/dL indicate higher risk for individuals with known cardiovascular disease and are often associated with cognitive impairment. Glucose <54 mg/dL is emerging as the key level to assess when comparing drugs or treatment strategies in clinical trials.

Time in Hyperglycemia (TIHyper). There are two CGM-defined cut points to define TIHyper and one clinically defined hyperglycemia level.

- Level 1: Glucose >180 mg/dL and ≤250 mg/dL, or 181–250 mg/dL
  - › Elevated or high glucose/need to monitor the situation
- Level 2: Glucose >250 mg/dL
  - › Clinically significant/very high/action required; consider correction insulin bolus, check insulin pump infusion set, increase hydration, address illness or excess stress if present, and consider checking urine or fingerstick ketones if persistent.
- Level 3: Diabetic ketoacidosis
  - › Ketones, acidosis, and usually hyperglycemia

It is important to note that no single metric of time in range (TIR, TIHyper, or TIHypo) can adequately characterize glucose control. An ideal CGM target is to maximize TIR with minimal TIHypo.

Glucose Variability (GV). GV refers to how much the glucose reading varies from the mean or median glucose, the degree of up and down fluctuation (amplitude), and the frequency of variations (6). There are dozens of well-established GV metrics. Most measure the amplitude of GV, including coefficient of variation (CV), standard deviation (SD), interquartile range (IQR), and mean amplitude of glycemic excursion (MAGE). CV, consistently the most reliable GV marker, is not directly correlated with mean glucose or A1C. Current research shows that a CV value <36% represents low GV and a relatively stable glucose profile, whereas a CV value ≥36% indicates an unstable glucose profile. SD is the most familiar GV measure and highly correlates with mean glucose and A1C. It is most reliable if glucose values are normally distributed around the mean, which is rarely the case with CGM values. If the SD is less than the mean glucose divided by 3 (with the mean glucose being 120–180 mg/dL), it is reasonable to assume low GV and a stable glucose profile.

Interpreting AGP

Although the aforementioned glucose metrics are helpful in quantitating glucose control in a group or an individual, visualization of the 24-hour modal (or standard) day AGP report is emerging as an essential personalized management tool.

Figure 1 represents 14 daily glucose profiles collapsed to create a single AGP visual display. The solid line is the median or 50% line; half of all glucose values are above and half are below this value. The 25th and 75th percentile curves shaded in dark blue represent the interquartile range or 50% of all values and are a good visual indicator of the degree of GV. The dashed outer lines (the 10th to 90th percentile curves) indicate that only 10% of glucose readings were above or below these values over the 2-week period.

At a glance, clinicians and patients can determine the extent to which values are within the target range (70–180 mg/dL) and the times of day that pose potentially dangerous low or high patterns requiring immediate attention. The overall management goal is to make or keep the curve as narrow and flat as possible within the designated target range.

Following are tips for effective review of the AGP with patients to guide clinical decision making (7,8).

1. Make sure there are adequate data for decision making (see Data Sufficiency above).
2. Mark directly on the profile sheet:
   - Type and duration of diabetes, age, weight (kg), and, if on insulin, daily dose (units/kg)
   - Usual times for waking (W), breakfast (B), lunch (L), dinner (D), and bedtime (BT)
   - Medication time and doses directly under the curve at the time usually taken (This is a good time to emphasize how critical it is to take bolus insulin before meals.)
   - If there is a consistent time of exercise or snacking (which should also be marked below the curve)
3. Once the report is "marked up," ask the patient to briefly describe and explain what he or she sees and why. Patients often provide honest, helpful insights to explain the glucose patterns.
4. Look for patterns of low glucose readings.
   - Remember, if the 10% lower line is touching the 70 mg/dL target line during a particular period of the day, 10% of all glucose values are <70 mg/dL at that time. Some action should be taken. If the 25% line is touching or below the 70 mg/dL target line or the 10% line reaches 54 mg/dL, immediate action is required.
   - Look at the separate printout of daily views to double-check patterns of low glucose and see if they are clustered on weekends or special activity days.

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5. Look for patterns of high glucose values.
   - Remember to ask how many times per week a medication is forgotten or if insulin is actually taken before meals.
   - Look at your meal markers and discuss whether high values are before or after usual mealtimes.
   - Ask about usual differences in weekend versus weekday times for waking, meals, and bedtime.
   - Look at the separate printout of daily views to double-check patterns of high glucose and see if they are clustered on weekends or special activity days.
6. Discuss areas where dark blue (50% of values) or light blue (80% of values) shaded areas are very wide (corresponding to high GV).
   - Can the patient do anything to reduce GV by adjusting the timing or amount of food intake, carbohydrate counting, timing of medications, exercise times or amounts, and/or stress?
   - Match food and exercise log or electronic data, if available, with AGP.
7. Compare current AGP and CGM metrics to those from last visit (or contact), if available, and discuss progress.
8. Agree on an action plan consisting of one or two recommendations:
   - Always treat hypoglycemia first.
   - When treating a pattern of hyperglycemia, look at least 12–18 hours past the time of the hyperglycemia you plan to treat. If the solid or light blue curves are touching the 70 mg/dL line or lower, be very conservative or hold off on correcting hyperglycemia until the hypoglycemia is addressed.
9. Print a copy of the marked-up AGP for the patient, and enter the AGP into the EMR, if possible, or at least copy and paste the AGP into the EMR progress note.

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The Future of Continuous Glucose Monitoring

Tadej Battelino, MD, PhD, *University of Ljubljana, Ljubljana, Slovenia*

The historical vision for continuous glucose monitoring (CGM) is becoming reality in day-to-day diabetes management, with the prospect of rapid growth in the foreseeable future. The latest U.S. Food and Drug Administration (FDA) approval of the first factory-calibrated CGM sensor will strengthen the path toward total elimination of cumbersome manual CGM calibrations. Medium- and long-term implantable sensors recently received regulatory approval in the European Union (EU) (1) and have been tested in the United States (2). Google, Microsoft, and other large companies are supporting the development of several minimally invasive glucose monitoring methods (e.g., microneedle patch platforms for continuous sampling of the interstitial fluid and tattoo-sensing technology using hydrogel glucose-sensing microspheres), as well as noninvasive technologies (e.g., an electrochemical battery-operated glucose oxidase sensor in a microchip sandwiched between two layers of a soft contact lens and hydrophilic organic electrodes that also are amenable to a contact lens design requiring no energy source) (3).

Additionally, the need for platforms that help people with diabetes and their health care providers understand and manage CGM-derived data more quickly and efficiently is of highest priority (4). Several prominent academic health care institutions have formally adopted professional platforms for uniformly uploading, analyzing, and presenting data from diabetes-related technology. Recently, the FDA approved a stand-alone CGM system enhanced with the Sugar.IQ diabetes assistant (Medtronic, Northridge, CA), which continually analyzes how food intake, insulin doses, physical activity, and other daily dynamics influence glucose levels. Similarly, the DreaMed Advisor Pro (DreaMed Diabetes, Petah Tikva, Israel), an automated diabetes management platform for health care professionals, has received regulatory approval in the EU and is currently being used in a clinical trial in the United States. The advanced algorithms in the Advisor Pro learn users' glucose patterns and recommend optimal pump setting adjustments, significantly augment the clinical impact of CGM, and reduce the burden of disease management for people with diabetes and their health care teams.

Likewise, several CGM-based closed-loop insulin delivery systems that are currently in pivotal trials sponsored by the U.S. National Institutes of Health, the Juvenile Diabetes Research Foundation, the Helmsley Charitable Trust, and various academic institutions will soon provide a variety of routine artificial pancreas options for individuals with diabetes, especially those with type 1 diabetes or type 2 diabetes treated with multiple daily insulin injections.

With respect to metrics, novel CGM parameters such as time in range and coefficient of variation will provide more patient-centered treatment goals that better match the reality of people's day-to-day lives. Ideally, this progress will increase the adoption of CGM systems by a wider range of people with diabetes and, through demonstrable clinical benefits including more sustained glycemic control and considerably improved quality of life, trigger reimbursement by public and private insurance entities.

Health care teams will continue providing top-notch education and training to people with diabetes and their home and school caregivers using advanced technological solutions (5).

Finally, the imminent vision of CGM, already experienced by some early adopters, is an integrated, Cloud-based environment connecting, monitoring, guarding, and advising individuals with diabetes, with the feasible goal of independently managing and treating this chronic condition.

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