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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Flash & Continuous Glucose Monitoring in Primary Care

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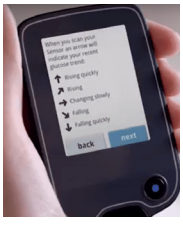
Managing diabetes has always been contingent on our awareness of patients' glucose levels. Since Benedict's 1908 copper reagent test for urine glucose, we've been edging closer to the ultimate goal of a real-time awareness of blood glucose levels. Ames Corporation introduced the Dextrostix™ in 1965, using glucose oxidase (on a platinum wire, embedded into a paper strip) to react with blood glucose, creating a colour that then needed physician interpretation to estimate the glucose level. A decade later, glucose meters containing photometers improved the colour interpretation and by 1980, the Dextrometer™ gave patients the direct ability to self-monitor their own blood glucose (SMBG).

SMBG technology continued to improve, producing increasing accuracy with less blood, along with the option of alternate site testing and eventually, nearly painless lancets. However, the next giant step forward has been the ability of repeated monitoring, using effectively the same technology, to produce a "continuous" awareness of blood glucose.

Flash and continuous glucose monitoring have evolved quickly in their nearly two-decade history. Four systems are approved in Canada: 2 flash glucose monitors; the Abbott FreeStyle Libre, and the recently approved FreeStyle Libre 2; and 2 continuous glucose monitors; the Dexcom G series, now at G6; and the Medtronic Guardian™ Connect. The Freestyle Libre Flash Glucose Monitoring System is a continuous glucose monitoring system according to Health Canada's review decision, so I'll be similarly considering both flash and continuous glucose monitors as continuous glucose monitoring (CGM) systems for this article. Their accuracy and manufacturing quality have improved to the point where three of the sensors in these systems (FreeStyle Libre, FreeStyle Libre 2 and Dexcom G6) are factory calibrated and do not require additional patient SMBG to verify accuracy. Each system has a wearable sensors that transmit glucose data to a remote reader or to a smartphone app. The FreeStyle Libre and FreeStyle Libre 2 sensor can be worn for 14 days, the G6 for 10 days and the Guardian Sensor 3 for 7 days. All systems now allow the user to define their target glucose ranges and then provide alerts to the user when they are out of range. Each system provides a viewer device to display continuous glucose data. The viewer provides a summary display of the glucose history and valuable statistical analyses that include the proportion of time in their target range (and below or above), the mean glucose, and measures of variability in glucose control. In Canada, all four systems also provide the hardware viewer in the form of a software app, which can be installed on most recent smartphones (iOS 7 and later; Android OS 5 and later).

FOR THE PERSON LIVING WITH DIABETES:

The adoption of flash and continuous glucose monitoring systems has been slow but continuous. These systems are reimbursed by the majority of private insurance companies across Canada and the Flash Glucose Monitoring system (FreeStyle Libre) is publicly reimbursed in several provinces which has allowed a faster uptake (for insulin-users in Ontario and Quebec, and for those with type 1 diabetes [T1D] in Yukon). After starting to wear a CGM system, my own patients describe a reduction in personal anxiety based on their chronic fears of unwanted hyperglycemia or of dangerous hypoglycemia.



For my patients with T1D, CGM system-driven awareness of their glucose level, and particularly the rapidity of glucose change (using trend arrows), has allowed them to progress more confidently in their favourite exercise and/or to experiment more freely with new food choices. Trend arrows show the rate of change, so that the user can see, for example, whether their exercise is causing a gradual decline (1 arrow or a 45° decline) or a rapid decline (2 arrows or a 90° decline). They can then react appropriately (compensatory carb intake) and not have to abandon their workout. Similarly, meal choices carry less automatic taboo, and restaurant meals contain less mystery, since users can simply track their post-meal glucose excursions and modify with additional insulin if needed.

My patients living with type 2 diabetes (T2D) have often reported that witnessing the impact of their food choices on their glucose levels has been eye-opening. I've seen these individuals then develop a greater engagement with their diabetes and a greater degree of self-empowerment. Not surprisingly, they also report that wearing a CGM sensor is far more convenient than daily (or more) capillary testing by finger pricking.

FOR THE PRIMARY CARE TEAM:

CGM systems are available directly to consumers and don't require a prescription other than for insurance purposes. Many of our patients will therefore adopt them directly. The primary care team can help to further convey the opportunity of using a CGM system to the rest of their patients and, once adopted, can then help guide patients to the greatest possible benefit from their CGM data.

Which patients should I discuss it with?

People living with T1D have shown improved glucose control, in both clinical trials and in real world evidence, using CGM. The benefits have been easiest to prove among adults, but children and adolescents also benefitted, in direct relation to the extent that they actually wore and used the CGM system. As with all diabetes interventions, the greatest gains were seen in those who had the poorest baseline control. The benefits seen were also independent of the insulin delivery system that patients used – either pump or multiple daily injections. Individuals with reduced awareness of hypoglycemia may particularly benefit – the IMPACT study showed that individuals using the Freestyle Libre for 6 months were able to cut their risk of serious hypoglycemia in half and experienced 40% less nocturnal hypoglycemia. Real world studies have shown even greater reductions in each of severe hypoglycemia events, EMS activation, and in patient fear of hypoglycemia.

> "The primary care team can help to further convey the opportunity of using a CGM system to the rest of their patients and, once adopted, can then help guide patients to the greatest possible benefit from their CGM data."

The DIAMOND and REPLACE trials showed that **people with T2D** using insulin also derived similar benefits in glucose control by adding a continuous and a flash glucose monitoring system, respectively. Studies with the Freestyle Libre have further shown that exposure to hypoglycemia can be reduced in these patients as well. The IMMEDIATE study, currently underway at LMC clinics in Canada, is exploring the specific value of providing a flash glucose monitor (FreeStyle Libre) to adults with T2D who are only using oral agent therapies (and not yet requiring insulin therapy).

Women with diabetes using CGM system in pregnancy have also shown improved neonatal outcomes. One study in Chinese women with gestational diabetes also reported similar benefits: lower mean birth weight, lower risk of preeclampsia and a lower rate of cesarean delivery.

3 tips for CGM-based guidance in Primary Care:

- → 1. Capitalize on the real-time glucose view that patients will now enjoy. Review dietary macronutrients and the general importance of improving the protein vs carbohydrate balance in each meal. It's a great opportunity to re-emphasize the importance of making our carbohydrate choices more complex and fiber-rich.
- → 2. Reinforce the value of an active lifestyle. The visible glucose decline often seen during a 30-minute walk can be very impactful and self-rewarding.
- → 3. Reinforce medication adherence. CGM system users will see the immediate effects of a missed insulin dose and the near-term effects of missed oral medications

FOR THE SPECIALIST CARE TEAM:

The lab A1C measure has long been our key outcome measure in population studies and in clinical research. It isn't going away soon. However, our modern care philosophy now guides us to find a patient-centred level of optimal glucose control with minimal hypoglycemia, information that a 90-day average measure cannot provide. Similarly, although the lab A1C is useful in population measurements, in individuals it is affected by each person's own particular red blood cell survival and variations in their hemoglobin. At best, the lab A1C is fully reliable in only 85% of individuals.

Current CGM systems now allow us to follow a more patient-centered measure: optimizing the number of glucose values that fall within an individualized target range, called "time in target range" (TIR, 3.9 – 10.0 mmol/L) while minimizing their time in low range. The TIR and lab A1C measures are closely correlated and TIR correlates well with diabetes complication risk. Current CGM systems also now allow us to share a view of our patient's data online, either

> "time in target range (TIR, 3.9 – 10.0 mmol/L)"

through the data cloud of a connected CGM, or by viewing the summary measures in the patient's own CGM management app.

What goes into the AGP (Ambulatory Glucose Profile) Report?

The online summary form of the CGM data is called the standardized **Ambulatory Glucose Profile (AGP).** Specialists and diabetes educators now use the AGP to assess the degree of hyperglycemia, hypoglycemia and to identify patterns that guide CGM system users to optimize their own self-care choices. The AGP summarizes 14, 30, 60 or 90 days of data. Typically a 14 day summary data can correlate well with three full months if >70% of the data are available.

Components (Fig 1):

- **Time in Range (TIR).** This time proportion is the CGM metric most commonly used to guide diabetes management. We ideally target 70% or more TIR and try to minimize Time in Low Range. Improvements of 5% or more in TIR are considered clinically significant.
- **Time in Low Range (3.0 – 3.8 mmol/L)** and **Time in Very Low Range (< 3.0 mmol/L)**
- **Time in High Range (10.1 – 13.9 mmol/L)** and **Time in Very High Range (< 13.9 mmol/L)**
- **Average Glucose:** The average glucose correlates well with lab A1C but doesn't provide insight on glycemic variability nor its most important outcome, hypoglycemia. On its own, it can be helpful in assessing overall control but it provides no insight into glucose patterns.
- **eA1C or Glucose Management Index (GMI):** both measures use CGM data to offer an estimated measure of the traditional lab A1C, intended as a convenience for healthcare providers.
- **Glucose Variability (GV):** generally, variability measures try to describe the frequency and the amplitude of glucose excursions from the mean, both high and low. The measure most commonly reported is the coefficient of variation (CV). A target value < 36% is considered to represent a stable glucose profile.

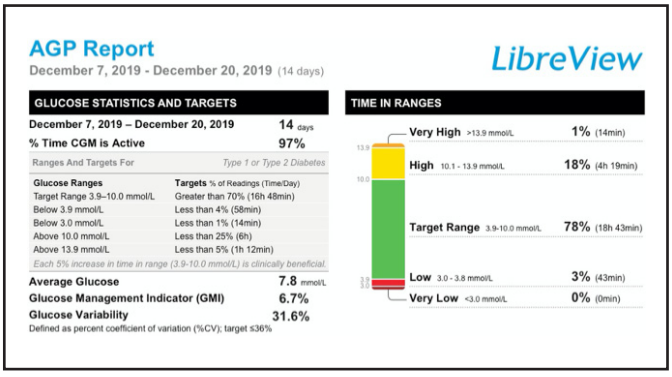


Fig 1

Daily and Summary Profiles (Fig 2):

- **24-hour modal day:** collapses 14 daily profiles into a summary view. The median glucose is shown as a solid line. Dark shading around the median line shows the areas containing glucose values that fall within the 25th to 75th percentiles. Lighter shading shows the 5th to 95th (FreeStyle Libre and FreeStyle Libre 2) or the 10th to 90th (Dexcom and Guardian) percentile regions. Our goal is a median line that is as flat as possible, within the target range, and with shaded variability areas as narrow as possible.

- **Daily glucose profiles:** a thumbnail of each day's glucose profile

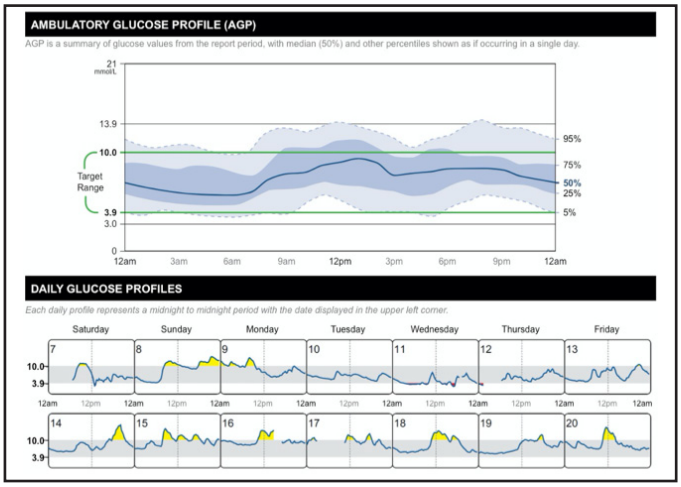


Fig 2

3 tips for CGM-based guidance in Specialist Care:

→ 1. Look for patterns of hypoglycemia. For over night hypoglycemia, is the basal insulin dose excessive? Is the person still using sulfonylureas that could be weaned? If mid-day, is exercise predictably lowering their glucose level?

→ 2. Look for more prolonged hyperglycemia. Explore whether an insulin dose was reduced or missed? Were oral medications missed for a longer period of time? For pumpers, was infusion site viability lost? Or was there a delay in a needed infusion site change?

→ 3. Confirm typical meal times and look for patterns of post-prandial hyperglycemia. Use any patterns to discuss the individual's typical carb choice and carb amounts at those meals.

CGM systems have emerged as a valuable tool in the self-care program for an individual living with diabetes. Those using insulin can expect improved glucose control, less hypoglycemia risk, and less fear of hypoglycemia. Introducing a CGM system into our patients' care routine may facilitate a new opportunity for them to re-engage with their diabetes in a more constructive and healthy way.

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FLASH & CONTINUOUS GLUCOSE MONITORING COMPARISON CHART

	Flash Glucose Monitoring Systems (Users can scan sensor to see glucose readings)		Continuous Glucose Monitoring Systems (Users can see glucose readings at all times)	
SYSTEM NAME	**FREESTYLE LIBRE**	**FREESTYLE LIBRE 2**	**DEXCOM G6**	**GUARDIAN CONNECT**
		 *Approved by Health Canada, but not launched yet.		
Accuracy (The lower the better)	9.5%	9.2%	9.8%	9.1-10.5% (with 2 calibrations) 8.7-9.6% (with 3-4 calibrations)
Insertion Site	Arm	Arm	Abdomen, arm and upper buttocks	Abdomen, upper buttocks and arm
Calibration (with finger prick)	No calibration needed.	No calibration needed.	No calibration needed. Calibration is needed only if the transmitter code is not entered.	At least 2x/day, recommended - 3-4x/day *Calibrations can only be done when BG is steady
Length of Sensor Wear	14 days	14 days	10 days	6 days
Receiver (where the data displays)	Smartphone or Standalone reader (also a BG and ketone monitor)	Smartphone or Standalone reader (also a BG and ketone monitor)	Smartphone, Smart watch or standalone receiver	Smartphone (iPhone only)
Integration with Insulin Pump	No	No	Yes - with Tandem (Basal IQ and Control IQ)	Medtronic
Able to use readings for treatment decisions?	Yes, unless: - BG is rapidly changing (straight up/down trend arrows present) - BG <4.0 mmol/L	Yes	Yes	No - fingerstick confirmation required
Low/High BG Alerts and Predictive alerts	No	Yes	Yes	Yes
Continuous Date Recording	Yes - scan every 8 hours	Yes - scan every 8 hours	Yes	Yes
Cost	**Reader:** $49 **Sensors:** 1 sensor $89 **Total Price:** **$2314/year** plus reader **Ontario & Quebec provide public reimbursement for patients managing diabetes with insulin	**Reader:** $49 **Sensors:** 1 sensor $89 **Total Price:** **$2314/year** plus reader	**Cost:** $299 / month x 12 payments **Total Price:** $3588 **Total Price:** **$4744 / year** (without receiver) **Standalone receiver available for purchase for $499	**Transmitter:** $599 per year (1 year warranty) **Sensor:** $399 (pack of 5) OR Single sensor: $69.95 **Total Price:** **$4759 / year** (*subscription package available)

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