

History of Glucose Monitoring

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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.

REFERENCES

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