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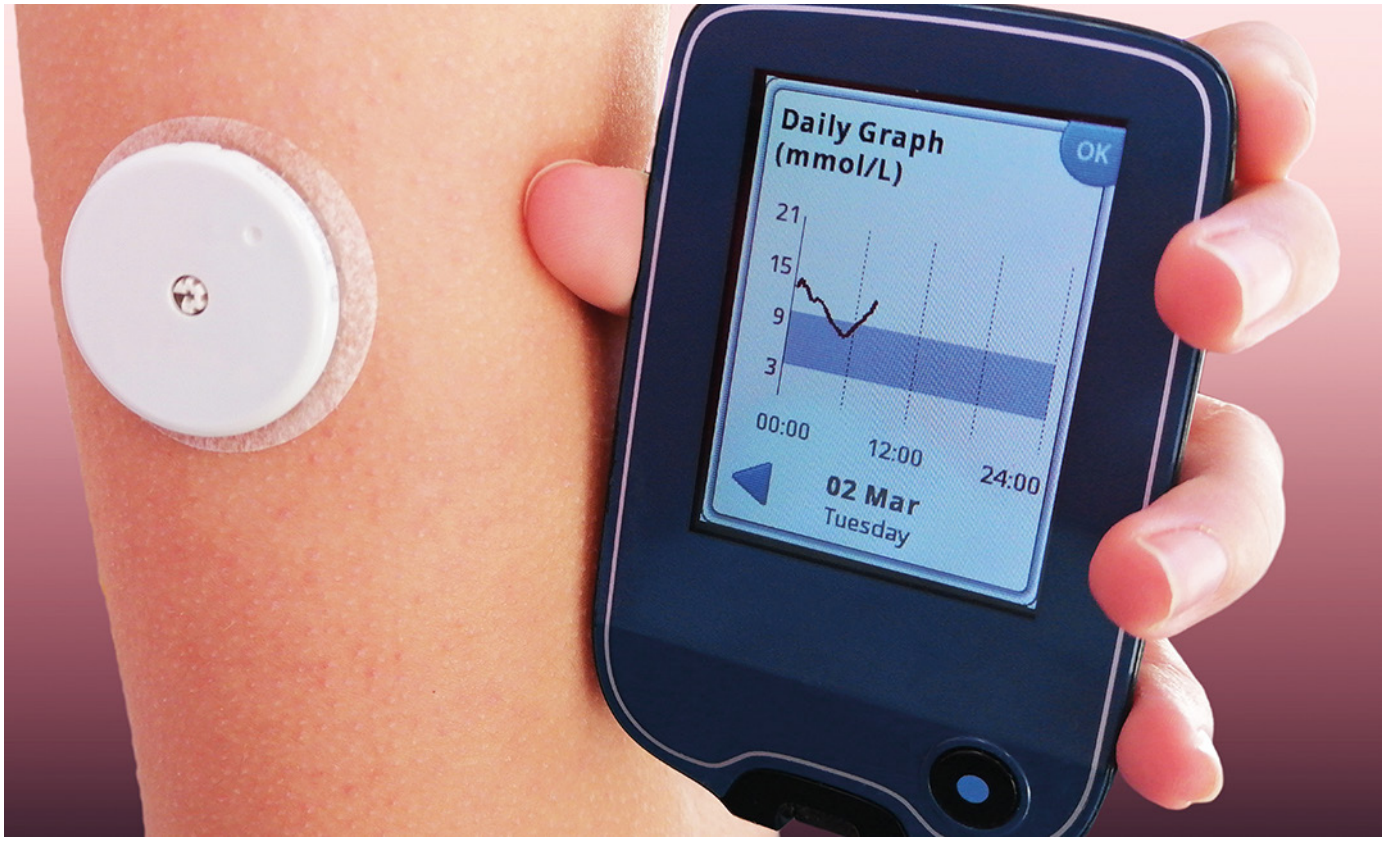

Innovations in Continuous Glucose Monitoring Systems

Diabetes mellitus (DM) constitutes one of the main global health problems due to its high economic, personal, and social costs, being considered one of the greatest health care emergencies of our century. It is a complex and heterogeneous disease with a highly variable clinical course. Regardless of the type of DM, maintaining blood glucose levels as close to normal as possible is essential to prevent micro and macrovascular complications that affect the quality of life of those who suffer from it and are associated with increased morbidity and mortality. However, achieving therapeutic targets often remains a challenge in routine clinical practice despite the pharmacological and technological advances of recent decades in the management of this condition.

In recent years, real-time continuous glucose monitoring (rtCGM) and intermittent continuous glucose monitoring (iCGM) systems have become highly valuable tools for improving metabolic control and quality of life for patients with type 1 and type 2 diabetes mellitus (DM). These devices allow for a more comprehensive understanding of glucose behavior than traditional measurement methods (capillary glucose), enabling both the patient and the healthcare professional to make more complex therapeutic decisions that lead to improvements in metabolic control.

CHARACTERISTICS, ACCURACY, CONNECTIVITY, AND ALARMS OF CGM SYSTEMS

Table 1 analyzes the characteristics of the different CGM systems available on the market.

The FreeStyle Libre 3 rtCGM and FreeStyle Libre 2 iCGM systems have direct connectivity with Novopen® 6 and Novopen Echo® plus insulin pens.

The SimpleraTM system has direct connectivity with the InpenTM insulin pen, which includes missed dose detection and a bolus calculator.

INNOVATIONS IN CGM FOR PEOPLE LIVING WITH T2DM

The use of CGM in people living with T2DM is associated with several advantages[1]: »

TABLE 1. Characteristics of MCG systems, accuracy, connectivity, and alarms

MCG System	MODY (%)	Usage Time	Warm-Up Time	Dimensions (cm)	Water Resistance	Connectivity	Alarms
FreeStyle Libre 2	9.2	14 days	60´	3.5 x 3.5 x 0.5	1 m	Monitor, Smartphone	High level, Low level, Prediction alert (< 70 mg/dL or > 250 mg/dLin 15 minutes), Screen message
FreeStyle Libre 3	7.9	14 days	60´	2.1 x 2.1 x 0.29	1 m	Smartphone	High level, Low level, Prediction alert (< 70 mg/dL or >250 mg/dL in 15 minutes), Screen message
Dexcom G6	9*	10 days sensor, 90 days transmitter	120´	4.57 x 3.05 x 1.52 Sensor + transmitter	2.4 m 24 h	Monitor, Smartphone Smartwatch	High level, Low level (one configurable, one mandatory at 55 mg/dL), Low imminent (will reach 55 mg/dL in 20 minutes), Rapid ascent and descent
Dexcom G7	8.2**	10 days + 12h grace period	30´	2.74 x 2.41 x 0.47	2.4 m 24 h	Monitor, Smartphone Smartwatch	High level, Postpone 1st high level alert, Low level (one configurable, one mandatory at 55 mg/dL), Low imminent (will reach 55 mg/dL in 20 minutes), Rapid ascent and descent, Alerts can be configured differently for day and night
Dexcom One+	8.2***	10 days + 12h grace period	30´	2.74 x 2.41 x 0.47	2.4 m 24 h	Monitor, Smartphone Smartwatch	High level, Postpone 1st high level alert, Low level
GuardianTM 4	10.6****	7 days	120´	3.8 x 6.7 x 5.2	2.4 m 30'	Smartphone	High level, Low level (one configurable, one mandatory at 54 mg/dL), Rapid ascent and descent, Alerts can be configured differently for day and night
SimpleraTM	10.2	7 days	120´	2.86 x 2.86 x 0.48	2.4 m 30'	Smartphone, Smartwatch	High level, Low level (one configurable, one mandatory at 54 mg/dL), Rapid ascent and descent, Alerts can be configured differently for day and night
Rechargeable removable transmitter Eversebse E3	8.5	6 months	24 h	4.8 x 3.76 x 8.8	1 m 30'	Monitor, Smartphone Smartwatch	High level, Low level, Change speed, Predictive high or low glucose alert (10´-20´-30´), Vibration alarm transmitter, Temporal profile configuration
GlucoMen Day	9.6	14 days	55´	3.5 x 2.5 x 0.7	1 m 30'	Smartphone, Smartwatch,	High level, Low level, Predictive high or low alert (15´), Rapid ascent and descent

MODY 9% in adults; 7.7% in pediatric population; ** MODY 8.2% in adults; 8.1% in pediatric population; *** MODY 8.2% in adults; 8.1% in pediatric population; **** MODY reduced to 9.54% with 2 calibrations (first at 2 hours post-insertion and second at 8 hours after first calibration).

CGM ALLOWS FOR OBTAINING MORE COMPREHENSIVE INFORMATION ON GLUCOSE BEHAVIOR THAN TRADITIONAL CAPILLARY GLUCOSE, ENABLING BOTH THE PATIENT AND THE HEALTH CARE PROFESSIONAL TO MAKE MORE COMPLEX THERAPEUTIC DECISIONS THAT LEAD TO BETTER METABOLIC CONTROL

- Improved glucose control: reduction in hypoglycemia episodes, decreased glucose variability, and improvement in glycated hemoglobin (HbA1c).

- Improvement in treatment adherence by patients.

- Improvement in therapeutic inertia of health care professionals.

- Improvement in satisfaction and quality of life.

- Reduction in barriers to insulin initiation due to the decrease in hypoglycemic episodes and the possibility offered by many devices to share glucose data.

Since 2017, studies have been published demonstrating the benefits of CGM in people with type 2 DM treated with multiple daily injections (MDI) of insulin. Later, data was published extending these benefits to people with type 2 DM treated with basal insulin. In 2023, studies were published regarding the use of CGM in people with DM who are on non-insulin therapies. The IMMEDIATE2 study is a randomized clinical trial that included people with type 2 DM treated with at least one non-insulin drug and an HbA1c ≥ 7.5%, with the exclusion criterion being insulin treatment for more than 3 months. The participants in this study were randomized into two groups: iCGM + diabetes education program (intervention) vs diabetes education program (control). The primary endpoint of the study was to evaluate the effectiveness and satisfaction level of iCGM. After 16 weeks, a statistically significant decrease was observed in time in range (TIR) by 9.9%, time above range (TAR) by 8.1%, and an 8.5% increase in time in tight range (TITR) in favor of the intervention group. A significant improvement was also observed in various quality of life tests within the intervention group. Additionally, a meta-analysis published in 2024 analyzed the impact of CGM on individuals with type 2 DM on non-insulin treatment. Both rtCGM and iCGM were associated with better glucose control as measured by HbA1c and other glucometry parameters, alongside a reduction in glucose variability. The increase in TIR was 8.6%, HbA1c decreased by 0.3%, glucose dropped by 11.2 mg/dL, time below range level 2 (TBR2) decreased by 0.3%, TAR decreased by 7.8%, and the standard deviation of glucose variation decreased by 4 mg/dL, along with better satisfaction with hypoglycemic treatment.

Recent studies have also demonstrated a decrease in hospitalizations for patients with type 2 DM after initiating iCGM. In a retrospective study including 38,312 people with type 2 DM over 65 years old, who were treated with MDI or continuous subcutaneous insulin infusion (CSII), a 40% decrease in hospitalizations for acute events related to DM (diabetic ketoacidosis, severe hypoglycemia, and hyperglycemia)4 was observed after 24 months of iCGM. Finally, in another retrospective study including 5933 people with type 2 DM, treated with MDI or basal insulin, with or without oral antidiabetic drugs, a 67% decrease in hospitalizations for acute events related to DM and a 7% reduction in hospitalizations for any cause were observed after 12 months of starting iCGM.

NEW GLUCOMETRY ANALYSES

The classic glucometry variables and control targets based on patient characteristics were already defined in the International Consensus on CGM published in 20196. These are visualized in the Ambulatory Glucose Profile (AGP) and are widely used in the routine clinical practice *(Table 2)*.

However, in recent years, emerging glucometry parameters have been introduced as complements to the classics:

- Time in Tight Range (TITR): the time that interstitial glucose remains between 70 and 140 mg/dL.

TABLE 2. Classic Glycometric Parameters

Time in Range (TIR) (%)	Time of interstitial glucose between 70-180 mg/dL
Time Above Range Level 1 (TAR1) (%)	Time of interstitial glucose between 181-250 mg/dL
Time Above Range Level 2 (TAR2) (%)	Time of interstitial glucose > 250 mg/dL
Time Below Range Level 1 (TBR1) (%)	Time of interstitial glucose between 54-69 mg/dL
Time Below Range Level 2 (TBR2) (%)	Time of interstitial glucose < 54 mg/dL
Coefficient of Variation (CV) (%)	Defines interday glycemic variability (GV). Mathematically associated with the mean, thus more descriptive of hypoglycemic excursions than the standard deviation (SD). Low GV is defined as CV < 36%, and high as CV ≥ 36%.
Glycemic Management Indicator (GMI) (%)	GMI (%): 3.31 + 0.02392 x (mean interstitial glucose mg/dL)

» Since the publication of the International Consensus on CGM in 2019, there has been debate about the need to review glucometry parameters and control targets, especially due to the increased use of hybrid closed-loop systems in routine clinical practice. Studies conducted in pediatric and adult populations (excluding pregnant individuals) without DM showed that these individuals' glucose levels were within the range of 70-140 mg/dL 96% of the time7, thus defining TITR as a new control parameter for individuals with DM. A recently published study analyzed TITR in 13,461 users of the MiniMed 780 g hybrid closed-loop system (Medtronic) and concluded that a TITR goal > 50% (which corresponds to an HbA1c < 6.5%) can be considered a reasonable and safe target for people living with type 1 DM8.

- Glycemic Risk Index (GRI): this is a new parameter derived from the analysis of various scores provided by 330 international experts in type 1 DM. It aims to summarize the quality of glycemic control in a single parameter. The formula for calculating the GRI is described in ***Figure 1***, giving a score from 0 to 100 points, where 0 represents the best control and 100 represents the worst possible glycemic control9.

Although HbA1c is the most scientifically supported parameter for predicting chronic complications, it does not optimally evaluate glycemic control as it does not provide information on glycemic variability or hypoglycemic episodes. On the other hand, TIR per se also has certain limitations, as it does not provide information on the direction of time out of range (hypo- or hyperglycemia) and does not give greater weight to extreme deviations from TIR. Additionally, the simultaneous evaluation of different parameters in the AGP report requires experience and time, so it seems logical to seek new glucometric parameters that synthesize the existing data. In this sense, GRI aims to summarize the overall quality of glycemic control for a specific patient in a single value. It allows the simultaneous evaluation of two essential components of metabolic control, such as TBR and TAR, in addition to providing a two-dimensional visualization of TAR vs. TBR, categorizing patients into five groups corresponding to five glycemic risk zones: Zone A (GRI percentile 0-20); Zone B (GRI percentile 21-40); Zone C (GRI percentile 41-60); Zone D (GRI percentile 61-80); Zone E (GRI percentile 81-100)9.

GRI gives greater weight to TBR and extreme glycemic values, unlike TIR or HbA1c, which are central values. It is also easily interpretable, and its changes can be assessed over time9. However, it is an emerging parameter, so there are no established cutoffs for GRI, nor for its Hypoglycemia Component (HypoC) or Hyperglycemia Component (HyperC), either in general or based on the age group and clinical characteristics of patients. Additionally, although studies have linked GRI with the development of microvascular complications10,11 and quality of life, there are no studies analyzing its association with macrovascular complications or mortality, and lastly, it is not automatically integrated into the AGP, which currently limits its widespread use.

- Glucodensity data: Glucodensity is a functional representation of CGM data that includes the information of each glucose value frequency across the entire glycemic range, rather than a roughly defined range (as broad as 70-180 for TIR, or above/below »

THE GLYCEMIC RISK INDEX (GRI) IS A NEW PARAMETER FOR GLUCOSE CONTROL THAT INCLUDES EXTREME GLUCOSE VALUES, BEING MORE COMPREHENSIVE THAN TRADITIONAL GLYCATED HEMOGLOBIN. HOWEVER, THERE IS A LACK OF EVIDENCE REGARDING ITS RELATIONSHIP TO MORBIDITY AND MORTALITY DUE TO DIABETES

FIGURE 1. Formula to calculate the Glycemic Risk Index (GRI)9.

Hypoglycemia component (HypoC) = TBR2 + (0.8 × TBR1)
Hyperglycemia component (HyperC) = TAR2 + (0.5 × TAR1)
GRI = (3.0 × HypoC) + (1.6 × HyperC)

Alternatively:
GRI = (3.0 × Low) + (2.4 × Moderate Low) + (1.6 × Moderate High) + (0.8 × High)

» a threshold)12. As a result, glucodensity automatically and simultaneously captures all parameters derived from individual glucose distributions. The potential advantages of glucodensity data analysis are:

- It provides a comprehensive representation of glucose across the entire glycemic concentration range in a single variable.
- It informs each glucose value frequency rather than a sum of variables that report time spent in various predefined ranges.
- It allows a more thorough analysis of glycemic variability by comparing all glucose range values included in each glucodensity profile.
- It has greater sensitivity than TIR in predicting DM biomarkers and glucometric variables.

Although this glucodensity approach is not routinely used in clinical practice or epidemiological studies, it represents a novel analysis of glucose values.

DUAL GLUCOSE AND KETONE BODY CGM SYSTEM

Diabetic ketoacidosis (DKA) is an acute complication associated with DM, much more common in individuals with T1DM, and it increases morbidity and mortality. It is estimated that the prevalence of DKA at the time of type 1 DM diagnosis is 29.9% in children, while adults »

» have a prevalence between 5% and 8%.13 The risk factors for developing DKA include poor metabolic control, treatment with SGLT2 inhibitors (Sodium-Glucose Cotransporter 2 inhibitors), young age (children and adolescents), low socioeconomic status, low physical activity, intercurrent conditions (presence of infection, trauma, or surgery), and the presence of psychiatric conditions associated with DM such as depression.

Despite the advances and implementation of CGM in recent decades, little progress has been made in monitoring ketone bodies, which still relies on capillary ketonemia determination. Although it has been shown that the use of CGM reduces the incidence of DKA, knowing only glucose data may not be enough to prevent this complication in individuals with associated risk factors. Therefore, an International Consensus of Experts on DM14 has recommended the development of dual monitoring systems for both glucose and ketone bodies, which should be used in the following cases, although they are not yet available:

- Treatment with CSII

- Recurrent DKA episodes

- Sick days

- Stressful situations

- Low-carbohydrate diets/fasting/high-intensity exercise

- Treatment with SGLT2i

- Pregnancy

- Excessive alcohol consumption

- Prolonged sedentary behavior

CGM WITH HYPOGLYCEMIA PREDICTION

Recently, an innovative CGM device (Accu-Chek Smart-Guide, Roche Diabetes Care) was introduced, with a MODY of 9.2%, and utilizes artificial intelligence algorithms to forecast future glucose levels. However, it is not yet available for routine clinical practice. The device includes a 14-day CGM sensor and 2 applications designed to show current glucose values and predictions over 30 minutes and 2 hours. Additionally, it includes a prediction for nocturnal hypoglycemia risk. This is a CGM system that will allow for medium- and long-term therapeutic decisions, unlike currently available devices. This will aid in decision-making for individuals living with DM, providing security and enhancing patient confidence. These systems will also offer advantages to healthcare professionals, as they will help identify treatment aspects that need improvement more effectively and easily. D

CONCLUSIONS

The widespread use of CGM devices has given us the opportunity to access glucose data that was previously inaccessible in routine clinical practice, and they have become a fundamental tool in managing individuals living with DM. These systems are constantly evolving and have marked a turning point in disease management and in the quality of life of people living with DM. However, it is essential to manage the information they provide effectively and to ensure appropriate therapeutic education to make the most of this technology.

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