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The usefulness of continuous glucose monitoring in the diagnostic approach to hypoglycemia after metabolic surgery

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Abstract

Post-bariatric hypoglycemia (PBH) is an underdiagnosed complication of metabolic surgery, resulting in reduced quality of life and weight gain. There is currently no gold standard for the diagnosis of PBH. Although various guidelines and consensuses do not consider continuous glucose monitoring (CGM) a valid diagnostic tool, currently available CGM devices have adequate accuracy for euglycemia and hyperglycemia and have improved accuracy for hypoglycemia over time. This has expanded the use of CGM in the non-diabetic population and may be a useful tool in PBH, but evidence in this population is limited. CGM provides a real-time assessment of glucose fluctuations and variability, providing insights that standard diagnostic tools such as the oral glucose tolerance test (OGTT) and the mixed meal test (MMT) cannot capture in real-world settings. CGM can provide detailed information on the immediate dynamic changes in glucose levels and glycemic profile that reflect the patient's "real life" situation, assess risk factors for PBH such as postoperative glycemic variability, and enable objective assessment of clinical response to nutritional and pharmacological therapy. Currently, there are limitations to its use in patients with PBH, but evidence of its usefulness in the management of these patients has increased in recent years. The aim of this narrative review is to highlight the benefits of evaluating different CGM metrics in patients with PBH.

Keywords: Post-bariatric hypoglycemia, continuous glucose monitoring, time in range, time below range

INTRODUCTION

Post-bariatric hypoglycemia (PBH), a late complication of metabolic and upper gastrointestinal surgery, presents significant challenges due to its impact on patient quality of life, including symptoms of neuroglycopenia and vasomotor instability. In addition, a significantly higher number of patients with weight gain ≥ 10% reported experiencing symptoms of PBH (40.6% *vs.* 29.0%)[1]. Despite its clinical relevance, PBH remains underdiagnosed, emphasizing the need for improved diagnostic modalities[2]. Several tests, including the mixed meal test (MMT) and the modified oral glucose tolerance test (OGTT), are available to confirm this diagnosis[2,3]. However, the protocols for developing these tests are not standardized and the cut-off points are not defined, so there is no consensus on the gold standard for diagnosis. Additionally, these tests do not enable the establishment of a "pattern" of hypoglycemic events, which is useful in the clinic for differential diagnosis.

Continuous glucose monitoring (CGM) is a system that continuously measures and stores glucose levels and enables evaluation of additional glycemic control metrics such as time in range (%TIR), glycemic profile, and variability and detection of acute events such as hypo- and hyperglycemia. Its use has been associated with improved glycemic control in patients with diabetes, reducing hypoglycemic events and hospitalizations independent of insulin use[4]. Current devices have improved the accuracy of hypoglycemic readings[5,6], and use in the non-diabetic population has increased[7-9].

The aim of this narrative review is to highlight the usefulness of CGM, the advantages of evaluating different metrics, and the "pattern" of hypoglycemic events in the diagnosis and follow-up of patients with PBH. In addition, this paper summarizes various advantages of CGM compared to other diagnostic tools.

GENERALITIES OF PBH

PBH arises from postprandial hyperinsulinemia, driven by anatomical and hormonal changes after metabolic surgery. Rapid nutrient transit to the distal intestine triggers an exaggerated glucose peak, stimulating excessive insulin secretion and amplifying incretin release, primarily glucagon-like peptide-1 (GLP-1) and other incretins, which amplify insulin secretion[10,11]. This imbalance leads to recurrent hypoglycemia, especially in the postprandial state[12]. This is associated with decreased secretion of glycogenolytic hormones with reduced hepatic glucose production, exacerbating hypoglycemia[12]. Other mechanisms underlying the failure of regulatory and compensatory systems are not clear[13].

During long-term follow-up of patients treated with metabolic surgery, two phenomena may occur. Dumping syndrome and PBH share postprandial timing but differ mechanistically. Dumping syndrome arises from rapid gastric emptying and fluid shifts, causing vasomotor and gastrointestinal symptoms. PBH, in contrast, results from excessive insulin secretion following carbohydrate ingestion, leading to recurrent hypoglycemia[10] [Table 1].

Early dumping: occurs within a few minutes after eating and is characterized by a combination of gastrointestinal symptoms (pain, abdominal distention, nausea, diarrhea, and borborygmi) with vasomotor symptoms (fatigue, hot flashes, palpitations, sweating, tachycardia, hypotension, and syncope) without hypoglycemia[2,3].

PBH or late dumping: is generally defined as postprandial hypoglycemia occurring between 1 and 3 h after a meal, with documented hypoglycemia (venous glucose < 54 mg/dL) at the time of symptoms and resolution after carbohydrate ingestion[2,12,14]. The diagnostic criteria are:

Table 1. Dumping syndrome clinical presentation[38]

Classification	Incidence (%)	Presentation time	Triggering	Symptoms
Early dumping	9-21	First 60 min after ingestion	Consumption of simple carbohydrates (osmotic effect)	Abdominal symptoms: nausea, vomiting, abdominal pain and bloating, diarrhea Vasomotor symptoms: diaphoresis, flushing, palpitations, hypotension, fatigue, need to lie down, and syncope (rare) Hyperglycemia
Late Dumping or PBH	1-6	1-3 h after ingestion	Incretin-driven hyperinsulinemic response after carbohydrate ingestion	Hypoglycemia (main manifestation): fatigue, weakness, confusion, hunger, and syncope Vasomotor symptoms: diaphoresis, palpitations, and irritability

PBH: Post-bariatric hypoglycemia.

1. History of neuroglycopenia between 1 and 3 h after a meal in patients with a history of metabolic surgery more than 1 year postoperatively.
2. Absence of hypoglycemia during prolonged fasting (more than 12 h).
3. Exclusion of other causes of hypoglycemia such as: adrenal insufficiency, malnutrition associated with excessive weight loss or poor intake, and critical illness. In addition, although rare, insulinoma has been reported in patients with hypoglycemia after upper gastrointestinal surgery; it should be suspected in patients with hypoglycemia on fasting or associated with physical activity that occurs within 1 year after metabolic surgery[15-17].

In clinical practice, differentiating between these clinical conditions can be difficult and complementary studies such as CGM may be useful in diagnosis.

CGM OVERVIEW

CGM has become an essential tool for the assessment of daily glucose profiles. Currently, technical improvements and rapid evolution have led to increased accuracy (with a good correlation to plasma glucose) and widespread availability. This supports both self-monitoring by the patient and therapy assessment by healthcare professionals[6]. Modern CGM systems consist of a sensor that measures glucose in the interstitial fluid every 1 to 5 min, offering near real-time data. These systems not only detect hypoglycemic episodes missed by traditional methods but also provide metrics such as glycemic variability (CV%), time-in-range (TIR), and time-below-range (TBR), enabling a comprehensive glycemic assessment critical for managing PBH[4].

There are two basic types of devices: those that are patient-owned, intended for frequent or continuous use in real time or on demand, for intermittent scanning or flash, and those that are applied by health care professionals, obtaining blinded (or with the option of nonblinding) data for a discrete period of time (professional CGM)[18]. Compared to self-monitoring blood glucose, the use of CGM allows the documentation of a greater number of hypoglycemic events, including nocturnal hypoglycemia and hypoglycemia unawareness[19]. Given the large amount of information, it generates a more complete glycemic profile, allowing a dynamic assessment of glycemic variability and the impact of food consumption and physical activity on interstitial glucose levels[18]. According to international consensus, hypoglycemia in CGM is defined as[20]:

· Level 1: Glucose value below 70 mg/dL (3.9 mmol/L) for more than 15 min, or a percentage of time within range (%TBR) below 70 mg/dL (3.9 mmol/L) greater than 4%[20].

· Level 2: Glucose level below 54 mg/dL (3.9 mmol/L) for more than 15 min, or %TBR below 54 mg/dL (3.0 mmol/L) greater than 1%[12,20].
· Prolonged hypoglycemia: glucose level below 54 mg/dL (3.9 mmol/L) for more than 120 min[20].

PBH PREVALENCE IN THE ERA OF CGM

Registry-based studies report a prevalence of PBH of 0.1% to 0.9%, but this may be an underestimate[18]. Using self-report questionnaires such as the *Edinburgh Hypoglycemia Scale* and the *Arts Dumping Severity Score Questionnaire*, the prevalence varies from 2.6% to 66.4%[18]. Studies using CGM have reported a prevalence of between 25% and 75% using a glucose threshold of < 54 mg/dL[2], which is much higher than that reported with provocative tests such as OGTT (6.6% to 51.4%) and similar to that reported with MMT (29.4% to 78.6%)[12]. However, the prevalence of PBH using CGM may vary depending on the time frame evaluated and the type of metabolic surgery. For example, the prevalence of PBH in patients with Roux-En-Y gastric bypass (RYGB) varies from 6.7% to 12.5% when only postprandial hypoglycemia is assessed[18]. The incidence of hypoglycemia within 24 h was 41.9%-100% in patients undergoing RYGB and 25%-88.9% in patients undergoing surgery[18].

GLYCEMIC VARIABILITY AS A FACTOR ASSOCIATED WITH PBH

CGM provides a more comprehensive evaluation of glycemic variability compared to Modified OGTT and MMT. While traditional tests capture a single glucose response, CGM calculates CV% over a 24-h period[20]. Glycemic variability refers to the frequency and degree to which patients' glucose levels fluctuate between maximum and minimum values[18,20]. This metric has been studied in patients with diabetes, where it is associated with poor metabolic control, increased markers of oxidative stress, and is an independent predictor of hypoglycemia[21,22]. Glycemic variability in clinical practice is measured by CV%; in patients with diabetes, a CV% > 36% is associated with increased level 2 hypoglycemia independent of clinical factors[21,22].

Lu *et al.* described the increase in glycemic variability, defined as CV% > 32%, as the main risk factor associated with PBH in patients with a history of type 2 diabetes (T2D) treated with gastric bypass who met disease remission criteria[23]. Another study showed that patients with a history of PBH and no history of T2D had higher postoperative CV% compared to healthy controls without surgery (27.3% ± 6.8% *vs.* 17.9% ± 2.4%, $P > 0.0001$)[24]. Clinical factors associated with higher glycemic variability include a history of preoperative T2D and the absence of remission criteria in the postoperative period. Single-anastomosis gastric bypass and duodenal switch are associated with greater variability compared to RYGB and sleeve gastrectomy (SG). Other factors such as meal composition, glycemic index, and carbohydrate amount do not influence glycemic variability[18]. A systematic review described other risk factors for the development of PBH, which are summarized in Table 2[12].

PBH DIAGNOSTIC STRATEGIES COMPARED TO CGM

PBH may be an underestimated threat to patients undergoing metabolic surgery. HbA1c remains a limited tool in PBH, as it does not reflect episodic hypoglycemia. CGM provides a real-time assessment of glucose fluctuations; it could be especially useful in patients with normal HbA1c but clinically significant hypoglycemia. There are several methods to confirm the diagnosis, including the modified OGTT and MMT [Table 3]. However, their use in clinical practice is limited because provocation tests must be performed under standardized conditions and there is currently no consensus on a gold standard for diagnosis[14]. These tests are also limited due to safety concerns, and they should be performed in the hospital setting because inducing hypoglycemia in the office is not always safe.

Table 2. Clinical factors associated with PBH[12]

Preoperative factors	Related to metabolic surgery	Postoperative factors
· Female gender · Age < 40 years · Preoperative hypoglycemia in people with a history of T2D	· Gastric sleeve or bypass · Cholecystectomy before or after metabolic surgery	· Excessive weight loss · Low HbA1c levels · High Glycemic variability · SSRIs · SNRIs

PBH: Post-bariatric hypoglycemia; T2D: type 2 diabetes; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors.

Table 3. PBH diagnostic test strengths and limitations

Diagnostic tool	Strengths	Limitations
MMT	Identifies PBH	Limited standardization, single-time-point assessment. It should be performed in a hospital setting due to safety concerns
OGTT	Differentiate early dumping from PBH; validated	Non-physiological conditions; may induce false positives. It should be performed in a hospital setting due to safety concerns
CGM	Real-time, 24-h data; detects nocturnal hypoglycemia	High cost; not yet a diagnostic

PBH: Post-bariatric hypoglycemia; MMT: mixed meal test; OGTT: oral glucose tolerance test; CGM: continuous glucose monitoring.

Sigstad score

This score is mainly used to detect early dumping syndrome and assigns a score based on postprandial symptoms[25]. The diagnosis of dumping syndrome is made when the score is greater than 7, but if the score is less than 4, this diagnosis is unlikely[25]. However, PBH is underdiagnosed with this tool, leading to recommendations for a modified Sigstad score[26]. Therefore, it is important to identify more effective methods to detect PBH in patients undergoing bariatric surgery.

MMT *vs.* CGM

MMT can be a useful dynamic test to confirm the occurrence of hypoglycemia. Among the current diagnostic tests, the MMT is considered the more physiologically representative modality and is currently the preferred provocation method to confirm the diagnosis of PBH[12]. However, this test does not reflect the daily life of the patient[2]. Additionally, the lack of standardization in the composition of the food used to perform it, along with different cut-off points, limits its use in daily clinical practice. Nevertheless, the MMT remains a useful dynamic test to confirm the occurrence of hypoglycemia in a large number of patients with persistent and recurrent PBH during long-term follow-up after gastric bypass[14].

CGM is more sensitive than MMT for the detection of hypoglycemia after RYGB[21,24]. CGM detected hypoglycemic episodes of < 55 mg/dL (< 3.0 mmol/L) in 75% of patients, while MMT detected hypoglycemia in 29% of patients. CGM also detected nocturnal hypoglycemic episodes in 15 (38%) of the patients and a mean of 3 ± 1 hypoglycemic episodes per patient, with a mean duration of 71 ± 25 min[27]. Although CGM is not considered a confirmatory test, it is easy to use, does not require in-hospital monitoring, and enables the evaluation of hypoglycemic event frequency, the time of onset, and their triggers during the patient's daily life. Moreover, it allows for the evaluation of glucose levels during each meal, as well as other relevant data such as glycemic variability[2].

Modified OGTT *vs.* CGM

One of the main advantages of the OGTT is that it can differentiate early dumping from PBH and is considered the reference test for dumping syndrome, validated by an international expert panel in 2020[3,28].

The test is positive for early dumping syndrome in the presence of one or more of the following[29]:

· Early increase (first 30 min) in hematocrit > 3%.
· Increase in pulse rate greater than 10 beats per min 30 min after ingestion. This finding has a sensitivity of 100% and specificity of 94% for the diagnosis of early dumping.

The test is considered positive for PBH based on the late development (60-180 min after ingestion) of hypoglycemia, defined as plasma glucose ≤ 50 mg/dL. However, OGTT is often poorly tolerated, creates non-physiological conditions with the ingestion of a large amount of carbohydrates not associated with other nutrients, and may induce false positives[2,28,29]. When comparing patients with a positive OGTT for early or late dumping, no significant differences in CGM metrics were found compared to patients with a negative test result[28].

PATTERNS OF HYPOGLYCEMIA WITH THE USE OF CGM AND THEIR CLINICAL RELEVANCE

CGM has been used in patients with a history of metabolic surgery and symptomatic hypoglycemia to assess patterns of glycemic excursions in association with a food and physical activity diary[24]. Two dominant patterns have been described in patients with PBH: postprandial hypoglycemia and nocturnal hypoglycemia, which occur in 32% and 29% of patients, respectively[30]. However, almost 40% of patients have a mixed pattern[30].

Postprandial hypoglycemia

This pattern is more common in patients with gastric bypass and PBH[30]. The use of CGM has shown a significant increase in glycemic variability associated with an early peak of postprandial hyperglycemia generally > 180 mg/dL, followed by an abrupt drop in glucose levels < 54 mg/dL compared to normal controls [Figure 1A and B][18,24]. Symptoms of hypoglycemia are more common in subjects with a postprandial pattern than in those with a nocturnal pattern[30].

Nocturnal hypoglycemia

In patients with diabetes, hypoglycemia (< 70 mg/dL) with or without symptoms is more likely to be associated with complications such as cardiac ischemia[31]. This pattern is more common in GS and postgastrectomy patients[30,32], and half of these events are asymptomatic[18]. Although its clinical relevance is not established, careful long-term evaluation is needed to determine its impact in this population.

Compared to the normal population, patients with PBH have lower interstitial glucose levels during the first hours of the night between 2 and 4 a.m. When comparing CGM data in patients with PBH *vs.* healthy controls, an increase in nocturnal events < 70 mg/dL with a mean duration of 33 min was described [Figure 2]. However, no hypoglycemic events < 54 mg/dL were documented in either group[24]. In case of hypoglycemic events < 54 mg/dL, the investigation of other causes of hypoglycemia should be expanded, such as malnutrition, side effects of medications or supplements, critical illness, primary or secondary adrenal insufficiency, autoimmune hypoglycemia, and insulinoma[33].

Glycemic profile in patients with T2D mellitus treated with metabolic surgery

Metabolic surgery has a direct impact on glycemic control in patients with T2D. In the immediate postoperative period, the decrease in glucose levels allows the suspension of oral medications and even insulin independent of weight loss[34]. Previous studies described that CGM could be effective in detecting hypoglycemia one year after metabolic surgery[27,35]. However, a recent study compared CGM data before

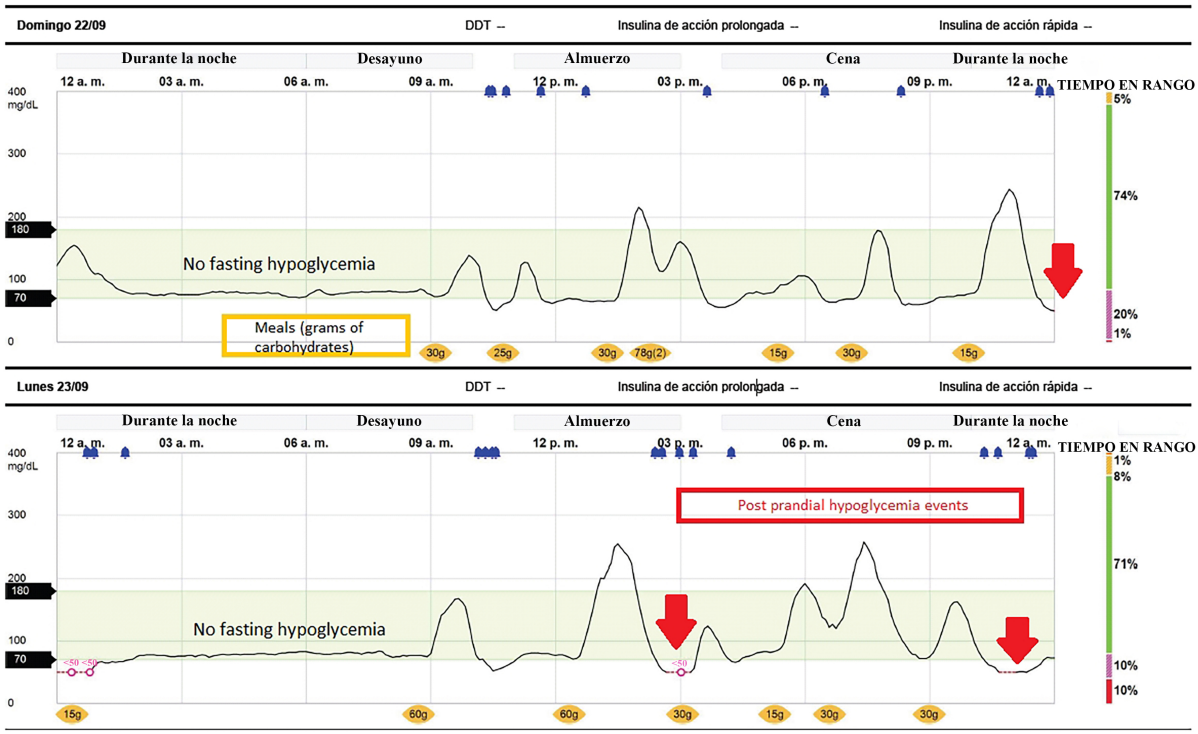

Figure 1. A 46-year-old female with a history of single anastomotic gastric bypass in 2021 with symptoms suggestive of postprandial hypoglycemia. AGP: TIR (70-180 mg/dL), TBR < 70 mg/dL: 16%, TBR < 54 mg/dL 4%, TAR > 180 mg/dL 5%, CV%: 41%. Source: Guardian 4 real-time CGM data (Medtronic, Northridge, California - USA). AGP: Ambulatory Glucose Profile; CV%: coefficient of variation; CGM: continuous glucose monitoring; TAR: time above range; TBR: time below range; TIR: time in range.

and after metabolic surgery in people with DM2 and observed a rapid change in glycemic pattern characterized by a significant increase in TBR < 70 mg/dL and < 54 mg/dL with a decrease in TAR > 180 mg/dL and > 250 mg/dL and glycemic variability independent of treatment, type of surgery, follow-up time, or DM2 remission[34].

CGM IN THE FOLLOW-UP OF PATIENTS WITH PBH

The goal of treatment is to reduce the frequency and severity of hypoglycemia. The patient should be advised that medical nutrition therapy (MNT) is unlikely to completely resolve hypoglycemia. This includes several key components, including small portions of low glycemic index carbohydrates (< 30 g), healthy fat intake, consumption of up to 1.5 g/kg of ideal body weight of protein, and dividing food intake into 6 small meals and snacks spaced every 3 to 4 h[2,33]. Although 90% of people achieve symptomatic improvement with dietary measures, a small percentage of patients will require pharmacologic treatment[2,36]. Acarbose is considered first-line therapy; somatostatin analogs (short-acting octreotide and pasireotide) and diazoxide are currently considered second- and third-line therapies, respectively[2].

In the clinic, CGM provides an objective measure of response to MNT and drug therapy [Figure 3]. In addition, CGM allows the patient to identify and modify foods that alter the glycemic profile. Cummings *et al.* described that the use of real-time CGM with hypoglycemia alarms allows patients to make dietary changes with a reduction in TBR < 70 mg/dL (4.7% ± 4.8% *vs.* 2.9% ± 2.5%, $P = 0.04$) and an increase in time in normoglycemia during the day (90.8% ± 5.2% *vs.* 94.8% ± 3.9%, $P = 0.004$) with a decrease in exposure to hyperglycemia compared to masked CGM[37]; however, additional studies with larger numbers of patients are needed.

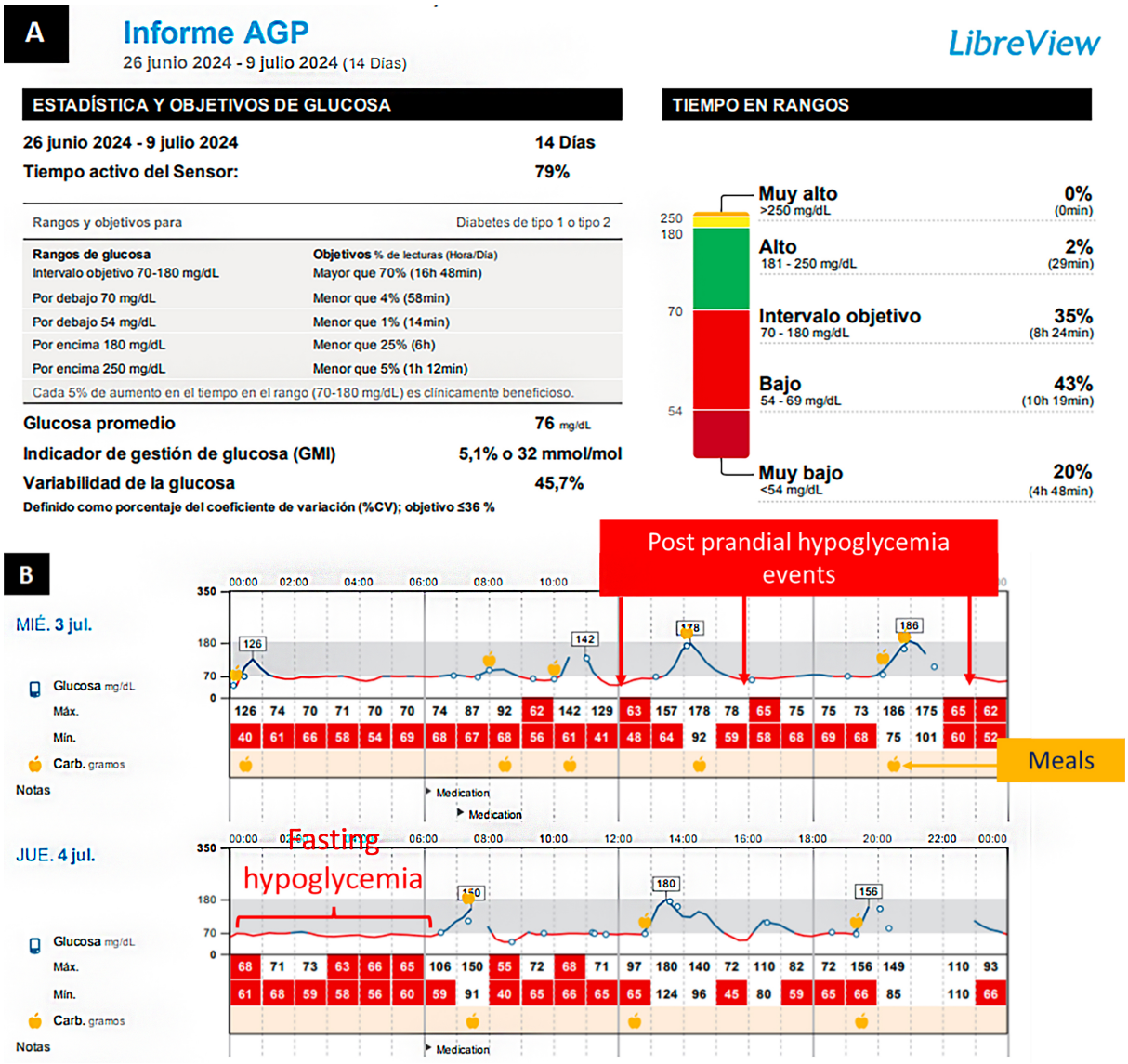

Figure 2. A 38-year-old female with a history of SG in 2015 and conversion to RYGB in 2021 due to gastroesophageal reflux. Presents with symptoms of fasting and postprandial hypoglycemia. (A) AGP data; (B) Prolonged hypoglycemia during the night and postprandial hypoglycemia. Source: FreeStyle Libre 2 CGM data (Abbott Diabetes Care, Alameda, California - USA). AGP: Ambulatory Glucose Profile; CV%: coefficient of variation; CGM: continuous glucose monitoring; RYGB: Roux-En-Y gastric bypass; SG: sleeve gastrectomy; TAR: time above range; TBR: time below range; TIR: time in range.

ADVANTAGES AND DISADVANTAGES OF CGM IN THE DIAGNOSIS OF PBH

Incorporating CGM into the diagnostic approach and follow-up of patients with PBH has several advantages. These include:

· Assessing postoperative glycemic variability to predict PBH.
· Detect a greater number of hypoglycemic events than existing tests.
· Assessment of hypoglycemic patterns: PBH should not be considered an exclusively postprandial phenomenon, and it is the only test capable of detecting hypoglycemic events, since the commonly used diagnostic tools (OGTT, MMT), by definition, can only detect hypoglycemia induced by meals, so it should be included in the diagnostic algorithm.

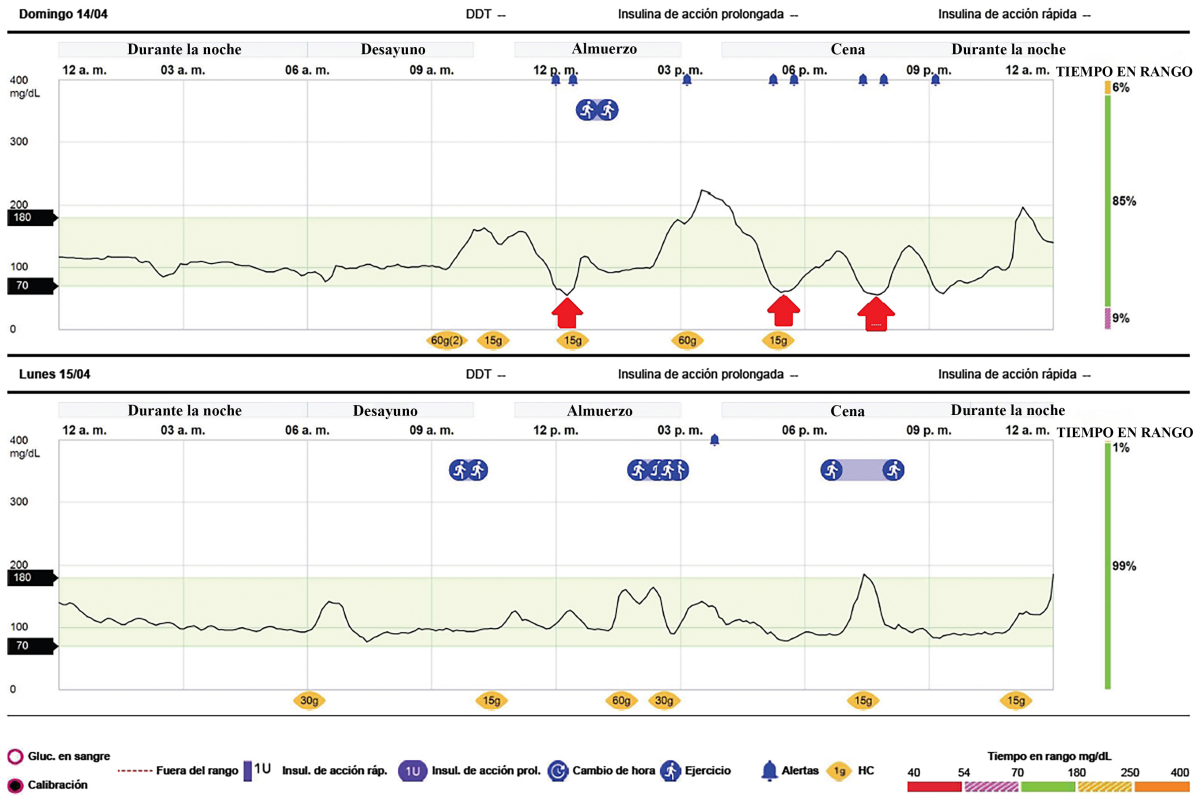

Figure 3. A 37-year-old woman with a history of gastric bypass in 2020 and PBH. CGM data after MNT. TIR (70-180 mg/dL): 92%, TBR < 70 mg/dL: 2%, TBR < 54 mg/dL 0%, TAR > 180 mg/dL 6%, CV%: 26%. (A) Multiple postprandial hypoglycemic events (red arrows) are observed when 165 g of carbohydrate is consumed during the day; (B) Reduction in postprandial hypoglycemic events after fractionation of the carbohydrate portion. Data source: Guardian 4 real-time continuous glucose monitoring data (Medtronic, Northridge, California - USA). AGP: Ambulatory Glucose Profile; CV%: coefficient of variation; CGM: continuous glucose monitoring; MNT: medical nutrition therapy; TAR: time above range; TBR: time below range; TIR: time in range.

· This device is easy to use and most CGMs can be connected to mobile devices, with alerts to prevent hypoglycemic events.
· Evaluating the glycemic profile over the 24 h of the day, which enables the evaluation of the patient's daily life, reveals episodes in real-life circumstances and can be used to monitor treatment effectiveness.

However, its implementation in guidelines for the diagnosis and management of PBH is limited for several reasons, including:

· Lack of standardized cut-off points: although the cut-off points for evaluating hypoglycemia in people with diabetes are already established, and the use of CGM in the non-diabetic population has increased. Given the physiological changes that occur in patients treated with metabolic surgery, the cut-off points for diagnosis of PBH using CGM and the impact on outcomes such as quality of life and weight gain have yet to be established.
· Cost: There are no studies evaluating the cost-effectiveness of CGM in patients with PBH at the time of this review.
· Availability: The use of CGM has increased due to its benefits in patients with diabetes independent of insulin use, and its use in the non-diabetic population has increased; however, factors such as cost and lack of coverage by insurers in patients without diabetes are limiting its use in patients with PBH.

· Accuracy: The accuracy of CGM devices has improved over time, but there is a need for devices with better accuracy in hypoglycemia.

CONCLUSION

PBH is a late complication of metabolic surgery, and although CGM is not approved as a diagnostic tool, the use of CGM provides a unique opportunity to assess glycemic patterns in real-world situations, including nocturnal and mealtime glucose fluctuations that are often missed by OGTT and MMT. It enables the assessment of parameters associated with PBH, such as glycemic variability, and the evaluation of treatment response in an objective manner. Even the use of alarms could reduce hypoglycemic events. Its incorporation into clinical practice in the management of PBH could transform diagnosis and treatment, but further studies are needed to establish standardized cut-off values and assess cost-effectiveness.

DECLARATIONS

Authors' contributions

Contributed to the conception and design of the manuscript: Henao DC
Involved in literature searches: Robledo S
Wrote the article: Henao DC, Gómez AM, Rosero R
All the authors critically reviewed the manuscript for important intellectual content and approved the final version to be published.

Availability of data and materials

Not applicable.

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Henao DC received speaker fees from Novo Nordisk, Sanofi, and Abbott. Gómez AM received speaker fees from Novo Nordisk, Elli Lilly, Boehringer Ingelheim, Abbott, and Medtronic. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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