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Viewpoint

Benefits and limitations of hypo/hyperglycemic alarms associated with continuous glucose monitoring in individuals with diabetes

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ABSTRACT

Continuous Glucose Monitoring (CGM) has improved the diabetes follow up. The use of CGM can be expected to reduce the long-term complications of diabetes. To achieve this, education of physicians and diabetic individuals is essential. The latest CGMs have alarms to improve glycemic control by avoiding hypoglycemia and hyperglycemia, hence the importance of proper setting of these alarms. Although useful to signal these events, we have noted that these alarms do not necessarily meet with unanimity in consultations... Are alarms considered a comfort or a possible disturbance ?

1. Introduction

A hemoglobin A_1c level (HbA_1c) ≤ 7.0% (53 mmol/mol) has long been considered a therapeutic goal for many people with diabetes. But this goal is not easy to reach, and hypoglycemia remains a major limiting factor in achieving it. Less than 30% of people with type 1 diabetes achieve an HbA_1 *c* < 7.5% (< 58 mmol/mol) [1]. Over the past decade, numerous studies have demonstrated that interstitial glucose monitoring via CGM is more effective than capillary glucose measurement. In parallel with technological advances, an international consensus [2] has proposed new interstitial glucose targets to achieve HbA_1c at 7.0%. The concept of time in range (TIR), defined as the percentage of time spent between 70 and 180 mg/dL of blood glucose over a given period of time, has thus been introduced.

To achieve an HbA_1 c of 7.0%, a high IRR of 70% and a reduction in the time in large glycemic ranges, i.e., the time spent in hypo and hyperglycemia, are required.

For this, the consensus recommends for hypoglycemia: < 4% of time spent below a glycemic value of ≤ 70 mg/dL or 3.9 mmol/l and < 1% of time spent below a glycemic value of ≤ 54 mg/dL or 3 mmol/l. For hyperglycemia: < 25% of time spent above a blood glucose value of 180 mg/dL (10 mmol/l) and < 5% above a blood glucose value of 250 mg/dL (14 mmol/l).

To reduce the time spent in hypo- or hyperglycemia, it is better to be warned of the imminence of these extreme situations - which do not always cause premonitory symptoms - hence the need for alarms. For example, people with type 1 diabetes who use CGMs with hypo- or hyperglycemic alarms achieve better glycemic control [3] with fewer severe hypoglycemic episodes and fewer hospitalizations for severe hypoglycemia [4].

1.1. Characteristics of CGMs

CGMs have three components: the sensor, consisting of an electrode placed through the epidermis into the interstitial fluid and stuck to the skin on the arm or abdomen; a transmitter that attaches to the sensor; and a receiver (a personal meter or a smartphone) that displays blood glucose readings in real time. There are two categories of CGMs:

- The flash glucose monitoring (**FGM**) or intermittent scan CGM (**isCGM)** system, which includes Abbott Diabetes Care's Free Style

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Libre® (FSL) 1 and 2. This system requires scanning the sensor with a meter to obtain the glucose value. It uses two components: a combination glucose sensor/transmitter (inserted in the arm) and a separate touchscreen or smartphone reader device. The sensor generates a new glucose value every minute for 14 days. The FGM does not require calibration. The FSL 2 has customizable glucose threshold crossing alarms for hypo and hyperglycemia.

- The real time CGM (**rtCGM**) system such as Dexcom®, Medtronic Guardian™, GlucoMen Day® Menarini and the Free Style Libre 3® automatically transmits blood glucose levels every minute to an application downloaded to smartphones. The advantage of the rtCGM is the presence of alarms for crossing a glycemic threshold and for some of them, alarms for predicting hypoglycemia, i.e., these devices anticipate the fall or rise in blood glucose before they occur.

The isCGM and rtCGM with properly scheduled alerts - and with proper training by a specialized diabetes team - can provide real added value and make diabetes monitoring more "comfortable" [5] .

2. Types of alarms

2.1. Hypoglycemic alarms

The symptoms of hypoglycemia are associated with "malaise". These occur when certain low glucose thresholds are reached. Hypoglycemia is mild (level 1) if the capillary or interstitial glucose level is less than < 70 mg/dL (or 3.9 mmol/L), the symptoms experienced are sweating, nervousness, tremors, palpitations and sometimes a feeling of hunger. Hypoglycemia is profound (level 2) if the blood sugar is < 54 mg/dL (or 3 mmol/l), the symptoms are: dizziness, fatigue, weakness, headache, inability to concentrate, slurred speech, and blurred vision [6] . Severe hypoglycemia (level 3): the comatose person requires the help of a third person to receive for example glucagon or glucose.

The symptoms of hypoglycemia are unpleasant and trigger excessive sugar intake, resulting in reactive hyperglycemia. Thus, the management of hypoglycemia to avoid and treat it is complex and requires structured education of people living with diabetes. We will not elaborate on the care of hypoglycemia but its avoidance via CGM alarms.

Education will begin with judicious alarm settings. In the majority of cases, the selected hypoglycemic alarm threshold is around 70 mg/dl, and if taken into consideration, allows $a > 50\%$ reduction in the time spent in hypoglycemia [7] .

However, this alarm threshold is not universal and must be adjusted with the health care team according to age, medical history and the threshold of hypoglycemia perception. It is also possible to activate the alarms only during periods when hypoglycemia occurs more frequently (at night, during intense physical activities, during fasting etc.).

If the hypoglycemia alarm is deactivated, depending on the device, there is an urgent low blood glucose alarm (< 54 mg/dl) which cannot be changed or deactivated (factory setting).

2.1.1. Who are the hypoglycemia alarms for?

Studies specifically designed to reduce the risk of hypoglycemia have been conducted in individuals at high risk of hypoglycemia or unawareness hypoglycemia . They have demonstrated a reduction in hypoglycemia, suggesting that real-time continuous glucose monitoring can prevent hypoglycemia when used specifically for this indication [8] .

CGMs with alarms will be indicated for diabetic individuals at increased risk of hypoglycemia, for example:

- Pregnant women with type 1 diabetes are at an increased risk of hypoglycemia because of the tighter glycemic control sought. Recent recommendations [9] call for less than 4% of time spent with glucose values ≤ 63 mg/dl (3.5 mmol/l), more than 70% of time spent with glucose values between 63 and 140 mg/dl (3.5-7.7 mmol/l), and less than 25% of time spent with glucose values ≥ 140 mg/dl (7.7 mmol/l).
- Children under 6 years of age, as hypoglycemia is often not recognized. They are unable to observe the early symptoms of hypoglycemia themselves [10].
- Fragile people who need support for their health care or who have lost their autonomy.
- People with unfeeling hypoglycemia or nocturnal hypoglycemia that are less well perceived. Indeed 25 to 30% of people with type 1 diabetes do not feel the symptoms of hypoglycemia. It is possible to assess this risk in consultation using the Clarke or Golden scores (≥ 4 the risk of unperceived hypoglycemia is high) [11]. These diabetic individuals are usually older, with a longer duration of diabetes, and higher glycemic variability [12]. A retrospective study has shown that these individuals have more severe hypoglycemia requiring the use of glucagon [13] Indeed, the counter-regulatory mechanisms limiting hypoglycemia are impaired [14] . Thus, for those not experiencing symptoms of mild hypoglycemia, higher hypoglycemia alarm levels of 75 or even 80 mg/dl are needed to allow for timely response. These alert levels should inform people quickly enough to give them time to consume glucose properly. In a recent study, the optimal alarm level for spending less than 1% of the time in hypoglycemia was 75 mg/dL [7] .

2.1.2. How to manage hypoglycemic alarms?

In current clinical practice, 3 situations are frequently encountered:

The person shows symptoms of hypoglycemia, but the alarm does not go off.

The situation is "*I do feel my hypoglycemia, but I feel it well before the sensor alarms warn me…*". In fact, some people experience symptoms before the 70 mg/dl blood glucose threshold. It is the rapid drop in blood glucose (the glycemic delta) that is felt, not the low blood glucose value per se. Always keep in mind that the CGM, which measures interstitial glucose, lags significantly behind capillary glucose changes. The CGM actually measures the interstitial glucose level with a certain delay of about 5 min compared to capillary glucose. If the latter decreases too quickly, faster than the one under the skin, the sensor does not have time to react.

It is not uncommon for the person who has experienced hypoglycemia to re-sugarize and for the alarm to sound afterwards!

This can be observed in case of intense physical activity, for example, the drop in blood sugar may be faster than measured by the meter. Therefore, the person is exposed to hypoglycemia before the sensor detects it. In this case, the hypoglycemic threshold alert will be ineffective. It will be necessary to rely on the direction of the glucose trend arrows which, depending on the brand of the sensor, will inform on the speed at which the glucose decreases. Finally here the choice of an rtCGM with hypoglycemia prediction seems more interesting.

Blood glucose is < 70 mg/dl at the meter, but no symptoms are experienced

These are people who do not feel hypoglycemia (see above). In this case, a detection alarm at a higher threshold should be set according to the advice of the health care team. If the person is warned earlier, he/she will be able to act accordingly in order to avoid hypoglycemia. Finally, if the sensor is not sufficient, the use of an insulin pump to stop the delivery of insulin when a too rapid decrease in blood glucose is detected may be indicated.

The person is experiencing symptoms, but there is a discrepancy between the sensor glucose value and the capillary glucose value.

This situation is very common: the person with diabetes does not know which indicator is reliable/ the symptoms; the glucose value measured by the sensor; or the one measured at capillary level? When the glucose values obtained by the sensor and the capillary sample do not match, it may mean that the blood glucose is rising or falling rapidly.

As previously mentioned, it is important to know that CGM values always lag behind capillary or blood values. In a stable situation, capillary and interstitial blood glucose levels will be almost equivalent. But in case of strong glycemic variations, such as during a rapid hypoglycemia, a difference will appear between the blood glucose measured by the finger and that measured by the CGM. The analysis of the glucose trend arrows will then be decisive.

In other situations, the CGM will tend to overestimate hypoglycemia (e.g. when the sensor is faulty).

There are situations where hypoglycemia is not reported:

- if the sensor is not recognized by the reader or smartphone, it rings. This is a disconnection alert. Beware of this since hypoglycemia may not be detected!
- if an anti NFC (Near Field Communication) smartphone shell is present, it will interrupt the data communication between the CGM and the smartphone.
- Some CGMs ask for a calibration with the blood glucose. Sometimes the app asks to do a calibration... at 2am. "I didn't hear it, but I did see the message 2 h later... when I woke up because I felt hypo: the blood glucose indicated a result of 33... and of course no alarm from the CGM, since it was no longer reading blood glucose and was waiting for a calibration!"

Finally, as we have pointed out, the CGM indicates a glucose level that is out of sync with capillary glucose even in hypoglycemia, so be careful not to consume too many carbohydrates, because the CGM will also indicate hypoglycemia with a delay, whereas the glucose level on the glucometer has already recovered.

2.2. Hyperglycemic alarms

In the majority of cases, the symptoms of hyperglycemia are discreet. It is necessary to reach very high blood glucose values (> 250 mg/dl) to observe symptoms such as thirst, the need to urinate more frequently, especially at night. Special attention should be paid to symptoms such as nausea, vomiting and fruity breath, which indicate the presence of ketosis or even ketoacidosis.

2.2.1. Who is the target group for hyperglycemic alarms?

- Pregnant women who need to have strict control of their blood sugar [15]
- Children at higher risk of ketosis [16]
- Frail individuals with comorbidities.
- People on insulin pumps.
- All people wishing to increase the time between 70 and 180 mg/dL (TIR)

2.2.2. How to manage hyperglycemic alarms?

The alarms warn the user in case of hyperglycemia, starting from a threshold defined in collaboration with the health care team. A study [7] has shown that an alarm threshold set at 170 mg/dL is associated with both a shorter time in hyperglycemia and an HbA1c close to 7.0%.

Hyperglycemia alerts are useful for people treated with insulin pumps in order to warn them in case of defective equipment (alert of an abnormally high glycemic excursion secondary to a blocked catheter, bent, etc.).

A programmed alert at 250 mg/dl, also allows to check the ketone bodies in order to avoid a ketosis crisis.

As with hypoglycemia, setting a low threshold for detection of hyperglycemia may imply a higher frequency of alerts and, therefore, nuisance.

It is therefore advisable to set a high threshold (e.g. 250 mg/dl) and to lower it gradually thereafter in order to improve glycemic control.

The risk is to see the development of an "untimely" behavior of the person who, faced with a hyperglycemic alert, will inject more insulin increasing the risk of hypoglycemic episodes. Appropriate education in the correction of hyperglycemia by insulin supplementation should be carried out by taking into account residual insulin (duration of insulin action) and insulin sensitivity.

Finally, most CGMs allow for data sharing. The ability to share data with family members and friends is another important feature. It acts as a safety net. This data sharing also allows access to telemedicine.

3. Discussion

CGM has made impressive scientific, technological, technical, and clinical advances, and offers benefits to many people with diabetes.

CGMs with alarms have been shown to decrease the risk of severe hypoglycemia in people with diabetes who have unintended hypoglycemia [8].

Which CGM to choose isCGM or rtCGM for hypoglycemic alarms?

A Belgian study (ALERTT1), comparing rtCGM and isCGM in adults with type 1 diabetes, was a prospective, double-arm, multicenter, randomized controlled trial in six hospitals. Adults with type 1 diabetes who were previously using isCGM without alarms were randomly assigned to rtCGM with alarms (intervention) or isCGM without alarms (control). After 6 months, in the rtCGM group HbA1c was lower (7.1% vs 7.4%; $p<0.0001$), and fewer participants on rtCGM experienced severe hypoglycemia (n = 3 vs n = 13; p = 0−0082). In this study, switching from isCGM to rtCGM significantly improved the reduction in hypoglycemia [17].

Another study, I-HART CGM showed that rtCGM monitoring had a significant beneficial impact on severe hypoglycemia (HS) in adults with type 1 diabetes at high risk for HS (Gold score ≥4) [18]. Indeed, the study examined whether the predictive hypoglycemia alert provided additional benefit over traditional low-threshold alerts. The percentage of times <54 mg.dl, <70, and >250 mg/dL decreased significantly after transitioning to an rtCGM regardless of the low-threshold alert setting [19].

However, if the detection thresholds for hypoglycemia are too high or too low for hyperglycemia, there is a risk of increasing the frequency of alarms, with a consequent impact on quality of life [20]. Optimal hypoglycemic alarm thresholds have been identified for lower percentages of time in hypoglycemia (e.g., <1%); with the consequence that CGM alarms further reduce the time spent in hypoglycemia. But these alarms can be tiring. Some people complain about repeated alarms (real or false).

Recently, the concept of "alarm fatigue" has emerged [21,22]. Alarm fatigue occurs when the user of a CGM is exposed to a high frequency of alarms whose significance is no longer perceived (in particular, false or useless alarms), with the corollary risk of neglecting true alarms.

It is usually recommended that CGM users set the hypoglycemia and hyperglycemia alarm thresholds at extremely low and high values, respectively, to minimize initial "false alarms" and correspondingly increase the likelihood of effective long-term use. However,

CGMs can be wrong, especially in detecting hypoglycemia, leading some diabetologists to set artificially high hypoglycemic thresholds. The danger, then, is to induce an "alarm fatigue" phenomenon. Alarms that are ignored are of no use and do not help to optimize glycemic control.

The problem with CGM monitoring systems is that there is an inverse relationship between sensitivity and specificity [23]. The higher the number of true events detected, the higher the number of false alarms. At the same time, specificity will be lower since the false positive rate will be higher, meaning that more alarms will be triggered unnecessarily. Frustration with the inaccuracy of the sensor may cause some people to stop using the CGM altogether. The key point is to encourage the person with diabetes to review all past alarms in the last week/week, determine when they occur, understand the cause of the alarm, and then ensure that the frequency of alarms is reduced with time and experience. The person with diabetes should not have to endure the alarms but understand them. The alarms should be adjusted according to the lifestyle with activation or inactivation, especially on days off or sick, in case of physical activity, etc. ....

One of the main research directions is the development of algorithms for learning individual glucose profiles to analyze continuous glucose monitoring data and provide earlier and more accurate individual prediction of hypoglycemia [24]

4. Conclusion

CGM systems equipped with both threshold and predictive alarms not only significantly reduce the risk of severe hypoglycemia, but also the fear of hypoglycemia. It is hoped that further interventional studies will help to support the view that alarms associated with CGM do indeed improve glycemic parameters (mean, variability, time in hypoglycemia, time in hyperglycemia, time on target), but more importantly, the long-term consequences of diabetes, as well as the quality of life of people with diabetes.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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