Emergent technologies applied to diabetes: What do we need to integrate continuous glucose monitoring into daily practice?

Where the long-term use of continuous glucose monitoring stands in 2011

A. Sola-Gazagnes*, C Vigeral

Service de diabétologie, hôpital Hôtel-Dieu, APHP, 1, place du Parvis Notre Dame, 75004 Paris, France

Abstract

The earliest continuous glucose monitoring (CGM) devices did not permit real-time readouts of glucose measurements. Instead, they were used to determine the glucose profile of patients in “real life” and as educational tools. In contrast, the latest real-time devices, whether linked or not to an insulin pump, give the patient access to glucose measurements and incorporate alarms that can be set. Thus, they are the newest self-management tools for patients with type 1 diabetes requiring an intensive insulin regimen. Some long-term studies in a selected population of patients with type 1 diabetes have shown improvement of glycaemic control as measured by HbA1c. Although the characteristics of “responsive” patients have yet to be identified, the ability of the patient to use the system on a near-daily basis (about 80% of the time) is a key point. Initial training of the patient by a professional team with expertise in CGM is also of the utmost importance. To date, CGM is not reimbursed by Social Security in France.

Keywords: Type 1 diabetes; Continuous glucose monitoring; Intensive insulin regimen; CSII; Insulin pump; Therapeutic education; Interstitial glucose; Review

1. Introduction

Continuous glucose monitoring (CGM) devices provide an estimated value of blood glucose by measuring interstitial glucose and using mathematical algorithms. Every 5 min, a new measurement is available, resulting in 288 measurements a day. However, CGM does not obviate self-monitoring of blood glucose (SMBG), for which the device has to be calibrated one to three times a day. The first CGM devices were approved by the US Food and Drug Administration (FDA) in 1999. With those delayed-readout devices, the patient remains unaware of the glucose measurements until they are downloaded. In contrast, with the latest real-time devices, glucose values are continuously available to the wearer. Each device comprises a

*Corresponding author.
E-mail address: agnes.sola@htd.aphp.fr (A. Sola-Gazagnes).

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sensor, transmitter and receiver (Fig. 1). In certain cases, the receiver can be an insulin pump (Paradigm Veo®, Medtronic; Animas Vibe®, Dexcom); in other cases, it can serve as a regular glucose meter (Navigator®, Abbott) (Fig. 2). If the receiver is a pump, there are as yet no automated adjustments made to the insulin infusion based on the glucose values obtained by CGM (closed-loop system).

2. Short-term glucose monitoring on demand

The short-term use of a CGM device or “glycaemic Holter” makes it possible to collect the glucose profile of a patient in real life over 3 to 5 days. The data are then downloaded and analyzed. The choice of a real-time or delayed-readout device is determined by the indication being monitored. Review of the CGM results is a helpful teaching tool that enables the patient, with the help of the health-care professional, to appreciate the effects of food, insulin timing and exercise on glucose levels. It can also provide diagnostic and management advice. However, the contribution of short-term CGM to better metabolic control remains unreliable and often disappointing [1].

Fig. 1. Continuous glucose monitoring devices consist of three parts: a sensor, a transmitter and a receiver which can be linked to an insulin pump or not. (1) the sensor (electrode); (2) the transmitter (radio frequency); (3) the receiver.

3. Long-term CGM

Real-time readout devices are used for the long term (Fig. 2). The glucose results are continuously available to the wearer, as is the rate of change in estimated glucose levels (trend arrows). Also, the devices can be set so that an alarm alerts the wearer to a glucose value that is projected to fall below or above the target within 10-30 min, based on the rate of change of interstitial glucose (Fig. 3). CGM provides information on glucose variability over periods of time that are seldom or never explored by SMBG (such as at night and post-meals). As hyperglycaemia and asymptomatic hypoglycaemia are detected by the device, the patient is alerted, thereby preventing their occurrence.

The reliability of the measurements makes it possible to use CGM in current practice; according to the manufacturer, the Medtronic Enlite® sensor has a mean absolute percent difference of 14.1% between the estimated glucose value and venous plasma glycaemia. However, during periods of rapid changes in blood glucose, there are time-lag errors between the interstitial-space glucose measure and SMBG. This is the case after meals, after supplementary insulin injection or after sugar intakes to correct low blood glucose, and it needs to be considered when reviewing the data [2]. The American Diabetes Association (ADA) [3] recommends SMBG before making any immediate management decisions (supplementary insulin, sugar intake).

4. Selecting patients for the best outcomes

Any patients with diabetes requiring an intensive insulin regimen are potentially good candidates for this technology. A number of randomized controlled clinical trials have been
undertaken to evaluate the impact of CGM in patients with type 1 diabetes, mostly using an insulin pump or multiple daily injections (MDI). Depending on the trial, HbA1c was reduced by 0.30–0.60% in “good candidates” [4]; this benefit was present at 3 months [5,6], and was also confirmed at the 6-month [7-9] and 1-year follow-ups (the Capteur-Evadiac study, publication in progress).

Frequent personal use of the system is a key determinant of success [7,8]. The best outcomes are observed when the CGM device is used >70% [7,10] or 80% [5,7,8] of the time. The more consistently CGM is used, the greater the metabolic benefits [11]. The near-daily use of CGM yields more information that patients can incorporate into their diabetes management, but it can also serve as a marker for patients who are more engaged in their

Fig. 3. Information available on a real-time device. Navigator®, Abbott. Data before (A) and after (B) upload.
diabetes self-management. In the Juvenile Diabetes Research Foundation (JDRF) trial [8], the benefit to glucose control could be observed only in adults aged over 25 who made more sustained use of the device than did younger patients: 83% of the subjects over 25 used it on 6 or more days a week vs 30% of those aged 15-24 years [11]. However, in patients < 25 years of age, greater CGM use was associated with a similar reduction of HbA1c. In the same trial, none of the psychosocial variables studied were predictive of the frequency of CGM use [11].

Before randomization, patients were performing an average of more than four blood glucose measurements per day, and their mean HbA1c ranged from 6.9% to 9.6% [5,8,9,12]. Also, CGM is not confined to patients with insulin pumps, although, in one trial, an additional benefit was found in patients using a pump vs MDI (Capteur-Evadiac, publication in progress). On comparing patients using a sensor-augmented insulin pump with those using MDI and SMBG, decreases of 0.6% (P < 0.01) [10] and 1.1% (P < 0.001) [13] in HbA1c were found. Supplementary benefit was observed after CGM use in patients with type 1 diabetes who had already achieved excellent control of their HbA1c, with levels at 6.5% [14] and 6.9% [9]; HbA1c was reduced by 0.27% with no increase in severe hypoglycaemic events, and less time was spent below 60 mg/dL [13] or 70 mg/dL [9].

Nevertheless, evidence of the benefits of CGM in certain populations is lacking. There has been no randomized study of patients with poorly controlled diabetes or of those who perform little or no SMBG. There are also scarcely any studies [15] supporting the benefit of CGM during pregnancy, or in patients with hypoglycaemia unawareness and/or frequent severe hypoglycaemic events. The bulkiness of the CGM devices (even when miniaturized) and the alarms can impair patients’ quality of life. However, in the JDRF study, no evidence was found of any changes in quality of life [16], although certain indicators of well-being were improved (Capteur-Evadiac, publication in progress). In addition, there was a reduced fear of hypoglycaemia in adult patients [16,17].

Furthermore, the impact of CGM on patients with diabetes is yet to be explored. The characteristics of responsive patients – those most likely to benefit from CGM use – are not yet known. As a high degree of early use (during the first 4 weeks) may be a predictor of sustained long-term use [11], a 4-week trial of CGM should be made available for patients who request it.

5. Patients’ training with CGM:
What is the key to success?

Together with the selection of appropriate patients, the training of health-care professionals is an important precondition of success. This was emphasized by the authors of the Small Troubles, Adaptive Responses (STAR-1) study [18], who partly attributed the failure of CGM in their study to the novelty of the tool and the insufficiently trained health-care team.

In addition, the training of patients should be both technical – to provide the required knowledge of the device – and educational – for better diabetes self-management. The basic knowledge of diabetes self-management should also be supplemented by training in functional insulin treatment (different types of insulin, delay in action of insulin, algorithms for the correction of high blood glucose, prevention and treatment of low blood glucose) [19,20].

As a glucose value is available every 5 min, it is clear that special training is required to properly analyze and apply the information. At the start of CGM, patients should undergo a specific educational programme delivered by a well-trained professional. This takes time and should be considered in the organization of the health-care team’s schedule. Training should provide information about the device, such as the requirements for calibration, and details of the time delay between SMBG and CGM values during periods of glucose variation [21]. Information on the glucose trend arrow should also be explained and emphasized. Also, algorithms for making diabetes management decisions using glucose values have been proposed but, so far, there has been no consensus on their use [21-24]. If an aberrant or unexplained result shows up on the device, the accuracy of the device needs to be questioned and SMBG performed.

There are different ways to use CGM, ranging from the simple use of alarms to prevent severe hypoglycaemic events in patients with hypoglycaemia unawareness [25] to the intensive use of the data for real-time adjustments to insulin doses and retrospective (after uploading the data) decisions for diabetes self-management. However, the unnecessary prescription of CGM or insufficient training of the patient can lead, at best, to unjustified extra costs and, at worst, to risks to the patient due to misuse of the data (such as iterative supplementary insulin injections or inappropriate sugar intakes) and inappropriate therapeutic decisions (Fig. 4) [26]. For these reasons, an educational diagnosis prior to the prescription is mandatory.

Follow-ups with a health-care professional, such as a face-to-face meeting, require the allocation of extra time. The use of telemedicine [27], at least at the start of CGM, could be a time-saver. Review of the downloaded data makes retrospective adjustment of insulin doses possible, and also determines the accuracy of decisions made by the patient in terms of supplementary insulin, sugar intake and management of physical activities. If the patient is using a sensor-augmented insulin pump, the insulin profile is superimposed on the glucose profile. In a motivated patient, this can lead to improvement in the glucose profile after 6 days of CGM (Fig. 5).

To date, there are hardly any automated interactions between the results of CGM and the rate of insulin infusion by the pump. However, one function in the Paradigm Veo pump enables a 2 h suspension of insulin infusion if the CGM value falls below a programmed glucose level. Some studies [28] have favoured the efficacy and safety of such a function, but further studies are needed on the subject. The ADA [3] and the American Association of Clinical Endocrinologists [29] have published some guidelines, while French guidelines [by the French Society of Diabetes (Société Francophone du Diabète)] are still in the process of being written.
Fig. 4. A patient misuses CGM: inappropriate interruption of the basal infusion of insulin in a patient with a pump (from [26]).

- J1

- J6

Fig. 5. A patient masters the use of CGM: example of an improvement of the glucose profile after 6 days of use.
6. Conclusion

The use of CGM devices can bring about metabolic improvements in some patients with type 1 diabetes requiring an intensive insulin regimen. Therefore, to implement the daily use of CGM in outpatients with the best cost/benefit balance, it is necessary to target those patients who are most likely to benefit from the technology. The metabolic benefits are correlated with sustained use of the device for more than 80% of the time. A trial of CGM should be made available to patients with type 1 diabetes to identify responsive subjects. It is absolutely necessary that the training and initial steps in the use of CGM be guided by a health-care team that is experienced in the education of diabetic patients and well schooled in CGM. Also, during the first trimester, the benefit to the patient of keeping the device should be evaluated. Last but not least, access to the device by all concerned patients will depend on its being reimbursed by Social Security. A recent study suggests that, among the appropriate targeted patients, CGM has a favourable cost/benefit rate [30].

Conflicts of interest statement

No conflict of interest to declare in relation with this article.

References