Value and limitations of the Continuous Glucose Monitoring System in the management of type 1 diabetes

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SUMMARY
The CGMS (Continuous Glucose Monitoring System) is a portable device allowing continuous measuring of glucose. It provides recordings of at least 72 h, during which 288 measures/day are performed. Results are visualised in the form of a set of curves, illustrating the variations in blood glucose levels over time. The quality of the records has often been questioned by several authors. Some of the system’s physiologically related limitations can be explained by the less than perfect coincidence of variations in glucose levels observed in the interstitial tissue, where CGMS measurings are done, and in the blood, where calibrations are performed. Other limitations, such as defects in accuracy or in reproducibility of tracings or premature curtailments of recordings, are due to technical weaknesses which were considerably improved during the past few years, particularly with regard to the quality of the electrodes providing a more stable signal over time. In clinical practice, CGMS is a tool for investigating the glycaemic patterns of diabetic patients in conjunction with SMBG. It allows the identification of overlooked hyper- or hypoglycaemia. Generally well accepted, it is a useful tool to analyse the nocturnal period, or any situation where glucose checks are rare. The visual nature of its results provides a facilitating support in the discussion between the patient and the care-provider during consultations or educational sessions. CGMS utilisation was proposed for guiding treatment adjustment. At present, it is still difficult to state with certainty that this tool allows effective improvement in the metabolic control of patients with type 1 diabetes, in view of the paucity of controlled studies showing an impact on HbA1c values or on the frequency of hypoglycaemia, even if such a tendency emerges from most non-controlled intervention trials.

Key-words: Type 1 diabetes - CGMS - Glucose sensor - Hypoglycaemia.
In recent years, continuous monitoring of glucose levels has become an indispensable tool for investigating the glycaemic patterns of patients with type 1 diabetes. The “Continuous Glucose Monitoring System” or CGMS® (Medtronic-Minimed, USA) was the first device allowing continuous recording of glucose levels to be granted a CE mark, and has been available for routine use in France since 2000. Despite the initial enthusiasm of diabetes specialists (and their patients), numerous authors have expressed reserve with regard to the quality of the information provided by this system and even its utility for investigating glucose profiles.

The objective of this review is to report the experience of various teams with the CGMS, to illustrate both its limitations and its value in clinical practice, and to explore the possibility of drawing definitive conclusions with regard to its utility in the investigation and treatment of type 1 diabetes.

CGMS: description and mode of operation

The CGMS has already been described elsewhere [1]. Briefly, it comprises an electrode reacting with glucose, inserted into the subcutaneous tissue, connected via a cable to a pager-sized monitor, capable of storing the 288 daily measurements made by the device over the recording period. The CGMS is fitted to the patient for three days and, for optimal recording, must be calibrated at least four times a day by entering measurements of capillary blood glucose [2]. At the end of this period, the data are downloaded on to a computer via a communication module (Com-Station). A dedicated data-processing software (Solutions™ CGMS® System Software 3.0) permits visualisation of the results in the form of a summary table, enabling a check of whether the criteria for optimal accuracy of the measurements (correlation coefficient, mean absolute deviation) are met, and a set of curves, graphically illustrating the variations in glucose concentration observed during each day of recording (figure 1).

The following points are worth emphasising:

- The CGMS does not directly measure glycaemia. It provides a signal that is proportional in intensity to the variations in glucose level in the interstitial fluid of the subcutaneous tissue, considered to mimic the fluctuations in blood glucose [3].
- This signal, stored in the monitor throughout the recording period, is subsequently converted into estimated mean values of glycaemia, via the software provided by the manufacturer, on the basis of the capillary blood glucose values recorded by the patients as calibration points during monitoring.

This means that a CGMS recording can provide reliable information about variations in blood glucose level only if 1) the variations in interstitial glucose levels perfectly mimic the fluctuations in blood glucose, 2) the mode of transformation of the sensor signal into blood glucose values is efficient and adapted to the system [4], 3) the signal is adequate, proportional to interstitial glucose levels and reproducible. We shall see in the following two sections that these conditions are not always met and review the measures taken to improve the results obtained using the CGMS.

Limitations of the CGMS

Physiological limitations of continuous monitoring of interstitial glucose: less than perfect coincidence of variations in blood and interstitial glucose levels

During substantial fluctuations in glycaemia, certain authors consider that there is a time difference between the variations in blood glucose and those observed in the subcutaneous interstitial fluid. In a study directly analysing the signal generated by the CGMS sensor, Boyne et al. [5] reported a mean time difference of 4 to 10 minutes between the rises, peaks, falls and nadirs of glucose in the vascular and interstitial compartments in patients with type 1 diabetes, following the ingestion of two liquid meals. In this study, the variations in interstitial glucose level lagged behind the blood glucose fluctuations in 81% of the cases. An other study [6] has suggested that interstitial glucose levels slightly fell before blood glucose levels in the initial stage of hypoglycaemia, but lagged behind blood glucose levels (with an average of 26 minutes) in rising again during the recovery phase. Monsod et al. [7] also noted a delayed and incomplete recovery of subcutaneous glucose levels measured by CGMS on transition from hypoglycaemia to hyperglycaemia. But they even observed a fall in those levels on introduction of a euglycaemic-hyperinsulinaemic clamp, while blood glucose levels remained perfectly stable.

These phenomena, consistent with a physiological effect of insulin on interstitial glucose uptake by peripheral tissues...
[8,9], inevitably affect the accuracy of the results obtained by continuous glucose sensors based on subcutaneous measurements, and by the CGMS in particular. Given that the variations in blood and interstitial glucose levels do not mimic one another exactly, it is difficult to extrapolate with certitude glycaemia values measured at a particular instant on the basis of interstitial glucose measurements. In contrast, the value of subcutaneous glucose sensors for the analysis of variations in glycaemia appears to be little affected by these phenomena, even though they result in a time shift and blunting of the tracings. The recommendations for use of the CGMS issued by the FDA [10] are categorical in this respect, stating that this device does not provide exact data on blood glucose levels but may be used to detect changes in glycaemia. Awareness of these phenomena enables one to put in perspective, if not explain, certain results observed with the CGMS, “accused” in particular of overestimating the duration and depth of hypoglycaemias [11], for which the nature of the fluctuations in interstitial glucose levels is partly responsible.

Initial limitations of the CGMS and technical improvements

Signal transformation

In the first versions of the data-processing software (version 1.6), the mode of transformation of the initial electric signal into blood glucose levels, based on a linear regression calculation, failed to adequately take into account the steady decrease in the electrical signal during the recording. Furthermore, a shift in the tracing at midnight was generally evident [12], resulting from the different calibration line used for each day of recording. This problem was resolved in the current versions of the software (the scientific version 1.7A and Solution 3.0), which employ a more continuous “floating” mode of calibration. In this system, each point on the tracing is determined on the basis of capillary glucose levels measured during the 12 hours preceding and following that point.

Quality of the signal generated by the glucose sensor

The quality of the signal emitted by the sensor is a crucial determinant of the accuracy and duration of the recordings.

In a study [13] of 50 recordings from patients with type 1 diabetes, we noted a significant attenuation of the intensity of the electrical signal (ISIG) throughout the three days of recording, even though the glucose levels of the patients remained stable. The signal/noise ratio was lower at the end of the recording, resulting in a corresponding deterioration in the quality of the CGMS measurements. In practice, this resulted in much more irregular recordings, with substantial oscillations in the curve devoid of clinical significance. However, the main consequence of the signal deterioration over time is premature curtailment of recording, in principle performed over a period of 72 h. Several authors report durations closer to 36 h than three days in the case of ambulatory recordings, as a result of premature interruptions in the tracings or failure to meet the criteria of accuracy during the final part of the recording [12,14,15]. Fading of the signal, by far the most frequent problem, reflected in repeated Cal/Error alarms, is not the only culprit. Interruptions of the tracings have also been reported as a result of connection problems between the electrode and the cable or between the cable and the monitor [13].

The reproducibility of the results obtained using this system has been questioned by several authors. In the study reported by Boyne et al. [5], cited above, in which each patient wore two CGMS at the same time, the authors noted time differences in the signal response of each of the devices during variations in glycaemia. This intra-patient variability in sensor reactivity, estimated to range between 5.7 and 7.6 min, may explain some, but no doubt not all, of the discrepancies in the CGMS tracings. Metzger et al. [12] showed considerable differences in glycaemic profiles obtained during simultaneous recordings, 69% of the measurements deviating by 10% from one device to another and in the case of 7% of the devices, by up to 50%. Some of these discrepancies between the recordings could have led to radically different interpretations and prompted erroneous clinical decisions.

Guerci et al. [16] confirmed this defect in reproducibility and, above all, despite using more efficient software, demonstrated the insufficient accuracy of the measurements, only 39% of which deviated by less than 10% from the simultaneously recorded reference values provided by a Beckman glucose analyser. On average, the values obtained by CGMS were underestimated by 12 mg/dL. The study performed by the Diabetes Research in Children Network (DirecNet) confirmed these results and highlighted the lower accuracy of the system for low glucose values than for high values [17].

Improvements in the equipment

These technical weaknesses have recently been addressed by the manufacturer. Several improvements have been introduced into the devices, including reinforcement of the cable and above all, from November 2002, modifications of the sensor leading to enhanced performance. The DirecNet study [17], comparing the performances of previous and current sensors, confirmed the beneficial impact of these modifications on several criteria of accuracy. The results showed that 78% and 98% of the measurements made by the new sensors lay within zone A and zones A + B, respectively, of the Clarke Error Grid, in contrast to 58% and 93%, respectively, with the previous sensors (P < 0.001) These results are in accordance with ours [18]. Since these modifications, we have observed not only a significant improvement in all criteria of optimal accuracy of the tracings, but also a longer duration of recording, with
a larger number of days responding to the optimal precision criteria. These improvements seem to be principally related to a greater stability of the sensor signal over time, sensor performance generally remaining satisfactory even after 72 h of use.

**Value of the CGMS in the management of type 1 diabetes**

**An exploratory tool**

The CGMS is a tool for investigating control of blood glucose levels. Its main value lies in completing the data obtained during self-monitoring of blood glucose (SMBG) by permitting the visualisation of glucose fluctuations between checks of capillary glucose. This has led to the proposal of its use for the detection of hyper- and above all hypoglycaemic excursions, unsuspected or overlooked with classical monitoring. The investigation of periods when checks of blood glucose levels are rare, e.g. during the night or after meals, has also become one of the principal indications of continuous recording in routine practice. The nocturnal period has been most extensively studied, in view of the paucity of blood glucose checks and the decrease in patient perceptiveness at this time.

**Exploration of hypoglycaemic phenomena**

In our experience, the investigation of nocturnal hypoglycaemia accounts for close to two-thirds of the motives for performing CGMS recordings in routine practice [13]. Numerous authors have reported that the CGMS permits the detection of asymptomatic hypoglycaemic episodes during the night, even in subjects with normal awareness of such episodes. In view of the poor accuracy of the CGMS in measuring low glucose values and the physiological limitations of the technique discussed above, the results of such studies must be analysed with caution. The incidence of such episodes varies from study to study, notably in relation to the threshold defined for hypoglycaemia. In a study on 10 adults with poorly controlled type 1 diabetes (HbA1c = 8.7%) and with normal awareness of hypoglycaemic episodes, Cheyne et al. [19] observed in eight patients between one and three episodes of nocturnal hypoglycaemia < 3 mmol/L (< 60 mg/dl) unsuspected by the patients but detected by the CGMS. More recently, another team [20] found that among 16 adult patients with type 1 diabetes, studied for approximately 3 days using the CGMS, 76% experienced at least one hypoglycaemic excursion (< 70 mg/dl) during the night. In children, also, nocturnal hypoglycaemic episodes < 40 mg/dL were evident in 30% of the recordings (and in almost 70% if the threshold for hypoglycaemia was set at 60 mg/dl), approximately 20% of the 56 patients in this study presenting this phenomenon during all three nights of the recording period [21]. Similarly, in an analysis of recordings made during 167 nights in 47 children, Kaufman et al. [22] noted the occurrence of hypoglycaemic episodes (< 40 mg/dl) in 27% of the children and in 35% if hypoglycaemia was defined as blood glucose levels < 50 mg/dl.

These authors also observed that the CGMS could detect asymptomatic hypoglycaemic episodes occurring during the day [19,21].

The reported duration of hypoglycaemic episodes is most often extremely long, frequently representing a total of several hours per day spent in a state of hypoglycaemia [19,23]. However, for the reasons cited above, this duration is no doubt overestimated.

**Detection of hyperglycaemic phenomena**

The CGMS is also of indisputable value in all situations in which periods of hyperglycaemia occurring during the daytime may be overlooked as a result of insufficient self-monitoring of glucose levels or simply monitoring not correctly covering the entire day. Boland et al. [21] emphasise the usefulness of CGMS to reveal postprandial hyperglycaemic phases undetected as a result of self-monitoring performed exclusively before meals and at bedtime. These results, obtained in children, may be compared with those reported by Schaepeleync-Belicar et al. [24] in poorly controlled adolescents (HbA1c = 10.1%) performing very few checks of blood glucose level (< 1 per day in 5/12 patients, < 3/day in the remaining 7 patients). The CGMS recordings permitted the detection of a very large number of postprandial hyperglycaemic episodes (24 in 10 patients), as well as prolonged periods of nocturnal hyperglycaemia (seven episodes) in five patients and a dawn phenomenon in four patients. The CGMS appears to be an ideal tool to detect dawn phenomena [25] and to differentiate these from asymptomatic nocturnal hypoglycaemic episodes.

**A tool for guiding treatment adjustment**

In routine practice, the CGMS is used in conjunction with SMBG, to adjust patients’ treatment according to the complementary information provided by continuous recording. Several authors have attempted to demonstrate that the use of this device permits an improvement in glucose control. The results are far from unequivocal. Few of the studies are methodologically satisfactory, as the impact of using the CGMS is rarely assessed in comparison to a control group or a control period, in which only SMBG data are used as a basis for adjusting treatment. Among the four randomised studies identified, only one found an improvement in HbA1c.

This crossover study [26], including 27 diabetic children (mean age: 12.5 years) receiving treatment via either multiple injections or a pump, compared the effect of adjusting treatment on the basis of CGMS recordings performed every two weeks or SMBG. The authors showed that the level of HbA1c diminished significantly over three months during the period of treatment adjustment based on the
CGMS (from 7.7% to 7.31%), whereas the level remained unchanged during the other period (7.75% and 7.65% at the beginning and end of the period, respectively). However, it must be emphasised that this difference was achieved at the cost of extremely intensive monitoring, distinct from normal routine use of the CGMS.

Similarly, the randomised study reported by Chase et al. [27], conducted on a small sample (n = 11) of young children (aged from 2.1 to 11.6 years), comprised an adjustment period of one month, during which treatment was adjusted every five days on the basis of the SMBG checks or the CGMS recordings (six recordings over one month). The authors reported a significant improvement in HbA1c at the end of the intensive treatment adjustment period in the CGMS group in comparison with the control (SMBG) group, but this difference tended to disappear by the end of the study, at three months.

The study published by Chico et al. [28], performed on adults with type 1 (and 2) diabetes, is more interesting and representative as the authors evaluated the impact of a single three-day recording by CGMS in comparison to a group of patients who performed reinforced SMBG during three days, including checks of glucose levels before and after meals, at bedtime and during the night. In this study, HbA1c improved in both arms, but without any significant difference between them, suggesting that the information provided by the CGMS is not superior to that furnished by reinforced SMBG for the purpose of treatment adjustment.

Nonetheless, it would be interesting to know the degree of acceptability of each method, in other words, whether it might not be easier in practice to persuade patients to wear a CGMS for three days than to impose nocturnal awakenings during three consecutive nights for the purpose of checking blood glucose levels. This hypothesis seems to be confirmed by a recent work from the DirecNet study group [29], in which the authors reported a poor compliance to intensified SMBG (10% of subjects completing a 8-point testing for 3 days) whereas they observed few problems in obtaining nearly complete CGMS profiles (median duration 70 h).

A fourth randomized study [30] also failed to demonstrate that therapy adjustments based on CGMS recordings was superior to those based on SMBG (performed at least 4 time per day), according to the results of HbA1c, which were similar in the two groups of patients at the end of the trial (12 weeks).

The other, non-controlled studies of interventions [24,25,31,32], all tend to show an improvement in diabetes control, often with substantial gains in terms of HbA1c or a reduction in hypoglycaemic episodes (table I). Although these studies may be challenged from the methodological standpoint, they are much less open to criticism in terms of the way in which the CGMS was used, corresponding more closely to the traditional mode of use in routine practice (from three to six days of recording, followed by treatment adjustment and re-evaluation of glucose control at two or three months).

### Table I

Design and results of intervention studies, using CGMS to adjust patients’ treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>design</th>
<th>n</th>
<th>population</th>
<th>main results at the end of the study: difference vs baseline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludvingsson 2003 [26]</td>
<td>Randomized, cross over, 2x3months</td>
<td>27</td>
<td>type 1 children</td>
<td>ΔHbA1c: CGMS -0.39% vs control: -0.10%</td>
<td>0.011*</td>
</tr>
<tr>
<td>Chase 2001 [27]</td>
<td>Randomized, parallel 3 months</td>
<td>11</td>
<td>type 1 children</td>
<td>ΔHbA1c: CGMS -1.2% vs control: -0.6%</td>
<td>ns*</td>
</tr>
<tr>
<td>Chico 2003 [28]</td>
<td>Randomized, parallel 3 months</td>
<td>80</td>
<td>type 1 adults</td>
<td>ΔHbA1c: CGMS -0.8% vs control: -0.5%</td>
<td>ns*</td>
</tr>
<tr>
<td>Tanenberg 2004 [30]</td>
<td>Randomized, parallel, 12 weeks</td>
<td>128</td>
<td>Type 1 and 2 adults</td>
<td>ΔHbA1c: CGMS -0.8% vs control: -0.7% Duration of hypoglycaemic event (min): CGMS: 49.4 vs control: 81.0</td>
<td>0.009*</td>
</tr>
<tr>
<td>Kaufmann 2001 [25]</td>
<td>Uncontrolled 6 months</td>
<td>47</td>
<td>type 1 children</td>
<td>ΔHbA1c: -0.3%</td>
<td>0.04#</td>
</tr>
<tr>
<td>Salardi 2002 [31]</td>
<td>Uncontrolled 6 months</td>
<td>44</td>
<td>type 1 children and adults</td>
<td>ΔHbA1c: -0.43%</td>
<td>0.032*</td>
</tr>
<tr>
<td>Schiaffini 2002 [32]</td>
<td>Uncontrolled 6 weeks</td>
<td>18</td>
<td>type 1 children</td>
<td>ΔFructosamine: -19µmol/l Reduction in hypoglycaemia events: -1.4 event/72h</td>
<td>&lt; 0.05#</td>
</tr>
<tr>
<td>Schaepeleyck-Bélicar 2003 [24]</td>
<td>Uncontrolled 2 months</td>
<td>12</td>
<td>type 1 adolescents</td>
<td>ΔHbA1c (%): -1.55%</td>
<td>&lt; 0.05#</td>
</tr>
</tbody>
</table>

*CGMS vs control group or period. #end vs baseline.
A means of patient education

In view of their visual nature, the tracings obtained using the CGMS constitute a tool for patient education on either an individual or a group basis.

For the healthcare professional, they represent a particularly effective aid for explaining to the individual patient the hyper- or hypoglycaemic phenomena occurring during the recording period, facilitating discussion between the patient and the care-provider to jointly seek solutions.

For the patient, the illustrative nature of the tracings makes them more meaningful than a logbook. The tracing provides a graphical representation of the “dynamic process” underlying the fluctuations in glucose levels, whereas the logbook merely presents a sequence of “states” expressed as juxtaposed glucose levels. Even a simple notion, such as the magnitude of the increase in glucose levels after a meal, immediately apparent on the tracing, necessitates an effort of extrapolation in the case of pre- and postprandial glucose levels entered in a logbook. The patient’s understanding of these phenomena is consequently enhanced. In addition, the possibility for the patients to finally view their hitherto unknown results, at the end of an examination lasting several days, often has a considerable impact and is even a revelation for some patients.

These elements no doubt contribute to a better acceptance of the treatment adjustments proposed by the care-provider. Even if no study, to the best of our knowledge, has specifically focused on this topic, several authors have emphasised the beneficial effect of using the CGMS with respect to patient motivation [24,26]. Schaeppelync-Belicar et al., for example, reported that radical treatment modifications were possible following CGMS recordings in poorly compliant adolescents, probably reluctant to accept any modification in their SMBG or their treatment prior to visualization of their results.

Tracings illustrating particularly well a problem of glucose control can also serve as a basis for group education sessions. By virtue of their immediately recognisable authenticity, as they represent real examples, they possess a “force” lacking in diagrams illustrating the same phenomena. In our practice, we use certain tracings from our patients to demonstrate the duration of action of prandial insulins, to illustrate the impact on glycaemia of a catheter obstruction during treatment via an external pump, or to emphasize the importance of postprandial checks of blood glucose level through tracings showing major postprandial hyperglycaemias even though preprandial glucose levels were correct.

Conclusion

Despite the physiological limitations of continuous glucose monitoring methods involving sensors inserted subcu-

taneously, and the initial technical deficiencies of the device, the CGMS seems to us to be a useful investigational tool in the management of type 1 diabetes to identify or confirm certain problems of glucose control. At present, it is still difficult to state with certainty that this tool allows effective improvement in the metabolic control of patients with type 1 diabetes, in view of the paucity of controlled studies showing an impact on HbA1c values or on the frequency of hypoglycaemias. Nevertheless, it would be surprising if the extra information provided by the CGMS compared with classical self-monitoring, when taken into account, did not result in more precise and more efficient treatment adjustment. Personally, we are convinced of the value of this device to aid adjustment of the treatment of our patients, if only because of its potential as an effective aid to discussion and comprehension of the results, leading to better acceptance of treatment proposals. The device has benefited from various technical improvements during the last few years, particularly with regard to the quality of the subcutaneous sensors, resulting in an enhanced duration and accuracy of the recordings. These changes are likely to have a positive impact on the results of future clinical studies seeking to demonstrate the value of this system in the management of type 1 diabetes.

References

5. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes 2003;51:2790-4


28. Chico A, Vidal-Rios P, Subirá M, Novials A. The Continuous Glucose Monitoring System is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care 2003;26:1153-7


Value of the CGMS in type 1 diabetes management