Mini Review

Real-time continuous glucose monitoring using Guardian®RT: from research to clinical practice

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Abstract

The limited number of self-monitoring blood glucose measurements is an obstacle for good metabolic control in patients with type 1 diabetes. However, continuous glucose measurement with real-time data and alarms is a recent technology that promises to improve the efficacy of treatment in diabetic patients. Guardian®RT uses a continuous telemetry display of real-time glucose values, and automatic alerts at preset hypo- and hyperglycaemic levels. Three calibrations a day are required, and the sensor must be changed every three days. The GuardControl study showed that, within three months, real-time continuous glucose monitoring with the Guardian®RT led to significantly improved HbA1c values in 162 poorly controlled patients (children and adults) with type 1 diabetes despite intensive insulin therapy. The continuous availability of glucose measurements permitted the patients to adjust their own insulin doses, food intake and physical activity and, thus, improve their glycaemic control. This report summarizes the available data on this tool and details how best to use this state-of-the-art modality in diabetic patients in clinical practice.

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Keywords: Diabetes; Blood-glucose monitoring; Continuous glucose monitoring; Sensors; Review

Résumé

Mesure continue du glucose en temps réel avec le Guardian®RT : de la recherche à la clinique

Le nombre limité d’autocontrôles glycémiques est un facteur limitant majeur d’un bon contrôle glycémique chez les patients diabétiques de type 1. La mesure continue du glucose avec lecture directe et alarmes est une technique récente prometteuse pour améliorer l’efficacité du traitement des patients diabétiques. Guardian®RT comprend un capteur qui mesure en continu le glucose interstitiel et transmet par télémétrie les mesures à un moniteur. Le patient dispose en temps réel de ces mesures sur un écran et d’alarmes en hypoglycémie et en hyperglycémie. Le Guardian®RT nécessite trois calibrations quotidiennes par mesures de la glycémie capillaire. Le capteur doit être changé tous les trois jours. L’étude GuardControl a montré que cet outil permettait d’améliorer significativement en trois mois l’HbA1c de 162 enfants et adultes diabétiques de type 1 dont l’équilibre était insuffisant malgré une insulinothérapie intensive. La disponibilité permanente des mesures de glucose a permis aux patients d’ajuster eux-mêmes leurs doses d’insuline, l’alimentation, l’activité physique et d’améliorer ainsi leur équilibre glycémique. Cet article fait le point des données disponibles sur ce dispositif et précise les modalités de son utilisation en pratique clinique en diabétologie, en l’état actuel des connaissances.

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Mots clés : Diabète ; Mesures de la glycémie ; Mesures continues de la glycémie ; Capteurs ; Revue générale

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Intensive insulin therapy with frequent glucose self-monitoring is crucial in patients with type 1 diabetes to ensure tight blood glucose control, thereby decreasing the risk of long-term complications [1–3]. However, conventional self-monitoring requires that the patient obtain multiple daily blood samples for glucose measurement. Devices that ensure continuous and non-invasive glucose monitoring have been long awaited by patients with diabetes. The first such device was the CGMS® (Medtronic MiniMed, Northridge, CA), introduced in France in 2000 as a diagnostic device for physicians. The CGMS® continuously measures glucose levels in interstitial fluid, but does not provide real-time data and has no alarm system. The device retrospectively provides interstitial glucose measurements at 5-min intervals for 3 days. Many published studies have established that the CGMS® is helpful for investigating unstable diabetes, improving the detection of hypoglycaemic and hyperglycaemic episodes compared with invasive blood glucose self-monitoring, and adjusting the insulin dosage or adapting other components of the treatment [4–8]. A single study found that repeated use of the CGMS® led to lower HbA1c levels [6].

Continuous glucose monitoring devices that display real-time values for the patient to read have recently been introduced into the market. The usefulness of the GlucoWatch® device is limited by a high rate of skin irritation [9]. The Guardian®RT (Medtronic MiniMed, Northridge, CA) is an electrode-based device that supplies the patient with real-time glucose values and sounds an alarm (or vibrates) when the values fall below, or rise above, preprogrammed thresholds. The GuardControl Trial was a multicenter randomized trial to evaluate the efficacy of the Guardian®RT device in both adult and pediatric patients across Europe and in Israel [10]. The results showed a clinically meaningful improvement in HbA1c values with the device. This discussion of the Guardian®RT and its modalities of use are based on the results of the GuardControl Trial and our own experience.

1. Guardian®RT: description, technical features, and practical considerations

The device is composed of a glucose sensor connected to a radiofrequency transmitter that wirelessly sends the data to a monitor.

The glucose sensor is a tiny glucose-oxidase-filled electrode that is inserted under the skin and changed every 3 days by the patient, and works in the same way as the CGMS® sensor. Interstitial glucose is converted to H2O2 by the enzyme, then to electrons that travel to the transmitter along a 4-inch cable. Glucose is measured at 10-s intervals. The electron flow is proportional to the concentration of glucose in the interstitial fluid. Fingerstick blood-glucose measurements are needed to calibrate the device.

Sensor accuracy was evaluated by comparing the Guardian®RT values to plasma glucose values measured by the reference technique, using the Beckman glucose analyzer [11–14]. The sensor proved reliable: coefficients of correlation ranged from 0.80 to 0.92, the mean absolute difference ranged from 12.8% to 18%, and 98.9% of values were in the A+B zone of the Clarke error grid [11]. Accuracy decreased during episodes of hypoglycaemia [14], when only 61.6% of values fell within the A+B zone.

The transmitter uses radio frequencies to send data to the monitor. It is attached to the skin by an adhesive patch.

The monitor is similar in size to an insulin pump. It receives the data wirelessly from the sensor via the transmitter. Values obtained at 10-s intervals are recorded and used to compute means over 5-min periods, which are then displayed. Thus, there are 288 readings over each 24-h cycle. The monitor can be placed up to 2 m away from the transmitter.

Alarms can be programmed to alert the patient to both hypoglycaemia and hyperglycaemia. The physician and patient decide together on the alarm thresholds. Repeated alarms in the event of persistent undesirable glucose levels can be set for 20–60 min for hypoglycaemia and 60–180 min for hyperglycaemia. The patient can choose to have the alarm either ring or vibrate.

Alarm accuracy was tested by Bode et al. [13]. With a threshold of 70 mg/dL, hypoglycaemia was detected with 67% sensitivity, 90% specificity and 47% false alarms. The best sensitivity/specificity ratio for hypoglycaemia was obtained using a higher threshold of about 82 mg/dL, which yielded 52% false alerts. At a threshold of 250 mg/dL, hyperglycaemia was detected with 63% sensitivity, 97% specificity and 19% false alarms. The best sensitivity/specificity ratio for hyperglycaemia occurred with a lower threshold of 192 mg/dL, which yielded 43% false alerts.

Clinicians should be aware of these performance data as they can help to adjust thresholds according to the needs of the individual patient. For instance, in a young child or a patient with unstable diabetes and a high risk of nocturnal hypoglycaemia, detection of all hypoglycaemic episodes is desirable. Therefore, a high hypoglycaemia threshold, for instance, 85 mg/dL, should be used during the treatment-adjustment phase, despite the higher rate of false alerts at that threshold. In contrast, a lower hypoglycaemia threshold may be desirable initially in a poorly controlled patient to decrease the false-alarm rate, as too many false alerts may lead the patient to turn the alarm off.

Calibration of the device at 12-h intervals is recommended by the manufacturer but, in our experience, calibration three times per 24-h cycle is optimal. One advantage of more frequent calibrations is that it reduces the additional calibrations requested by the device at unpredictable and perhaps inconvenient times. Calibration timing deserves attention. Accuracy improves when blood-glucose levels differ markedly across calibration measurements [15]. A recent study [16] found little improvement in accuracy when the number of calibration measurements was more than four times every 24 h. More relevant to sensor accuracy is appropriate calibration timing, most notably for accuracy of nocturnal measurements (calibration at 9 pm and 6 am), and calibration during periods of relative stability rather than during rapid blood-glucose changes. To date, there are no published studies of the impact of calibration pat-
terms on the accuracy of Guardian®RT, which uses the same sensor, but different algorithms, as the CGMS® device. In practice, we recommend three calibrations per day ideally before each of the three main meals, when blood-glucose levels are fairly stable.

**Downloading data:** Up to 21 days of information can be stored in the Guardian®RT device before being downloaded to a computer. Solutions® software can be used by the diabetologist to create graphs or Tables of glucose values, alerts and other information.

**EC labeling and marketing:** Guardian®RT obtained the EC label on 25 May 2005 (EC 0459, certificate n°1285/B2P4O4/2, report D020102-7), specifying that the device is reserved for patients with diabetes and that the data supplied by the device must be confirmed by a fingerstick measurement before decisions are made concerning any treatment or lifestyle changes. Guardian®RT has been available for purchase by hospitals in France since January 2006.

**2. The GuardControl trial**

Real-time continuous glucose monitoring was found to be helpful in decreasing hyperglycaemic and hypoglycaemic episodes in adults with type 1 diabetes [17]. Earlier studies of the device evaluated measurement accuracy and alarm usefulness for detecting hypoglycaemia and hyperglycaemia [13]. The GuardControl Trial was the first clinical study of the impact of using the Guardian®RT for metabolic control [10]. The primary objective of this prospective multicenter randomized study, conducted in Europe and Israel, was to investigate whether the device improved metabolic control in patients with poorly controlled type 1 diabetes.

The 162 adults and children had HbA1c levels greater than 8.0% (mean, 9.6%) despite optimal insulin therapy with multiple daily injections or a pump. They were randomly allocated to conventional glucose self-monitoring (control group), continuous use of Guardian®RT or use of the Guardian®RT for 3 days every 15 days.

Over the 3-month study period, a mean HbA1c decrease of 1% was seen in the continuous-use group, a significant 0.6% difference compared with the controls. This benefit was achieved with no increase in the rate of hypoglycaemic episodes. Continuous real-time glucose monitoring allowed the patients themselves to take action to improve their metabolic control, which was previously inadequate despite optimal insulin therapy. Thus, the device constitutes a breakthrough in the field of diabetes.

Further studies are needed to investigate the long-term benefits of real-time continuous glucose monitoring on metabolic control, optimal patterns of use (frequency and duration), indications other than poorly controlled diabetes, patient response to alerts, long-term acceptability, and usefulness in target populations.

**3. Use of Guardian®RT in clinical practice**

At present, Guardian®RT has proved beneficial in patients with inadequate diabetes control despite intensive therapy. Other potential indications need to be evaluated.

The introduction of Guardian®RT monitoring in a patient with diabetes is a multistep procedure.

**3.1. Installation of the device and initial technical training of the patient**

The device should be installed by two trained healthcare professionals—namely, a diabetologist and a nurse. The patient is taught how to insert the sensor. Sensor placement was accomplished without difficulty by the patients in the GuardControl Trial. The patient also receives instruction on how the device works and how it should be handled, most notably for calibration and setting the alarms. Patients benefit from being shown how to conduct reviews, upon awakening, of all nocturnal values stored in the monitor’s memory.

**Initializing the device:** After inserting the sensor and connecting the cable, a 140-min initialization period is required, during which no glucose values are given. This time can be used for patient education. When initialization is complete, the device should then be calibrated, after which glucose values are displayed at 5-minute intervals. Subsequently, the patient should change the sensor every 72 h. Sensors should be transported in thermal insulation bags. Patients should be told that they can engage in their usual activities while using the device, most notably, while showering (with the monitor within 6 feet of the transmitter) and during sports activities.

**3.2. Optimal use of the information supplied by Guardian®RT**

The instructions given to patients at installation of the device are crucial, as they ensure optimal use of the device and, therefore, optimal benefits for metabolic control. The initiation of continuous glucose monitoring provides an opportunity for reminding patients of the basic treatment-adjustment rules, which they will be able to follow to greater benefit using the additional information supplied by the device, particularly the glucose values after meals and at night. Patients should be encouraged to use the device for insulin injections that anticipate changes, instead of only for injections that correct changes. Decisions concerning duration of use and patient support should be made by the diabetologist for each individual patient.

In our experience, benefits are derived from using a sequence of three or four sensors (Fig. 1). The first 3 days (first sensor) are used by the patient to collect information on basal insulin and postprandial variations. Basal insulin needs can be determined by reading the nocturnal values in the device’s memory and, where appropriate, by reading the glucose plateau during a carbohydrate fast and adjusting the basal insulin dosage accordingly. The impact of meals is shown by
the postprandial values supplied by Guardian®RT. The rapid insulin/carbohydrate intake can be evaluated when the postprandial values fall outside the desired range. During the next 6 days (second and third sensors), the patient makes and validates changes to the treatment regimen. A fourth sensor (days 10 through 12) may be useful for checking insulin doses under specific circumstances such as physical activity or following an unusually rich meal. The sequence of four sensors can be repeated as often as needed to improve metabolic control, depending on the goals of the given patient.

Data in the Guardian®RT memory can be downloaded at any time to a computer equipped with Solutions® software. Graphs of glucose values taken over the previous 21 days can help the diabetologist and the patient to further tailor the treatment.

4. Advantages, limitations and perspectives

The Guardian®RT is an innovative tool for improving the management of diabetes. Despite its many advantages, it has a number of limitations (Table 1). The following clinical examples illustrate some of these advantages and limitations.

4.1. Advantages

Many adults and pediatric patients or their parents have expressed considerable enthusiasm for the Guardian®RT device. It provides reassurance, especially when fear (or phobia) of hypoglycaemic episodes keeps the patient from optimizing the insulin dose. In such cases, the Guardian®RT alert system provides the patient with the confidence needed to increase the insulin dose, thereby achieving better metabolic control.

In both adolescents and adults, the device enables better adjustment of food intake and/or insulin doses during strenuous physical activity. Adolescents also discover the glucose highs induced by uncontrolled snacking, which helps them limit this behavior on their own accord.

4.2. Limitations and perspectives

The main disadvantage reported by patients is the high rate of false alerts, particularly for hypoglycemia, which is a source of many complaints particularly when the alerts occur at night. On the other hand, the alarm may fail to go off when it should. One reason for missed hypoglycaemic episodes is the time lag...
between changes in blood and interstitial-fluid glucose levels, particularly when blood-glucose levels drop sharply. The next-generation Guardian® REAL Time device comes equipped with a slope alarm system for detecting sharp glucose drops. Nevertheless, the expected reduction in false alerts will need to be confirmed.

Some patients complain that the device is too bulky. The Guardian® REAL Time will use a miniaturized wireless transmitter.

Concerns have been voiced by physicians over this new technology, but any misgivings of several investigators in the GuardControl Trial were appeased by clinical experience:

Acceptability of Guardian®RT by patients: most of the patients who used the device for 3 months wished to continue using it, as they felt the benefits outweighed the disadvantages.

How did patients handle the large amounts of information provided by the device? Compulsive administration of rapid insulin followed by recurrent hypoglycaemic episodes has been suggested as a theoretical area of concern. However, this behavior did not occur in our experience. No increase in hypoglycaemic episodes has been seen. Patient education regarding use of the data and support until the patient becomes a confident user is crucial in this respect.

5. Conclusion

Guardian®RT is an innovative device that can substantially improve metabolic control in adult and pediatric patients with uncontrolled type 1 diabetes. The device is a breakthrough that leads us into the era of continuous glucose monitoring. An insulin pump equipped with a real-time continuous monitoring system is now available (Paradigm®RT, Medtronic). Research is ongoing for a move to the next stage, involving automated, closed-loop, feedback-controlled, subcutaneous insulin delivery, with algorithms for matching insulin dose to glucose level [18,19]. The artificial pancreas is almost here.

Table 1
Advantages, limits of the Guardian®RT

<table>
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<tr>
<th>Advantages</th>
<th>Limits</th>
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<tbody>
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<td>Continuous Glucose Measurement</td>
<td>Permanent availability of the glucose measurements on a screen</td>
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<tr>
<td>Alarms</td>
<td>Detection of hypo/hyperglycaemia</td>
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* Improvements scheduled for the future version of the Guardian® Real Time.

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References

[8] Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent


