Use of Continuous Glucose Monitoring Can Address Patient Fears and Facilitate Improved Glycaemic Management

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Abstract

Effective diabetes management can delay or prevent many of the complications of diabetes. Achieving optimal glycaemic control, however, often requires intensive insulin treatment, which is associated with an increased risk of severe hypoglycaemia. Many intensively managed patients are reluctant to follow and/or adjust their insulin regimens as needed because of fear of hypoglycaemia. This lack of adherence can result in exposure to chronic hyperglycaemia, oxidative stress and long-term complications. Severe hypoglycaemia can be prevented through vigilance in identifying patients at risk, using appropriate medications and medication regimens, and effective glucose monitoring strategies and technologies. This article reviews some evidence relevant to hypoglycaemia in intensively managed patients and discusses how tools such as continuous glucose monitoring (CGM) can help patients overcome their fear of hypoglycaemia and safely achieve optimal glycaemic control.

Keywords

Hypoglycaemia, type 1 diabetes, type 2 diabetes, continuous glucose monitoring (CGM), self-monitoring of blood glucose (SMBG), intensive insulin management, multiple daily injections (MDI)

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Glycaemic Control is a Challenge in Diabetes

Large controlled clinical trials have demonstrated that intensive management of glycaemia and other diabetes risk factors can significantly decrease the development and/or progression of macrovascular and microvascular disease.[1–4] Achieving optimal glycaemic control requires a high level of daily self-management. For patients with type 1 diabetes, this often includes intensive insulin therapy with dose adjustment (based upon carbohydrate intake and activity) and frequent glucose monitoring.[1,5] Despite the proven benefits of effective diabetes management, many people with diabetes are reluctant or unable to follow and/or adjust their insulin regimens as needed, due to concerns about hypoglycaemia.[6–8]

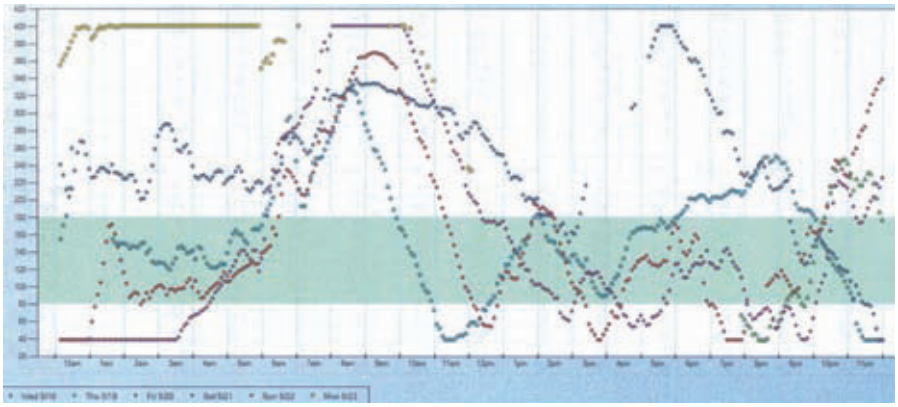
Impact of Hypoglycaemia on Diabetes Management

Hypoglycaemia occurs when blood glucose concentrations drop below the level necessary to properly maintain the body's requirement for energy and stability.[9] Plasma glucose ≤70 mg/dl (3.9 mmol/l) is generally considered the cut-off point for hypoglycaemia; however, severe hypoglycaemia is usually defined as having plasma glucose <50 mg/dl (2.8 mmol/l), seizure, coma and/or requiring the assistance of another person.[1,10]

Retrospective studies of severe hypoglycaemia in type 1 diabetes have reported the incidence to be 1.3 (n=1,076) to 1.5 (n=195) episodes per patient-year; the percentage of patients affected ranged from 36.7 % to 40.5 %, respectively.[11,12] Although the reported incidence rates in type 2 diabetes are more varied, depending on the treatment, duration of the disease and the cut-off points used to define severe hypoglycaemia,[13–20] the frequency of severe hypoglycaemia in type 2 diabetes, including episodes that require emergency medical treatment, is similar to that seen in type 1 diabetes when matched for duration of insulin therapy.[21–23] Patients affected by hypoglycaemia unawareness – a condition that occurs when a person with diabetes no longer experiences the symptoms of impending hypoglycaemia – have a three- to sixfold increased risk of severe hypoglycaemia because they are no longer alerted to take action (ingest carbohydrates) to prevent it.[24–26]

Patients treated with insulin or insulin secretagogues experience severe hypoglycaemia more frequently when glucose control is intensified.[27–29] In the Action to control cardiovascular risk in diabetes (ACCORD) trial, Gerstein et al. found that intensive therapy to target normal glycated haemoglobin (HbA_{1c}) levels significantly increased the occurrence of hypoglycaemia requiring assistance compared with standard care: 538 (10.5 %) versus 179 (3.5 %), respectively, p<0.001.[28] At one year, stable median HbA_{1c} levels of 6.4 % and 7.5 % were achieved in the intensive-therapy group and the standard-therapy group, respectively; however, higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.

Figure 1: Example of Continuous Glucose Monitoring Data Download



This is the continuous glucose monitor (CGM) trace of an 82-year-old patient with type 1 diabetes, who uses an insulin pump. Over the past year, the patient has presented to accident and emergency eight times with episodes of severe hypoglycaemia. The horizontal bar in the middle of the trace represents the targeted blood glucose range of 80–180 mg/dl (4.4–10 mmol/l). When placed on the CGM, one can clearly identify that the patient is becoming hypoglycaemic in between the hours of 11 am and 12 pm, and again from 2 pm to 9 pm. The dotted lines represent trends of interstitial glucose readings on six consecutive days.

Numerous studies have shown significant differences between continuous subcutaneous insulin infusion (CSII) therapy and multiple daily injection (MDI) treatment in the occurrence of severe hypoglycaemia.[30–34] A meta-analysis by Pickup and Sutton looked at 22 studies, involving 1,414 type 1 diabetes subjects and found both improved HbA_{1c} levels and reductions in severe hypoglycaemia in CSII-treated subjects compared with those treated by MDI.[34] Although differences in hypoglycaemia reduction in type 2 diabetes studies are not as apparent, studies have shown that use of CSII in this population significantly reduces HbA_{1c} without increasing severe hypoglycaemia when compared with MDI therapy.[33,35,36]

Severe Hypoglycaemia and Adverse Clinical Events

Severe hypoglycaemia has been the suspected cause of the higher mortality in the ACCORD trial; however, a causal relationship between hypoglycaemia and cardiovascular events has not yet been shown. A recent study by Zoungas et al.[37] examined the relationship between severe hypoglycaemia and subsequent risks of vascular complications and death among the 11,140 subjects with type 2 diabetes who participated in the Action in diabetes and vascular disease (ADVANCE) trial.[28] During a median follow-up period of five years, 231 subjects (2.1 %) had at least one episode of severe hypoglycaemia: 150 (2.7 %) in the intensive group and 81 (1.5 %) in the control group. Within both groups, severe hypoglycaemia was associated with a significant ($p<0.001$) increase in the adjusted risks of major macrovascular events, major microvascular events, death from a cardiovascular cause and death from any cause. Although these findings demonstrated a strong link between severe hypoglycaemia and adverse clinical events, the analysis indicated that hypoglycaemia is just as likely to be a marker of vulnerability to such events as it is to be the cause.

The relationship between severe hypoglycaemia and macrovascular events remains unclear, yet the inevitable consequences of untreated severe hypoglycaemia are significant, including morbidity or even death.[38,39] One of the most significant consequences of severe hypoglycaemia, however, is fear,[40–43] which often becomes a key obstacle to intensifying therapy and/or adhering to prescribed insulin regimens.[9,38,44] This, in turn, can lead to poor metabolic control and subsequent health outcomes.[45] A large study by Anderbro et al. identified frequency of severe hypoglycaemia as the most significant factor associated with fear of hypoglycaemia in adults with type 1 diabetes.[40]

Prevention of Severe Hypoglycaemia

Several strategies have been proposed for the prevention of severe hypoglycaemia, which include adjusting glycaemic goals, using insulin analogues whenever possible and switching patients from MDI therapy to insulin pumps.[46]

The cornerstone of hypoglycaemia prevention, however, is glucose monitoring, using self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM). Frequent glucose monitoring enables patients to detect glycaemic excursions, identify current or impending hypoglycaemia, monitor resolution of hypoglycaemia, identify recurring patterns of hypoglycaemia and obtain valuable feedback about the effect of medication (dosages, timing), meals and activity on their glycaemic control.[47] This, in turn, enables them to make appropriate changes in their treatment regimen, insulin and lifestyle. It also provides valuable information that allows clinicians to make more informed decisions about changes in therapy.

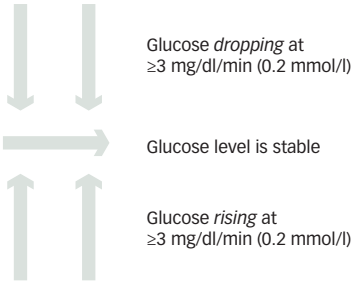
Self-monitoring of Blood Glucose

When using SMBG, testing should occur at or before the peak insulin effect throughout the day to assess glycaemic patterns and periodically during the night to detect night-time and/or early morning hypoglycaemia. SMBG should be matched to the specific therapy. Although use of seven-point glucose profiles can help identify asymptomatic hypoglycaemia or high-risk patterns,[48] some peaks and troughs may be missed.

Continuous Glucose Monitoring

CGM systems provide 24-hour coverage, measuring glucose levels in interstitial fluid at one-minute or five-minute intervals, depending on the system (see *Figure 1*). Currently, only three manufacturers offer CGM systems that are approved by the US Food and Drug Administration (FDA): Abbott, DexCom and Medtronic. These systems are available by prescription[49] and are often covered by insurance in the US, especially in poorly controlled patients or those with problematic hypoglycaemia. However, reimbursement for CGM in Europe is sparse.

Figure 2: Glycaemic Arrow Indicators on Continuous Glucose Monitoring Devices



An audible or vibratory alarm is triggered when glucose levels are changing rapidly. Two down arrows, accompanied by an auditory or vibrating alarm, produced by the DexCom continuous glucose monitoring (CGM) device would warn the user that his/her blood glucose level is dropping at the rate of ≥3 mg/dl (0.2 mmol/l) per minute; double arrows down for the Medtronic CGM device mean ≥2 mg/dl/min (0.1 mmol/l). Blood glucose levels that are stable over time would be demonstrated on the sensor with a horizontal arrow. If the glucose level is rising at greater than 3 mg/dl/min (0.2 mmol/l) an alarm would sound alerting the patient to appropriately manage their hyperglycaemic event; double arrows up for the Medtronic CGM device mean ≥2 mg/dl/min (0.1 mmol/l).

CGM devices are made up of three main components: 1) a disposable sensor that measures glucose levels; 2) a transmitter that is attached to the sensor; and 3) a receiver that displays and stores glucose data. Patients, using an insertion device, place a thin plastic sensor just under the skin. The transmitter sends an electrical signal to the receiver where it is processed into a glucose value and adjusted based on periodic calibration using capillary blood glucose. Realtime glucose values and glucose trends are then presented in the display. The data can also be downloaded to a computer for review and analysis.

An important feature of the CGM devices is an audible or vibratory alarm that is triggered if glucose rises above or falls below a defined threshold or changes rapidly, thus predicting an impending hyperglycaemic or hypoglycaemic event. Arrows in the display indicate both the direction and rate of glucose change (see *Figure 2*).

Several studies have shown realtime CGM use to be effective in helping type 1 and type 2 diabetes patients achieve good glycaemic control with a reduced risk of hypoglycaemia.[50–55] In a recent randomised controlled multicentre study, 120 intensively managed type 1 diabetes children and adults were randomly assigned to conventional home monitoring with a blood glucose metre and wearing a masked continuous glucose monitor every second week for five days, or to a group with realtime CGM.[56] At 26 weeks, the time per day spent in hypoglycaemia (interstitial glucose concentration <63 mg/dl [<3.5 mmol/l]) was significantly shorter in the continuous monitoring group than in the control group: mean (standard deviation [SD]) hours per day, 0.48 (0.57) versus 0.97 (1.55), respectively (p=0.03). Time spent in normoglycaemia (70–180 mg/dl [3.9–10 mmol/l]) was significantly longer in the CGM group compared with the control group: mean (SD) hours per day, 17.6 (3.2) versus 16.0 (3.4), respectively (p=0.009). At study end, HbA_{1c} in the CGM group was significantly lower than in the control group: 6.69 % versus 6.95 %, respectively (p=0.008).

An earlier study by Garg et al. reported findings from a randomised controlled trial that looked at the accuracy, safety and clinical effectiveness of CGM use in 91 insulin-requiring subjects with type 1 diabetes (n=75) and type 2 diabetes (n=16).[54] Subjects were randomised to control (CGM with no data provided) for three consecutive 72-hour periods and experimental (realtime CGM with data masked during the first period but available for periods two and three). When compared with control subjects, the experimental group spent 21 % less time hypoglycaemic (<55 mg/dl [<3.1 mmol/l]), 23 % less time hyperglycaemic (≥240 mg/dl [>13.3 mmol/l]) and 26 % more time within the target glucose range (81–140 mg/dl [4.5–7.8 mmol/l]) (p<0.001). Nocturnal hypoglycaemia was also reduced by 38 % in experimental subjects compared with control subjects (p<0.001).

Other trials have demonstrated that CGM is beneficial for type 1 diabetes patients who have already achieved excellent control (HbA_{1c} <7.0%),[56–58] and that safe and efficacious CGM use in children and adults can be sustained over time.[59,60] In a recent study, paediatric patients and their caregivers identified prevention of hypoglycaemia and decreased anxiety about hypoglycaemic events as the most common perceived benefit of CGM use.[61]

Professional Use of Continuous Glucose Monitoring – Masked Data

Use of masked data is one option for intensive monitoring. Short-term periodic use of CGM devices over three to seven days, without patient access to data, often reveals patterns of previously undetected hyperglycaemia and hypoglycaemia.[62] This option allows clinicians to interpret data retrospectively, identify issues and then adjust the insulin regimen accordingly. Reviewing the CGM data with patients also creates opportunities for more meaningful discussions, enhancing patient understanding and encouraging adherence to treatment. There are limitations, however, to professional CGM use. For example, it does not empower patients with immediate feedback that would allow them to make treatment changes (insulin and/or lifestyle). Furthermore, if patients know they are being monitored, they may alter their behaviour. Another factor to consider is the duration of CGM use; three to seven days of monitoring may be inadequate to detect important glycaemic patterns.

Patient Use – Realtime Data

Use of realtime CGM provides the ability to view realtime glucose values, analyse graphs of recent glucose trends and receive alarms/alerts for impending hypoglycaemia or hyperglycaemia. This allows patients to immediately identify acute or impending episodes of previously undetected hypoglycaemia[63] and then take appropriate action to resolve or prevent the hypoglycaemia.[64]

Conclusions

Severe hypoglycaemia is a significant health risk of insulin-treated diabetes, particularly in those treated with MDI therapy.[31,35,65] Given its associated morbidity and mortality, many patients are reluctant to follow their prescribed insulin regimens,[9,38,44] thereby increasing their risk of developing the microvascular and macrovascular complications of hyperglycaemia.[1–4] Given the evidence in support of glycaemic control, clinicians have an obligation to recommend and use the most effective treatments and technologies that will enable patients to safely manage their diabetes. A key challenge is helping patients obtain reimbursement for tools such as CGM; some payers (public and private) only allow CGM in patients who are using CSII or who already have documented hypoglycaemia. This automatically excludes many patients on MDI therapy who would potentially benefit from this technology. Appropriate use of medication and CGM technology will enable clinicians to initiate treatment regimens that will help patients safely achieve optimal glycaemic control and overcome their fear of hypoglycaemia. ■

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