Real-Time Continuous Glucose Monitoring Significantly Reduces Severe Hypoglycemia in Hypoglycemia-Unaware Patients With Type 1 Diabetes

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OBJECTIVE—To evaluate the effect of continuous glucose monitoring (CGM) on the frequency of severe hypoglycemia (SH) in patients with established hypoglycemia unawareness.

RESEARCH DESIGN AND METHODS—We conducted a retrospective audit of 35 patients with type 1 diabetes and problematic hypoglycemia unawareness, despite optimized medical therapy (continuous subcutaneous insulin infusion/multiple daily insulin injections), who used CGM for >1 year.

RESULTS—Over a 1-year follow-up period, the median rates of SH were reduced from 4.0 (interquartile range [IQR] 0.75–7.25) episodes/patient-year to 0.0 (0.0–1.25) episodes/patient-year ($P < 0.001$), and the mean (±SD) rates were reduced from 8.1 ± 13 to 0.6 ± 1.2 episodes/year ($P = 0.005$). HbA_{1c} was reduced from 8.1 ± 1.2% to 7.6 ± 1.0% over the year ($P = 0.005$). The mean Gold score, measured in 19 patients, did not change: 5.1 ± 1.5 vs. 5.2 ± 1.9 ($P = 0.67$).

CONCLUSIONS—In a specialist experienced insulin pump center, in carefully selected patients, CGM reduced SH while improving HbA_{1c} but failed to restore hypoglycemia awareness.

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Although real-time continuous glucose monitoring (CGM) has been shown in randomized controlled trials to improve glycemic control and mild-to-moderate hypoglycemia, studies to date have not shown convincing reductions in severe hypoglycemia (SH) (1,2). Clinically, CGM may benefit patients with impaired awareness of hypoglycemia (IAH), who have an increased risk of SH (3), by alerting them to impending hypoglycemia, and thus providing them with "technological" awareness to replace the loss of their "physiological" awareness. In our clinical service, across two associated tertiary hospitals, we have obtained case-specific funding for CGM for 35 patients with type 1 diabetes, IAH, and problematic hypoglycemia limiting daily activities during intensified insulin therapy. This audit evaluates outcomes at 1 year to see whether the use of CGM can reduce SH or improve awareness.

RESEARCH DESIGN AND METHODS

—A retrospective case-note audit was carried out in adult type 1 diabetes patients with ongoing problematic hypoglycemia leading to limitation in daily activities and IAH (Gold score [a Likert linear analog scale in which patients are asked to score between 1 and 7, respectively, if they are always aware or never aware of the onset of hypoglycemia] >4) (4) despite structured education with or without continuous subcutaneous insulin infusion (CSII), who then used CGM in addition to CSII or multiple daily injection (MDI) for at least 12 months. Patients were seen in a specialized clinic with expertise in structured education in flexible insulin therapy and CSII (>700 pump patients across two sites). CGM is not routinely funded in the U.K., so a multidisciplinary team evaluated each case, ensured that routine therapy was optimized on CSII or MDI, and sought patient-specific funding from local health boards. We compared HbA_{1c}, SH rates (episodes requiring third-party assistance), and awareness status using the Gold score at baseline and at 1 year.

Twenty-three subjects used the Medtronic (Northridge, CA) Paradigm Veo system, which can suspend basal insulin delivery automatically for up to 2 h if sensor glucose readings fall below a preset threshold and the patient fails to respond (termed low glucose suspend [LGS]) (5); 7 patients used the Medtronic Paradigm RT system, and 3 patients used Dexcom (San Diego, CA) G4 sensors in combination with an Animas Vibe pump (Johnson & Johnson, New Brunswick, NJ). One patient continued receiving MDIs, and one pump user used the Freestyle Navigator CGM system (Abbott Diabetes Care, Alameda, CA).

Results are reported as the mean ± SD or median (interquartile range [IQR]), unless otherwise stated. Groups were compared using the paired *t* test or Wilcoxon test, as appropriate.

RESULTS

—The mean age of the patients was 43.2 ± 12.4 years, the duration of diabetes was 29.6 ± 13.6 years, 24 patients were female, 33 of 35 patients were receiving CSIIs prior to starting CGM, and 1 more patient converted to CSII within 2 months of starting CGM. The median duration of CSII use was 40 months (range 8–352 months) prior to CGM start.

The median rate (IQR) of SH was reduced from 4.0 (0.75–7.25) episodes/patient-year at baseline to 0.0 (0.0–1.25)

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episodes/patient-year ($P < 0.001$) (mean 8.1 ± 13 to 0.6 ± 1.2 episodes/year; $P = 0.005$) after 1 year of CGM (Fig. 1). There was no difference between those patients receiving treatment with or without LGS in final mean HbA_{1c} level (7.7 ± 0.7% vs. 7.8 ± 1.5%; $P = 0.9$) or median SH rate (0.0 [0–0] vs. 0.0 [0–2.0]; $P = 0.3$), but three patients were transferred onto LGS pumps after having SH on standard CGM and did not have any further episodes. HbA_{1c} levels for all patients were reduced from 8.1 ± 1.2% to 7.8 ± 1.0% (65 ± 10 to 62 ± 10 mmol/mol) at 1 year ($P = 0.007$).

Nineteen patients (54%) reported subjective improvement in awareness, with 13 reporting no change and 3 reporting a slight worsening in awareness. Paired Gold scores were available in 19 of 34 subjects, showing no change over the year: 5.0 ± 1.5 vs. 5.0 ± 1.9 at 1 year ($P = 0.67$).

CONCLUSIONS—This study describes the efficacy of CGM in reducing SH in patients with type 1 diabetes and IAH who had problematic hypoglycemia limiting daily activities despite structured education and (predominantly) treatment by CSII. Thirty to 40% of patients with long-duration type 1 diabetes have IAH, and such patients have a threefold to sixfold increase in the risk of SH (3), and experience a negative impact on quality of life through time off work, injury, and fear of hypoglycemia (6), in addition to having an increased risk of mortality (7). Strategies for improving the management of these patients are urgently required.

Structured education in flexible insulin therapy can significantly reduce SH and restore awareness in almost half of those who report unawareness (8). CSII can reduce SH by a mean of about fourfold versus MDI, with the greatest reductions occurring in those with the most hypoglycemia at baseline (9). It was because the subjects in our study had failed to resolve their disabling SH with such measures that a trial of CGM was instigated. Randomized controlled trials have demonstrated a benefit of CGM in reducing mild-to-moderate hypoglycemia but not SH (1,2), perhaps because of the deliberate exclusion of patients with problematic hypoglycemia and low SH rates at baseline in these studies. We hypothesized that SH might be reduced by CGM when used in clinical practice in those patients with problematic SH.

A proportion of our patients used CGM in conjunction with an insulin pump with automatic suspension of basal insulin during hypoglycemia (LGS). Prolonged overnight hypoglycemia still occurs commonly during CGM (10), and patients may sleep through up to 71% of nocturnal alarms (11). Even 30 min of mild hypoglycemia can impair epinephrine responses to subsequent hypoglycemia (12). CSII with LGS is known to reduce CGM-recorded nocturnal hypoglycemia (5) and to increase epinephrine responses to experimental hypoglycemia in adolescents with IAH (13), but its effect on SH has not been documented. We found that both HbA_{1c} and SH were reduced by CGM used with LGS, but to a similar extent to CGM used conventionally. However, we caution that we studied small numbers of patients in a nonrandomized study, and a randomized controlled trial of the two types of CGM pump use would be required to compare the effects on SH.

The strength of our study is that we specifically selected patients who reported problematic hypoglycemia. The study is limited by being a nonrandomized clinical observation, and it is possible that factors other than CGM use (e.g., training, education, and contact with healthcare professionals when starting CGM) contributed to the benefit that was observed. Nevertheless, all subjects had previously undergone structured education, and 33 of 35 subjects had already used CSII for a considerable period. Although more than half of the patients reported subjective improvement in awareness, there was no change in reported Gold scores. Because complete avoidance of hypoglycemia can restore awareness of hypoglycemia (14), we had anticipated an improvement in this measure. It is possible that, although CGM was able to reduce the profound and extended hypoglycemia requiring third-party support, the lag between sensor and capillary glucose concentrations (15) prevented a substantial reduction in the milder, shorter, and more frequent biochemical hypoglycemia that is needed to restore awareness.

This study is the first report of the ability to significantly reduce the incidence of SH in a carefully selected group of patients who were struggling with hypoglycemia despite optimized therapy. These findings serve as proof of principle; they contrast with previous reports that suggested a limited role for CGM in avoiding SH and lay the foundation for further randomized studies in this group of patients.

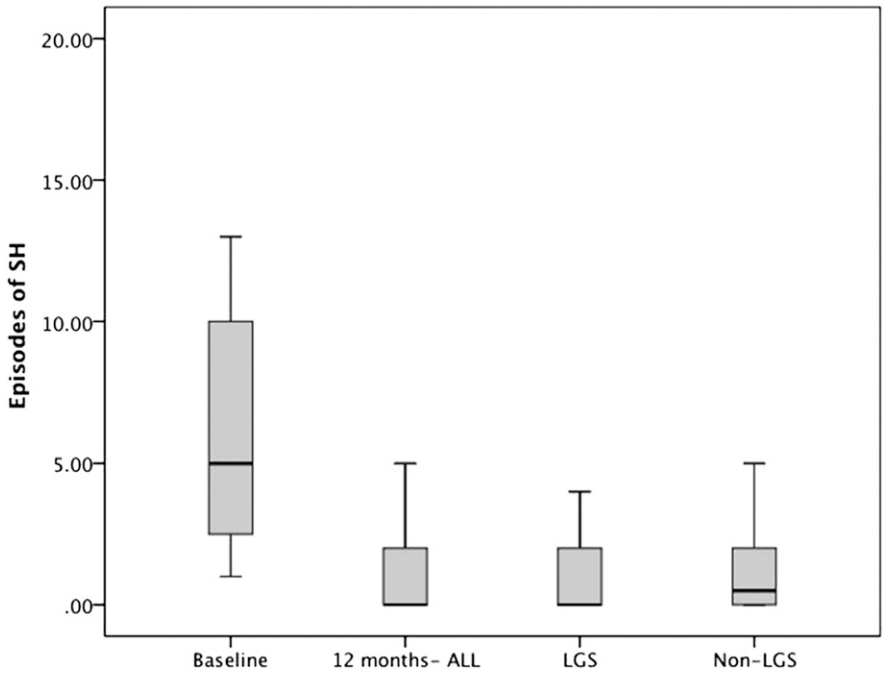

Figure 1—*Annual rates of SH, requiring third-party help at baseline and 12 months after starting CGM. Also shown are the 12-month rates divided into those treated with or without LGS.*

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