Effect of real-time continuous glucose monitoring on hypoglycemia in adult type 1 diabetes patients

Hypoglycemia is one of the major challenges in diabetes management for most patients, especially among those with type 1 diabetes. Clinical studies have shown that hypoglycemia can lead to cognitive dysfunction and behavioral impairment. Continuous glucose monitoring (CGM) can provide continuous, comprehensive and reliable blood glucose information, and facilitate the early detection and evaluation of hypoglycemia, thereby providing guidance for the treatment for hypoglycemia.

In this article by van Beers et al.[1], the authors carried out a randomized, open-label, cross-over trial. Participants were type 1 diabetes patients with impaired awareness of hypoglycemia, and were treated with either continuous subcutaneous insulin infusion or multiple daily insulin injections. The authors randomly assigned 52 patients (1:1) to either the real-time CGM followed by self-monitoring of blood glucose group or the self-monitoring of blood glucose followed by real-time CGM group. In both groups, the self-monitoring of blood glucose phase acted as the control. The authors found that intervention with CGM significantly improved time that patients spent in normoglycemic state, with reductions in time spent in both hypoglycemia and hyperglycemia.

Previous studies of CGM in type 1 diabetes have usually included three aspects. First, the application of retrospective CGM in detecting hypoglycemia. A typical example is the application of CGM in detecting 'dead-in-bed

syndrome'. Tanenberg et al.[2] reported a case of sudden death as a result of hypoglycemia confirmed by CGM: a 23-year-old, type 1 diabetes patient treated with insulin pump suffered sudden death during sleep. The CGM showed that the patient had a linear drop in blood glucose at midnight after injection of insulin, and his blood glucose was <1.7 mmol/L at death. This was the first case with CGM-based evidence to show that hypoglycemia caused dead-in-bed syndrome, which refers to the unexpected sudden death of young people with type 1 diabetes. Second, the application of real-time CGM in preventing hypoglycemia in advance. Pettus et al.[3] surveyed 222 patients with type 1 diabetes who used real-time CGM, and found that when the CGM device showed two arrows down ('↓↓'), 42% of the respondents would reduce their insulin dosage to prevent hypoglycemia. With a glucose value of 6.67 mmol/L and a falling glucose trend, 70% of respondents would consume carbohydrates to avoid hypoglycemia. Third, the comparison between real-time CGM and usual care in reducing hypoglycemia (Table 1). A previous retrospective study suggested that CGM reduces the risk of severe hypoglycemia in patients with type 1 diabetes and impaired awareness of hypoglycemia[4]. A randomized controlled trial showed that a sensor-augmented insulin pump with an automated low-glucose insulin suspension reduced the combined rate of severe and moderate hypoglycemia in patients with type 1 diabetes[5]. Recently, Beck et al.[6] carried out a randomized clinical trial that included 158 adults with type 1 diabetes with a mean age of 48 years. Mean glycated hemoglobin reduction from baseline was

1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group, and 0.5% and 0.4%, respectively, in the control group (repeated measures model $P < 0.001$). The median duration of hypoglycemia at <3.9 mmol/L was 43 min/day in the CGM group, and 80 min/day in the control group ($P = 0.002$). Therefore, the authors concluded that among adults with type 1 diabetes, the use of CGM resulted in a greater decrease in glycated hemoglobin level and a shorter duration of hypoglycemia compared with usual care. The current study by van Beers et al.[1] also supported the claim that CGM improves glycemic control and diminishes severe hypoglycemia in adult patients with type 1 diabetes who were at high risk of severe hypoglycemia. This well-designed randomized study is particularly intriguing, as it added the value of real-time CGM to clinical practice. Another randomized controlled trial (HypoCOMPaSS) focused on adults with type 1 diabetes and impaired awareness of hypoglycemia reported improved hypoglycemia awareness and glycemic control from baseline to end-point (24 weeks) with the use of extensive patient guidance, but no added benefit of CGM was shown[7]. It was pointed out that sensors were only used for a median of 57% of the time in the HypoCOMPaSS study, whereas in typical adult patients with long-standing type 1 diabetes and impaired awareness of hypoglycemia, CGM with median sensor usage of 89.4% reduced severe hypoglycemia[1].

This study is solid and convincing due to its following strengths. First, the study focused on adults with type 1 diabetes, aged 18–75 years, with a mean age of 48.6 years and a median diabetes

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Table 1 | Examples of studies using continuous glucose monitoring system in patients with type 1 diabetes

Trial	n	Age (years)	Study design	Study detail	End-points
van Beers et al.[1]	52	48.6 ± 11.6	Randomized controlled cross-over trial (46 weeks in total)	CGM-washout-SMBG (n = 26) or SMBG-washout-CGM (n = 26)	Mean difference in percentage of time spent in normoglycemia; severe hypoglycemia
Ly et al.[5]	95	18.6 ± 11.8	RCT (6 months)	Standard-pump (n = 49) or low-glucose suspension pump (n = 46)	Combined incidence of severe and moderate hypoglycemia
Beck et al.[6]	158	48 ± 13	RCT (24 weeks)	CGM (n = 105) or control group (n = 53)	The difference in change in HbA1c level
Little et al.[7]	96	48.6 ± 12.2	2 × 2 factorial RCT (24 weeks)	MDI/CSII × SMBG/RT–CGM	Between-intervention difference in 24-week hypoglycemia awareness
Choudhary et al.[4]	35	43.2 ± 12.4	Retrospective study (1 year)	Retrospective analysis	Median rates of severe hypoglycemia; HbA1c; the mean Gold score

CGM, continuous glucose monitoring; CMDI, multiple daily insulin injections; HbA1c, glycated hemoglobin; RCT, randomized controlled trial; RT–CGM, real-time continuous glucose monitoring; SII, continuous subcutaneous insulin infusion; SMBG, self-monitoring blood glucose.

duration of 30.5 years. As most patients with impaired awareness of hypoglycemia are aged >40 years and have had diabetes for >25 years, this study focused on the typical adult type 1 diabetes population, whereas some earlier studies included juvenile or adolescent populations. Second, this is a randomized, open-label, cross-over trial. The sample size was calculated carefully, its cross-over design removed between-patient variation and the washout period prevented any substantial carryover effects. Third, the authors included several outcomes. Not only did the study include parameters of time spent in normoglycemia, hypoglycemia and hyperglycemia, but it also discussed the within-day and between-day glucose variability (standard deviation of glucose concentration, coefficient of variation, mean absolute change in glucose concentration, mean of daily differences and continuous overall net glycemic action). A variety of parameters of glycemic variability as end-points enriched the study and expanded the scope of the study to include the discussion of glucose variability.

Furthermore, the study revealed some important characteristics of CGM for clinical use. First, the use of CGM did not prevent all incidents of hypoglycemia, but reduced the duration and severity. Second, CGM does not have an effect beyond the actual intervention because withdrawal of CGM resulted in a reversal of the time spent in the normoglycemic state to baseline values. Third, the equal benefit of CGM for patients on both continuous subcutaneous insulin infusion and multiple daily insulin injections was noted, which suggests that CGM can be used in various patient groups, including those unwilling or unable to change to continuous subcutaneous insulin infusion.

Recurrent hypoglycemia increases the risk of severe hypoglycemia and the development of hypoglycemia unawareness. Real-time CGM, by virtue of its ability to show the direction and rate of change of glucose concentrations, allows users to alter multiple aspects of their diabetes care, including the timing and adjustment of insulin doses, and to take action in hypoglycemia prevention. Further research is required to assess long-term effectiveness, as well as clinical outcomes and adverse effects. Based on real-time CGM, we believe that the artificial pancreas, which couples a CGM to an insulin pump through sophisticated predictive algorithms, holds the promise of eliminating hypoglycemia in the near future.

DISCLOSURE

The author declares no conflict of interest.

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