Editorial

Real-time continuous glucose monitoring decreases the risk of severe hypoglycemia in people with type 1 diabetes and impaired awareness of hypoglycemia

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Hypoglycemia in persons with type 1 diabetes (T1DM) is the consequence of the insulin therapy necessary to control hyperglycemia and prevent its long-term complications. Hypoglycemia also, however, has important clinical consequences, as it is a risk factor for morbidity and mortality and heavily impacts the quality of life of people with diabetes. Unquestionably hypoglycemia contributes to increased health expenditures. Prevention of the risk of hypoglycemia must be one of the main objectives in the treatment of diabetes, especially if the glycemic target is ambitious.

One of the most significant risk factors affecting the frequency and severity of hypoglycemia in persons with T1DM is impaired awareness of hypoglycemia (1,2). This condition is generally associated with defective glucose counter-regulation. Both conditions are caused by frequent, recurrent hypoglycemia and together comprise the "Cryer syndrome" (hypoglycemia-associated autonomic failure, referred to as HAAF) in diabetes (3). Details of the mechanisms of Cryer syndrome have been reviewed elsewhere (3,4). Reducing the number and frequency of hypoglycemic episodes is critical to improving impaired hypoglycemia awareness and the accompanying defective glucose counter-regulation, as shown already more than 25 years ago (5). The first step in the management of a patient's hypoglycemia should be a broad review of possible causes, which can then guide the creation of an individualized, structured treatment program. Such a program should include (I) flexible insulin doses, either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), related both to the carbohydrate content of meals and to physical activity; (II) patient education to develop patient awareness and recognition of activities and situations that are risk-precipitating factors for hypoglycemia; (III) self-monitoring blood glucose (SMBG) to detect hypoglycemia paired with appropriate treatment, most importantly promptly correcting any blood glucose value <70 mg/dL; and (IV) measurement of nighttime glycemia 1–2 times per week (at 03:00–04:00 h) (6). Of all these elements, SMBG is crucial in managing glucose control and preventing hypoglycemia during intensified insulin therapy (7) because it allows dose adjustment of insulin, therapy effectiveness monitoring, and verification of glycemic fluctuations. The difficulty is that, to achieve maximum effectiveness, SMBG must be undertaken multiple times during the day, but such frequent SMBG monitoring is burdensome for many patients and becomes expensive in those countries with limited reimbursement. The recent introduction of continuous glucose monitors (CGM) which can measure the glucose concentration in the interstitial liquid, using a minimally invasive needle sensor placed in the subcutaneous tissue, offers

patients more than an alternative to traditional SMBG, a new approach to interpret indirectly the dynamics of plasma glucose over the 24 h. This reduces the number of daily finger sticks while providing a great deal of data on daily glucose concentration/fluctuation which can be used to better manage treatment. Modern CGM devices can visualize in real-time current glucose and its trend (rtCGM) and generate visual and auditory alerts for hypo/hyperglycemia (8). Due to these features, rtCGM has the potential to reduce the risk of hypoglycemia and should help those at risk of severe hypoglycemia, particularly those affected by impaired awareness of hypoglycemia. Unfortunately, patients at high risk of hypoglycemia have generally been excluded from clinical studies. Until now, only a few small studies have examined the impact of this technology on hypoglycemia risk reduction in people with impaired awareness of hypoglycemia. In fact, even though the majority of people with T1DM are treated with MDI, evidence on using rtCGM in people treating with MDI who have impaired awareness of hypoglycemia is limited to only two studies (9,10). One study on long-lasting T1DM with impaired awareness of hypoglycemia concluded that impaired awareness could be improved, and severe and recurrent hypoglycemia prevented without worsening glycemic control in those using SMBG as well as those using rtCGM (in MDI or CSII) (9). Another study, enrolling a similar group of patients (29 in MDI and 23 in CSII) with hypoglycemia unawareness and at high risk of severe hypoglycemic (10), showed that the number of severe hypoglycemic episodes decreased with rtCGM *vs*. SMBG (14 *vs*. 34 events, P=0.03) with similar results in patients on either CSII or MDI. Overall, the evidence from these relatively small studies points favorably to usage of rtCGM in T1DM, not only in those who are on CSII therapy, but also those treated with MDI who, as said, represent the majority of type 1 treated subjects and for whom this technology may well help to prevent hypoglycemia.

A recent study by Heinemann *et al*. (11) that has evaluated the effectiveness of rtCGM in prevention of hypoglycemia among high-risk individuals with T1DM in SMBG using MDI might have potential for broad application. The primary goal of the study was to determine whether the incidence and severity of hypoglycemia could be reduced by rtCGM (11). In this 6-month, multicenter, open-label, parallel, randomized controlled trial done at 12 diabetes practices in Germany (HypoDE, Hypoglycemia in Deutschland), participants all used MDI (n=149) and were at risk for hypoglycemia [a history of hypoglycemia unawareness (93%) or severe hypoglycemia (60%) in the prior year]. Their main demographic and medical characteristics were: – mean [standard deviation (SD)] age: 46 [11] yrs; diabetes duration 21 (13.6) yrs; body mass index (BMI) 26 [6] kg/m^2; A1C 7.5% (1.0%)/58.3 [11] mmol/mol; females 40%. The participants initially wore masked rtCGM devices for 4 weeks to establish baseline glycemic control. Patients were then randomized to utilize rtCGM or continue SMBG to adjust insulin for 22 weeks. During the final 4-week follow-up period, participants in rtCGM continued its use, while those in SMBG again used masked rtCGM devices. The most significant endpoint was in the baseline-adjusted number of hypoglycemic events [defined as glucose ≤3.0 mmol/L (≤54 mg/dL) for ≥20 min] during the follow-up phase. Between the baseline and follow-up periods, mean hypoglycemic episodes per 28 days decreased from 10.8 to 3.5 in rtCGM patients but remained essentially unchanged (14.4 *vs*. 13.7) in those using SMBG. The occurrence of hypoglycemic events decreased by 72% with rtCGM. Both groups' mean HbA1c values remained the same. A smaller number of severe hypoglycemic events were observed during the treatment and follow-up phases in the rtCGM group (24 episodes) than in the control group (39 episodes). In the latter, the incidence of severe hypoglycemia requiring third party assistance in the follow-up phase was almost twice that observed in the rtCGM group. Both groups' hypoglycemia unawareness scores (Clarke questionnaire) improved by approximately 40%. Glycemic variability, as assessed by coefficient of variation, decreased from the baseline to the follow-up phase in the rtCGM group (from 39.3% to 34.1%), whereas it did not change in SMBG (from 40.5% to 41.1%). Similarly, mean low blood glucose index (LBGI), a risk indicator of severe hypoglycemia (12), decreased in the rtCGM group (from 1.26 to 0.52), while it did not change in SMBG (from 1.6 to 1.53). In sum, this study shows that T1DM patients using MDI who are at high risk for hypoglycemia, rtCGM can reduce this risk without impairing overall glycemic control. Given that the majority of T1DM patients use SMBG and MDI, these findings demonstrate that those T1DM patients could achieve a significant reduction of occurrences of hypoglycemia and hypoglycemia unawareness if rtCGM were more widely implemented. In addition, because treating hypoglycemia carries significant costs and so creates a significant economic burden for national healthcare systems (4), the study by Heinemann *et al*. (11) demonstrates that by using rtCGM in T1DM patients treating with MDI, the cost of treating

episodes of severe hypoglycemia could be reduced and those funds could then be available for use to improve diabetes care. Recently, an international panel of experts (13) has formulated recommendations on CGM use, either rtCGM or intermittently viewed (iCGM). The recommendations are based on the results of the many studies that have shown that rtCGM improves glycemic control and quality of life in both children and adults with T1DM, whether treated with CSII or multiple daily insulin injection therapy. rtCGM improves HbA1c, shortens the length of hypoglycemia and hyperglycemia episodes, and reduces moderate-to-severe hypoglycemia (13). The positive results of the study by Heinemann *et al*. (11) using rtCGM in stand-alone mode (that is not as a part of a sensor-integrated pump system) add important additional information that needs to be integrated into the panel's recommendations. By focusing research on T1DM people with impaired awareness of hypoglycemia and severe hypoglycemia, the Heinemann study represents a meaningful step forward in the transition from the era of SMBG to that of continuous monitoring in these people. These results, if widely disseminated to the community of practitioners treating T1DM patients and to the T1DM patients themselves, could provide an impetus to increased use of rtCGM in clinical practice. Ultimately the goal should be for every T1DM patient, whether in CSII or MDI, particularly those with problematic hypoglycemia, to use rtCGM.

If the use of rtCGM is deeply desirable in T1DM, its use is also possible in the management of other types of diabetes. For example, people with T2DM managed with intensive insulin treatment, experience hypoglycemia more often than they realize and also often do not recognize it when it occurs. In an observational prospective study comprised of 63 stable, insulin-treated patients with T2DM, the patients sequentially recorded two daily capillary blood glucose readings, pre- and/or postprandial, over 8 consecutive weeks and wore a blind CGM system for one more week. More hypoglycemic events were recorded by CGM than by SMBG (3.8% *vs*. 1.7%; P=0.016), especially at night (14). In a 24-week clinical trial in people with T2DM rates of hypoglycemia were found not to be different in those receiving rtCGM and SMBG, although glucose control was a bit better in the rtCGM group (14). It is of note that in the trial hypoglycemia rates were low at baseline and only 11% of people had reduced awareness of hypoglycemia in both groups (15). Therefore, although benefits of rtCGM use have been reported in individuals with T2DM who are managed with or without intensive insulin treatment (13), more studies are needed, particularly in intensively treated T2DM people with problematic hypoglycemia, as in Heinemann's trial in T1DM, to better understand the use of sensor technology to prevent hypoglycemia in T2DM.

Finally, another possible use of rtCGM is in the management of insulin treated diabetes in pregnancy (13). However, in order to better define the role of these technologies, more studies are needed in pregnant women with T1DM to assess their role in improving glucose control and limiting adverse maternal and neonatal outcomes associated with hypoglycemia. Due to limited data, the same can be said about the benefit of rtCGM for individuals with gestational diabetes mellitus not requiring insulin (13).

In closing, one should remember that the risk for severe hypoglycemia follows the onset of hypoglycemia unawareness and impaired counter-regulation which, in turn, develop shortly after repeated daily episodes of mild hypoglycemia. The modern regimens of insulin treatment of T1DM (MDI with new insulin analogues, CSII) should be combined with CGM in all patients, even those who do not suffer yet from hypoglycemia unawareness and impaired counter-regulation, to prevent it.

Also, it must be recognized that while glucose monitoring is a very important component of diabetes management, it is, even with the increased effectiveness enabled by rtCGM, only one component. Other equally important treatment factors must be employed in order to limit severe hypoglycemia in people with diabetes suffering from impaired awareness of hypoglycemia. Among these factors, educating patients about hypoglycemia prevention, determining individual glycemic targets and utilizing flexible insulin doses, both in CSII and MDI, all are necessary elements in a comprehensive and effective diabetes treatment program. Modern technology for T1DM does not work itself if not combined with continuing education of patients and close long-term contact between the patient and the diabetes team.

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Footnote

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