Current Application of Continuous Glucose Monitoring in the Treatment of Diabetes

Pros and cons

JEROEN HERMANIDES, MD[1]
MOSHE PHILLIP, MD, PHD[2]
J. HANS DEVRIES, MD, PHD[1]

The ultimate goal of diabetes technology is to create an artificial pancreas, or closed-loop system. In the early 1970s, the first prototypes became available (1). Although recent advances are promising, the closed-loop system is currently confined to the clinical research center (2). The continuous subcutaneous insulin infusion (CSII) pump became commercially available in the 1980s, and it is now a common and accepted way of providing insulin (3,4). The emergence of continuous glucose monitoring (CGM) followed in the 1990s, with the first reports on CGM by microdialysis in 1992 (5,6). Retrospective needle-type CGM systems were introduced just before the turn of the century (7–10). Currently, there are four subcutaneous CGM systems on the market that have real-time glucose values on display every 1–5 min and feature an alarm function for hypo- and hyperglycemia: the Freestyle Navigator (Abbot Diabetes Care, Alameda, CA), the Guardian Real-Time (Medtronic MiniMed, Northridge, CA), the Dexcom SEVEN (Dexcom, San Diego, CA), and the GlucoDay (Menarini Diagnostics). The first three are needle-type CGMs and the latter is a microdialysis-type sensor. All of these measure glucose via the glucose-oxidase reaction. In this article, we will discuss the pros and cons of the current application of CGM in the treatment of diabetes.

PROS OF CGM—From the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, we learned that lowering HbA_{1c} reduces morbidity and mortality (11,12) and that tight glycemic control is associated with an increased rate of severe hypoglycemic episodes. We therefore should judge the pros of CGM by its HbA_{1c}-lowering potency and its influence on severe hypoglycemia rates. Table 1 summarizes all intervention trials that have been performed with real-time CGM regarding HbA_{1c} and the incidence of severe hypoglycemia.

The Juvenile Diabetes Research Foundation (JDRF) landmark study randomized 322 adults, adolescents, and children with type 1 diabetes at a baseline HbA_{1c} of 7.0–10.0% to CGM or self-monitoring of blood glucose (SMBG). CGM use for 26 weeks significantly reduced HbA_{1c} by 0.5% in adult patients (13). Although the intention-to-treat analyses did not show a significant HbA_{1c} reduction in children and adolescents, it was demonstrated among all age groups that there was a significant HbA_{1c} reduction in patients who used CGM for ≥6 days/week (14). The adolescents were the most infrequent users of CGM devices. In a follow-up study of the JDRF trial, patients initially randomized to the control group were put on CGM after the trial. Again, HbA_{1c} decrease was significantly associated with CGM use among all age groups (15). Previously, Deiss et al. (16) randomized type 1 diabetic patients with baseline HbA_{1c} of ≥8.1% to 3 months of continuous CGM use, biweekly CGM use, or intensive insulin treatment with SMBG. Continuous CGM use resulted in a significant HbA_{1c} reduction of 0.6% compared with conventional treatment, whereas biweekly use did not improve HbA_{1c} compared with conventional treatment. Thus, it seems that the frequency of CGM use is important. This is also evident from the Sensor-Augmented Pump Therapy for A1C Reduction 1 (STAR-1) trial and the RealTrend study (Table 1), in which the efficacy of CGM with CSII was investigated in CSII users and insulin pump–naive type 1 diabetic patients, respectively (17,18). Although there was no significant between-group difference in HbA_{1c} decrease in both studies, subanalyses showed that sensor use of at least 60–70% of the time did result in a significant HbA_{1c} decrease. The importance of frequency of CGM use is further substantiated by results from O'Connell et al. (19), who randomized 62 patients with well-controlled type 1 diabetes using CSII to intervention with CGM or conventional SMBG for 3 months. HbA_{1c} improved by 0.4% in favor of the intervention group, but within the intervention group, HbA_{1c} was 0.5% lower in patients using CGM ≥70% of the time compared with <70% use. Thus, CGM is effective in lowering HbA_{1c} in patients who actually use it. In daily practice, patients who are noncompliant are easy to identify by accessing downloaded data, and (dis)continuation of CGM treatment can be openly discussed.

In addition, initiating CGM treatment might even be more effective when combined with the initiation of CSII. This

From the [1]Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; and the [2]Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
Corresponding author: Jeroen Hermanides, j.hermanides@amc.uva.nl.
This publication is based on the presentations at the 3rd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, F. Hoffmann-La Roche, Janssen-Cilag, Johnson & Johnson, Novo Nordisk, Medtronic, and Pfizer.
DOI: 10.2337/dc11-s219

Table 1—*CGM trials in type 1 diabetes*

Study	Population	Inclusion HbA_{1c}	Prestudy treatment (*n*)	Duration	Comparison	Dropout	Outcome HbA_{1c}	Severe hypoglycemia (*n*)
Deiss et al. (16)	81 children; 81 adults; type 1 diabetes	≥8.1%	CSII (78); MDI (84)	3 months	*1*) CGM continuously; *2*) CGM biweekly; *3*) SMBG	*1*) $n = 4$; *2*) $n = 1$; *3*) $n = 0$	*1*) vs. *3*): −0.6%, $P = 0.003$; *2*) vs. *3*): NR, P = NS; *1*) vs. *2*): NR, P = NS	*1*) 1; *2*) 1; *3*) 0
Hirsch et al. (17) (STAR-1)	146 adults and children; type 1 diabetes	≥7.5%	CSII (146); MDI (0)	6 months	*1*) CGM; *2*) SMBG	*1*) $n = 6$; *2*) $n = 2$	*1*) vs. *2*): −0.11, $P = 0.37$	*1*) 21*; *2*) 18
JDRF study group (13) (JDRF-CGM trial)	114 children; 110 adolescents; 98 adults; type 1 diabetes	7.0–10%	CSII (256); MDI (66)	6 months	*1*) CGM; *2*) SMBG	*1*) $n = 3$; *2*) $n = 2$	Adults *1*) vs. *2*): −0.5%, $P < 0.001$; Adolescents *1*) vs. *2*): 0.08%, $P = 0.52$; Children *1*) vs. *2*): −0.1%, $P = 0.29$	*1*) 14; *2*) 11
O'Connell et al. (19)	62 children and adults; type 1 diabetes	≤8.5%	CSII (62); MDI (0)	3 months	*1*) CGM; *2*) SMBG	*1*) $n = 5$; *2*) $n = 2$	*1*) vs. *2*): −0.4%, $P = 0.009$	*1*) 0; *2*) 0
JDRF study group (34)	29 children; 33 adolescents; 67 adults; type 1 diabetes	<7.0%	CSII (111); MDI (18)	6 months	*1*) CGM; *2*) SMBG	*1*) $n = 1$; *2*) $n = 1$	*1*) vs. *2*): −0.3%, $P < 0.001$	*1*) 9; *2*) 10
Raccah et al. (18) (RealTrend study)	51 children; 81 adults; type 1 diabetes	≥8.0%	CSII (0); MDI (132)	6 months	*1*) CGM and CSII; *2*) SMBG and CSII	*1*) $n = 14$; *2*) $n = 6$	*1*) vs. *2*): −0.2%, $P = 0.09$; Per protocol analyses: *1*) vs. *2*): −0.4%, $P = 0.004$	*1*) 1†; *2*) 0
Hermanides et al. (20) (Eurythmics trial)	83 adults; type 1 diabetes	≥8.2%	CSII (0); MDI (83)	6 months	*1*) CGM and CSII; *2*) SMBG	*1*) $n = 1$; *2*) $n = 4$	*1*) vs. *2*): −1.2%, $P < 0.001$	*1*) 4; *2*) 1
Bergenstal et al. (21) (STAR-3 trial)	156 children; 329 adults; type 1 diabetes	7.4–9.5%	CSII (0); MDI (385)	1 year	*1*) CGM and CSII; *2*) SMBG	*1*) $n = 19$; *2*) $n = 13$	Adults *1*) vs. *2*): −0.6%, $P < 0.001$; Children *1*) vs. *2*): −0.5%, $P < 0.001$	*1*) 32; *2*) 27

*$P < 0.05$. †Number of total severe hypoglycemic episodes per group not given, only episode with seizure/coma. NR, not reported. NS, not significant.

result is relevant, since most type 1 diabetic patients use multiple daily injection (MDI) therapy with SMBG as standard care, especially in Europe (3). In a multicenter randomized controlled trial (RCT) (the Eurythmics trial), adult type 1 diabetic patients (HbA_{1c} at entry ≥8.2%) on intensive treatment were allocated to CGM, augmented with CSII or continuation of their multiple daily injections and SMBG regimen (20). After 26 weeks, this regimen resulted in an HbA_{1c} decrease in the CGM-augmented CSII group of 1.2%. Recently, the STAR-3 trial was published with a design similar to the Eurythmics trial. HbA_{1c} decreased after 1 year in the CSII augmented with CGM group compared with continuation of injection treatment and SMBG in both children and adults (Table 1) (21). In the previously mentioned RealTrend study, initiating CGM-augmented CSII treatment was also superior to starting CSII treatment alone in the per-protocol analysis, indicated by an HbA_{1c} improvement of 0.4% in favor of the CGM-augmented CSII group (18).

It is important to emphasize that these reductions in HbA_{1c} with CGM was not associated with an increase in the number or severity of hypoglycemic episodes.

Next to its effects on HbA_{1c}, CGM seems to have a positive impact on patient-reported outcomes. Despite being confronted throughout the day with diabetes through CGM alarms and the discomfort of the device itself, results from an Internet survey administered to 162 patients using CGM-augmented CSII and 149 patients using CSII alone demonstrated that patients using CGM were more satisfied with their treatment and had better quality of life (22). In the Eurythmics trial, patients randomized to CGM-augmented CSII experienced significantly less problems with their diabetes and increased treatment satisfaction as measured by the Problem Area In Diabetes questionnaire and the Diabetes Treatment Satisfaction questionnaire (20,23,24).

Two other patient groups in which CGM might be of importance are pregnant women with diabetes and hospitalized patients (25,26). In an Australian RCT, 71 women with type 1 diabetes were randomized to antenatal care with CGM at 4- to- 6-week intervals during pregnancy or to standard antenatal care (27). Patients who were allocated to CGM had lower HbA_{1c} levels at the end

of pregnancy and an odds ratio for macrosomia of 0.36 (95% CI 0.13–0.98).

For hospitalized patients, the application of CGM is being investigated, especially with regard to tight glycemic control in the intensive care unit (28). Although concerns exist about the accuracy of sensors in this setting, a recent trial showed that CGMs may prevent hypoglycemia in the intensive care unit (29).

Finally, CGM is an essential part in the development of the closed-loop or artificial pancreas. In the last years, much research has been performed to develop and improve closed-loop systems (30–32). In particular, algorithms are being developed that use the continuous stream of data to control insulin titration (33,34). In a recent publication by Hovorka et al. (2), the efficacy of a closed-loop format was investigated in a controlled trial. The closed-loop comprised different commercially available CGMs for data input, a control algorithm, and a nurse adjusting the insulin pump. Type 1 diabetic patients using CSII were studied overnight, after a meal and after exercise. During the application of the closed-loop system, glucose was significantly more often in the target range and less in the hypoglycemic range compared with the standard CSII regimen. These results are promising, and future studies will have to work toward investigating the closed loop in outpatient settings, most preferably at home.

CONS OF CGM—CGM is effective in specific patient groups with regard to HbA_{1c} lowering. First, and most evidently, poorly controlled type 1 diabetic patients seem to benefit from CGM when they use it frequently enough. This result reveals the first problem, because especially children and adolescents are noncompliant with CGM use, and its value in this patient group is therefore limited to only the most motivated patients (13,35). Second, there are many patients that do not tolerate the CGM devices. This scenario is illustrated by the higher dropout rates in the CGM arms of the RCTs (Table 1). Also, in the JDRF trial and the Eurythmics trial, patients were already exposed to (blinded) CGMs before inclusion or randomization to obtain a baseline CGM measurement for all patients (13,20). This resulted in 23 of 345 and 4 of 87 patients dropping out before randomization in the JDRF trial and Eurythmics trial, respectively—probably patients not tolerating the device. Clearly, CGM is not for everyone.

Furthermore, in most trials summarized in Table 1, patients were either already on CSII before randomization or were put on CSII during the trial. Consequently, we have to be cautious when extrapolating the RCT results to patients using CGM in combination with MDI therapy.

Now that the first substantial randomized controlled trials on CGM have been performed, another conclusion is that CGM does not seem to prevent severe hypoglycemia. This is in contrast with early expectations and current beliefs. Table 1 shows the incidences of severe hypoglycemia across several CGM trials that are mostly comparable in the intervention and control groups. In the STAR-1 trial, there were even significantly more severe hypoglycemic events in the CGM arm that in the control arm (17). There seem to be three possible explanations for the inability of CGM to prevent severe hypoglycemia. First, there is CGM inaccuracy. When compared with actual plasma glucose values, CGMs have an inaccuracy up to 21% (expressed as mean absolute difference, |CGM glucose − plasma glucose|/plasma glucose). This number is even higher in the hypoglycemic range or during rapid rise and fall of the plasma glucose (36). Probably a physiologic and instrumental delay, inherent to the current real-time CGMs, contribute to the inaccuracy of the devices (37).

Second, during severe hypoglycemia, there is a decline of cognitive function and patients are less adequate in responding to acoustic or vibration alarms (38). Third, during intensive sport activities, which bring along an increased risk of hypoglycemia, the CGM device is more likely to be put aside. However, we have to note that no trials so far were specifically designed and powered to investigate CGM in relation to prevention of severe hypoglycemia. One multicenter trial is underway and the results are eagerly awaited (NCT00843609). In an observational follow-up study from the JDRF-CGM study group, CGM use was associated with both HbA_{1c} reduction and reduction in severe hypoglycemia rate (15). This association indicates the need for controlled trials, perhaps with a longer duration than 6 months, to allow for the possibility that a longer user learning phase is needed to learn to avoid severe hypoglycemia. Such trials investigating the value of CGM in preventing severe hypoglycemia should be targeted to patients at high risk for severe hypoglycemia. This is also important for reimbursement of CGM in well-controlled type 1 diabetic patients. Because these patients have already achieved their HbA_{1c} targets without CGM, the incremental CGM value has to come from preventing hypoglycemia and gaining quality of life.

In addition, CGM is always discussed in the context of type 1 diabetes, whereas the vast majority of the diabetes population consists of type 2 diabetic patients. Blood glucose monitoring with SMBG is the standard of care, but its effectiveness is debated (39). Having this in mind, the evidence on CGM in the type 2 diabetic population is surprisingly scarce. Yoo et al. (40) performed an RCT in 65 patients with type 2 diabetes, comparing 12 weeks of intermittent real-time CGM use (3 days per month) with standard care using SMBG. In both groups, HbA_{1c} decreased, but it decreased significantly more (-0.5%, $P = 0.004$) in the CGM arm. To our knowledge, this is the only RCT that specifically assessed HbA_{1c} decrease by CGM in type 2 diabetes. Adequate powered trials with sufficient follow-up time are needed.

Finally, the costs of the CGM devices are a major con. Treatment with CGM costs about $4,930–7,120 per person-year compared with $550–2,740 for SMBG (41). It can be assumed that CGM would be cost-effective in poorly controlled type 1 diabetic patients because of the gain in long-term health benefits, as indicated by HbA_{1c} lowering. However, the cost-effectiveness of CGM in other patient groups or in preventing hypoglycemia is hard to assess because of the existing lack of evidence. This result is reflected in the current reimbursement status of CGMs. In the U.S., federal Medicare and most other health plans reimburse real-time CGM only for type 1 diabetic patients who are not meeting the ADA HbA_{1c} targets or experience severe hypoglycemic events. In Europe, real-time CGM is only reimbursed in Sweden and Slovenia. CSII-using patients in Sweden with two or more severe hypoglycemic episodes per year, patients with HbA_{1c} >10% while receiving intensive insulin therapy, and children who require at least 10 plasma glucose tests per 24 h are eligible for reimbursement. If CGM does not have the desired effect after 3 months, it should be discontinued. In Israel, real-time CGM is included in the National Health Basket and is reimbursed

by the Sickness Funds. Children (aged 6–18 years) with type 1 diabetes and severe hypoglycemia unawareness, experiencing two severe episodes of hypoglycemia in the past 12 months (requiring ambulance assistance or emergency ward treatment), can apply for reimbursement.

CONCLUSIONS—According to currently available evidence, CGM lowers HbA_{1c} without increase in the incidence of severe hypoglycemic episodes in patients with type 1 diabetes who use the device frequently. Furthermore, CGM seems to have a positive impact on quality of life in this patient group. Treating adolescents and children with CGM requires additional attention, since these patients tend to use CGM less frequently. So far, CGM is not indicated for preventing severe hypoglycemia or treating type 2 diabetes because supporting evidence is pending. Results of the application of CGM in pregnant women with diabetes or in-hospital hyperglycemia are promising but need further investigation. Future studies should address the patient groups that have been neglected so far and analyze cost-effectiveness. Finally, CGM accuracy needs improvement, as does the user-friendliness of the devices. Predictions on the feasibility of the closed-loop system have proven too optimistic too often; however, we do believe that major steps forward have been made in the last few years.

Acknowledgments—M.P. received research grants from Abbott Diabetes Care and Medtronic. J.H.D. received fees for speaking engagements and research support from Abbott Diabetes Care, Dexcom, and Medtronic. No other potential conflicts of interest relevant to this article were reported.

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