Current Application of Continuous Glucose Monitoring in the Treatment of Diabetes

Pros and cons

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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 hypoglycemia 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 HbA1c 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 HbA1c-lowering potency and its influence on severe hypoglycemia rates. Table 1 summarizes all intervention trials that have been performed with real-time CGM regarding HbA1c 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 HbA1c of 7.0–10.0% to CGM or self-monitoring of blood glucose (SMBG). CGM use for 26 weeks significantly reduced HbA1c by 0.5% in adult patients (13). Although the intention-to-treat analyses did not show a significant HbA1c reduction in children and adolescents, it was demonstrated among all age groups that there was a significant HbA1c 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, HbA1c decrease was significantly associated with CGM use among all age groups (15). Previously, Deiss et al. (16) randomized type 1 diabetic patients with baseline HbA1c of ≥8.1% to 3 months of continuous CGM use, bi-weekly CGM use, or intensive insulin treatment with SMBG. Continuous CGM use resulted in a significant HbA1c reduction of 0.6% compared with conventional treatment, whereas biweekly use did not improve HbA1c 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 HbA1c decrease in both studies, subanalyses showed that sensor use of at least 60–70% of the time did result in a significant HbA1c 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. HbA1c improved by 0.4% in favor of the intervention group, but within the intervention group, HbA1c was 0.5% lower in patients using CGM ≥70% of the time compared with <70% use. Thus, CGM is effective in lowering HbA1c 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...
### Table 1—CGM trials in type 1 diabetes

| Study                                      | Population                        | Inclusion HbA1c | Prestudy treatment (n) | Duration | Comparison | Dropout | Outcome HbA1c | 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 | n = 4; 1) vs. 3): −0.6%, P = 0.003; 2) vs. 3): NR, P = NS; 3) n = 0; 1) vs. 2): NR, P = NS | 1) 1; 2) 1; 3) 0 | 1) 0; 2) 5; 3) 3 |
| Hirsch et al. (17)                         | 146 adults and children; type 1 diabetes | ≥7.5%           | CSII (146); MDI (0)   | 6 months | 1) CGM; 2) SMBG; 3) SMBG | n = 6; 1) vs. 2): −0.11, P = 0.37 | 1) 21*; 2) 18 | 1) 0; 2) 0; 3) 0 |
| JDRF study group (13)                      | 114 children; 110 adolescents; type 1 diabetes | 7.0–10%         | CSII (256); MDI (66)  | 6 months | 1) CGM; 2) SMBG | n = 3; Adults 1) vs. 2): −0.5%, P < 0.001; 2) n = 2 | 1) 14; 2) 11 | 1) 10; 2) 10; 3) 0 |
| JDRF-CGM trial                             | 98 adults; type 1 diabetes         |                 |                        |          |            |         |               |                         |
| Connell et al. (19)                        | 62 children and adults; type 1 diabetes | ≤8.5%           | CSII (62); MDI (0)    | 3 months | 1) CGM; 2) SMBG | n = 5; 1) vs. 2): −0.4%, P = 0.009 | 1) 0; 2) 2 | 1) 0; 2) 0; 3) 0 |
| JDRF study group (34)                      | 29 children; 33 adolescents; type 1 diabetes | <7.0%           | CSII (111); MDI (18) | 6 months | 1) CGM; 2) SMBG | n = 1; 1) vs. 2): −0.3%, P < 0.001 | 1) 9; 2) 10 | 1) 0; 2) 0; 3) 0 |
| Raccab et al. (18)                         | 51 children; 81 adults; type 1 diabetes | ≥8.0%           | CSII (0); MDI (132)  | 6 months | 1) CGM and CSII; 2) SMBG and CSII | n = 6; 1) vs. 2): −0.2%, P = 0.09; 2) Per protocol analyses: 1) vs. 2): −0.4%, P = 0.004 | 1) 1′; 2) 0 | 1) 0; 2) 0; 3) 0 |
| Hermanides et al. (20)                     | 83 adults; type 1 diabetes         | ≥8.2%           | CSII (0); MDI (83)   | 6 months | 1) CGM and CSII; 2) SMBG | n = 1; 1) vs. 2): −1.2%, P < 0.001 | 1) 4; 2) 1 | 1) 0; 2) 0; 3) 0 |
| Bergenstal et al. (21)                     | 156 children; 329 adults; type 1 diabetes | ≥7.4–9.5%       | CSII (0); MDI (385)  | 1 year   | 1) CGM and CSII; 2) SMBG | n = 13; Adults 1) vs. 2): −0.6%, P < 0.001; 2) n = 2 | 1) 32; 2) 27 | 1) 0; 2) 0; 3) 0 |
| Eurythmics trial                           |                                    |                 |                        |          |            |         |               |                         |
| Hermanides et al. (20)                     | 83 adults; type 1 diabetes         | ≥8.2%           | CSII (0); MDI (83)   | 6 months | 1) CGM and CSII; 2) SMBG | n = 1; 1) vs. 2): −1.2%, P < 0.001 | 1) 4; 2) 1 | 1) 0; 2) 0; 3) 0 |
| STAR-3 trial                               |                                    |                 |                        |          |            |         |               |                         |

*P < 0.05. †Number of total severe hypoglycemic episodes per group not given, only episode with seizure/coma. NR, not reported. NS, not significant.
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 HbA1c 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 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 HbA1c 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 HbA1c 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, HbA1c 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 HbA1c 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 concern. 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 HbA1c 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 HbA1c 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 HbA1c >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.
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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 reimbursements.

CONCLUSIONS—According to currently available evidence, CGM lowers HbA1c, 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.

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References

1. Albisser AM, Leibl BS. The artificial pancreas. Clin Endocrinol Metab 1977;6: 457–479
2. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751
3. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. Diabetes Care 2002;25:593–598
4. Shalitin S, Philip M. The use of insulin pump therapy in the pediatric age group. Horm Res 2008;70:14–21
5. Bolinder J, Ungerstedt U, Arner P. Microdialysis measurement of the absolute glucose concentration in subcutaneous adipose tissue allowing glucose monitoring in diabetic patients. Diabetologia 1992;35: 1177–1180
6. Bolinder J, Ungerstedt U, Arner P. Long-term continuous glucose monitoring with microdialysis in ambulatory insulin-dependent diabetic patients. Lancet 1993; 342:1080–1085
7. Bode BW, Gross TM, Thornton KR, Mastrostato J. Continuous glucose monitoring used to adjust diabetes therapy improves glycylated hemoglobin: a pilot study. Diabetes Res Clin Pract 1998;46: 183–190
8. Chase HP, Kim LM, Owen SL, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. Pediatrics 2001;107:222–226
9. Ludvigsson J, Hansa R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003;111:933–938
10. Tänenberg R, Bode B, Lane W, et al. Use of the continuous glucose monitoring system to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clin Proc 2004;79: 1521–1526
11. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetic patients. N Engl J Med 1993;329:977–986
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837–853
13. Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 1998;338:984–986
14. Beck RW, Buckingham B, Miller K, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care 2009;32: 1947–1953
15. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (JDRF-CGM) trial. Diabetes Care 2010;33:17–22
16. Deiss D, Bolinder J, Riveline J, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732
17. Hirsch IB, Abelson J, Bode BW, et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol Ther 2008; 10:377–383
18. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: The RealTrend study. Diabetes Care 2009;32:2245–2250
19. O’Connell MA, Donath S, O’Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009;52:1250–1257
20. Hermanides J, Nørgaard K, Bruttomesso D, et al. Sensor-augmented pump therapy substantially lowers HbA1c. Diabet Med. 5 February 2011 [Epub ahead of print]
21. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010;363:311–320
22. Peyrot M, Rubin RR. Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system. Diabetes Technol Ther 2009;11: 57–62
23. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. In Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice. Bradley C, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 111–132
24. Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. Diabetes Care 1995;18:754–760
25. Hermanides J, DeVries JH. Sense and nonsense in sensors. Diabetologia 2010; 53:593–596
26. Yogev Y, Chen R, Ben-Harroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes melitus. Obstet Gynecol 2003;101:633–638
27. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008;337: a1680
28. Logtenberg SJ, Kleeistra N, Snellen FT, et al. Pre- and postoperative accuracy and safety of a real-time continuous glucose monitoring system in cardiac surgical patients: a randomized pilot study. Diabetes Technol Ther 2009;11:31–37
29. Holzinger U, Warszawski J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. Diabetes Care 2010;33:467–472
30. Clarke WL, Anderson S, Breton M, Patek S, Kashmer L, Kovatchev B. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. J Diabetes Sci Tech 2009;3: 1051–1058
31. Renard E, Place J, Cantwell M, Chevassus H, Palerm CC. Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery: feasibility study testing a new model for the artificial pancreas. Diabetes Care 2010;33:121–127
32. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934–939
33. Hanaire H. Continuous glucose monitoring and external insulin pump: towards a subcutaneous closed loop. Diabetes Metab 2006;32:534–538
34. Atlas E, Nimri R, Miller S, Gurmberg EA, Phillip M. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. Diabetes Care 2010;33:1072–1076
35. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383
36. Wentholt IM, Hoekstra JB, DeVries JH. Continuous glucose monitors: the long-awaited watch dogs? Diabetes Technol Ther 2007;9:399–409
37. Wentholt IM, Hart AA, Hoekstra JB, DeVries JH. Relationship between interstitial and blood glucose in type 1 diabetes patients: delay and the push-pull phenomenon revisited. Diabetes Technol Ther 2007;9:169–175
38. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26:1902–1912
39. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A, Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ 2008;336:1177–1180
40. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2008;82:73–79
41. Pham M. Medtronic diabetes: sizing the market for realtime, continuous blood glucose monitors from MDT, DXCM, and ABT [article online], 2006. Available from http://www.research.hsbc.com. Accessed 28 September 2009