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COMMENTARY

Sense and nonsense in sensors

J. Hermanides · J. H. DeVries

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Abstract Continuous subcutaneous glucose monitoring (CGM) is a developing technology in the treatment of diabetes mellitus. The first randomised controlled trials on its efficacy have been performed. In several studies, CGM lowered HbA_{1c} in adult patients with suboptimally controlled type 1 diabetes mellitus, when selecting compliant patients who tolerate the device. However, as a preventive tool for hypoglycaemia, CGM has not fulfilled the great expectations. Increasing reimbursement of CGM is expected in the near future, awaiting studies on cost-effectiveness.

Keywords Continuous glucose monitoring · HbA_{1c} · Reimbursement · Severe hypoglycaemia

Abbreviations

CGM	Continuous subcutaneous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
JDRF	Juvenile Diabetes Research Foundation
RCT	Randomised controlled trial
SMBG	Self-monitoring of blood glucose

Pioneering work of artificially replacing the glucose-monitoring function of the pancreas started in the 1970s [1]. With the introduction of the microdialysis technique in the early 1990s, the future of continuous subcutaneous glucose monitoring (CGM) seemed bright and shiny [2, 3]. The great expectation was that, by providing the patient with a continuous stream of data and alarms for otherwise unrecognised (nocturnal) hypo- and hyperglycaemia, the HbA_{1c} target of <7% was in reach and the main barrier to effective diabetes treatment—the occurrence of severe hypoglycaemia—could be overcome [4–6]. Even more, integrating CGM and continuous subcutaneous insulin infusion (CSII) would mean it would be a matter of time before the closed-loop system would be available [7]. Several years later, the first needle-type sensor became clinically available, though it could only be read out retrospectively [8]. Currently, there are three real-time CGM systems on the market that are approved by the US Food and Drug Administration (FDA) and have the Conformité Européenne (CE) mark: the Freestyle Navigator (Abbott Diabetes Care, Alameda, CA, USA); the Guardian Real-Time (Medtronic MiniMed, Northridge, CA, USA); and the DexCom SEVEN (DexCom, San Diego, CA, USA; only available in the USA). All these systems measure glucose in the subcutaneous tissue and provide real-time glucose measurements every 1–5 min. The first randomised controlled trials (RCTs) have now been performed with real-time CGM, prompting the next questions: did the sensor fulfil expectations and is this reflected in the current reimbursement status of the device?

Effect on HbA_{1c}

The first RCT, performed by Deiss and colleagues, investigated a needle-type continuous subcutaneous glucose monitor in patients with poorly controlled type 1 diabetes (HbA_{1c} ≥8.1% on intensive treatment) [9]. There was a difference in HbA_{1c} reduction of 0.6% after 3 months in favour of patients who were instructed to use the device continuously, as compared with patients using conventional

J. Hermanides · J. H. DeVries (✉)
Department of Internal Medicine, Academic Medical Centre,
P.O. Box 22660, 1100 DD Amsterdam, the Netherlands
e-mail: J.H.DeVries@amc.uva.nl

treatment. In a third arm, patients used CGM biweekly, and this did not result in a significant HbA_{1c} improvement. A subsequent 26 week randomised treat-to-target study performed by Hirsch and coworkers (the STAR 1 trial) yielded disappointing results [10]. There was no significant difference in change in HbA_{1c} between type 1 diabetes patients using CSII randomised to either augmenting their current therapy with CGM or continuing with their standard self-monitoring of blood glucose (SMBG). In both groups, there was a decrease in HbA_{1c} of 0.6–0.7%. That the decreases in HbA_{1c} were comparable in both groups was attributed to intensification of the treatment in both the control and intervention groups. It seems that in an attempt to assure equal attention times in both groups, the control group was treated more intensively than would be feasible in daily practice. In the Juvenile Diabetes Research Foundation (JDRF) study, three different age groups (≥25, 15–24 and 8–14 years) were randomised to either CGM or SMBG continuation [11]. All patients had type 1 diabetes and the vast majority were already using CSII. The mean difference in HbA_{1c} change was 0.5% after 26 weeks in favour of patients using CGM, but this was only in those aged 25 years and older. No significant difference in HbA_{1c} change was detected in the other age groups. In both the STAR 1 and the JDRF trials, the frequency of sensor usage was strongly correlated to the decrease in HbA_{1c}. This is in line with the study from Deiss et al. [9] and the recently published RealTrend study [12]. In this latter study, patients administering multiple daily injections and with an HbA_{1c}≥ 8% at inclusion started with either CSII therapy or sensor-augmented pump therapy for 26 weeks. From a predefined analysis, HbA_{1c} improved compared with the CSII group only in patients using the sensor >70% of the time. Unfortunately, patients in the sensor-augmented pump group had already used CGM for 9 days before the baseline HbA_{1c} measurement was performed and therefore the observed HbA_{1c} difference, 0.41%, may have been underestimated. The combination of CGM and CSII has also been investigated in the recently presented Eurythmics trial, where a difference in HbA_{1c} improvement of 1.21% in favour of the sensor-augmented pump group was found when type 1 diabetes patients (HbA_{1c} at entry ≥8.2%), who were using multiple daily injection therapy and SMBG, were randomised to continuing their current therapy or starting CGM-augmented insulin-pump therapy [13]. It is interesting that the JDRF trial and the Eurythmics trial, both showing a significant HbA_{1c} improvement in the intervention group, confronted patients with a short period of blinded CGM usage at baseline before randomisation. Patients who did not tolerate the device, and therefore would be likely to drop out or be non-compliant during the study course, were at least partly filtered out before randomisation.

Effect on severe hypoglycaemia

The improvement in HbA_{1c} in the different RCTs was not accompanied by a significant increase in severe hypoglycaemia [9–13]. This seems reassuring, but CGM did not fulfil the expectation that its use would reduce the frequency of severe hypoglycaemic events [14]. Even more, in the STAR 1 trial, the use of CGM was associated with a significant increase in severe hypoglycaemia. This is most likely related to the reduced awareness of auditory and vibratory alarms during hypoglycaemia and non-use of the device during high-risk activities, such as intensive sports. No study so far has shown a decrease in the frequency of severe hypoglycaemia in a CGM arm as compared with the control arm in type 1 diabetes. Indeed, sensors have an inaccuracy of up to 21% when comparing plasma glucose values with subcutaneous glucose values [15]. This inaccuracy is even more pronounced in the hypoglycaemic range. In addition, the usefulness of the CGM devices for detecting forthcoming hypoglycaemia is limited by a putative physiological delay between the blood glucose and glucose concentration in the subcutaneous tissue, which is accompanied by an instrumental delay of the sensor [16]. In other words, patients need more time to prevent hypoglycaemia, especially when they have hypoglycaemia unawareness. Perhaps the developing technology will result in an alarm function for predicting hypoglycaemia by using the rate of change in glucose in the lower euglycaemic range. For now, CGM is insufficient for the prevention of severe hypoglycaemia.

Costs and reimbursement

Interestingly, it is the argument of possibly preventing severe hypoglycaemia that has persuaded healthcare organisations in Israel to reimburse CGM use. Children with type 1 diabetes who have experienced more than two severe hypoglycaemic episodes within 1 year are entitled to CGM compensation. In addition, real-time CGM is now covered by the majority of health plans in the USA, including the federal Medicare program. Reimbursement is generally available for type 1 patients with severe hypoglycaemia or those who are not meeting American Diabetes Association HbA_{1c} targets. In the Netherlands and part of Italy, retrospective CGM is currently reimbursed. The Czech Republic covers up to four sensors per year for retrospective CGM and in Sweden, real-time CGM is reimbursed for patients using CSII and having two or more severe hypoglycaemic episodes per year, children who require at least ten plasma glucose tests per 24 h and patients with HbA_{1c} >10% while receiving optimised insulin therapy. The reimbursement indication of hypoglycaemia illustrates that so far, coverage was based on

feeling rather than the (scarce) evidence. This is not to say that CGM is not able to reduce severe hypoglycaemia, but we need randomised trials in patients at high risk for severe hypoglycaemia (i.e. those suffering from hypoglycaemia unawareness). From the results of the clinical trials to date, we can now argue that CGM offers a clear health benefit, expressed as HbA_{1c} lowering, for type 1 diabetes patients with HbA_{1c} values above 8%. The additional costs for sensors are US$4380 per person year compared with US $550–2740 when using SMBG [17]. Consequently, we need to calculate whether the long-term health benefits of CGM following from ascertained lowering of HbA_{1c} outweigh the costs when compared with standard care with multiple daily injections and/or insulin pumps. A similar comparison was performed by Roze and colleagues indicating that the cost-effectiveness of CSII is acceptable [18]. A technical appraisal from the National Institute for Health and Clinical Excellence (England and Wales) seems timely.

Other patient groups

The application of CGM in patient groups other than those with type 1 diabetes is limited. No trials with adequate duration assessing HbA_{1c} change have been performed for patients with type 2 diabetes [19]. One particular patient group that warrants special attention is pregnant women with diabetes. CGM has proven effective in improving glucose control at the end of pregnancy [20]. It resulted in fewer cases of macrosomia in the offspring, with an odds ratio of 0.36 (95% CI 0.13 to 0.98) [21]. As it concerns a limited time span, reimbursement of CGM in this group should impose no significant financial burden on the healthcare system.

Finally, the use of CGM for treating in-hospital hyperglycaemia could be valuable, and the first randomised studies are awaited. However, the advantage of CGM in this setting may be less evident, as frequent blood sampling is standard practice in the intensive care unit and CGM accuracy may suffer if the circulation is compromised [22].

Conclusion

CGM with or without CSII has been proven to lower HbA_{1c} in adult patients with type 1 diabetes mellitus and HbA_{1c} values above 8%, when compliant patients who tolerate the device are selected. However, CGM is not the final answer to severe hypoglycaemia. Awaiting a cost-effectiveness analysis, increasing reimbursement of CGM is expected.

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