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CHAPTER 5

TECHNOLOGY FOR HYPOGLYCAEMIA: CSII AND CGM

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J Hans De Vries

ABSTRACT

This chapter describes the technology with the potential to prevent or limit exposure to hypoglycaemia. These include continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) systems. An overview of the impact of these methods on the occurrence of hypoglycaemic events compared to standard treatment (multiple daily injections or home blood glucose monitoring) in patients with type 1 diabetes is given. CSII is effective to reduce the frequency of severe hypoglycaemia. Against expectations, CGM seems unable to prevent hypoglycaemia. The reasons why CGM seems unable to limit exposure to severe, mild and nocturnal hypoglycaemia in patients with type 1 diabetes with and without impaired hypoglycaemia awareness are discussed. We also point to future research that may help reduce hypoglycaemia exposure.
INTRODUCTION

Advances in technology that have the potential to prevent or limit exposure to hypoglycaemia, include continuous subcutaneous insulin infusion and continuous glucose monitoring systems. An overview of their impact on the occurrence of hypoglycaemic events compared to standard treatment in patients with type 1 diabetes is given. The reasons why continuous glucose monitoring seems unable to prevent severe hypoglycaemia are discussed. This is followed by a section on cost and reimbursement status and finishes with future expectations.

INSULIN PUMP THERAPY

Insulin pump therapy or continuous subcutaneous insulin infusion (CSII) emerged in the late 70s. It is now a common and accepted way of administering insulin.

An insulin pump continuously infuses fast acting insulin subcutaneously at variable rates. In addition, the user can administer additional doses at meal times or to correct for a high glucose concentration. The difference between insulin delivered by CSII or multiple daily injections (MDI) lies in the pump’s ability to differentiate the supply of basal insulin throughout the 24 hours of the day. This better mimics the physiological situation than injections of basal insulin. Also, insulin delivery can be decreased or even temporarily stopped in case of unanticipated exercise, a situation that can only be dealt with by ingesting food in case of MDI treatment. The most important indication for CSII is the desire for better glycaemic control in those with suboptimal glucose levels. The patient’s motivation, educational level and interaction with the treatment team are important determinants of success.

Adverse events that may arise with CSII are pump malfunction, infection at the injection site, irritation or discomfort 13.

Meta-analyses of studies comparing CSII and MDI treatment demonstrated improved glycaemic control with the use of CSII therapy in patients with type 1 diabetes mellitus 4–5. In addition, they also show that insulin pump therapy reduces the risk of severe hypoglycaemia with a rate ratio of 2.89 (95% CI 1.45 to 5.76) for randomised controlled trials. The reduction was greatest in those with the highest initial severe hypoglycaemia rates on MDI 6. Another recent meta-analysis shows an odds ratio for severe hypoglycaemia of 0.48 in favour of CSII 7.

MONITORING

The current recommendations of the American Diabetes Association suggest that type 1 diabetes patients undertake home blood glucose monitoring (HBGM) three or more times
This provides an incomplete picture of blood glucose fluctuations. In addition, finger stick measurements are painful and regular testing requires great devotion from the subjects. It is estimated that 46% of patients with insulin treated diabetes self-monitor their blood glucose less than 3 times each day.

**Continuous glucose monitoring**

Continuous glucose monitoring (CGM) devices date from the nineties of the last century. CGM systems measure glucose via the glucose-oxidase reaction in interstitial fluid and translate this via a calibration into a value resembling blood glucose. This semi-continuous information identifies fluctuations that would not be identified with self-monitoring. CGM is considered to be particularly useful for children, patients with poorly controlled diabetes, women during pregnancy and patients with impaired awareness of hypoglycaemia. Currently, the use of CGM is not common practice, with only sporadic reimbursement in Europe (see subsection COST AND REIMBURSEMENT).

Most CGM systems use a small needle type sensor inserted in the subcutaneous adipose tissue. Two types of CGM systems can be discriminated:

- systems that measure the glucose concentration during a number of days: the information is stored in a monitor and can be downloaded later;
- real-time systems that continuously provide the actual glucose concentration on a display for longer periods of time.

There are four real-time CGM systems on the market that display glucose values every 1-5 minutes and feature an alarm function for hypo- and hyperglycaemia:

- The Freestyle Navigator (Abbot Diabetes Care, Alameda, CA, USA)
- The Guardian Real-Time (Medtronic MiniMed, Northridge, CA, USA)
- The Dexcom SEVEN (Dexcom, San Diego, CA, USA)
- The GlucoDay (Menarini Diagnostics, Florence, Italy)

Although HbA1c is lowered more when real-time CGM is used continuously, it is often used intermittently (e.g. a couple of days per month or in intervals of five to seven days) to reduce costs. The current evidence of CGM for the prevention of severe, mild and nocturnal hypoglycaemia and hypoglycaemia prevention in patients with impaired awareness will be discussed.
Severe hypoglycaemia

Early expectations were that CGM would prevent severe hypoglycaemia, but evidence is still lacking (Table 1). In the STAR-1 Trial, there were even significantly more severe hypoglycaemic events in the CGM arm than in the control arm 10. Meta-analysis of CGM intervention trials in type 1 diabetes for the occurrence of severe hypoglycaemia shows a non-significant odds ratio of 1.37 (95% CI: 0.83, 2.25) with CGM use compared to HBGM in a random effects model (Figure 1). There are at least six possible explanations for the inability of CGM to prevent severe hypoglycaemia:

- improved glycaemic control
- long learning phase
- CGM inaccuracy
- inadequate response to hypoglycaemic alarm
- intolerance of the CGM device
- insufficient study design

These will be discussed in more detail below.

Improved glycaemic control

In a recent meta-analysis an overall difference of 0.30% (3 mmol/mol) in HbA1c was shown in favour of CGM compared to HBGM that was statistically significant 11. The improvement in glycaemic control following from CGM use may lead to an increase in

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CGM Events</th>
<th>Total</th>
<th>HBGM Events</th>
<th>Total</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
<th>Odd Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Battellino 2011</td>
<td>0</td>
<td>62</td>
<td>0</td>
<td>58</td>
<td>Not estimable</td>
<td></td>
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<td>Bergenstal 2010</td>
<td>32</td>
<td>247</td>
<td>27</td>
<td>248</td>
<td>1.22 [0.71, 2.01]</td>
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<tr>
<td>Dei 2006</td>
<td>2</td>
<td>103</td>
<td>0</td>
<td>53</td>
<td>2.64 [0.12, 55.89]</td>
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<td>Hermanides 2011</td>
<td>4</td>
<td>43</td>
<td>1</td>
<td>35</td>
<td>3.49 [0.37, 32.72]</td>
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<tr>
<td>Hirsch 2008</td>
<td>11</td>
<td>66</td>
<td>3</td>
<td>72</td>
<td>4.60 [1.22, 17.30]</td>
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<tr>
<td>JDRF CGM Study Group 2008</td>
<td>14</td>
<td>162</td>
<td>11</td>
<td>155</td>
<td>1.24 [0.54, 2.82]</td>
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<tr>
<td>JDRF CGM Study Group 2009</td>
<td>9</td>
<td>67</td>
<td>10</td>
<td>62</td>
<td>0.81 [0.30, 2.14]</td>
<td></td>
</tr>
<tr>
<td>Kordonouri 2010</td>
<td>0</td>
<td>76</td>
<td>4</td>
<td>78</td>
<td>0.11 [0.01, 2.04]</td>
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<tr>
<td>O’Connell 2009</td>
<td>0</td>
<td>29</td>
<td>0</td>
<td>29</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Racah 2009</td>
<td>1</td>
<td>30</td>
<td>0</td>
<td>53</td>
<td>5.44 [0.25, 137.82]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>885</strong></td>
<td></td>
<td><strong>843</strong></td>
<td></td>
<td><strong>1.37 [0.83, 2.25]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events 73 56
Heterogeneity: Tau² = 0.10; CH² = 8.93, df = 7 (p = 0.26); P = 22%
Test for overall effect: Z = 1.24 (p = 0.22)

Figure 1 - Forest plot of the incidence of severe hypoglycaemia in CGM intervention trials. CGM: continuous glucose monitoring, HBGM: home blood glucose monitoring, Events: severe hypoglycaemic events, Total: number of subjects
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Inclusion HbA1c</th>
<th>Pre-study</th>
<th>Duration</th>
<th>Comparison</th>
<th>Drop out</th>
<th>Outcome HbA1c</th>
<th>Severe hypoglycaemia (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battelino</td>
<td>2011</td>
<td>120 adults and children</td>
<td>&lt;7.5%</td>
<td>CSII (81); MDI (39)</td>
<td>26 weeks</td>
<td>1) CGM; 2) HBGM</td>
<td>1) n=10; 2) n = 9</td>
<td>1 vs. 2: -0.4%, ( p &lt; 0.008 )</td>
<td>1) 0; 2) 0</td>
</tr>
<tr>
<td>Bergenstal (STAR-3 Trial)</td>
<td>2010</td>
<td>156 children</td>
<td>7.4%-9.5%</td>
<td>CSII (0); MDI (385)</td>
<td>1 year</td>
<td>1) CGM and CSII; 2) HBGM</td>
<td>1) n=19; 2) n = 13</td>
<td>adults 1 vs. 2: -0.6%, ( p &lt; 0.001 ); children 1 vs. 2: -0.5%, ( p &lt; 0.001 )</td>
<td>1) 32; 2) 27</td>
</tr>
<tr>
<td>Deiss</td>
<td>2006</td>
<td>81 children</td>
<td>≥8.1%</td>
<td>CSII (78); MDI (84)</td>
<td>3 months</td>
<td>1) CGM continuously; 2) CGM biweekly; 3) HBGM</td>
<td>1) n=4; 2) n=1; 3) n=0</td>
<td>1 vs. 3: -0.6%, ( p = 0.003 )</td>
<td>1) 1; 2) 1; 3) 0</td>
</tr>
<tr>
<td>Hermanides (Eurythmics Trial)</td>
<td>2011</td>
<td>83 adults</td>
<td>≥8.2%</td>
<td>CSII (0); MDI (83)</td>
<td>6 months</td>
<td>1) CGM and CSII; 2) HBGM</td>
<td>1) n=1; 2) n=4</td>
<td>1 vs. 2: -1.2%, ( p &lt; 0.001 )</td>
<td>1) 4; 2) 1</td>
</tr>
<tr>
<td>Hirsch (STAR-1 Trial)</td>
<td>2008</td>
<td>146 adults and children</td>
<td>≥8.5%</td>
<td>CSII (146); MDI (0)</td>
<td>6 months</td>
<td>1) CGM; 2) HBGM</td>
<td>1) n=6; 2) n=2</td>
<td>1 vs. 2: -0.11, ( p = 0.37 )</td>
<td>1) 11*; 2) 3</td>
</tr>
<tr>
<td>JDRF CGM Study Group</td>
<td>2008</td>
<td>114 children</td>
<td>7.0-10%</td>
<td>CSII (256); MDI (66)</td>
<td>6 months</td>
<td>1) CGM; 2) HBGM</td>
<td>1) n=3; 2) n=2</td>
<td>adults 1 vs. 2: -0.5%, ( p &lt; 0.001 ); adolescents 1 vs. 2: 0.08%, ( p = 0.52 ); children 1 vs. 2: -0.1%, ( p = 0.29 )</td>
<td>1) 14; 2) 11</td>
</tr>
<tr>
<td>JDRF CGM Study Group</td>
<td>2009</td>
<td>29 children</td>
<td>&lt;7.0%</td>
<td>CSII (111); MDI (18)</td>
<td>6 months</td>
<td>1) CGM; 2) HBGM</td>
<td>1) n=1; 2) n=1</td>
<td>1 vs. 2: -0.3%, ( p &lt; 0.001 )</td>
<td>1) 9; 2) 10</td>
</tr>
<tr>
<td>Kordonouri</td>
<td>2010</td>
<td>160 children</td>
<td>≥8.0%</td>
<td>CSII (160); MDI (0)</td>
<td>12 months</td>
<td>1) CGM and CSII; 2) HBGM</td>
<td>1) n=4; 2) n=2</td>
<td>1 vs. 2: -0.2%, ( p = NS )</td>
<td>1) 0; 2) 4</td>
</tr>
<tr>
<td>O’Connell</td>
<td>2009</td>
<td>62 children and adults</td>
<td>≥8.5%</td>
<td>CSII (62); MDI (0)</td>
<td>3 months</td>
<td>1) CGM; 2) HBGM</td>
<td>1) n=5; 2) n=2</td>
<td>1 vs. 2: -0.4%, ( p = 0.009 )</td>
<td>1) 0; 2) 0</td>
</tr>
<tr>
<td>Raccah (RealTrend Study)</td>
<td>2009</td>
<td>51 children</td>
<td>≥8.0%</td>
<td>CSII (0); MDI (128)</td>
<td>6 months</td>
<td>1) CGM and CSII; 2) HBGM and CSII</td>
<td>1) n=14; 2) n=6</td>
<td>1 vs. 2: -0.2%, ( p = 0.09 ); per protocol analyses: 1 vs. 2: -0.4%, ( p = 0.004 )</td>
<td>1) 11; 2) 0</td>
</tr>
</tbody>
</table>

*P < 0.05. †Number of total severe hypoglycaemic episodes per group not given, only episode with seizure/coma. NR, not reported. NS, not significant, CGM, continuous glucose monitoring HBGM, home blood glucose monitoring, CSII, continuous subcutaneous insulin infusion, MDI, multiple daily injections.
the incidence of hypoglycaemia. This might explain why the incidence of hypoglycaemia remains unchanged or is perhaps slightly increasing with CGM use (in our meta-analysis presented in Figure 1 numerically 73 vs. 56 severe hypoglycaemic events with CGM and HBGM, respectively).

**Long learning phase**

In an observational follow-up study from the JDRF CGM Study Group (2008) \(^1\), extending CGM use from 6 to 12 months was associated with an HbA1c that remained in the target range combined with a rate of severe hypoglycaemia that was reduced by almost 70% compared with the former 6-month monitoring period. \(^1\). This suggests that a longer user experience is required to learn to avoid severe hypoglycaemia with CGM. However, this is inconsistent with an observational study in sixteen subjects with type 1 diabetes on MDI treatment \(^4\). All included subjects had experienced at least 1 episode of severe hypoglycaemia in the previous year. After the baseline (HBGM) month they had one month to get used to the CGM device, thereafter the study month (CGM) followed. The number of severe hypoglycaemic episodes dropped from 16 in the month with HBGM to 3 in the month when CGM was used, \(p = 0.064\). The overall number of hypoglycaemic episodes (<3.0 mmol/L) dropped from 8.6 to 4.7 (\(p = 0.01\)). Subjects expressed less fear of hypoglycaemia when they used CGM. Therefore it seems sensible investigating the value of CGM in preventing severe hypoglycaemia in patients at high risk.

**CGM inaccuracy**

The accuracy of CGM remains subject of debate. There are some technical issues to consider:

- lag between interstitial glucose and blood glucose
- instrumental delay
- necessity of finger stick blood testing for calibration purposes
- potential error in recording values at the limit of the detection range

Interstitial glucose values are partially determined by the rate of glucose diffusion from plasma to the interstitial fluid and the rate of glucose uptake by subcutaneous tissue cells, but it is also influenced by many other factors \(^5\). The relationship between blood and interstitial glucose is not well understood.

The physiological delay that occurs in the equilibration of blood with interstitial tissue glucose may be increased when blood glucose falls rapidly \(^6\). During experimental hypoglycaemia in people with type 1 diabetes, CGM underestimated plasma glucose concentrations and thus
potentially overestimated the frequency of hypoglycaemia. Interestingly, comparison of glucose values detected by CGM and HBGM in a crossover study revealed that in the hypoglycaemic range CGM values overestimated blood glucose levels with an average of 0.83 mmol/L.

On top of the physiologic delay in the equilibration of blood glucose and interstitial glucose, if any, there is also an instrumental delay, inherent to the current real-time CGM systems. Both are probably contributors to the inaccuracy of the CGM devices.

For the current CGM devices it is essential to perform frequent calibration with capillary samples. Recordings by the CGM are markedly influenced when this is not done correctly. When compared with actual blood glucose values, CGM devices have an inaccuracy of approximately 15% (expressed as mean absolute difference (MAD [sensor value - blood glucose] / blood glucose). The performance of these devices is worse during hypoglycaemia, when inaccuracy may increase up to 25%. This indicates that the accuracy of CGM requires improvement, especially in hypoglycaemia, which is the clinically most important range for adequate sensor performance.

Inadequate response to hypoglycaemic alarm
When the sensor alerts the patient for a hypoglycaemic event it is not guaranteed that the patient is warned timely enough to take appropriate action before neuroglycopenia has occurred. Cognitive function declines during severe hypoglycaemia leading to a less adequate response to acoustic or vibration alarms. During the night, patients may not hear alarms when they are asleep, especially when the device is covered with blankets. It is reported that patients sleep through half of all alarms.

Intolerance of the CGM device
There are many patients who do not tolerate CGM devices. This is illustrated by the higher drop-out rates in the CGM arms of the RCTs (Table 1). In many trials, patients were already exposed to (blinded) CGM systems before inclusion or randomization to obtain a baseline CGM measurement for all patients. This led to a premature drop-out of 4 of 87, 23 of 345 and 4 of 132 patients before randomization in the Eurythmics, JDRF trial and RealTrend study, respectively, probably patients that did not tolerate the device. There are also questionnaire studies that support this. A questionnaire study to determine barriers to CGM showed that 27 of 54 subjects stopped using CGM. A third reported adhesive issues with the device and that the device was too ponderous. Another study identified perceived barriers to CGM in about 30% of 624 responders. Commonly reported problems
were insertion pain, (false) system alarms, problems with insertion sites and the size of the transmitter or receiver.

Hirsch et al. 10, mentioned above, reported eleven severe hypoglycaemic events in the CGM group and three in the HBGM group (Table 1). Six of eleven events occurred when patients were not wearing or not using the CGM device. The remaining 5 events occurred during use of the device. The following was established: subjects ignored alarms that warned for low sensor readings and subjects based treatment decisions on sensor readings only, without confirming the blood glucose with a capillary test.

**Insufficient study design**

It is known that the incidence of severe hypoglycaemia is skewed 27, meaning that most patients experience no severe hypoglycaemia, while others experience very high numbers of severe hypoglycaemic episodes. By excluding the patients with previous severe hypoglycaemic episodes the incidence of severe hypoglycaemia may have been artificially low in some CGM trials 28, 29. The studies performed so far might have been insufficiently powered to detect a difference in hypoglycaemia rates between treatment groups.

Table 1 largely contains trials designed for patients that used CSII before randomization or switched to CSII during the trial. Consequently, we have to interpret these data with care when we extrapolate the results to patients using CGM in combination with MDI treatment.

**Mild hypoglycaemia**

Mild hypoglycaemia detected with CGM is often represented as ‘time spent in the hypoglycaemic range’ or as ‘area under the curve’ which makes comparison with hypoglycaemia detected by HBGM difficult. Frequently it is not clear whether the reported episodes of hypoglycaemia were symptomatic or asymptomatic and only a few studies report whether patients have hypoglycaemia awareness.

Many CGM intervention studies do not provide enough detail to allow inclusion in a meta-analysis. To this day it seems that there is no reduction in time spent in the hypoglycaemic range with CGM (Figure 2), although one trial reported a reduction in patients in good control 30.

**Nocturnal hypoglycaemia**

Nocturnal hypoglycaemia is a common problem for people with type 1 diabetes. It is
estimated that up to 75% of hypoglycaemic episodes associated with coma or seizures occur at night when the counterregulatory response is impaired. The reported prevalence of nocturnal hypoglycaemia has been studied previously with HBGM in outpatient and inpatient settings and is ranging from 10 to 56%. It is believed that the real prevalence of nocturnal hypoglycaemia might be higher, because the testing with HBGM is intermittent and is depending on the initiative of the patient. The introduction of CGM provided a method of measuring glucose levels every few minutes and led to increased monitoring. The prevalence of nocturnal hypoglycaemia that has been assessed with CGM devices is up to 68%. However, the higher prevalence based on the utilization of CGM has been debated. The CGM devices may have a tendency to report lower glucose values at night.

CGM as preventive therapy for nocturnal hypoglycaemia is desired. Until now the evidence supporting the usefulness of CGM in the detection and treatment of nocturnal hypoglycaemia is very sparse. Garg et al. studied 91 insulin dependent patients with type 1 (n= 75) and type 2 (n=16) who all used a CGM device. The subjects were assigned to a display group and a control group (CGM data blinded to patient). Nocturnal hypoglycaemia was 38% lower in the display group compared with the control group. The role for CGM for a reduction in nocturnal hypoglycaemia needs to be established in the future.

**Impaired awareness of hypoglycaemia**

Recurrent episodes of mild hypoglycaemia, even in the absence of symptoms, are not benign as they can induce defects in counterregulatory hormonal responses and modification of warning symptoms, thereby increasing the risk of severe hypoglycaemia. It is assumed that if episodes of asymptomatic hypoglycaemia are detected and treated, severe hypoglycaemia will be prevented. In theory those with impaired awareness of hypoglycaemia could benefit...
from continuous glucose monitoring. Clinical practice recommendations suggest that CGM is useful in patients with impaired awareness of hypoglycaemia and/or frequent episodes of hypoglycaemia. However, the hypoglycaemia preventive effect of CGM has not been established. There has been no randomized trial with this specific group of patients so far.

One short-term study included a substantial proportion (43%) of patients with impaired awareness of hypoglycaemia. The subjects were randomized into a group with real-time CGM or a blinded sensor. The group with real-time CGM demonstrated a significant decrease in duration of hypoglycaemic excursions compared to the control group with a blinded sensor, but this was accompanied with an increase in hyperglycaemic excursions.

There are a few other studies that provide more in-depth knowledge about impaired awareness of hypoglycaemia with the use of CGM devices. Kubiak et al. investigated hypoglycaemia awareness using CGM during 72-hours. Patients with impaired awareness of hypoglycaemia showed a significantly higher total number of hypoglycaemic episodes, number of undetected hypoglycaemic episodes, and mean glucose levels. However, these results were not confirmed by Choudhary et al. The UK group performed a post-hoc analysis of data collected as part of the UK Hypoglycaemia Group Study and after the 5 days of CGM utilization no significant differences were observed either in frequency, duration or severity of hypoglycaemia between those with normal and impaired awareness of hypoglycaemia. When hypoglycaemia exposure was assessed prospectively over 9-12 months using weekly 4-point HBGM, the subjects with impaired awareness had a significant higher risk for mild and severe hypoglycaemia. The latter was reported in previous studies. The difference between the two studies might be that Kubiak et al. selected patients with strongly impaired awareness of hypoglycaemia based on patient interviews and a history of severe hypoglycaemia, while Choudhary et al. used a questionnaire. This suggests that the two study cohorts may have differed in degree or prevalence of impaired awareness of hypoglycaemia.

Ly et al. used real-time CGM during 4 weeks in six subjects to prevent hypoglycaemic episodes compared to five subjects with standard treatment. All patients had impaired awareness of hypoglycaemia and underwent hyperinsulinaemic hypoglycaemic clamp studies at baseline and after 4 weeks. The group with real-time CGM reported a greater percentage change and peak epinephrine response to induced hypoglycaemia than subjects in the control group. Also, subjects in the CGM group reported higher adrenergic symptom scores. There was no change in glucagon, cortisol and growth hormone responses during hypoglycaemia for both groups. The greater epinephrine response and
partial restoration of adrenergic symptoms suggest that real-time CGM might be useful for the restoration of the symptomatic and counterregulatory response to hypoglycaemia in patients with impaired awareness of hypoglycaemia. Future research should elucidate this further.

COST AND REIMBURSEMENT

Insulin pump therapy
The main cost of CSII is for consumables, such as tubing and cannulas – about €4000 per year. The cost of the pump, assuming a 4-year life, adds another €950 per annum. It is assumed that insulin pump therapy compared to MDI is cost-effective in adults and children with type 1 diabetes patients in Europe and the U.S.A. 57-59. This is calculated on basis of the improvement in glycaemic control, fewer problems with hypoglycaemia and quality of life. Insulin pump therapy is reimbursed in most European countries and in the U.S.

Continuous glucose monitoring
Treatment with CGM costs about €3800 per person per year (based on use of the device 80% of the time) compared with €1625 for HBGM (based on 4-times daily testing). 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 hypoglycaemia is hard to assess because of the currently existing lack of evidence. This is only partially reflected in the current reimbursement status of CGM devices.

In Europe, real-time CGM is only reimbursed in Sweden, Slovenia and the Netherlands. CSII-using patients in Sweden with two or more severe hypoglycaemic episodes per year, patients with HbA1c > 10% while receiving intensive insulin therapy and children who require at least 10 HBGM tests per day are eligible for reimbursement. If CGM is not having its desired effect after 3 months, it should be discontinued. Reimbursement in Slovenia is possible for children with type 1 diabetes until the age of 7, patients with hypoglycaemia unawareness with a history of severe hypoglycaemia or pregnant type 1 or type 2 diabetes patients on intensive insulin treatment. Selected hospitals in the Netherlands get a specific amount reimbursed from third party payers for the treatment of each patient with diabetes. Physicians then determine which patient gets a CGM device. Likely, only a limited number of patients will be selected.

In the U.S., health plans reimburse real-CGM for type 1 diabetes patients who are not meeting the American Diabetes Association HbA1c targets or experience severe hypoglycaemic events.
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 hypoglycaemia unawareness, experiencing two severe episodes of hypoglycaemia in the past 12 months (requiring ambulance assistance or emergency ward treatment), can apply for reimbursement.

**FUTURE EXPECTATIONS**

Current developments include overnight and hybrid closed loop (artificial pancreas) insulin delivery systems, dual hormone delivery and other modifications to existing therapies that offer the potential to reduce the risk of hypoglycaemia for people with diabetes. Two groups reported that closed-loop compared to open-loop treatment may reduce risks of nocturnal hypoglycaemia \(^{60,61}\).

Whether continuous glucose monitoring is useful in patients with impaired awareness of hypoglycaemia and/or frequent episodes of hypoglycaemia should be elucidated. One multicenter trial is underway and the results are eagerly expected (ISRCTN52164803).

**CONCLUSIONS**

- CSII is effective to reduce the frequency of severe hypoglycaemia
- CGM lowers HbA1c without an increase in the incidence of severe hypoglycaemic episodes
- Against expectations, CGM has not been able to lower the incidence of severe hypoglycaemia.
- CGM may be a supplemental tool to home blood glucose monitoring in those with hypoglycaemia unawareness and/or frequent hypoglycaemic episodes, but this needs confirmation in trials targeting this population.

**REFERENCES**


37. Kaufman F.R., Austin J., Neinstein A. et al. Nocturnal hypoglycaemia detected with the


