Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas
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Chapter 6

Continuous glucose monitoring systems for type 1 diabetes mellitus

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Summary version, the integral version may be found in the Cochrane Library
BACKGROUND

Self-monitoring of blood glucose is essential to optimise glycaemic control in type 1 diabetes mellitus. Continuous glucose monitoring (CGM) systems measure interstitial fluid glucose levels to provide semi-continuous information about glucose levels, which identifies fluctuations that would not have been identified with conventional self-monitoring. Two types of CGM systems can be defined: retrospective systems and real-time systems. Real-time systems continuously provide the actual glucose concentration on a display. Currently, the use of CGM is not common practice and its reimbursement status is a point of debate in many countries.
OBJECTIVES

To assess the effects of CGM systems compared to conventional self-monitoring of blood glucose (SMBG) in patients with diabetes mellitus type 1.

SEARCH METHODS

We searched The Cochrane Library, MEDLINE, EMBASE and CINAHL for the identification of studies. Last search date was June 8, 2011.

SELECTION CRITERIA

Randomised controlled trials (RCTs) comparing retrospective or real-time CGM with conventional self-monitoring of blood glucose levels or with another type of CGM system in patients with type 1 diabetes mellitus. Primary outcomes were glycaemic control, e.g. level of glycosylated haemoglobin A1c (HbA1c) and health-related quality of life. Secondary outcomes were adverse events and complications, CGM derived glycaemic control, death and costs.

DATA COLLECTION AND ANALYSIS

Two authors independently selected the studies, assessed the risk of bias and performed data-extraction. Although there was clinical and methodological heterogeneity between studies an exploratory meta-analysis was performed on those outcomes the authors felt could be pooled without losing clinical merit.

RESULTS

The search identified 1366 references. Twenty-two RCTs meeting the inclusion criteria of this review were identified. The results of the meta-analyses (across all age groups) indicate benefit of CGM for patients starting on CGM sensor augmented insulin pump therapy compared to patients using multiple daily injections of insulin.
(MDI) and standard monitoring blood glucose (SMBG). After six months there was a significant larger decline in HbA1c level for real-time CGM users starting insulin pump therapy compared to patients using MDI and SMBG (mean difference (MD) in change in HbA1c level -0.7%, 95% confidence interval (CI) -0.8% to -0.5%, 2 RCTs, 562 patients, I²=84%). The risk of hypoglycaemia was increased for CGM users, but CIs were wide and included unity (4/43 versus 1/35; RR 3.26, 95% CI 0.38 to 27.82 and 21/247 versus 17/248; RR 1.24, 95% CI 0.67 to 2.29). One study reported the occurrence of ketoacidosis from baseline to six months; there was however only one event. Both RCTs were in patients with poorly controlled diabetes.

For patients starting with CGM only, the average decline in HbA1c level six months after baseline was also statistically significantly larger for CGM users compared to SMBG users, but much smaller than for patients starting using an insulin pump and CGM at the same time (MD change in HbA1c level -0.2%, 95% CI -0.4% to -0.1%, 6 RCTs, 963 patients, I²=55%). On average, there was no significant difference in risk of severe hypoglycaemia or ketoacidosis between CGM and SMBG users. The confidence interval however, was wide and included a decreased as well as an increased risk for CGM users compared to the control group (severe hypoglycaemia: 36/411 versus 33/407; RR 1.02, 95% CI 0.65 to 1.62, 4 RCTs, I²=0% and ketoacidosis: 8/411 versus 8/407; RR 0.94, 95% CI 0.36 to 2.40, 4 RCTs, I²=0%).

Health-related quality of life was reported in five of the 22 studies. In none of these studies a significant difference between CGM and SMBG was found. Diabetes complications, death and costs were not measured.

There were no studies in pregnant women with diabetes type 1 and in patients with hypoglycaemia unawareness.
AUTHORS’ CONCLUSIONS

There is limited evidence for the effectiveness of real-time continuous glucose monitoring (CGM) use in children, adults and patients with poorly controlled diabetes. The largest improvements in glycaemic control were seen for sensor-augmented insulin pump therapy in patients with poorly controlled diabetes who had not used an insulin pump before. The risk of severe hypoglycaemia or ketoacidosis was not significantly increased for CGM users, but as these events occurred infrequent these results have to be interpreted cautiously. There are indications that higher compliance of wearing the CGM device improves glycosylated haemoglobin A1c level (HbA1c) to a larger extent.
Summary of Findings: CGM for type 1 diabetes mellitus

Patient or population: patients with type 1 diabetes mellitus

Intervention: Continuous real-time glucose monitoring

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95%CI)</th>
<th>Relative effect (95%CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed risk</td>
<td>Control</td>
<td>Continuous Real-time CGM</td>
<td></td>
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<tr>
<td>Severe hypoglycaemia</td>
<td>75 per 1000 (47 to 133)</td>
<td>RR 1.05 (0.63 to 1.77)</td>
<td>689 (5 studies)</td>
<td>low¹</td>
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<tr>
<td>Follow-up: 6 months</td>
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<tr>
<td>Ketoacidosis</td>
<td>23 per 1000 (7 to 52)</td>
<td>RR 0.85 (0.32 to 2.26)</td>
<td>689 (5 studies)</td>
<td>low¹</td>
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<tr>
<td>Follow-up: 6 months</td>
<td></td>
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<tr>
<td>Quality of life - Physical health domain</td>
<td>The mean quality of life - physical health in the control groups was 54</td>
<td>The mean quality of life - physical health in the intervention groups was 1.4 higher (0.2 lower to 3 higher)</td>
<td>226 (1 study)</td>
<td>very low²,³</td>
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<tr>
<td>SF-12 Follow-up: 6 months</td>
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<tr>
<td>Quality of life - Mental health domain</td>
<td>The mean quality of life - mental health in the control groups was 75</td>
<td>The mean quality of life - mental health in the intervention groups was 1.9 higher (1.4 lower to 5.2 higher)</td>
<td>226 (1 study)</td>
<td>very low²,³</td>
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<tr>
<td>SF-12 Follow-up: 6 months</td>
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<tr>
<td>Quality of life - Parents</td>
<td>The mean quality of life - parents in the control groups was 49</td>
<td>The mean quality of life - parents in the intervention groups was 0.3 lower (2.9 lower to 2.3 higher)</td>
<td>226 (1 study)</td>
<td>very low²,⁴</td>
</tr>
<tr>
<td>SF-12 Follow-up: 6 months</td>
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<tr>
<td>Change in HbA1c (%)</td>
<td>The mean change in HbA1c ranged across control groups from -0.6 to 0</td>
<td>The mean change in HbA1c in the intervention groups was 0.2 lower (0.4 to 0.1 lower)</td>
<td>963 (6 studies)</td>
<td>moderate⁵</td>
</tr>
<tr>
<td>Follow-up: 6 months</td>
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</table>
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 Substantial imprecision because of very low number of events; 95% CI includes appreciable benefit as well as appreciable harm.
2 Only one study.
3 Substantial imprecision because of small population size; 95% CI includes no effect as well as improved quality of life.
4 Substantial imprecision because of small population size; 95% CI includes improved as well as worsened quality of life.
5 Inconsistency because of heterogeneity (different study designs and patient populations; $I^2 = 55\%$).