Hypoglycaemia in diabetes
Schopman, J.E.

Citation for published version (APA):
Schopman, J. E. (2013). Hypoglycaemia in diabetes
CHAPTER 6

DIAGNOSTIC ACCURACY OF CONTINUOUS GLUCOSE MONITORING FOR THE DETECTION OF HYPOGLYCAEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Josefine E Schopman
Floor van Wijk
Brian M Frier
J Hans de Vries
Frits Holleman

Manuscript in preparation
ABSTRACT

Aims
To evaluate the diagnostic accuracy of continuous glucose monitoring (CGM) for the detection of hypoglycaemic events.

Materials and methods
A MEDLINE search was performed until January 2012 to identify all potentially relevant publications regarding hypoglycaemia and CGM systems. Abstract books of the annual meetings of the European Association of the Study of Diabetes and the American Diabetes Association of 2010 and 2011 were screened for relevant studies. Two reviewers independently selected studies for inclusion, extracted data and assessed the risk of bias with the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Sensitivity and specificity of CGM systems were pooled using a random effects model.

Results
Ten studies met the eligibility criteria. Selected studies were divided in two groups by reference methods: home blood glucose monitoring (HBGM) and laboratory methods. A high risk of bias was observed in some studies that did not always verify CGM-detected hypoglycaemia. Pooling of the studies with HBGM as reference method showed a sensitivity of 0.70 (Confidence Interval 95% 0.65-0.73) and specificity of 0.95 (CI 0.92-0.97) to detect hypoglycaemia with CGM. The studies that used laboratory measurements found a lower sensitivity (range 0.33-0.61) and a similar specificity (range 0.96-0.98). The overall positive predictive values ranged from 17-90%.

Conclusions
Only a few studies report the performance of CGM from a patient perspective and the quality of some studies is dubious. Accuracy of Continuous Glucose Monitoring needs improvement to detect hypoglycaemia with greater reliability.
INTRODUCTION

Since insulin has been used to treat type 1 diabetes, hypoglycaemia has been an impediment to good glycaemic control, despite many advances in insulin therapy and patient education. While the direct harm of incidental mild hypoglycaemia is debatable, recurrent episodes of mild hypoglycaemia, even in the absence of symptoms, are not benign because they can diminish counterregulatory hormonal responses and warning symptoms, thus increasing the risk of severe hypoglycaemia 1.

At home, hypoglycaemia may be detected using capillary home blood glucose monitoring (HBGM), which is the standard of glucose monitoring in everyday life. The detection of hypoglycaemia using HBGM is limited by its dependency on the frequency and timing of testing. It is estimated that half of all those who are treated with insulin self-monitor their blood glucose less than three times daily 2. Many episodes of biochemical hypoglycaemia will therefore be missed. Continuous glucose monitoring systems (CGMS) measure interstitial tissue glucose every few minutes for a period of up to seven days. The monitoring of glucose levels with CGM in real-time potentially enables patients to be alerted when glucose levels become low and may therefore help them to avoid progressing to severe hypoglycaemia. Some specialists consider the use of continuous glucose monitoring systems to be the ‘gold standard’ for the detection of (asymptomatic) hypoglycaemia. However, concerns have been raised about the accuracy of CGM measurements, particularly within the hypoglycaemic range. 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 least good during hypoglycaemia, when inaccuracy may rise to 25% 3. Most accuracy studies report their data as MAD values, but data on sensitivity and the positive predictive value of hypoglycaemic alerts are more relevant outcomes from the patient’s viewpoint as both missed hypoglycaemic events and too many false alarms may reduce the patients’ confidence in CGMS 4, 5.

We have performed a systematic review to evaluate the accuracy of continuous glucose monitoring systems for hypoglycaemia detection as compared to home blood glucose monitoring using conventional glucose meters and/or laboratory devices in people with type 1 diabetes.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting systematic reviews and meta-analyses.
Data sources and search strategy
An electronic search was performed in Medline until January 2012. The following text terms and medical subheadings (MeSH) terms were combined: “Diabetes Mellitus, type 1”[Mesh], insulin dependent diabetes mellitus[tiab], diabetes mellitus type 1[tiab], continuous glucose monitoring[tiab], continuous subcutaneous glucose monitoring[tiab], CGMS[tiab], CGM[tiab], “Blood Glucose Self-Monitoring”[Mesh] and continuous[tiab]. We limited our search to original research performed in humans and use of the English language. Abstract books of the annual meetings of the European Association of the Study of Diabetes and the American Diabetes Association of 2010 and 2011 were screened manually for additional relevant studies.

Study selection
Two reviewers (JES and FvW) independently screened the records. Inclusion and exclusion criteria were defined a priori. A study was included when it reported crude data on paired values of hypoglycaemia episodes detected with CGM and a reference test (HBGM or a laboratory method) or when it reported sensitivity and/or specificity. A publication was excluded when the CGM system used was a prototype and not available for commercial purposes.

Data extraction
From the included publications the following data were extracted: first author, year of publication, study design, number of patients, number of paired hypoglycaemia tests, characteristics of the study population, CGMS type, reference test method, definition of hypoglycaemia. Subsequently the number of detected true hypoglycaemic episodes with CGM (true positives, TP), number of false detected hypoglycaemic episodes with CGM (false positives, FP), number of missed hypoglycaemic episodes with CGM (false negatives, FN) and the number of true non-hypoglycaemic episodes with CGM (true negatives, TN) were collected. We contacted the corresponding author for additional information when the publication reported only a value for sensitivity and/or specificity for hypoglycaemia detection with CGM, without the crude number of hypoglycaemia episodes.

Study quality
Two reviewers independently assessed the risk of bias of included studies by means of a modified version of the Quality Assessment for Diagnostic Accuracy Studies 2 (QUADAS-2) checklist. The QUADAS-2 tool comprises four domains: patient selection, index test, reference standard and flow and timing of the tests. Each domain is assessed in terms of risk of bias (low, high or unclear risk). The first three domains are also assessed in terms of
concerns regarding applicability of the primary study data to the review’s research question. Following recommendations of the QUADAS-2 authors, we modified the QUADAS-2 checklist as follows: signalling question 1 of domain 2 (Were the index test results interpreted without knowledge of the results of the reference standard?) and signalling question 2 of domain 3 (Were the reference standard results interpreted without knowledge of the results of the index test?) were omitted. The potential of bias is related to the potential influence of previous knowledge on the interpretation of the test. In the current review both the index and reference test are objective tests. We therefore judged it appropriate to remove these questions. Signalling question 2 of domain 4 (flow and timing) (Did all patients receive the same reference standard?) was also removed because we already differentiated between the two utilized reference standards HBGM and laboratory methods. Signalling question 3 of domain 4 (Did all patients receive a reference standard) was modified to: Was a reference test performed for each index test indicating a low blood glucose level? Disagreements between both reviewers were discussed and resolved by consensus.

Data synthesis
By combining the reference method outcome (dichotomized into hypoglycaemia or no hypoglycaemia) with the CGM test results (hypoglycaemic value or no hypoglycaemic value), sensitivity, specificity and positive predictive value were calculated.

Review Manager Version 5.2 (The Cochrane Collaboration, Oxford, UK) was used to calculate the 95% confidence intervals of the sensitivity and specificity and to generate the forest plots. Meta-analysis was performed using MetaDiSc using a random effects model. Heterogeneity was assessed using the I² statistic. The I² expresses the variation across the studies according to heterogeneity rather than from chance, in the form of a percentage. Heterogeneity was not further explored by subgroup analysis due to the limited number of studies.

RESULTS
Figure 1 summarizes the study identification and selection process. With the search in MEDLINE and by the manual search of the abstract books, 533 studies of potential interest were identified. Of these we excluded 459 publications after reviewing the abstract. After reading the full text of 74 studies, 61 were excluded either because no data on hypoglycaemia were reported or data of CGM measurements and a reference method were not paired.

Three records were excluded during the data extraction process as only sensitivity and specificity of the CGM system were presented and after contacting the authors the raw numbers of hypoglycaemia could not be retrieved. Ultimately, 10 studies were selected for
this systematic review. Six studies used HBGM as a reference method, three studies used a laboratory method as reference method and one study used both methods. A large variation in blood glucose cut-off values for the definition of hypoglycaemia was observed among the selected studies. Table 1 contains the characteristics of the 10 studies included.

**Figure 1 - Summary of the study identification and selection process**

HBGM = home blood glucose monitoring, TP = true positives, FP = false positives, FN = false negatives, TN = true negatives. For the sake of clear arrangement of this figure no division was made in < or ≤ for glucose cut-off levels.
Table 1 - Characteristics of the 10 studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>No. of subjects</th>
<th>No. of tests</th>
<th>Age ± SD (yrs)</th>
<th>Duration of diabetes ± SD (yrs)</th>
<th>HbA1c baseline ± SD (%)</th>
<th>% IAH</th>
<th>Type of CGMS</th>
<th>Reference method</th>
<th>Hypoglycaemia blood glucose cut-off (mg/dL (mmol/L))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolfsson</td>
<td>2009</td>
<td>Accuracy study</td>
<td>12</td>
<td>182</td>
<td>31</td>
<td>12.2 ± 7.1</td>
<td>7.1 n.s.</td>
<td>CGMS (Medtronic)</td>
<td>HemoCue</td>
<td>Gold and Ipro (Medtronic)</td>
<td>&lt;70 (3.9)</td>
</tr>
<tr>
<td>Ahmet</td>
<td>2011</td>
<td>Observational</td>
<td>25</td>
<td>277</td>
<td>11.7 ± 3.9</td>
<td>4.9 ± 4.0</td>
<td>8.3 ± 1.8</td>
<td>n.s.</td>
<td>Gold and Ipro (Medtronic)</td>
<td>One-Touch Ultra glucose meter (LifeScan)</td>
<td>&lt;70 (3.9)</td>
</tr>
<tr>
<td>Bode</td>
<td>2004</td>
<td>Accuracy study</td>
<td>71</td>
<td>4453</td>
<td>44 ± 11.4</td>
<td>23.6 ± 10.6</td>
<td>7.6 ± 1.1</td>
<td>78%</td>
<td>CGMS (Medtronic)</td>
<td>Accu-Chek (Roche Diagnostics Corp.)</td>
<td>&lt;70 (3.9)</td>
</tr>
<tr>
<td>DirecNet</td>
<td>2004</td>
<td>Accuracy study</td>
<td>91</td>
<td>1449</td>
<td>9.9</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>CGMS (Medtronic)</td>
<td>.</td>
<td>&lt;60 (3.3) &lt;70 (3.9)</td>
</tr>
<tr>
<td>Garg</td>
<td>2009</td>
<td>Accuracy study</td>
<td>30</td>
<td>HBGM: 1802</td>
<td>35.3 ± 7.8</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>SEVEN (Dexcom)</td>
<td>Yellow Springs Instruments</td>
<td>&lt;80 (4.4)</td>
</tr>
<tr>
<td>Guerci</td>
<td>2003</td>
<td>Accuracy study</td>
<td>18</td>
<td>276</td>
<td>40.4 ± 12.5</td>
<td>21.4 ± 15.7</td>
<td>7.9 ± 0.8</td>
<td>n.s.</td>
<td>CGMS (Medtronic)</td>
<td>.</td>
<td>&lt;55 (3.0)</td>
</tr>
<tr>
<td>Høi-Hansen</td>
<td>2005</td>
<td>Accuracy study</td>
<td>29</td>
<td>643</td>
<td>49.7</td>
<td>21.9</td>
<td>8.1 ± 0.8</td>
<td>41%</td>
<td>CGMS (Medtronic)</td>
<td>HemoCue</td>
<td>≤63 (3.5)</td>
</tr>
<tr>
<td>Jeha</td>
<td>2004</td>
<td>Accuracy study</td>
<td>10</td>
<td>379</td>
<td>3.7 ± 1.3</td>
<td>1.9 ± 1.4</td>
<td>8.6 ± 0.8</td>
<td>n.s.</td>
<td>CGMS (Medtronic)</td>
<td>Free-Style glucometer (TheraSense)</td>
<td>&lt;60 (3.3)</td>
</tr>
<tr>
<td>Wentholt</td>
<td>2006</td>
<td>Observational</td>
<td>75</td>
<td>560</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>GlucoDay (Menarini)</td>
<td>.</td>
<td>≤60 (3.3) &lt;70 (3.9)</td>
</tr>
<tr>
<td>Zijlstra</td>
<td>2012</td>
<td>Accuracy study</td>
<td>18</td>
<td>2317</td>
<td>43 ± 11</td>
<td>18 ± 10</td>
<td>8.3 ± 0.5</td>
<td>none</td>
<td>CGMS (Medtronic)</td>
<td>Super GL Analyzer (Hitado Diagnostic Systems)</td>
<td>&lt;70 (3.9)</td>
</tr>
</tbody>
</table>

yrs = years, n.s. = not specified; IAH = impaired awareness of hypoglycaemia, CGMS = continuous glucose monitoring system, HBGM = home blood glucose monitoring device, Lab = laboratory device.
Methodological quality
A summary of the QUADAS-2 quality assessment is given in Figure 2. We found a variable risk of bias in the domain flow and timing. This is due to the fact that only two studies clearly stated that for all CGM-detected hypoglycaemic events a reference test was performed (low risk of bias), in four studies this was unclear (unclear risk of bias) and in four studies some CGM detected hypoglycaemic events were excluded from the original study analysis (high risk of bias). We documented a high applicability concern for six studies where CGM data were read out retrospectively and the sensor did not have a hypoglycaemia alert.

![Figure 2 - Review authors’ judgments about methodological quality of the included studies evaluated by QUADAS-2.](image)

Diagnostic accuracy
The analysis contained 13,355 paired CGM and reference tests. The diagnostic accuracy data and forest plots of the sensitivity and specificity of the included studies are presented in figures 3a and 3b. Pooling of the studies with HBGM as reference method showed a sensitivity of 0.70 (CI 0.65-0.73, I²=37%) and specificity of 0.95 (CI 0.92-0.97, I²=93%) to detect
The sensitivity was 75%. This phenomenon may be explained by the fact that the CGMS in 61% when compared with colleagues and ranged from 0.33-0.75. The CGM sensitivity was found to be worse in studies that use the detection of hypoglycaemia with CGM. We judged that statistical pooling of the studies with laboratory measurements as reference method was not feasible because of the wide heterogeneity visualized by the forest plot. The positive predictive values for all studies are shown in online supplement 1 and ranged from 17-90%.

DISCUSSION

The aim of this systematic review was to evaluate the diagnostic accuracy of CGM for the detection of hypoglycaemia. Sensitivity in the selected publications was low to moderate and ranged from 0.33-0.75. The CGM sensitivity was found to be worse in studies that use a laboratory method as the reference method. This is also illustrated in the study of Garg and colleagues 19 that used both reference methods: the CGM system had a sensitivity of 61% when compared with YSI readings, but when compared with HBGM measurements the sensitivity was 75%. This phenomenon may be explained by the fact that the CGMS in
this study and another study were calibrated with HBGM measurements while the sensor performance was assessed by a laboratory method. However, this does not explain the low sensitivity that was observed by Zijlstra et al., because the CGMS was calibrated with the same laboratory method that was used to assess its performance.

Overall specificity of CGM for the detection of hypoglycaemia was high and ranged from 0.90-0.99. This is a somewhat spurious finding resulting from the fact that CGM measures continuously and the number of true negatives, or in other words ‘episodes’ of euglycaemia, far exceed the number of detected false positives.

It is important to note that not all studies had a reference test performed for all CGM-detected hypoglycaemia episodes. For example, no reference tests were performed during the night when the subjects were asleep. These episodes were simply excluded from the original study analyses. It is possible that some of these episodes of “hypoglycaemia” had been falsely detected by CGM so that if these episodes had been included, a lower positive predictive value and specificity would have resulted.

The positive predictive value is very informative for the accuracy of CGMS and informs us about false alarms. The percentage of false alarms in the studies with CGMS hypoglycaemic alerts ranged from 10 to 83%. Too many false alarms may reduce the patients’ confidence, and consequently their enthusiasm, to use CGM. To illustrate this, in the Juvenile Diabetes Research Foundation study, the use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. Before inclusion or randomization, these patients had already been exposed to (blinded) CGM systems to obtain a baseline CGM measurement for all participants. This led to a pre-randomization drop-out of 23 of 345 patients, probably because they could not tolerate the device. Questionnaire studies identify barriers to the use of CGM in 30-50% of the patients and false system alarms are considered to be one of the important reasons to stop using CGM.

Clinicians should be aware of the limitations of CGM for the detection of hypoglycaemia. Analyses of sensitivity and positive predictive values as measure of the accuracy of CGM systems for the detection of hypoglycaemia should consistently form a part of future studies. Technical developments for continuous glucose monitoring systems should focus on the problem of hypoglycaemia from the patient’s perspective. Accuracy of Continuous Glucose Monitoring needs improvement to detect hypoglycaemia with greater reliability.
REFERENCES


