Assessing Impaired Hypoglycemia Awareness in Type 1 Diabetes

Agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycemia

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OBJECTIVE — The aim of our study was to determine the agreement of two noninvasive methods, a self-report and a field study method, for the assessment of impaired hypoglycemia awareness with a gold standard criterion of hypoglycemia awareness, the autonomic symptom threshold during experimental hypoglycemia.

RESEARCH DESIGN AND METHODS — A total of 19 type 1 diabetic patients completed a standardized questionnaire to assess impaired hypoglycemia awareness and performed a hand-held computer (HHC) study to assess their recognition of hypoglycemic episodes occurring during 2–4 weeks. Patients subsequently underwent a stepped hypoglycemic clamp to study responses to standardized hypoglycemia. Diagnoses of impaired hypoglycemia awareness were based on the separate self-report questions, a composite self-report score, and three different cutoff levels for the percentage of accurately recognized hypoglycemic episodes during the field study. Agreement of these noninvasive measures with the hypoglycemic clamp measure were tested by calculating kappa values, sensitivity, and specificity.

RESULTS — The composite self-report score agreed reasonably well with the hypoglycemic clamp measure (kappa 0.49, sensitivity 66.7%, and specificity 85.7%) and showed a better agreement than the separate self-report questions. The HHC criterion of impaired hypoglycemia awareness did not agree with the hypoglycemic clamp criterion at any of the cutoff levels tested.

CONCLUSIONS — The composite self-report tested in this study is a reasonably reliable assessment method for the diagnosis of impaired hypoglycemia awareness, using the physiological definition of an absence of autonomic symptoms at a blood glucose level of 3 mmol/l. In contrast, the recognition of hypoglycemic events in everyday life as measured using the HHC method is not related to the hypoglycemic clamp criterion.

Diabetes Care 23:529–532, 2000

A reduced symptomatic recognition of hypoglycemia, known as impaired hypoglycemia awareness, has been shown to increase the risk of severe hypoglycemia (SH) in type 1 diabetic patients (1). The term impaired hypoglycemia awareness should be preferred over the term hypoglycemia unawareness, since this syndrome does not represent an all-or-none phenomenon. Nevertheless, classification of patients with normal and impaired hypoglycemia awareness is relevant for both clinical and research purposes. The comparison of studies on impaired hypoglycemia awareness is complicated by the use of different definitions and assessment methods. In general, three approaches to the assessment of impaired hypoglycemia awareness can be distinguished. The first and most common approach is to classify awareness on the basis of self-reports, which range from questions concerning symptom changes since the diagnosis of diabetes (1, 2) or absence of autonomic symptoms (3, 4) to SH history (2, 4). A second, less common approach is to determine impaired awareness of hypoglycemia on the basis of actual recognition of hypoglycemic episodes occurring over a certain period of time. A suitable method for this purpose, developed by Cox et al. (2, 5), is a field study using a hand-held computer (HHC). Finally, impaired hypoglycemia awareness can be assessed using experimentally induced hypoglycemia in the laboratory, by defining the glycaemic threshold for the occurrence of autonomic symptoms (6). In contrast to the self-report and field study methods, the third technique measures responses to a standardized hypoglycemic stimulus and may therefore be employed as gold standard to assess hypoglycemia awareness. The aim of the present study was to determine to what extent different assessment methods of impaired hypoglycemia awareness diagnose the same patients. For this purpose, we studied the agreement of a number of standard self-report questions and of the HHC data with the autonomic symptom threshold during experimentally induced hypoglycemia.

RESEARCH DESIGN AND METHODS

Patients and study design

We studied 19 type 1 diabetic patients in reasonable glycaemic control (HbA1c ≤8.3%) using basal bolus therapy with regular insulin before meals and NPH insulin at bedtime. Results for this study were obtained during the 8- to 10-week lead-in period of an insulin analog trial (7). During this period, patients completed a standard-
Assessment methods of impaired hypoglycemia awareness

ized questionnaire to assess hypoglycemia awareness, performed the HHC program for 2–4 weeks, and subsequently underwent a stepped hypoglycemic clamp to study counterregulatory hormone and symptom responses to standardized hypoglycemia. The study was approved by the local Medical Ethics Committee, and written informed consent was obtained from all participants.

Self-report of impaired hypoglycemia awareness

At the start of the study, patients completed a standard self-report (2) with five items to assess impaired hypoglycemia awareness. Based on these items, which are specified below, we tested six different diagnostic self-report criteria of impaired hypoglycemia awareness. The first criterion (change criterion) was based on the experience of a loss of symptoms that used to occur during hypoglycemia. The second criterion (recognition criterion) was based on the patient's ability to recognize hypoglycemia on the basis of symptoms, defining the answer categories “never,” “seldom,” and “sometimes” as impaired and “often” and “always” as normal hypoglycemia awareness. The third criterion (threshold criterion) was based on how low blood glucose needed to be for the patient to experience symptoms, defining a level <3 mmol/l as impaired hypoglycemia awareness. The fourth criterion (moderate hypoglycemia criterion) was based on the experience of moderate hypoglycemia in the past year (one or more episodes in which the patient was too confused, disoriented, or lethargic to perform self-treatment). The fifth criterion (SH criterion) was based on the experience of severe hypoglycemia in the past year (one or more episodes with unconsciousness or seizures and/or requiring glucagon or intravenous glucose treatment). Finally, for the sixth criterion (composite criterion), impaired hypoglycemia awareness was diagnosed when indicated by a minimum of three of five of the self-report criteria mentioned above.

Field study data

After instruction and a few days’ practice, patients were asked to complete 40–70 blood glucose estimations followed by home blood glucose measurements (HBGM) within 2–4 weeks, at random times and performing a maximum of five trials within 1 day. Both estimate and HBGM were entered in the HHC (5). In addition, for each HHC trial, patients entered the degree (on a scale of 0 to 6) to which they were experiencing each of six autonomic symptoms (palpitations, tremor, sweating, visual disturbances, irritability, and anxiety) and five neuroglycopenic symptoms (difficulty concentrating, light-headedness, confusion, difficulty speaking, and weakness). For this study, the percentage of hypoglycemic readings (HBGM ≤3.9 mmol/l) accurately estimated as hypoglycemia was used as measure of impaired hypoglycemia awareness. For this calculation, we used only data from patients with a minimum of four hypoglycemic HHC readings. In previous studies, accurate estimation percentages ~30% have been observed in reduced awareness and ~50% in normal aware subjects (2). We studied the effect of using cutoff levels of 30, 40, and 50% for diagnosing impaired hypoglycemia awareness.

Hypoglycemic clamp tests

The stepped hypoglycemic clamp experiments have been described in detail elsewhere (4). In short, during these experiments, blood glucose was stabilized at 4.0 mmol/l within 60 min and kept at 4 mmol/l for another 60 min by means of a continuous regular insulin infusion and a variable glucose infusion. After 120 min of euglycemia, blood glucose was lowered to 3.5 mmol/l within 15 min and was kept at that level for another 45 min. This procedure was repeated twice to reach blood glucose plateaus of 3 and 2.5 mmol/l, respectively. To assess hypoglycemic symptom responses throughout the clamps, patients were given the HHC used for the field study to complete the hypoglycemic symptom questionnaire described above. For the purpose of this study, we used the total autonomic symptom score based on the six autonomic symptoms described above. Before participation, patients received the information that their blood glucose level would be lowered at some time during the test, but they did not know that their blood glucose level would be lowered in a stepwise fashion, and they were not informed about their blood glucose level at any time during the test. Hypoglycemia had to be avoided vigorously for 24 h, and patients abstained from caffeine consumption for at least 12h before the test.

Statistical analysis

Thresholds for autonomic symptom responses during the hypoglycemic clamp were defined as the time point at which an elevation of the total autonomic symptom score of more than 2SD above the mean of the euglycemic levels was observed on two or more consecutive samples. An autonomic symptom threshold at a blood glucose level <3 mmol/l was defined as the gold standard criterion of impaired hypoglycemia awareness. For the HHC data, the percentage of hypoglycemic readings accurately estimated as hypoglycemia (percentage detection of BG ≤3.9 mmol/l) was determined. As a measure of agreement of the self-report and the field study criteria with the gold standard, we calculated the kappa value (a measure of the observed agreement compared with the agreement expected by chance, ranging from 0 to 1) as well as sensitivity (percentage of impaired aware patients correctly identified by the criterion) and specificity (percentage of normal aware patients correctly identified by the criterion) of the different criteria (8). A commercially available software package (SPSS 7.5 for Windows 95; SPSS, Chicago) was used for all statistical analyses.

RESULTS — We studied 19 type 1 diabetes patients (15 men and 4 women), age (± SD) 30.4 ± 6.4 years, diabetes duration 12.8 ± 7.2 years, and HbA1c 7.2 ± 0.6% (reference range 4.3–6.1%). All patients were treated with basal bolus therapy with regular and NPH insulin.

Self-report and hypoglycemic clamp data were analyzed for all patients. The HHC data were analyzed for 16 patients, because 2 patients did not complete the minimum of 40 HHC trials, and data from 1 patient could not be retrieved because of a technical defect of the HHC. Twelve of nineteen patients (63.2%) were classified as impaired aware according to the hypoglycemic clamp. Based on the composite self-report, 9 of 19 patients (47.4%) were diagnosed with impaired hypoglycemia awareness, as were 7 of 16 (43.8%) based on the HHC method. The agreement of the different self-report measures and the HHC measure with the gold standard are shown in Table 1. As for the self-report measures, the change and moderate hypoglycemia criterion showed poor agreement with the hypoglycemic clamp criterion, whereas the recognition, threshold, and SH criteria performed somewhat better. The composite self-report criterion showed the best agreement (kappa 0.49), with a sensitivity of 66.7% and specificity of 85.7%. The HHC criterion based on a cut-off level of 40% agreed poorly with the
hypoglycemic clamp measure, with a negative kappa (the observed agreement between the two methods was lower than the agreement expected by chance). The agreement of the percentage recognized hypoglycemia with the gold standard did not improve with cutoff levels of 30 and 50%. As for the relationship between the composite self-report and HHC criterion (based on a cutoff level of 40%), a very poor agreement was observed, with a kappa of 0 and sensitivity and specificity of 50% each.

**CONCLUSIONS** — Results from this study demonstrate that the classification of impaired hypoglycemia awareness based on a standard self-report agrees reasonably well with the physiological classification of impaired hypoglycemia awareness based on the absence of autonomic symptoms at a blood glucose level of 3 mmol/l. In contrast, the field method classification did not agree with the hypoglycemic clamp classification.

The agreement between the self-report and physiological classification of hypoglycemia awareness shows that patients are to some extent aware of changes or impairments in the biological responses of their body to hypoglycemia. The composite self-report criterion tested in this study showed the best agreement with the physiological classification of impaired hypoglycemia awareness, followed by the SH, threshold, and recognition criterion, whereas the moderate hypoglycemia and change criterion agreed poorly. These results demonstrate that the use of different self-report criteria results in the diagnosis of different patients. In some studies, our definition of moderate hypoglycemia is used as definition of severe hypoglycemia. From our data, it appears worthwhile to distinguish between self-reported moderate and severe hypoglycemic episodes, since these were shown to have the highest sensitivity and specificity, respectively, in diagnosing impaired hypoglycemia awareness.

Because the field method measures recognition of hypoglycemic episodes occurring spontaneously over a period of time, we had expected this method to be an ecologically valid as well as accurate measure of impaired hypoglycemia awareness. In contrast to our expectation, this method did not agree with the hypoglycemic clamp criterion. A possible explanation is that the blood glucose levels of the hypoglycemic HHC events differ between patients, which may bias the percentage of recognized hypoglycemia. Possibly, this problem could be solved by calculating the percentage recognized hypoglycemic events of episodes <3 mmol/l. However, in our study, this did not leave a sufficient number of episodes for most patients. In addition, the recognition of mild biochemical hypoglycemia in everyday life is known to be influenced not only by impairments of counterregulatory hormone and (autonomic) symptom responses to hypoglycemia, but also by a large number of situational and behavioral factors (9,10). Supporting this concept is the finding of average percentages of accurately recognized hypoglycemic events as low as 50% even in normal aware patients (2).

In conclusion, the composite self-report tested in this study can be recommended as a standard criterion of the physiologically defined syndrome of impaired hypoglycemia awareness (based on the absence of autonomic symptoms at a blood glucose level of 3 mmol/l). In contrast, the recognition of hypoglycemic events in everyday life as measured using the HHC method is not related to the hypoglycemic clamp criterion. These data demonstrate that the application of different methods for the classification of hypoglycemia awareness may result in the identification of different patient groups. It is not possible to conclude from this study that either of the assessment methods tested is superior to the other methods. The clinical relevance of identifying patients with impaired hypoglycemia awareness is that these patients run a higher risk of severe hypoglycemia, thus further research is required to test the relationship between these assessment methods of hypoglycemia and the future occurrence of severe hypoglycemic episodes. In addition, further studies are required to characterize the different patient-related and situational determinants of hypoglycemia recognition in everyday life.

**Table 1** — Agreement of the self-report and HHC diagnostic criteria of impaired hypoglycemia awareness with the gold standard, defined as a threshold for autonomic symptoms <3 mmol/l during the stepped hypoglycemic clamp test

<table>
<thead>
<tr>
<th>criteria</th>
<th>Kappa</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tr>
<td>Self-reports</td>
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<tr>
<td>Change criterion</td>
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<tr>
<td>Recognition criterion</td>
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<td>75</td>
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<tr>
<td>Severe hypoglycemia criterion</td>
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<tr>
<td>Composite criterion</td>
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<td>66.7</td>
<td>85.7</td>
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<tr>
<td>HHC</td>
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<td>Detection of blood glucose ≤3.9 mmol/l</td>
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<td>&lt;30%</td>
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<tr>
<td>&lt;40%</td>
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**References**
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