

**AN EVALUATION OF METHODS OF ASSESSING IMPAIRED
AWARENESS OF HYPOGLYCEMIA IN TYPE 1 DIABETES**

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INTRODUCTION

Subjective recognition of the warning symptoms of hypoglycemia is fundamental to allow self-treatment and prevent progression to severe hypoglycemia (SH) ^{1,2}. Recognition of the onset of these premonitory symptoms constitutes “awareness” of hypoglycemia ³. With increasing duration of insulin therapy, many people with type 1 diabetes experience a change in their hypoglycemia awareness associated with either a reduction in symptom intensity or a change in symptom profile, or both ³⁻⁶. Impaired awareness of hypoglycemia (IAH) is associated with a six-fold greater frequency of SH and is a recognised risk factor for this problem ^{7,8}.

Accurate identification of individuals with IAH is important to allow modification of their glycemic targets and to adjust insulin therapy to minimise hypoglycemia risk. Three methods have been proposed to assess awareness of hypoglycemia for clinical application ⁷⁻⁹, but to date have not been compared directly. The present study was performed in a randomly selected cohort of people with type 1 diabetes to assess the concordance between these methods in ascertaining the prevalence of IAH and whether the methods have equivalent sensitivity in identifying affected individuals.

SUBJECTS AND METHODS

Subjects

One hundred and forty participants were recruited; 80 completed the study. Those who completed the study (n = 80) were significantly older than those who did not (n = 60), (47.6 (12.7) vs 41.1 (12.6) years, p = 0.04). No differences in duration of diabetes (p = 0.7) or in glycemic control (p = 0.35) were observed between these two groups. All completed a questionnaire to assess

awareness of hypoglycemia using each of the three methods (Gold⁷, Clarke⁸, Pedersen-Bjergaard⁹). The participants were then asked to perform capillary blood glucose measurements (using their own blood glucose meters) four times daily, prospectively over a four-week period. When any blood glucose value was recorded < 3 mmol/L (54mg/dl), the subjects were asked to complete a validated symptom questionnaire (the Edinburgh Hypoglycemia Score¹⁰) to document the nature (autonomic, neuroglycopenic and malaise) and the intensity of the hypoglycemic symptoms that were experienced. Completed diaries and information sheets (n=80) were returned at the conclusion of the monitoring period. Methods of assessing awareness of hypoglycemia

The Gold method⁷ poses the question: “do you know when your hypos are commencing?” The respondent then completes a 7-point Likert scale with 1 representing “always aware” and 7 representing “never aware”. A score of 4 or more implies impaired awareness of hypoglycemia.

The Clarke method⁸ comprises eight questions characterising the participant’s exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to, hypoglycemia. A score of 4 or more implies impaired awareness of hypoglycemia.

The Pedersen-Bjergaard method⁹ requires the patient to respond to the question: “do you have symptoms when you have a hypo?” requiring the selection of one response from “always”, “sometimes” or “never”. Only patients who answer “always” are considered to have normal symptomatic awareness of hypoglycemia, the others are designated as having impaired or absent awareness”.

Differences between groups (normal awareness versus IAH) were analyzed using the two-sample t test/Mann-Whitney-U test or the χ^2 /Fishers exact test. To assess the linear relationship between two variables a Spearman rank correlation coefficient was calculated. All analyses were performed using SPSS version 12.0 for Microsoft Windows.

RESULTS

Prevalence of impaired awareness of hypoglycemia

The prevalences of IAH as identified by the *Gold*, *Clarke* and *Pedersen-Bjergaard* methods were 24%, 26% and 62.5% respectively. A strong association, using Spearman's test was found between the *Gold* and *Clarke* methods for identifying impaired awareness ($r_s = 0.868$, $p = 0.001$). If the *Pedersen-Bjergaard* method was revised to include "always and usually" representing normal awareness and "occasionally and never" representing IAH in response to the question "do you have symptoms when you have a hypo?" the percentage of IAH fell substantially to 15.4%. A poorer correlation was also demonstrated between this revised method and with the other methods of assessment (*Gold* $r = 0.531$, *Clarke* $r = 0.536$).

Those patients with IAH identified by the *Gold* method ($p = 0.001$) and the *Clarke* method ($p = 0.007$) were significantly older than those with normal awareness. No such age difference was observed using the *Pedersen-Bjergaard* method ($p = 0.10$). The duration of diabetes was significantly longer in the IAH group of patients using all three methods but no statistical difference was observed in HbA1c between the two groups, subdivided by state of awareness.

Frequency of biochemical hypoglycemia (Table 1)

The patients designated as having IAH using the *Gold* and *Clarke* methods reported a significantly higher number of episodes of biochemical hypoglycemia over the four-week monitoring period than those patients considered to have normal awareness. No statistical differences were observed between the two sub-groups using the *Pedersen-Bjergaard* method ($p = 0.06$). During this period the reported intensity of autonomic symptoms was lower during biochemical hypoglycemia in those in whom IAH had been identified using the *Clarke* and *Gold* methods, compared to patients designated as having normal awareness. No symptomatic differences were observed between the groups identified using the *Pedersen-Bjergaard* method ($p = 0.22$). Using all three methods no statistical differences were observed between the groups in either self-reported neuroglycopenic symptoms or mean incidence of severe hypoglycemia in the year preceding the study.

DISCUSSION

In the present study the three methods currently available to assess symptomatic awareness of hypoglycemia were evaluated for their concordance in identifying impaired awareness of hypoglycaemia. In the present randomly selected cohort of adults with type 1 diabetes, equivalent prevalences of impaired awareness (24% and 26%), with a strong correlation ($r_s = 0.868$,) were obtained with two of the methods (*Gold* and *Clarke*). This is consistent with previous population surveys, which have suggested that, based on clinical history; approximately 25% of unselected adults with type 1 diabetes have some form of this acquired syndrome^{4,11,12}. A much higher (62.5%) prevalence was observed

using the method of *Pedersen-Bjergaard*. Differences between the methods were also apparent with respect to patients considered to be at high risk of impaired awareness. With the *Clarke* and *Gold* methods, the patients identified as having IAH were older, had a longer duration of diabetes, had experienced more episodes of severe hypoglycemia during the preceding year and recorded frequent mild biochemical hypoglycaemia during the monitoring period. Those with IAH according to the *Gold* and *Clarke* methods had significantly lower autonomic and non-significantly higher neuroglycopenic symptom scores during hypoglycemia compared to those with intact awareness, which are recognised characteristics of this syndrome⁷. The *Pedersen-Bjergaard* method appears to over-estimate the prevalence of IAH and identified only those people who had a long duration of diabetes and a history of previous SH as characteristics relevant to those who had impaired symptomatic awareness.

When methods that utilise questionnaires are used to ascertain awareness of hypoglycemia, some overlap may occur. No currently available method can be considered to be fully reliable and valid. However, the *Pedersen-Bjergaard* method to identify patients with impaired awareness of hypoglycemia offers too simplified an approach to this complex clinical condition and appears to be insensitive and indiscriminating, so over-estimating its prevalence. It cannot therefore be endorsed for routine clinical use.

In conclusion, for clinical and research use, the *Clarke* and *Gold* methods should be used preferentially, either separately or in combination, to identify people with type 1 diabetes who have impaired awareness of hypoglycemia.

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Table 1 The frequency of episodes of biochemical hypoglycemia over the 4 week period and recollect total number of episodes of severe hypoglycemia (SH) during the preceeding year.

| Method of assessment | <i>Gold⁷</i> | | | <i>Clarke⁸</i> | | | <i>Pedersen-Bjergaard⁹</i> | | |
|--|-------------------------|-------------|-------|---------------------------|-------------|-------|---------------------------------------|-------------|------|
| | Normal | Impaired | p | Normal | Impaired | p | Normal | Impaired | p |
| From record sheets (%) | | | | | | | | | |
| Total biochemical glucose values < 3.0mmol/L | 3.49 (3.64) | 7.62 (5.35) | 0.003 | 3.40 (2.65) | 7.86 (5.10) | 0.001 | 3.31 (3.51) | 5.37 (4.90) | 0.06 |
| Biochemical glucose values 2.5-2.9 mmol/ | 2.38 (2.64) | 4.14 (2.92) | 0.02 | 2.33 (2.65) | 4.29 (2.81) | 0.006 | 2.26 (2.55) | 3.24 (2.91) | 0.11 |
| Biochemical glucose values <2.5mmol/l | 1.11 (1.71) | 3.47 (3.81) | 0.01 | 1.02 (1.67) | 3.57 (3.80) | 0.005 | 1.05 (1.51) | 2.08 (3.11) | 0.11 |
| Severe hypoglycemic reactions | 0 (0) | 0.1 (0.7) | 0.10 | 0.05 (0.47) | 0 (0) | 0.55 | 0 (0) | 0.05 (0.43) | 0.44 |
| Autonomic symptoms | 2.88 (1.06) | 2.09 (0.99) | 0.005 | 2.96 (1.05) | 1.89 (0.79) | 0.001 | 2.87 (1.08) | 2.54 (1.09) | 0.22 |
| Neuro-glycopenic symptoms | 2.25 (1.02) | 2.45 (1.14) | 0.47 | 2.29 (1.06) | 2.35 (1.06) | 0.83 | 2.12 (1.00) | 2.41 (1.08) | 0.27 |
| From questionnaire | | | | | | | | | |
| Incidence of SH (episodes per patient year) | 0.07 (0.32) | 1.57 (2.82) | 0.001 | 0.05 (0.29) | 1.62 (2.80) | 0.001 | 0 (0) | 0.76 (1.98) | 0.04 |
| Prevalence of SH | 5% | 53% | - | 5% | 57% | - | 0% | 26% | - |