An Evaluation of Methods of Assessing Impaired Awareness of Hypoglycemia in Type 1 Diabetes

JACQUELINE GEDDES, MRCP[1]
ROHANA J. WRIGHT, MRCP[1]
NICOLA N. ZAMMITT, MRCP[1]
IAN J. DEARY, PHD[2]
BRIAN M. FRIER, MD[1]

Subjective recognition of the warning symptoms of hypoglycemia is fundamental to allow self-treatment and prevent progression to severe hypoglycemia (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 sixfold greater frequency of severe hypoglycemia and is a recognized risk factor for this problem (7,8).

Accurate identification of individuals with IAH is important to allow modification of glycemic targets and to adjust insulin therapy to minimize 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 individuals 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.

RESEARCH DESIGN AND METHODS

— A total of 140 participants were recruited; 80 completed the study. Those who completed the study were significantly older than those who did not ($n = 60$) (mean ± SD age 47.6 ± 12.7 vs. 41.1 ± 12.6 years, respectively, $P = 0.04$). 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 methods presented by Gold et al. (7), Clarke et al. (8), and Pedersen-Bjergaard et al. (9). The participants were then asked to perform capillary blood glucose measurements (using their own blood glucose meters) four times daily, prospectively over a 4-week period. When any blood glucose value <3 mmol/l (54 mg/dl) was recorded, the subjects were asked to complete a validated symptom questionnaire, the Edinburgh Hypoglycemia Score (10), to document the nature (autonomic, neuroglycopenic, or 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 method (7) 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 implies impaired awareness of hypoglycemia.

The Clarke method (8) comprises eight questions characterizing 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 four or more implies impaired awareness of hypoglycemia.

The Pedersen-Bjergaard method (9) requires the patient to respond to the question "can you feel when you are low?" requiring the selection of one response from "always," "usually," "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 vs. IAH) were analyzed using the two-sample *t* test/Mann-Whitney *U* test or the χ^2/Fisher's 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 IAH

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 "can you feel when you are low?" the percentage of IAH fell substantially to 15.4%. A poorer correlation was also demonstrated between this revised method and the other methods of assessment (Gold $r_s = 0.531$, Clarke $r_s = 0.536$).

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

From the [1]Diabetes Department, Royal Infirmary of Edinburgh, Edinburgh, U.K.; and the [2]Department of Psychology, University of Edinburgh, Edinburgh, U.K.
Address correspondence and reprint requests to Prof. Brian M. Frier, The Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, Scotland, U.K. E-mail: brian.frier@luht.scot.nhs.uk.
Received for publication 26 December 2006 and accepted in revised form 28 March 2007.
Published ahead of print at http://care.diabetesjournals.org on 6 April 2007. DOI: 10.2337/dc06-2556.
Abbreviations: IAH, impaired awareness of hypoglycemia.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*The frequency of episodes of biochemical hypoglycemia over the 4-week period and recollected total number of episodes of severe hypoglycemia (SH) during the preceding year*

	Gold			Clarke			Pedersen-Bjergaard		
	Normal	IAH	*P*	Normal	IAH	*P*	Normal	IAH	*P*
From record sheets									
Total biochemical glucose values <3.0 mmol/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/l	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 <2.5 mmol/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
Neuroglycopenic 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%	—

Data are means (SD).

group of patients using all three methods, but no statistical difference was observed in A1C between the two groups, subdivided by state of awareness.

Frequency of biochemical hypoglycemia

Data regarding the frequency of biochemical hypoglycemia can be found in 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 4-week monitoring period than those considered to have normal awareness. No statistical differences were observed between the two subgroups 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 with 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 difference was observed between the groups in self-reported neuroglycopenic symptoms. The mean incidence of severe hypoglycemia in the year preceding the study was statistically different between those identified as having IAH compared with those with normal awareness using all three methods.

CONCLUSIONS — 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 hypoglycemia. In the present randomly selected cohort of adults with type 1 diabetes, equivalent prevalences of impaired awareness (24 and 26%, respectively), 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, ~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 hypoglycemia during the monitoring period. Those with IAH according to the Gold and Clarke methods had significantly lower autonomic and nonsignificantly higher neuroglycopenic symptom scores during hypoglycemia compared with those with intact awareness, which are recognized characteristics of this syndrome (7). The Pedersen-Bjergaard method appears to overestimate the prevalence of IAH and identified only a long duration of diabetes and a history of previous severe hypoglycemia as characteristics relevant to those who had impaired symptomatic awareness.

When methods that utilize 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 undiscriminating, thus overestimating 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.

Acknowledgments — J.G. was supported by a research grant from the Chief Scientist Office of Health of the Scottish Executive.

References

1. Deary IJ: Symptoms of hypoglycaemia and effects on mental performance and

emotions. In *Hypoglycaemia in Clinical Diabetes*. Fisher BM, Frier BM, Eds. John Wiley & Sons, Chichester, U.K., 1999, p. 29–54
2. McAulay V, Deary IJ, Frier BM: Symptoms of hypoglycaemia in people with diabetes. *Diabet Med* 18:690–705, 2001
3. Frier BM, Fisher BM: Impaired hypoglycaemia awareness. In *Hypoglycaemia in Clinical Diabetes*. Fisher BM, Frier BM, Eds. John Wiley & Sons, Chichester, U.K., 1999, p. 111–146
4. Pramming S, Thorsteinsson B, Bendtson I, Binder C: Symptomatic hypoglycaemia in 411 type 1 diabetic patients. *Diabet Med* 8:217–222, 1991
5. Cryer P, Binder C, Bolli G, Cherrington A, Gale E, Gerich J, Sherwin R: Hypoglycemia in IDDM. *Diabetes* 38:1193–1199, 1989
6. Gerich JE, Mokan M, Veneman T, Korytkowski M, Mitrakou A: Hypoglycemia unawareness. *Endocrine Reviews* 12:164–179, 1991
7. Gold AE, MacLeod KM, Frier BM: Frequency of severe hypoglycemia in patients with type 1 diabetes and impaired awareness of hypoglycemia. *Diabetes Care* 17:697–703, 1994
8. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W: Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 18:517–522, 1995
9. Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B: Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. *Lancet* 357: 1248–1253, 2001
10. Deary IJ, Hepburn DA, MacLeod KM, Frier BM: Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* 36: 771–777, 1993
11. Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM: Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. *Diabet Med* 7: 711–717, 1990
12. Muhlhauser I, Heinemann L, Fritsche E, von Lennek K, Berger M: Hypoglycemic symptoms and frequency of severe hypoglycemia in patients treated with human and animal insulin preparations. *Diabetes Care* 14:745–749, 1991