Reduced Awareness of Hypoglycemia in Adults With IDDM

A prospective study of hypoglycemic frequency and associated symptoms

WILLIAM L. CLARKE, MD
DANIEL J. COX, PHD
LINDA A. GONDER-FREDERICK, PHD
DIANA JULIAN, MA
DAVID SCHLUNDT, PHD
WILLIAM POLONSKY, PHD

OBJECTIVE — To prospectively evaluate the frequency and severity of hypoglycemic episodes in IDDM subjects who declare themselves to have reduced awareness of hypoglycemia, to validate their self-designations in their natural environment, and to determine objectively the presence or absence of autonomic and neuroglycopenic symptoms associated with their low blood glucose (BG) levels.

RESEARCH DESIGN AND METHODS — A total of 78 insulin-dependent diabetes mellitus (IDDM) subjects (mean age 38.3 ± 9.2 years; duration of diabetes 19.3 ± 10.4 years) completed two sets of assessments separated by 6 months. The assessments included reports of frequency and severity of low BG, symptoms associated with low BG, and a BG symptom/estimation trial using a hand-held computer (HHC). Diaries of hypoglycemic episodes were kept for the intervening 6 months. HbA_1 levels were determined at each assessment.

RESULTS — Of the subjects, 39 declared themselves as having reduced awareness of hypoglycemia (reduced-awareness subjects). There were no differences between these reduced-awareness subjects and aware subjects with regard to age, sex, disease duration, insulin dose, or HbA_1. During the HHC trials, reduced-awareness subjects were significantly less accurate in detecting BG <3.9 mmol/l (33.2 ± 47 vs. 47.6 ± 50% detection, $P = 0.001$) and had significantly fewer autonomic (0.41 ± 0.82 vs. 1.08 ± 1.22, $P = 0.006$, reduced-awareness vs. aware) and neuroglycopenic (0.44 ± 0.85 vs. 1.18 ± 1.32, $P = 0.004$, reduced-awareness vs. aware) symptoms per subject. Prospective diary records revealed that reduced-awareness subjects experienced more moderate (351 vs. 238, $P = 0.026$) and severe (50 vs. 17, $P = 0.0062$) hypoglycemic events. The second assessment results were similar to the first and verified the reliability of the data.

CONCLUSIONS — IDDM subjects who believe they have reduced awareness of hypoglycemia are generally correct. They have a history of more moderate and severe hypoglycemia, are less accurate at detecting BG <3.9 mmol/l, and prospectively experience more moderate and severe hypoglycemia than do aware subjects. Neither disease duration nor level of glucose control explains their reduced awareness of hypoglycemia. Reduced-awareness individuals may benefit from interventions designed to teach them to recognize all of their potential early warning symptoms.

From the Departments of Pediatrics and of Psychiatric Medicine, the University of Virginia Health Sciences Center, Charlottesville, Virginia; the Diabetes Research and Training Center (D.S.), Vanderbilt University, Nashville, Tennessee; and the Joslin Diabetes Clinic (W.P.), Boston, Massachusetts.

Address correspondence and reprint requests to William L. Clarke, MD, Box 386, Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville, VA 22908.

Received for publication 7 July 1994 and accepted in revised form 22 December 1994.

BG, blood glucose; HFS, Hypoglycemia Fear Survey; HHC, hand-held computer; IDDM, insulin-dependent diabetes mellitus; SMBG, self-monitoring of blood glucose.

Reduced awareness of hypoglycemia is a commonly reported phenomenon among patients with long-standing insulin-dependent diabetes mellitus (IDDM). Up to 50% of IDDM patients 15–20 years postdiagnosis report having lost their ability to perceive autonomic symptoms associated with low blood glucose (BG) levels and thus often fail to act to prevent severe hypoglycemia (1,2). Indeed severe hypoglycemia, e.g., loss of consciousness and/or seizures, has been reported to occur up to five times more frequently in patients with reduced awareness (3). The mechanism of this reduced awareness is not currently known. However, it has been shown to be associated with improved glucose control and defective glucose counterregulation, as well as with longer disease duration (4,5). In addition, recent low BG (<3.9 mmol/l within the previous 72 h) may be associated with an acute transient reduction in hypoglycemic symptom awareness (6–9).

Reduced awareness is usually declared by patients themselves in response to questioning. However, confirmation of their designations (aware, partially aware, or unaware) has been validated in only one laboratory study (10). Nine subjects identifying themselves as aware, partially aware, or unaware were infused with insulin in the laboratory to produce hypoglycemia, while autonomic and neuroglycopenic symptoms were monitored. Only one of nine subjects self-designated as unaware was able to identify either autonomic or neuroglycopenic symptoms as BG was lowered. In the other subjects, severe neuroglycopenia developed at higher BG levels than did autonomic symptoms (1.33 ± 0.15 vs. 0.94 ± 0.11 mmol/l, $P < 0.02$) and prevented the recognition of hypoglycemia. In subsequent prospective analyses, 66% of IDDM subjects declaring themselves unaware of hypoglycemic symptoms experienced severe hypoglycemia within the next 12 months compared with 25% of aware patients (11).

The present study was designed to

evaluate prospectively the frequency, severity, and consequences of reduced awareness of hypoglycemia as declared by IDDM subjects, to validate their designations in their natural environment, and to identify characteristics that might be useful in distinguishing people with reduced awareness. Such information could be particularly helpful in designing interventions that might prevent or interrupt severe hypoglycemic episodes and improve patients' awareness.

RESEARCH DESIGN AND METHODS

— Subjects in this study were recruited from the University of Virginia, Vanderbilt University, and the Joslin Diabetes Clinic for a larger study of blood glucose awareness training (12,13). Adults who had IDDM for at least 2 years, who were between 21 and 55 years old, and who were routinely performing self-monitoring of blood glucose (SMBG) were solicited by newspaper announcements to participate in a study involving "improved metabolic control and awareness of hypoglycemia." Particular efforts were made to recruit and include subjects with extreme degrees of hypoglycemic awareness. Subjects attended an orientation meeting at which the study was explained, and informed consent was obtained.

The study consisted of two assessments separated by 6 months. Each assessment included a battery of questionnaires and a BG symptom rating/estimation trial. During the intervening 6 months, subjects completed diaries of hypoglycemic events, which they mailed in monthly. HbA_1 was determined before the initial assessment and after the second assessment. No other intervention occurred during this time.

Assessments

Assessments included demographic, disease management, and hypoglycemic awareness questionnaires. Subjects answered questions concerning personal experiences with hypoglycemia including a history of mild, moderate, and severe episodes, and symptoms that are believed to be associated with low BG. The following definitions of hypoglycemia, similar to those used in the Diabetes Control and Complications Trial feasibility study, were used: mild—symptoms such as shakiness, headache, or sweating, relieved with simple carbohydrate; moderate—lethargy, confusion, or requiring assistance for treatment; severe—unconscious, seizure, or requiring glucagon or intravenous glucose (14). Each subject completed the Hypoglycemia Fear Survey (HFS) to measure their worry associated with low BG (15). Glycosylated hemoglobin (HbA_1) was measured for each subject to determine glucose control over the previous 6–8 weeks. All HbA_1 levels were assayed at the University of Virginia Clinical Laboratory, where the nondiabetic range was 4.4–6.9%.

BG symptom rating/estimation trial

Subjects were taught to use a hand-held computer (HHC) (Psion P-250) programmed to collect BG estimates, symptoms ratings, and SMBG determinations. The HHC prompts subjects to estimate their current BG, enter the value into the computer, and rate (on a scale of 0–6) the degree to which they are currently experiencing each of five neuroglycopenic symptoms (dizziness, uncoordination, tiredness, visual disturbance, and difficulty concentrating) and four autonomic symptoms (sweatiness, pounding heart, trembling, and nervous/tense). Subjects next performed SMBG and entered that result as well. The HHC records the date and time of each entry. Actual SMBG values entered sooner than 45 s after the prompt "Measure your BG" are designated false, since an insufficient length of time would have occurred for the determination of BG using most meters; such data are disregarded. We have previously demonstrated that the HHC BG symptom rating/estimation procedure permits accurate identification of symptoms that are sensitive and specific to high and low BG levels for each individual (12,13,16,17). Subjects in the present study completed 50 HHC trials over 3 weeks at both assessments.

Monthly diaries

During the 6 months between assessments, subjects kept hypoglycemia diaries in which they recorded information concerning mild, moderate, and severe hypoglycemic episodes. In addition to actual BG level and time of occurrence, subjects recorded information regarding driving errors (speeding, out of lane, etc.), violations, and accidents. Diaries were mailed in on a monthly basis.

Statistical analysis

Subjects were divided into those who were aware of hypoglycemia (aware group) and those who had reduced awareness (reduced-awareness group) based on their responses to questions 1–8 in Table 1. Four or more answers designated R categorized a subject as having reduced awareness, while two or fewer R answers categorized a subject as aware. Group assignments using these criteria were compared with potential aware/reduced-awareness group assignments based on subjects' answers to the single question, "To what extent can you tell by your symptoms that your sugar is low? (never, sometimes, often, always)." Agreement of categorization between the two methods was demonstrated by a cross-table ($\chi^2 = 40.29$, $P < 0.0001$).

The means of information from assessment questionnaires, HHC trials, and HbA_1 levels were obtained, and data from the two groups were analyzed after a Bonferroni correction using nonpaired Student's *t* tests. In addition, data from the assessments, HHC trials, and HbA_1 levels obtained after the prospective diary recordings were compared with the initial findings to assess reliability. Monthly diary data were added over the 6-month period and analyzed using the Mann-Whitney *U* test.

Table 1—*Survey items used to categorize aware or having reduced awareness of hypoglycemia in subjects*

1) Check the category that best describes you: (check one only)
_____ I always have symptoms when my blood sugar is low (A)
_____ I sometimes have symptoms when my blood sugar is low (R)
_____ I no longer have symptoms when my blood sugar is low (R)

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
_____ yes (R) _____ no (A)

3) In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)
_____ Never (A) _____ Once or twice (R) _____ Every other month (R)
_____ Once a month (R) _____ More than once a month (R)

4) In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)
_____ Never (A) _____ 1 time (R) _____ 2 times (R) _____ 3 times (R)
_____ 5 times (R) _____ 6 times (R) _____ 7 times (R) _____ 8 times (R)
_____ 9 times (R) _____ 10 times (R) _____ 11 times (R)
_____ 12 or more times (U)

5) How often in the last month have you had readings <70 mg/dl with symptoms?
___ Never ___ 1 to 3 times ___ 1 time/week ___ 2 to 3 times/week ___ 4 to 5 times/week
___ Almost daily

6) How often in the last month have you had readings <70 mg/dl without any symptoms?
_____ Never _____ 1 to 3 times _____ 1 time/week _____ 2 to 3 times/week
_____ 4 to 5 times/week _____ Almost daily

(R = answer to 5 < answer to 6, A = answer to 6 > answer to 5)

7) How low does your blood sugar need to go before you feel symptoms?
_____ 60–69 mg/dl (A) _____ 50–59 mg/dl (A) _____ 40–49 mg/dl (R)
_____ <40 mg/dl (R)

8) To what extent can you tell by your symptoms that your blood sugar is low?
_____ Never (R) _____ Rarely (R) _____ Sometimes (R) _____ Often (A)
_____ Always (A)

Four or more R responses = reduced awareness; 2 or fewer R responses = aware.

RESULTS

Subject characteristics

A total of 78 IDDM adults (28 men), aged 38.3 ± 9.2 (mean ± SD) years, with disease duration of 19.3 ± 10.4 years, were recruited. Of these, 39 were categorized as aware and 39 were categorized as having reduced awareness by the criteria listed above. There were no differences in mean age, disease duration, daily insulin dose, or initial HbA_1 between the two groups (Table 2). The number of subjects with known nephropathy or retinopathy was similar in both groups. More reduced-awareness subjects had known neuropathy than aware subjects (12 vs. 4), but the difference was not statistically significant.

Retrospective questionnaire data

On the retrospective questionnaire there were no differences between aware and reduced-awareness subjects in the reported frequencies of mild hypoglycemia during the month before the study. However, reduced-awareness subjects reported significantly more moderate hypoglycemia (1.9 ± 1.6 vs. 0.9 ± 1.3 episodes/month, $P = 0.002$) during the previous 6 months, and >10 times the number of severe hypoglycemic episodes during the previous year (2.6 ± 3.4 vs. 0.2 ± 0.7 episodes/year, $P < 0.0001$). Subjects rated the usefulness of the nine low BG symptoms to their recognition of hypoglycemia. Symptoms were considered to be significant for an individual if that subject rated a particular symptom as occurring often or always in association with low BG. The mean number of symptoms so endorsed was significantly greater in aware than in reduced-awareness subjects (4.32 ± 1.5 vs. 2.10 ± 1.7 symptoms/subject, $P < 0.001$). Despite these differences in frequencies of moderate and severe hypoglycemia and in symptom beliefs, fear of hypoglycemia, as measured by the HFS worry scale, did not differ in the two groups (22.3 ± 11.3 vs. 25.1 ± 9.3, NS, aware vs. reduced-awareness).

Prospective HHC data

To identify symptoms sensitive and specific to low BG (<3.9 mmol/l), the probability of a symptom being rated ≥1 when BG was low versus when it was not low (>3.9 mmol/l) was compared (17). The number of significant symptoms per subject was not linearly dependent on the number of low BG episodes ($r = 0.02$, NS). The HHC trial demonstrated significant differences in the actual number of significant symptoms per subject in the two groups (2.26 ± 2.23 vs. 0.85 ± 1.44 symptoms/subject, $P = 0.002$, aware vs. reduced-awareness). This was true for both autonomic and neuroglycopenic symptoms (Table 2). Similar numbers of subjects in each group had at least one significant symptom associated with their BG <3.9 mmol/l. In addition, detection of low BG (percentage of actual BG <3.9 mmol/l estimated as <3.9 mmol/l) was significantly lower in reduced-awareness subjects. Mean number of actual BG readings in the ranges <3.9 mmol/l, 2.8–3.9 mmol/l and <2.8 mmol/l, during the HHC trial were similar for both groups. Thus, reduced-awareness subjects believed (retrospective questionnaire) themselves to have fewer significant symptoms associated with their low BG

Table 2—*Characteristics of aware and reduced-awareness groups*

	Aware	Reduced awareness	*P* value
n	39	39	
Age (years)	36.6 ± 8.8	40.0 ± 9.3	NS
Duration (years)	16.5 ± 9.9	22.0 ± 10.3	NS
Insulin dose (U/day)	40 ± 15.9	37.2 ± 16.2	NS
HbA_1 (%)	10.7 ± 2.2	9.8 ± 1.9	NS
Retrospective data			
Moderate episodes in past 6 months (*n*)	0.9 ± 1.3	1.9 ± 1.6	<0.002*
Severe episodes in past 12 months (*n*)	0.2 ± 0.7	2.6 ± 3.4	<0.0001*
Low BG symptoms reported/subject (*n*)	4.3 ± 1.5	2.1 ± 1.7	<0.001
Prospective HHC data			
Autonomic symptoms/subject (*n*)	1.08 ± 1.22	0.41 ± 0.82	=0.007*
Neuroglycopenic symptoms/subject (*n*)	1.18 ± 1.32	0.44 ± 0.85	=0.003*
Detection of BG <3.9 mmol/l (%)	47.6 ± 50	33.2 ± 47	=0.001
BG <3.9 mmol · l^{-1} · $subject^{-1}$ (*n*)	6.5 ± 5.7	7.0 ± 4.5	NS

Data are means ± SD. * Data for these variables were not normally distributed. Thus, nonparametric Mann-Whitney *U* tests were used to compare these data.

and to be less accurate at detecting BG <3.9 mmol/l than aware subjects. This was confirmed by the HHC.

Reduced-awareness subjects may be specifically less sensitive to low BG events or generically less sensitive to internal events. Consequently, reduced-awareness and aware subjects were compared on symptoms and detection of high BG (>10 mmol/l) using HHC data. Both reduced-awareness and aware subjects had a similar number of high BG symptoms (need to urinate, dry mouth and nose, and sweet/funny taste in mouth). In addition, while reduced-awareness subjects were less accurate at detecting BG 3.9–2.8 mmol/l and <2.8 mmol/l, they were equally accurate at detecting high BG (Fig. 1). This indicates that reduced awareness is specific to low BG and not a generic insensitivity to internal bodily events.

Prospective documentation of hypoglycemic events

Reduced-awareness subjects had significantly fewer mild, but more moderate and more severe, hypoglycemic episodes during the 6-month period (Table 3). Reduced-awareness subjects had similar numbers of moderate and severe hypoglycemic events during the night as did aware subjects, but significantly more such events than aware subjects during the day ($P = 0.015$). Total driving errors (speeding, time out of lane, etc.) were greater in aware subjects (2,210 vs. 1,065, $P = 0.026$) as were driving violations (29 vs. 11, $P = 0.020$, aware vs. reduced-awareness). The number of accidents was not significantly different between the two groups.

Repeat assessment and HHC trial

After 6 months of diary recordings, all subjects repeated the HFS and the HHC trial. HbA_1 levels remained unchanged in both aware and reduced-awareness subjects. Fear of hypoglycemia scores, as reflected by HFS worry scale, also were unchanged. HHC results validated the reliability of the initial findings in terms of percentage detection of BG <3.9 mmol/l (45.9 ± 49% vs. 35.3 ± 48%, $P = 0.014$, aware vs. reduced-awareness) and number of significant hypoglycemic symptoms per subject (2.26 ± 2.26 vs. 1.0 ± 1.41, $P = 0.003$, aware vs. reduced-awareness) when BG <3.9 mmol/l. The number of subjects with at least one symptom significantly associated with BG <3.9 mmol/l was similar in both groups (25 vs. 18, NS, aware vs. reduced-awareness).

CONCLUSIONS — This is the first nonlaboratory study to examine the accuracy of IDDM subjects' self-categorization of their ability to recognize hypoglycemia. In their natural environment, IDDM

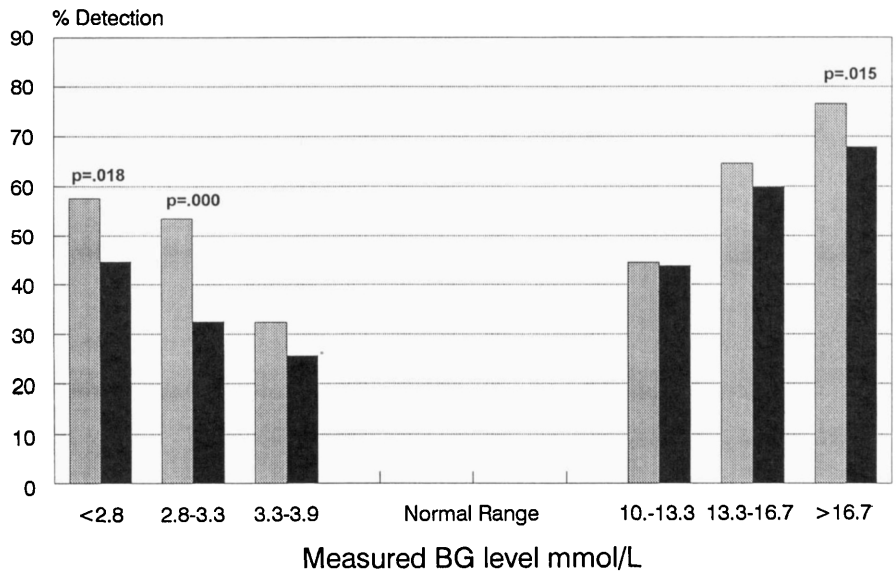

Figure 1—*Percent detection of hypo- or hyperglycemia.* ▩, *aware group;* ■, *reduced-awareness group.*

Table 3—*Six-month prospective hypoglycemia diaries*

	Aware group	Reduced-awareness group	*P* value
Mild episodes	1,064	799	0.021
Moderate episodes	238	351	0.026
Severe episodes	17	50	0.006
Driving errors	2,210	1,065	0.026
Driving violations	29	11	0.020
Driving accidents	7	5	NS

Data are *n*.

subjects who believe that they have a reduced ability to detect low BG are correct. HHC data, for both assessments, demonstrated that while reduced-awareness subjects had a similar number of BG <3.9 mmol/l measurements as aware subjects, they had fewer low BG symptoms and poorer detection of low BG. In addition, prospectively, reduced-awareness subjects experienced more moderate and severe hypoglycemic episodes. The relatively large number of subjects studied, their geographic diversity, and the stability of the findings over 6 months attest to the reliability of these data.

Previous studies have suggested that hypoglycemic unawareness is associated with long disease duration, improved glucose control, and defective glucose counterregulation (1,4,5). In the present study, reduced-awareness subjects had similar disease duration and HbA_1 levels as aware subjects. We did not test the ability of our subjects to counterregulate to hypoglycemia. However, since autonomic symptoms occurred less frequently in reduced-awareness than in aware subjects, it is possible that sympathochromaffin cell insufficiency may have contributed to their reduced awareness (18).

During insulin-induced hypoglycemia in the laboratory, unaware IDDM subjects have been shown to have neuroglycopenic symptoms at higher BG levels than autonomic symptoms (2). In addition, laboratory studies of normal adults with hypoglycemic unawareness induced transiently by repeated insulin infusions have demonstrated that neuroglycopenic symptoms are not affected by pharmacological autonomic blockade (18). Thus, it would appear that neuroglycopenic symptoms of low BG are important warning signs of impending severe hypoglycemia that are often present, but rarely used as prompts to raise BG levels.

It has been suggested that IDDM subjects with hypoglycemic unawareness are incapable of recognizing neuroglycopenic symptoms and have lost autonomic symptoms of hypoglycemia (18). The present study evaluated both autonomic and neuroglycopenic symptoms during the HHC trials. Despite a reduced number of hypoglycemic symptoms and a reduced ability to detect low BG, subjects with reduced awareness had some autonomic and neuroglycopenic symptoms. This finding, that autonomic and neuroglycopenic symptoms may be present in subjects with reduced awareness of hypoglycemia in their natural environment, emphasizes the need to improve IDDM subjects' attention to all of their potential warning signs of hypoglycemia.

Post hoc analysis of HHC data regarding symptoms associated with hyperglycemia has failed to demonstrate a correlation between the number of low and high BG symptoms per subject. In addition, these data demonstrate that reduced-awareness subjects are not generically unable to perceive symptoms of bodily events, but rather are uniquely unable to recognize low BG symptoms. The finding of no differences in the HFS worry scales between aware and reduced-awareness subjects at either assessment may be surprising. However, we have previously shown that fear of hypoglycemia as measured by this instrument is not related to the absolute number of hypoglycemic episodes (19). Rather, HFS worry scores are related to the degree of distress or trauma associated with hypoglycemic events. The difference between diary information with regard to driving errors, etc., in aware and reduced-awareness subjects may be the result of increased awareness by aware subjects of their driving skills and/or decisions by reduced-awareness subjects to drive more carefully or less frequently. Our data do not permit validation of these speculations.

The recognition of hypoglycemia is complex and requires at least four biopsychological processes: *1*) a physiological reaction, such as central nervous system dysfunction or counterregulation; 2) physical consequences, such as autonomic or neuroglycopenic symptoms; 3) symptom detection; and 4) accurate symptom interpretation (16). A variety of factors, including (but not limited to) recent low BG, autonomic neuropathy, inattention to one's symptoms, or lack of knowledge concerning the categorization of somatic symptoms as related to high or low BG, can modify these processes. Reduced awareness of hypoglycemia does not have a single cause in all IDDM subjects, nor may a single etiology explain all episodes of reduced awareness in a single subject.

In the present study, reduced-awareness subjects had similar numbers of significant autonomic and neuroglycopenic symptoms. Therefore, efforts to improve awareness in these subjects should focus on enhancing symptom detection and educating subjects with regard to symptom interpretation. Other strategies for improving awareness may be preferable in other groups of subjects. Hypoglycemia unawareness in patients with insulinomas is reversible with tumor removal (20). In addition, Fanelli et al. (21) have shown in IDDM subjects with shorter disease duration than our subjects that re-

duced awareness of hypoglycemia may be improved by raising overall mean BG levels (21). The latter, although potentially beneficial in terms of patient safety, may contribute to poor glucose control and ultimately lead to microvascular complications (22).

Clearly there is a need to identify causes of reduced awareness of hypoglycemia and develop intervention strategies to restore awareness without sacrificing metabolic control. Blood glucose awareness training, a behavioral intervention designed to assist IDDM subjects in recognizing hyperglycemic and hypoglycemic symptoms, has been shown to improve overall BG estimation accuracy without altering levels of metabolic control (12,13). Such an intervention, focused on improving autonomic and neuroglycopenic symptom detection and predicting and preventing hypoglycemia, could be an important adjunct to restoring awareness of hypoglycemia while preserving glucose control.

References

1. Cryer P, Binder C, Bolli G, Cherrington A, Gale E, Gerich J, Sherwin R: Hypoglycemia in IDDM. *Diabetes* 38:1193–1199, 1989
2. Pramming S, Thorsteeinsson B, Bendtson I, Binder C: Symptomatic hypoglycemia in 411 type I diabetic patients. *Diabetic Med* 8:217–222, 1991
3. Hepburn D, Patrick A, Eadington D, Ewing D, Frier B: Unawareness of hypoglycemia in insulin-treated patients: its prevalence and relationship to autonomic neuropathy. *Diabetic Med* 7:711–717, 1990
4. Clarke W, Gonder-Frederick L, Richards F, Cryer P: Multifactorial origin of hypoglycemic symptom unawareness in IDDM. *Diabetes* 40:680–685, 1991
5. Cryer P: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic function. *Diabetes* 41:255–260, 1992
6. Cox D, Gonder-Frederick L, Polansky W, Schlundt D, Korachev B, Clarke W: Frequency of hypoglycemia after a low BG (Abstract). *Diabetes* 42 (Suppl. 1):124A, 1993
7. Heller S, Cryer P: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
8. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J: Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42:1233–1237, 1993
9. Lingenfelser T, Renn W, Sommerwerck U, Jung M, Buettner U, Zaiser-Kaschel R, Eggstein M, Jakober B: Compromised hormonal counterregulation, symptom awareness and neuropsychological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. *Diabetes* 424:610–618, 1993
10. Hepburn D, Patrick A, Frier B: Severe hypoglycemia precedes autonomic activation in insulin-dependent diabetic patients with hypoglycemia unawareness (Abstract). *Diabetes* 38 (Suppl. 1):76A, 1989
11. MacLeod K, Gold A, Frier B: Frequency of severe hypoglycemia in insulin-dependent diabetic patients with altered awareness of hypoglycemia (Abstract). *Diabetes* 42 (Suppl. 1):73A, 1993
12. Cox D, Gonder-Frederick L, Julian D, Cryer P, Lee J, Richards F, Clarke W: Intensive versus standard blood glucose awareness training (BGAT) with insulin dependent diabetes: mechanism and ancillary effects. *Psychosom Med* 53:453–462, 1991
13. Cox D, Gonder-Frederick L, Julian D, Clarke W: Long-term follow-up of blood glucose awareness training. *Diabetes Care* 17:1–5, 1994
14. The Diabetes Control and Complications Trial Research Group: Diabetes Control and Complications Trial (DCCT): results of feasibility study. *Diabetes Care* 10:1–19, 1987
15. Cox D, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 10:617–621, 1987
16. Cox D, Gonder-Frederick L, Antoun B, Schroeder D, Clarke W: Perceived symptoms in the detection of hypoglycemia. *Diabetes Care* 16:519–527, 1993
17. Cox D, Gonder-Frederick L, Kovatchev B, Polonsky W, Schlundt D, Julian D, Clarke W: The identification and nature of hypoglycemic symptoms among individuals with insulin dependent diabetes mellitus. *Biol Psychol*. In press
18. Towler D, Havlin C, Crafts S, Cryer P: Mechanism of awareness of hypoglycemia. *Diabetes* 42:1791–1798, 1993
19. Irvine A, Cox D, Gonder-Frederick L: Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin-dependent diabetes mellitus. *Health Psychol* 11:135–138, 1992
20. Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Plantanisiotis D, Rambotti A, Raptis S, Brunetti P, Cryer P, Gerich J, Bolli G: Reversibility of unawareness of hypoglycemia in patients with insulinomas. *N Engl J Med* 329:834–839, 1993
21. Fanelli C, Epifano L, Rambotti A, Pampanelli S, DiVincenzo A, Modarelli F, Lepore M, Annibvale B, Ciofetta M, Bottini P, Porcellati F, Scionti L, Santeusanio F, Brunetti P, Bolli G: Meticulous prevention of hypoglycemia normalizes the glycemia thresholds and magnitude of most neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 42: 1683–1689, 1993
22. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993