Blood Glucose Awareness Training and Epinephrine Responses to Hypoglycemia During Intensive Treatment in Type 1 Diabetes

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OBJECTIVE — To determine the effect of blood glucose awareness training (BGAT) on epinephrine and symptom responses to hypoglycemia in patients with type 1 diabetes enrolled in an intensive diabetes treatment (IDT) program.

RESEARCH DESIGN AND METHODS — A total of 47 subjects with uncomplicated diabetes (duration 9 ± 3 years; HbA_{1c} 9.0 ± 1.2%; reference range 4–6%) enrolled in a 4-month outpatient IDT program were randomized to classes in BGAT (n = 25) (BGAT group) or cholesterol awareness (n = 22) (control group). Subjects underwent stepped hypoglycemic clamp studies before and at completion of IDT. Plasma glucose was lowered from 6.7 mmol/l (baseline) to 4.4, 3.9, 3.3, 2.8, and 2.2 mmol/l over 190 min. Symptoms, counterregulatory hormones, and ability of the subject to estimate their glucose level were assessed at each plateau. At home, subjects used a handheld computer to first estimate and then measure and record blood glucose levels for 70 trials over a 4-week period immediately before IDT and again immediately following the educational intervention.

RESULTS — HbA_{1c} decreased in both BGAT group (9.1 ± 1.4 to 7.9 ± 1.1%; $P < 0.001$) and control group (9.0 ± 1.1 to 7.8 ± 0.8%; $P < 0.001$) (NS between groups). Frequency of hypoglycemia (<3.9 mmol/l) increased in both groups, from 0.45 ± 0.06 to 0.69 ± 0.07 episodes per day ($P < 0.001$) in the BGAT group and from 0.50 ± 0.08 to 0.68 ± 0.06 episodes per day ($P < 0.05$) in the control group (NS between groups). Epinephrine responses after IDT were greater in the BGAT group (repeated measure analysis of variance [ANOVA], $F = 3.5$, $P < 0.05$). A separate analysis of subjects (n = 26) most at risk for hypoglycemia (HbA_{1c} after IDT <7.8% or an HbA_{1c} improvement of >2 percentage points) showed that frequency of hypoglycemia increased in both the groups: from 0.50 ± 0.09 to 0.80 ± 0.11 episodes per day ($P < 0.01$) in the BGAT group (n = 14) and from 0.43 ± 0.11 to 0.75 ± 0.07 episodes per day ($P < 0.05$) in the control group (n = 12) (NS between groups). However, the epinephrine response in control subjects decreased with IDT while the response in the BGAT subjects was preserved (repeated measure ANOVA, $F = 4.4$, $P < 0.02$).

CONCLUSIONS — BGAT is a useful intervention to decrease blunting of counterregulatory responses associated with improved glycemic control and may modify the severity of hypoglycemia associated with improved glycemic control in type 1 diabetes.

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Abbreviations: ANOVA, analysis of variance; BG, blood glucose; BGAT, blood glucose awareness training; DCCT, Diabetes Control and Complications Trial; hGH, growth hormone; IDT, intensive diabetes treatment; MSQ, mood and symptom questionnaire.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Intensive diabetes treatment (IDT) is associated with an increased frequency of hypoglycemic episodes in subjects with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) reported a threefold increase in the frequency of severe hypoglycemic episodes in the intensively treated group (1,2). This increased frequency of hypoglycemia has been shown to be associated with a decrease in the counterregulatory hormone and symptom responses to hypoglycemia (3–5). More recently, a number of studies have shown that avoidance of hypoglycemia may lead to restoration of some or all of the hypoglycemia-induced defects in counterregulation and symptom recognition (6–8). Fanelli et al. (6) found that restoration of counterregulatory and symptom responses occurred with a small, statistically significant deterioration in glycemic control. Cranston et al. (7) showed that hypoglycemia avoidance was associated with a small, statistically nonsignificant deterioration in glycemic control. Achievement of hypoglycemia avoidance required a major commitment of medical resources beyond that usually available to patients in a clinical setting. We hypothesized that specific training around the detection and avoidance of hypoglycemia during IDT would be beneficial in the preservation of counterregulatory responses, thereby allowing improvements in glycemic control with less hypoglycemia.

We chose blood glucose awareness training (BGAT) to accomplish this goal of improved detection and avoidance of hypoglycemia. BGAT appears to improve blood glucose estimation accuracy in type 1 diabetes (9–12) and may lead to a decrease in frequency of undetected hypoglycemia in these subjects (10–12). The BGAT program involves instruction in interpretation of physical symptoms, performance cues and moods, and feelings as internal cues to blood glucose awareness. It also involves instruction on food, exercise, insulin dosage and action, time of day, and last blood glucose reading as external cues to estimate blood glucose level. BGAT has

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Table 1—*Demographic characteristics of study subjects*

	Total group	At risk for hypoglycemia
n	47	26
Sex (M/F)	23/24	11/15
Age (years)	34 ± 8 (19–50)	33 ± 8 (19–50)
BMI (kg/m²)	25 ± 3 (19–31)	24 ± 3 (19–29)
Duration of type 1 diabetes (years)	9 ± 3 (3–15)	9 ± 3 (3–15)
Baseline HbA_{1c}(%)	9.0 ± 1.2 (7.4–13.0)	8.9 ± 1.4 (7.4–13.0)
Education (years)	16 ± 2 (11–20)	16 ± 2 (12–20)

Data are means ± SD (range).

not been used during IDT when subjects have increased risk of hypoglycemia, blunted counterregulation, and decreased symptom recognition.

We postulated that those subjects who underwent BGAT as part of IDT and improved their glycemic control (i.e., those most at risk for hypoglycemia) would exhibit a preservation of the counterregulatory and symptom responses to hypoglycemia, while control subjects who did not undergo BGAT would exhibit a blunting of the counterregulatory response to hypoglycemia.

RESEARCH DESIGN AND METHODS

Subjects

A total of 60 subjects enrolled in the study. However, eight subjects dropped because of either moving from the area (*n* = 3) or having a change in job and time involvement (*n* = 4) or a non–study-related injury (*n* = 1). Five subjects experienced technical difficulties either during one of the clamp procedures (*n* = 3) or with laboratory assays (*n* = 2). The final study sample consisted of 47 subjects (23 men, 24 women) with type 1 diabetes. Subjects had a mean age of 34 ± 8 years, had diabetes for between 3 and 15 years, and had no evidence of diabetic complications. Mean HbA_{1c} before the study was 9.0 ± 1.2%, (reference range 4–6%) (Table 1). Subjects were excluded if they had evidence of proliferative retinopathy, diabetic nephropathy, or autonomic or peripheral neuropathy. Retinopathy was assessed with dilated-eye examination by an ophthalmologist within the past 12 months. Nephropathy was defined as albumin excretion >300 mg/24 h. Autonomic neuropathy was assessed by measuring heart rate response to deep breathing and in response to the Valsalva maneuver (14). Subjects also were excluded if they had a history of severe unrecognized hypoglycemia, as defined in the DCCT, within the previous 2 years. Voluntary informed written consent was obtained from each person before the study, and the study protocol was approved by the Joslin Diabetes Center Committee on Human Studies.

All subjects were followed in an outpatient clinic over a 4- to 5-month period with a goal of improving glycemic control as near to the normal nondiabetic range as safely possible. Subjects were seen monthly by study physicians, nurse educators, and a nutritionist and had weekly telephone contact with their nurse educator to optimize glycemic control. During this period, subjects took 3–5 insulin injections per day and performed an average of five home blood glucose measurements per day. Subjects were randomized to a study group who received an eight-session group education program in BGAT (using the revised BGAT-3 version) (15) or randomized to a control group who received an equivalent number and duration of sessions in cholesterol education.

Stepped hypoglycemic insulin clamp

Before and after 4 months of intensive diabetes treatment, subjects underwent paired identical hypoglycemic insulin clamp procedures (16). Subjects arrived at the Clinical Research Center in the fasted state, having omitted their morning injection of insulin. With the patient seated, a catheter was inserted into an antecubital vein of the nondominant arm for administration of test substances. A second catheter was inserted in a retrograde fashion into a dorsal hand vein of the nondominant hand for blood sampling. This hand was placed in a heated box (70°C) to arterialize venous blood (17). Insulin was infused at 2 mU · kg^{-1} · min^{-1} (12 pmol · kg^{-1} · min^{-1}) and a variable infusion of 20% dextrose was used to lower blood glucose levels from 6.7 to 4.4, 3.9, 3.3, 2.8, and 2.2 mmol/l in a stepwise fashion every 30 min. At each glucose plateau, paired blood samples were drawn for estimation of insulin (18), catecholamines (19), cortisol (20), adrenocorticotropin (21), and growth hormone (hGH) (22).

At baseline and at each glucose level, subjects completed a 35-item self-administered mood and symptom questionnaire (MSQ). Subjects rated each item on a 7-point Likert scale, with 0 standing for feeling the symptom "not at all" and 6 standing for feeling the symptom "a lot". The mean score of trembling, sweating, pounding heart, and fast pulse was used to represent neurogenic symptoms, and the mean of being light headed, difficulty concentrating, uncoordinated, confused, and feeling weak to represent neuroglycopenic symptoms. This symptom and mood questionnaire has been used previously by our group and by others (23). On completion of each MSQ, subjects were asked to estimate and record their blood glucose level.

Other measures

HbA_{1c}. HbA_{1c} was measured at baseline, before the beginning of IDT (clamp 1), at each monthly clinic visit, at the completion of IDT (clamp 2), and at the final clinic visit.

Blood glucose meter data. Home blood glucose meter readings were downloaded to a personal computer on the day of each of the stepped hypoglycemic insulin clamp procedures, providing data on glucose levels for 4 weeks before each of the studies. These data were then used to analyze the frequency of hypoglycemia (<3.9 mmol/l) experienced by each of the study subjects.

Blood glucose estimation accuracy

This was assessed in two of the following ways for this study: *1*) At each glucose plateau during the hypoglycemic clamp studies study, subjects were asked to estimate and record their blood glucose level. We then calculated the blood glucose estimation error as measured blood glucose minus the estimated blood glucose. *2*) To assess blood glucose estimation accuracy using handheld computer data, study subjects estimated and then measured and recorded blood glucose for 70 trials over a 4-week period immediately preceding the initiation of IDT and again over a 4-week period immediately after BGAT group or control group education. Before each of the 70 glucose tests subjects recorded blood glucose, relevant symptoms, and

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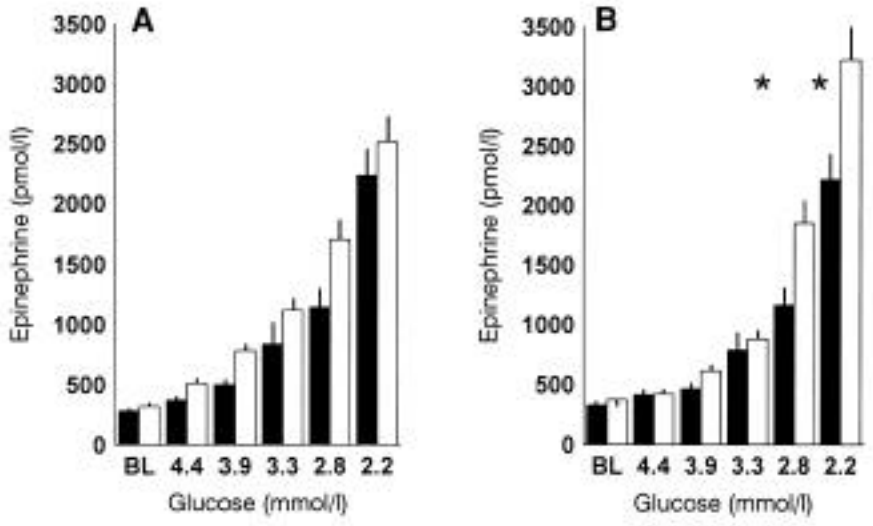

Figure 1—A: *Epinephrine levels during stepped hypoglycemic clamp study in control group (■) and in the BGAT group (□) before IDT.* B: *Epinephrine levels during stepped hypoglycemic clamp study in control group (■) and in the BGAT group (□) after IDT;* *P < *0.05 control group* (n = *25) vs. BGAT group* (n = *22)* (F = *3.5 repeated measure ANOVA)*

moods in a handheld computer (Psion P-250, London) (24). During each trial, the computer presented 13 of the moods and symptoms that were used in the mood and symptom questionnaire during the insulin clamp procedures, requiring that subjects rate their moods and symptoms on a Likert scale as described above. A built-in timer in the handheld computer ensured that subjects would not have time to perform home blood glucose testing before entering their glucose estimation. These data allowed us to assess the effect of BGAT on blood glucose estimation accuracy in the subject's home environment.

Using data from the handheld computer, we classified estimation errors according to their potential clinical impact, using criteria adapted from Cox et al. (9). According to these criteria, any estimate within 20% of the actual meter reading is correct, which allows for the ~10% difference between plasma glucose and whole blood concentration. The other error categories are the following: benign errors, unnecessary correction of an acceptable blood glucose level, dangerous failure to treat, and erroneous treatment. The latter two categories are considered serious errors. Handheld computer data were also used to calculate the low blood glucose (BG) index (25,26) and to obtain neurogenic and neuroglycopenic symptom scores. The low BG index was calculated to quantify the relative number and extent of low glucose readings. Also, the low BG index is obtained by summing the weighted values of each low glucose reading and dividing by the total number of blood glucose readings; thus a higher score indicates more low blood glucose readings (25,26).

Statistical analysis

Data are reported as mean ± SEM, except for demographic data (Table 1), which are presented as mean ± SD. Hypotheses related to between-group differences in glycemic control, hypoglycemia frequency, low BG index, and counterregulatory hormones at specific glucose levels were tested with Student's *t* tests, while within-group preintervention versus postintervention differences were tested with paired *t* tests. Overall differences in counterregulatory hormone response to hypoglycemia were tested with repeated measure analysis of variance (ANOVA). When the *P* value associated with the repeated measure ANOVA global *F* statistic was <0.05, contrasts were used to locate specific mean differences. Analysis was performed using SAS Version 6.12 (SAS Institute, Cary, NC).

RESULTS

Glycemic control and hypoglycemia frequency

During 4 months of IDT, glycemic control as measured by HbA_{1c} improved in both BGAT and control groups. HbA_{1c} fell from 9.0 ± 1.1 to 7.8 ± 0.8% in the control group ($P < 0.001$), and from 9.1 ± 1.4 to 7.9 ± 1.1% in the BGAT group ($P < 0.001$) (NS between groups). Hypoglycemia frequency (as measured by the daily number of readings <3.9 mmol/l) increased in both groups from 0.50 ± 0.08 to 0.68 ± 0.06 episodes per day in the control group ($P < 0.05$) and from 0.45 ± 0.06 to 0.69 ± 0.07 episodes per day in the BGAT group ($P < 0.001$) (NS between groups). Comparing the number of hypoglycemic episodes below 3.4, 2.8, and 2.2 mmol/l in the control and BGAT groups, no difference was noted in the severity of hypoglycemia (data not shown).

Counterregulatory hormones

Before IDT, epinephrine levels at baseline increased from 282 ± 33 to 2,234 ± 321 pmol/l at a glucose level of 2.2 mmol/l in the control group and increased from 318 ± 29 pmol/l at baseline to 2,516 ± 289 pmol/l at a glucose level of 2.2 mmol/l in the BGAT group (*P* = NS between groups; Fig. 1*A*). After 4 months of IDT, epinephrine levels increased from 328 ± 33 pmol/l at baseline to 2,217 ± 263 pmol/l at a glucose level of 2.2 mmol/l in the control group and from 373 ± 40 pmol/l at baseline to 3,220 ± 382 pmol/l at a glucose of 2.2 mmol/l in the BGAT group (Fig. 1*B*). After IDT, epinephrine levels were lower in the control group compared with the BGAT group at blood glucose levels of 2.8 mmol/l (1,162 ± 165 vs. 1,850 ± 255 pmol/l) and 2.2 mmol/l (2,217 ± 263 vs. 3,220 ± 382 pmol/l), $P < 0.05$ between groups (Fig. 1*B*). Levels of norepinephrine, ACTH, cortisol, and hGH did not differ between control and BGAT groups before or after IDT and the educational programs (Table 2).

Symptom scores

Neurogenic and neuroglycopenic symptom scores during the insulin clamp increased with hypoglycemia but did not differ between control and BGAT groups before or after 4 months of IDT (Table 3). In contrast to the control group, self-reported neurogenic symptoms (using the handheld computer) were reduced in those subjects undergoing BGAT during IDT ($P < 0.004$). Neuroglycopenic symptoms did not differ in BGAT and control groups with IDT.

Blood glucose estimation

Blood glucose estimation accuracy did not differ in control and BGAT groups before IDT (clamp 1). After IDT (clamp 2), blood glucose estimation errors at glucose levels of 3.3, 2.8, and 2.2 mmol/l steps were

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Table 2—*Counterregulatory hormone responses at baseline and at nadir hypoglycemia in groups before and after IDT*

	Control (n = 22)		BGAT (n = 25)	
	Baseline	Nadir	Baseline	Nadir
Norepinephrine (nmol/l)				
Before	1.08 ± 0.08	1.78 ± 0.19	1.14 ± 0.07	1.74 ± 0.17
After	1.24 ± 0.10	2.04 ± 0.19	1.28 ± 0.10	2.41 ± 0.22
ACTH (pmol/l)				
Before	3.0 ± 0.5	15.2 ± 3.2	3.3 ± 0.5	18.2 ± 3.6
After	5.4 ± 1.7	18.6 ± 3.3	5.2 ± 1.0	18.3 ± 2.9
Cortisol (nmol/l)				
Before	385 ± 27	573 ± 45	401 ± 25	617 ± 47
After	388 ± 30	576 ± 37	352 ± 19	604 ± 44
hGH (μg/l)				
Before	9 ± 2	55 ± 7	23 ± 7	37 ± 7
After	9 ± 3	48 ± 5	9 ± 2	46 ± 6

Data are means ± SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

−3.7 ± 1.1, −2.1 ± 0.9, and −1.0 ± 0.4 mmol/l in the control group and −3.7 ± 1.2, −2.4 ± 0.9, and −1.1 ± 0.5 mmol/l in the BGAT group (NS between groups).

Field trials performed using the handheld computer showed blood glucose estimation error did not differ between control and BGAT groups with IDT. Serious errors in glucose estimation at 3.3, 2.8, and 2.2 mmol/l were seen in 50, 27, and 15% of the control group and in 52, 20, and 12% of the BGAT group after IDT. There was no change in the low BG index after IDT (P = 0.08) for either the BGAT or the control groups. However, those subjects undergoing BGAT had a greater improvement in detection of low BG levels ($P < 0.04$) and fewer undetected low BG readings ($P < 0.05$).

Effect of BGAT on counterregulatory hormones and blood glucose awareness in subjects at high risk of hypoglycemia

As described in the section above, we identified 26 subjects as the subgroup most at risk for hypoglycemia during IDT (final HbA_{1c} <7.8 or >2% decrease in HbA_{1c} with IDT; Table 1) (mean final HbA_{1c} for at risk group = 7.3 vs. 8.5% for those at less risk of hypoglycemia). The remainder of the results will focus on this group.

Glycemic control and hypoglycemia

During 4 months of IDT, HbA_{1c} improved from 9.0 ± 0.4 to 7.4 ± 0.2% in the control group ($P < 0.01$) and from 8.8 ± 0.5 to 7.5 ± 0.2% in the BGAT group ($P < 0.01$) (NS between groups). Hypoglycemia frequency increased from 0.43 ± 0.11 episodes per day to 0.75 ± 0.07 episodes per day in the control group ($P < 0.05$) and from 0.50 ± 0.09 episodes per day to 0.80 ± 0.11 episodes per day in the BGAT group ($P < 0.05$) (NS between groups). Comparing the number of hypoglycemic episodes below 3.9, 3.3, 2.8, and 2.2 mmol/l in the control and BGAT groups, there was an increase in the proportion of hypoglycemic episodes <2.8 mmol/l from 20 ± 3 to 31 ± 4% of readings in the control group, while no increase was seen in the BGAT group from 33 ± 7 to 31 ± 4% (P = NS).

Counterregulatory hormones

In the subjects at risk for hypoglycemia, epinephrine levels before IDT increased from 278 ± 56 pmol/l at baseline to 2,556 ± 580 pmol/l at a glucose level of 2.2 mmol/l in the control group and from 304 ± 43 pmol/l at baseline to 2,346 ± 286 pmol/l at a glucose of 2.2 mmol/l in the BGAT group. Epinephrine levels did not differ between control and BGAT groups prior to IDT (Fig. 2*A*). After 4 months of IDT, epinephrine levels increased from 324 ± 47 pmol/l at baseline to 1,829 ± 322 pmol/l at a glucose level of 2.2 mmol/l in the control group and from 358 ± 66 pmol/l at baseline to 2,996 ± 569 pmol/l at a glucose of 2.2 mmol/l in the BGAT group (Fig. 2*B*). The change in epinephrine response to hypoglycemia with IDT differed in the control and BGAT groups (repeated measure ANOVA, F = 4.4; $P < 0.05$). The major contribution to this difference occurred at the 2.2 mmol/l level (Fig. 2*B*). Levels of norepinephrine, ACTH, cortisol, and hGH did not differ in control and BGAT groups before or after BGAT (Table 4).

Symptom scores

Neurogenic and neuroglycopenic symptom scores during the insulin clamp increased with hypoglycemia but did not differ between control and BGAT groups before and after 4 months of IDT (Table 5). There was no significant decrease in neurogenic (P = 0.11) or neuroglycopenic symptoms (P = 0.93) in the BGAT group compared with the control group with IDT in the data obtained from the handheld computer.

Blood glucose estimation

Blood glucose estimation accuracy, as assessed during the hypoglycemic insulin clamp studies, did not differ in the control and BGAT groups before and after IDT. After IDT, blood glucose estimation errors at glucose levels of 3.3, 2.8, and 2.2 mmol/l steps were −1.7 ± 0.9, −2.1 ± 1.1, and −1.6 ± 0.7 mmol/l in the control group and −2.2 ± 0.8, −2.1 ± 0.9, and −1.6 ± 0.9 mmol/l in the BGAT group. Trials performed using the handheld computer showed that blood glucose estimation error (including serious errors) did not differ

Table 3—*Symptom scores at baseline and at nadir hypoglycemia during a hypoglycemic clamp study in groups before and after IDT*

	Control (n = 22)		BGAT (n = 25)	
	Baseline	Nadir	Baseline	Nadir
Neurogenic				
Before	0.32 ± 0.11	2.14 ± 0.27	0.31 ± 0.10	2.2 ± 0.30
After	0.30 ± 0.08	1.82 ± 0.29	0.30 ± 0.11	1.78 ± 0.30
Neuroglycopenic				
Before	0.64 ± 0.12	2.30 ± 0.21	0.74 ± 0.14	2.18 ± 0.32
After	0.53 ± 0.12	1.87 ± 0.22	0.70 ± 0.18	1.56 ± 0.26

Data are means ± SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

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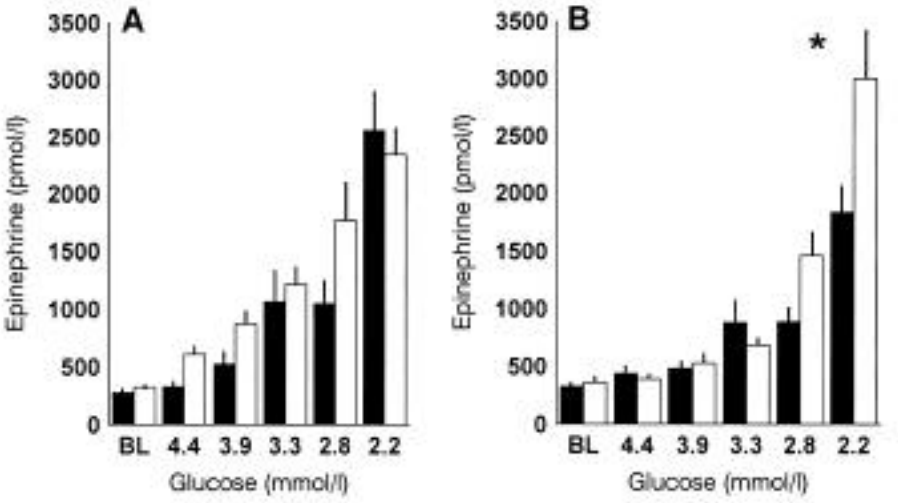

Figure 2—*Epinephrine levels during stepped hypoglycemic clamp study in 26 subjects at risk for hypoglycemia (BGAT, n = 14; control group, n = 12). A: Control group (■) and BGAT group (□) before IDT. B: Control group (■) and BGAT group (□) after IDT; *P < 0.02, (F = 4.4 repeated measures ANOVA) pre-IDT vs. post-IDT.*

between control and BGAT groups with IDT. Serious errors in glucose estimation at 3.3, 2.8, and 2.2 mmol/l were seen in 42, 25, and 17% of the control group and in 50, 28, and 14% of the BGAT group after IDT. However, those subjects undergoing BGAT had fewer undetected low BG readings compared with the control group ($P < 0.04$).

CONCLUSIONS — In this study, we examined the effect of BGAT on counterregulatory hormone and symptom responses to hypoglycemia during 4 months of IDT in type 1 diabetes. IDT, involving the use of multiple daily injections of insulin and frequent blood glucose monitoring, is designed to help subjects with type 1 diabetes improve their glycemic control. Many achieve levels of HbA_{1c} close to the nondiabetic range. However, IDT has been shown to be associated with an increased frequency of hypoglycemia in subjects with type 1 diabetes (1,2). The increased frequency of hypoglycemia leads to a reduction in the counterregulatory hormone (mainly epinephrine) response to subsequent acute hypoglycemia, initiating a cycle where exposure to hypoglycemia increases the risk of subsequent hypoglycemia for these subjects (3–5). Thus, an intervention, which could improve the detection and avoidance of hypoglycemia associated with improvements in glycemic control, should allow for maintenance of the epinephrine response to subsequent hypoglycemia and protection from more profound hypoglycemic episodes in these subjects.

BGAT is a psychoeducational intervention designed to improve patients' ability to detect both hyperglycemia and hypoglycemia. Skills training is focused on enhancing awareness of how internal cues (e.g., concentration difficulties) subtly covary with the individual's blood glucose shifts and how external factors (e.g., timing of insulin action) are associated with changes in blood glucose level. In an initial study, Cox et al. (9) found that BGAT leads to an increase in the accuracy of blood glucose estimation. This initial finding has been confirmed in other studies demonstrating an increase in estimation accuracy of 15–25% (10–13), particularly in the hypoglycemic range (10,11,13). In a study of outpatients, BGAT was found to promote a decrease in the percentage of undetected hypoglycemic episodes from 48 to 25% (11). A later study on hospital-based patients confirmed these findings (12). Cox et al. (25) reported an improvement in detection of both high and low BG levels and a reduction in the number of low readings during self-monitoring of blood glucose in 78 subjects who underwent BGAT. Improved detection of hypoglycemia was significant only for hypoglycemia unaware subjects, while the reduction in the number of low readings was significant only for subjects reporting awareness of hypoglycemia. The authors suggested that BGAT might be an effective behavioral adjunct during IDT to reduce the occurrence of severe hypoglycemia.

In this study, both control and BGAT groups achieved similar improvements in glycemic control. Both also had similar increases in the frequency of hypoglycemia with IDT, yet the epinephrine response in the BGAT group was not impaired despite an increase in frequency of hypoglycemia. Self-reported neurogenic and neuroglycopenic symptoms and blood glucose estimation accuracy did not differ during the insulin clamp studies in control and BGAT groups. Thus, the reason for the preservation of the epinephrine response in the BGAT group, despite an increase in the frequency of hypoglycemic episodes, was not initially apparent. However, subjects who underwent BGAT had better detection of low blood glucose compared with the control group. Thus, the preservation of the

Table 4—*Counterregulatory hormone responses at baseline and at nadir hypoglycemia in groups before and after IDT in the 26 subjects at risk for hypoglycemia*

	Control (n = 12)		BGAT (n = 14)	
	Baseline	Nadir	Baseline	Nadir
Norepinephrine (nmol/l)				
Before	1.12 ± 0.10	1.94 ± 0.30	1.16 ± 0.11	1.60 ± 0.16
After	1.30 ± 0.12	2.00 ± 0.15	1.08 ± 0.08	2.05 ± 0.20
ACTH (pmol/l)				
Before	3.7 ± 0.7	16.7 ± 5.1	3.5 ± 0.8	13.4 ± 3.2
After	7.6 ± 2.9	16.8 ± 5.4	5.1 ± 1.5	12.2 ± 1.6
Cortisol (nmol/l)				
Before	374 ± 36	565 ± 61	400 ± 34	660 ± 58
After	399 ± 53	531 ± 53	366 ± 30	600 ± 67
hGH (μg/l)				
Before	8 ± 3	55 ± 9	25 ± 5	30 ± 5
After	13 ± 4	53 ± 8	12 ± 3	41 ± 7

Data are means ± SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

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Table 5—*Symptom scores at baseline and at nadir hypoglycemia during a hypoglycemic clamp study in groups before and after IDT in those 26 subjects at risk for hypoglycemia*

	Control (n = 12)		BGAT (n = 14)	
	Baseline	Nadir	Baseline	Nadir
Neurogenic				
Before	0.52 ± 0.18	2.58 ± 0.30	0.29 ± 0.10	2.17 ± 0.38
After	0.42 ± 0.12	2.27 ± 0.36	0.13 ± 0.09	1.59 ± 0.40
Neuroglycopenic				
Before	0.75 ± 0.20	2.41 ± 0.25	0.44 ± 0.16	1.67 ± 0.34
After	0.47 ± 0.16	2.15 ± 0.28	0.20 ± 0.10	1.06 ± 0.24

Data are means ± SEM. BG levels were 6.7 mmol/l at baseline and 2.2 mmol/l at nadir.

epinephrine response may relate to the ability of those subjects who underwent BGAT to modify hypoglycemic exposure during IDT.

Data based on the entire study group reflect subjects who did not achieve a significant improvement in glycemic control during IDT. These subjects would not have been expected to have an increased frequency of hypoglycemia or an altered counterregulatory response. The original hypothesis was that those subjects who underwent BGAT and improved their glycemic control would experience fewer hypoglycemic episodes than control subjects who improved their glycemic control to a similar degree but did not receive BGAT. Therefore, to clarify the effect of BGAT in preserving the epinephrine response and in modifying the exposure to hypoglycemia during IDT, we specifically identified those study subjects who had the most clinically meaningful improvement in glycemic control and who would be considered most at risk for hypoglycemia.

In these 26 subjects, epinephrine levels were maintained after IDT in those subjects who underwent BGAT, while epinephrine levels decreased in the control group (Fig. 2). Daily hypoglycemia frequency increased to a similar degree in both control and BGAT groups. However, in these subjects who had improved their glycemic control, there was no increase in the percentage of hypoglycemic episodes <2.8 mmol/l in the BGAT group, while the percentage of hypoglycemic episodes <2.8 mmol/l increased in the control group. Moreover, field data from the handheld computer demonstrated a decrease in the number of undetected low blood glucose levels in the subjects who underwent BGAT. Thus, while all subjects experienced an increase in hypoglycemia frequency with IDT, the maintenance of the proportion of events <2.8 mmol/l and the decrease in the number of undetected episodes of hypoglycemia would be expected to result in fewer severe prolonged episodes of hypoglycemia in the BGAT group compared with the control group. These mild hypoglycemic episodes may not impact significantly on counterregulation and thus would be associated with a preservation of the epinephrine response to subsequent hypoglycemia.

In this study, two measurements of blood glucose estimation accuracy (a measure of internal clues to hypoglycemia) did not differ between control and BGAT groups with IDT. This suggests that the preservation of the epinephrine response and the shift in the distribution of the hypoglycemic episodes in the BGAT subjects who improved their glycemic control were due to their ability to use the information addressing insulin action, timing of injections, meals, and exercise (external clues) taught as an integral part of the BGAT course.

The findings on hypoglycemia frequency in the study were based on home blood glucose testing and have some limitations. Subjects may not have treated or recorded all of their low blood glucose readings, and we have no data on nocturnal hypoglycemic episodes in these subjects. Unrecognized nocturnal hypoglycemic episodes are known to affect counterregulatory hormone responses to subsequent hypoglycemia (27). However, in a study of this type which combines data from both a clinical research and field environment, self-monitoring of blood glucose levels using memory meters is the best method available to quantify hypoglycemia frequency.

In summary, this study shows an effect of a psychoeducational intervention (BGAT) on a physiological response (epinephrine), which ultimately may impact on the problem of hypoglycemia for individuals with type 1 diabetes. Among those subjects with type 1 diabetes who improved their glycemic control and who had increased frequency of hypoglycemia during 4 months of IDT, BGAT was associated with preservation of the epinephrine response to hypoglycemia and a reduction in the number of undetected hypoglycemic episodes, compared with those who achieved similar improvement in glycemic control with IDT but did not undergo BGAT. Therefore, BGAT may be useful in avoiding the downregulation in counterregulatory responses to hypoglycemia associated with intensive diabetes therapy in type 1 diabetes.

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