A Multicenter Evaluation of Blood Glucose Awareness Training-II

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OBJECTIVE — Blood glucose awareness training (BGAT) teaches individuals with insulin-dependent diabetes to more accurately estimate/detect their blood glucose (BG) fluctuations. It has not, however, consistently resulted in improved ability to detect low BG. To assess an enhanced version of BGAT (BGAT-II), with more focus on increasing sensitivity to low BG events, a multicenter study was undertaken. Following up on previous findings that BGAT is most effective with individuals who are least accurate in estimating BG, this study explicitly recruited subjects who did and did not report reduced awareness of hypoglycemia.

RESEARCH DESIGN AND METHODS — Seventy-eight subjects from three research sites participated in a repeated baseline design. Subjects' BG estimation accuracy and BG profiles were assessed 6 months before, immediately before, and immediately after BGAT-II.

RESULTS — Post-treatment, BGAT-II led to better overall accuracy in detecting BG fluctuations and better detection of both low and high BG levels. This was achieved while the number of low readings of self-monitoring of blood glucose (SMBG) was reduced. Reduction in the number of low SMBG events was significant only for subjects reporting awareness of hypoglycemia. Detection of low BG was significant only for subjects reporting reduced awareness of hypoglycemia. Both groups demonstrated equivalent improvements in detection of high BG levels.

CONCLUSIONS — BGAT may be an effective behavioral strategy for reversing hypoglycemic unawareness and an adjunct to intensive insulin therapy to reduce the occurrence of severe hypoglycemia.

A series of studies (1–8) has found that blood glucose awareness training (BGAT) effectively teaches individuals with insulin-dependent diabetes mellitus (IDDM) to more accurately recognize blood glucose (BG) fluctuations through symptom perception. The original BGAT involved both educational materials on symptoms of BG fluctuations and homework exercises. Homework involved rating experienced symptoms, estimating BG level on the basis of these symptoms, performing self-monitoring of blood glucose (SMBG), and then plotting estimated/actual BG readings on an error grid (9) to provide immediate feedback concerning estimation accuracy. While BGAT has led to consistent improvement in overall BG estimation accuracy, it has not specifically improved detection of extreme BG levels (<3.9 and >10 mmol/l). We recently followed up past BGAT subjects and, in comparison with control subjects, found that past BGAT subjects had fewer automobile crashes and had sustained improvement in metabolic control. In addition, past BGAT subjects who were given booster training demonstrated better detection of low BG events compared with past BGAT subjects who did not receive booster training (10). These data have potentially significant implications for patients undergoing intensive therapy, who are at increased risk of severe hypoglycemia.

In an attempt to enhance BGAT and to more thoroughly evaluate its impact, we conducted a multicenter evaluation. BGAT-II involved seven 1.5-h classes that followed a standardized training manual. This manual has an introductory chapter, three chapters on internal cues (autonomic, neuroglycopenic, and affective symptoms), and three chapters on external cues (timing, amount and type of insulin injections, food consumption, and exercise performance). BGAT-II differed from our original BGAT in several respects. The original manual was 74 pages, while the BGAT-II manual was 132 pages. While the original manual dealt with external cues in a single chapter, the new manual devoted separate chapters to insulin, food, and exercise. The original manual was written in 1985, and the new manual was written in 1992 and updated with all new information. The new man-

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AVOVA, analysis of variance; BG, blood glucose; BGAT, blood glucose awareness training; SMBG, self-monitoring of blood glucose.

ual had extensive input from diabetes experts across a wide range of disciplines.

Our previous work demonstrated that subjects with the poorest estimation accuracy at baseline benefited the most from BGAT (1–3). Therefore, our present study explicitly evaluated the effects of BGAT on subjects who either did report reduced hypoglycemic awareness (aware subjects) or did not (reduced-awareness subjects). Since several previous studies have failed to find a placebo effect on estimation accuracy (1–3), subjects in the present study served as their own control subjects in a repeated baseline design. Assessment of estimation accuracy and BG profiles occurred three times: 6 months before, immediately before, and 1 month after BGAT. To assess the ability to generalize BGAT's efficacy, three research sites and four trainers were used. Joslin Diabetes Center and Vanderbilt University were selected as the two additional research sites because of their geographic proximity to the University of Virginia, while being distinctly different from one another and University of Virginia in terms of region.

RESEARCH DESIGN AND METHODS

— All three sites recruited subjects through newsletters, notices posted in diabetes clinics, and direct physician referral. Subjects were requested to participate in a training program designed to enhance awareness/detection of BG fluctuations. All subjects were required to *1*) have had diabetes for at least 2 years, 2) have taken insulin since the time of diagnosis, 3) routinely measure their BG with a meter ≥2 times/day, and 4) not have a clinical history of depression or substance abuse. A total of 36, 29, and 35 subjects were recruited at the University of Virginia, Joslin Diabetes Center, and Vanderbilt University, respectively. Of these subjects, 22 did not complete all pretreatment and post-treatment assessments. All but one withdrawal from the study occurred during the 6-month repeated baseline phase before BGAT. Only the 78 subjects who completed all data collection are included in the data analyses. There were 28 men and 50 women, with mean age of 38.2 ± 9.0 years; mean duration of disease of 19.3 ± 10.4 years; mean insulin dose of 38.6 ± 16 U/day; and mean HbA_1 of 10.25 ± 2.13%. In our laboratory, the upper limit of normal HbA_1 is 6.9%. There was no difference between aware and reduced-awareness groups for any of these pretreatment variables (11).

Subjects were defined as hypoglycemic aware or as having reduced hypoglycemic awareness on the basis of clinical criteria, patients' reports of recent experience with severe hypoglycemia, and reported lost symptoms of hypoglycemia. The exact criteria are found in Table 1 of the accompanying article (11). Final subject selection and assignment to hypoglycemic aware or reduced-awareness groups was performed at the University of Virginia, keeping the other sites blind to conditions.

Procedure

Groups of 4–10 subjects were invited to a general orientation meeting, at which they were informed about the nature of the study and all questions were answered. Interested subjects then signed a consent form and initiated the first assessment. Each assessment was identical and included an HbA_1 assay and use of a hand-held computer. Subjects were instructed to use the Psion P-250 hand-held computer for 50 trials over a 3- to 4-week period just before their routine SMBG, whenever they felt symptoms of BG fluctuations and when they anticipated their BG to be either high or low. On each trial, subjects first entered an estimate of their current BG level. Then, the computer presented 12 symptoms, which subjects rated on a 0 (none) to 6 (extreme) scale. Finally, subjects performed SMBG and entered this reading. Once subjects entered a response, the data could not be changed. SMBG measurements were generated by subject's own meter, since that is the meter they were familiar with and since it contained the data from which they made clinical decisions.

For each trial, the computer stored each BG estimate, symptom ratings, SMBG reading, and elapsed time between the computer's prompt to "Measure your BG" and the subject's entry of his/her SMBG reading. Since at least 1 min is required for a subject to lance his/her finger, collect a blood sample, and generate a BG reading, data were considered unreliable if this elapsed time was <60 s. In addition, trials that were entered within 30 min of a previous trial were assumed to be dependent on that previous trial and were considered unreliable. Any trials with unreliable data were excluded from analyses. The same assessment procedure was repeated 6 months later, just before BGAT.

BGAT classes of 8–10 subjects followed the same training procedure. Subjects *1*) read a chapter before class, 2) discussed that chapter in class, 3) used information from that class to estimate their BG just before SMBG during the subsequent week, and 4) discussed these home observations in the next class. For example, if the class focused on the internal cue of neuroglycopenic symptoms, subjects were taught how low BG affects the brain, what the most common neuroglycopenic symptoms are (12), and how to detect subtle signs of neuroglycopenia (e.g., perform mental subtractions, and then they were given a BG diary listing the most common neuroglycopenic symptoms and how to test for them. Subjects considered these symptoms, recorded in their diaries any experienced symptoms, and then estimated and subsequently measured their BG levels. The error grid was reproduced on the back of this diary. Subjects plotted their estimated (*y*-axis) and actual (*x*-axis) readings on this error grid, noting whether their estimates were accurate (A zones) or dangerously inaccurate (C, D, or E zones). An example of an external cue chapter was the one dealing with insulin. Insulin kinetics of short-, intermediate-, and long-acting insulin were discussed (14). Information was pre-

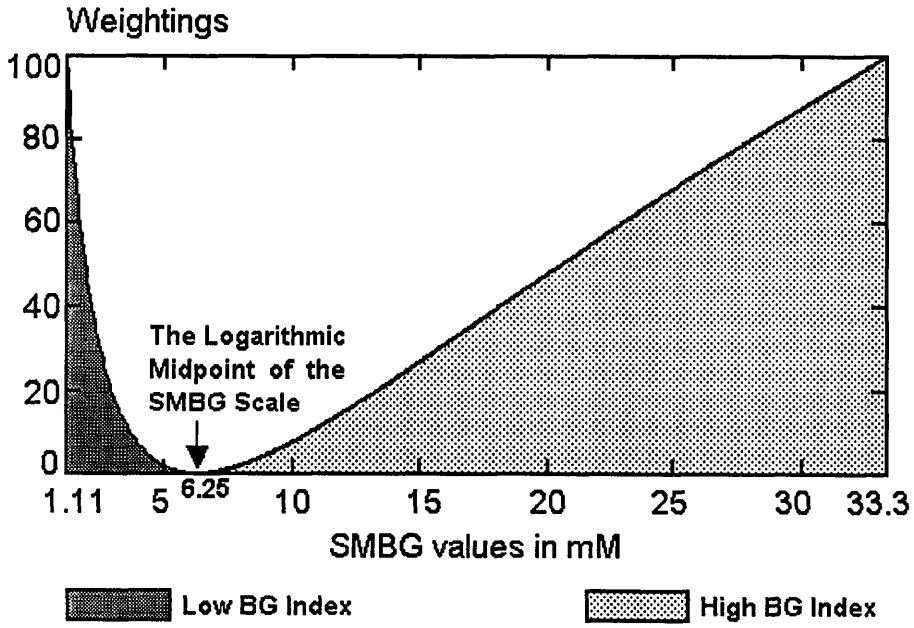

Figure 1—*Quadratic weighting functions of BG readings between 20 and 600 mg/dl.*

sented on how to predict the combined effects of subjects' personal insulin regimens, when their insulin actions were peaking or at their nadirs, and how to extrapolate when subjects were most vulnerable to low and high BG levels. For homework, subjects plotted their combined insulin curves, taking into account the time, amount, and type of insulin used. On the basis of this graphed information, subjects were to anticipate when their insulin action was most likely to be high or low, while concurrently considering the external cues of food, exercise, and last BG reading.

The third assessment began 1 week after class 7. The third HbA_1 assessment was done 1 month after completion of BGAT, when subjects turned in their hand-held computers.

Measures

Analyses focused on improvement in estimation accuracy and shifts in BG distributions for both aware and reduced-awareness subjects. Estimation accuracy was quantified in two ways. First, the accuracy index was calculated from the error grid analysis (2). This involved determining the percentage of estimates that are considered accurate (A zone estimates) minus the percentage of dangerously inaccurate estimates (C, D, and E zones). Second, using the assumptions of the error grid, the percentage of low (<3.89 mmol/l) and high (>10 mmol/l) BG levels detected was calculated. Detection occurred when the estimated and actual BG levels were either both <3.89 mmol/l or >10 mmol/l.

BG distribution was defined using the BG index (16), which quantifies the frequency and degree of extreme BG levels in an individual's SMBG records. The BG index is computed as the mean weight of the SMBGs. The weighting for each BG reading is based on a logarithmic rescaling of the BG readings and a quadratic weighting function known as a risk function in mathematical risk theory. The lowest (1.1 mmol/l or 20 mg/dl) and the highest (33.33 mmol/l or 600 mg/dl) possible SMBG readings, with most meters, are assigned the weight of 100. The logarithmic midpoint of the acceptable postprandial BG range of 3.89–10 mmol/l (17) is 6.25 mmol/l. BG readings at that midpoint are assigned a weight of 0. Values above and below 6.25 mmol/l are assigned exponentially increasing weights. The curve depicting the weighted risk for specific BG values is presented in Fig. 1. Two indexes can be generated. The high BG index involves weighting every reading >6.25 mmol/l, while readings below this midpoint are all given weightings of 0. The low BG index is the inverse, in which readings <6.25 mmol/l are weighted and those above are weighted 0. By adding this weight for each SMBG reading and dividing by the number of readings, this variable quantifies the frequency and severity of extreme high and low BG readings. We have found that the low BG index significantly predicts future occurrence of severe hypoglycemia (16), while the high BG index significantly correlates with HbA_1 ($r = 0.67$, $P < 0.001$) (D.J.C. and B. Kovatchev, unpublished observations).

Table 1—*Reliability and stability of primary dependent variables across the 6 and 0 months pre-BGAT repeated baseline*

	Correlation	Comparison of mean
Estimation accuracy measurements		
Accuracy index	0.48, $P = 0.000$	$t = 0.17$, $P = 0.86$
Detection (%)		
<3.9 mmol/l	0.65, $P = 0.000$	$t = 1.08$, $P = 0.28$
>10 mmol/l	0.66, $P = 0.000$	$t = 0.79$, $P = 0.43$
BG distribution measurements		
Low BG index	0.60, $P = 0.000$	$t = 0.98$, $P = 0.33$
High BG index	0.60, $P = 0.000$	$t = 0.18$, $P = 0.86$

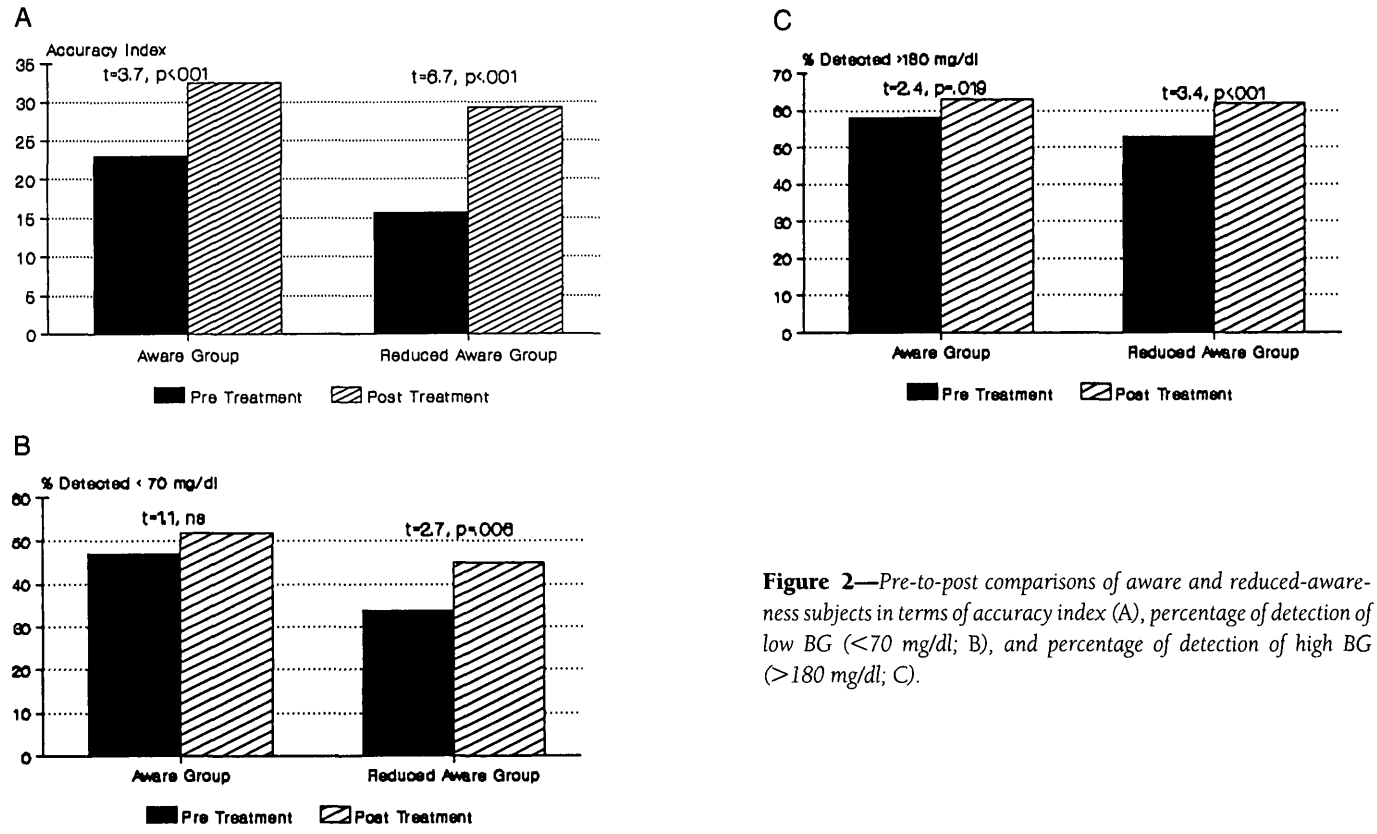

Figure 2—*Pre-to-post comparisons of aware and reduced-awareness subjects in terms of accuracy index (A), percentage of detection of low BG (<70 mg/dl; B), and percentage of detection of high BG (>180 mg/dl; C).*

RESULTS

Overview

Across-subject analyses were performed. Because baseline assessments 1 and 2 were highly correlated and not different (Table 1), affirming no beneficial effect with time or repeated use of the handheld computer, assessments 1 and 2 were combined. Analysis of variance (ANOVA) was used to compare this averaged baseline and assessment 3 for aware and reduced-awareness subjects.

Improvement in BG estimation accuracy

For the accuracy index, there were significant group ($F = 28.84$, $P \leq 0.001$), pre-to post-treatment ($F = 53.91$, $P \leq 0.0001$), and interaction ($F = 4.66$, $P = 0.03$) effects. Reduced-awareness subjects were less accurate at baseline but showed the greatest benefit from BGAT-II. Contrasts showed that both groups demonstrated significant pre-to-post improvements in accuracy index (Fig. 2*A*). Percentage of detection of low BG demonstrated significant group ($F = 15.9$, $P \leq 0.0001$), and pre-to-post ($F = 7.67$, $P = 0.006$) effects, but no interaction effect ($F = 0.89$, $P = 0.35$). Figure 2*B* indicates that reduced-awareness subjects were less accurate at detecting low BGs at baseline and, at posttreatment, their accuracy was equivalent to aware subjects' baseline performances. Contrasts showed that only reduced-awareness subjects demonstrated significant pre-to-post improvement in detection of low BG. In terms of detecting high BG, there were significant group ($F = 5.07$, $P = 0.02$) and pre-to-post ($F = 15.9$, $P \leq 0.0001$) effects, but no interaction effect ($F = 0.77$, $P = 0.38$; Fig. 2*C*). Both aware and reduced-awareness subjects demonstrated significant pre-to-post improvement in detection of high BG. In summary, these findings indicate that BGAT-II improved overall BG estimation accuracy and, specifically, detection of high BG for both aware and reduced-awareness subjects, but only reduced-awareness subjects demonstrated a significant improvement in detection of low BG.

Shifts in BG distributions

For the low BG index (Fig. 3*A*), there were significant group ($F = 9.35$, $P = 0.002$) and pre-to-post ($F = 3.69$, $P = 0.055$) effects, but no interaction effect. Contrasts showed that only the aware subjects demonstrated a significant pre-to-post improvement in their low BG indexes. For the high BG index, there were significant group ($F = 18.30$, $P \leq 0.001$) and interaction ($F = 3.95$ $P < 0.05$) effects, but not a pre-to-post effect. Only reduced-awareness subjects demonstrate

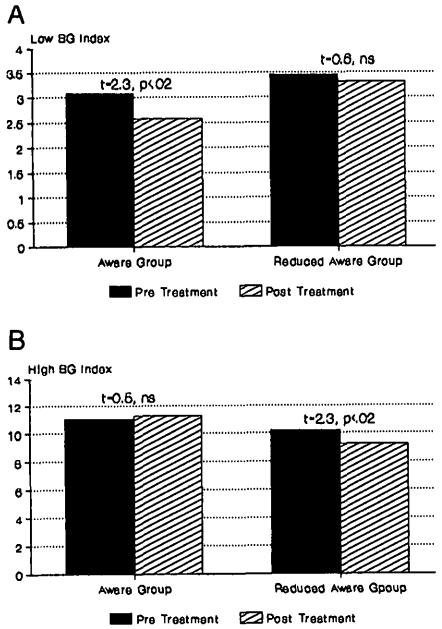

Figure 3—*Pre-to-post comparison of aware and reduced-awareness subjects in terms of low BG index (A) and high BG index (B).*

a significant pre-to-post improvement in high BG index (Fig. 3*B*).

CONCLUSIONS— BGAT-II was effective in improving overall accuracy of BG estimation, as well as specific detection of both low and high BG. Aware and reduced-awareness subjects demonstrated equivalent improvements in overall estimation accuracy and detection of hyperglycemia. However, only reduced-awareness subjects demonstrated pre-to-post BGAT-II benefits in terms of improved detection of hypoglycemia. In the accompanying paper (11), we report that, while reduced-awareness subjects had fewer autonomic and neuroglycopenic symptoms at baseline, they did have some hypoglycemic symptoms. Post hoc analysis indicated that improved detection of low BG was not associated with a pre-to-post increase in the number of perceived symptoms sensitive and specific to hypoglycemia. This would suggest that BGAT-II helped reduced-awareness subjects to more effectively utilize their available hypoglycemic cues.

Given that these findings come from three diverse diabetes centers at which BGAT was taught by four therapists, this methodology adds to the external validity/generalization of the efficacy of BGAT-II. This was formally confirmed with ANOVA analyses, which found no site × pre-to-post interactions with any of the dependent variables. Another issue of the ability to generalize relates to which patients will utilize BGAT. Of the 100 subjects, 22 dropped out. Dropouts did not differ from subjects who completed BGAT in terms of age, race, sex, education, treatment regimen, disease duration, locus of control, self-efficacy, or depression. In fact, only one of the subjects who began BGAT dropped out during training. The remaining dropouts withdrew during the 6-month repeated baseline phase. These results suggest that BGAT is acceptable to a range of patients and can be administered equally well by various professionals at various diabetes facilities.

In terms of preventing severe hypoglycemia, we have reported that the presence of frequent and extremely low BG readings during routine SMBG (low BG index) is a major predictor of severe hypoglycemic episodes during the subsequent 6 months (16). BGAT-II led to a significant reduction of such low SMBG readings, but only for those individuals who reported hypoglycemic awareness. Therefore, this group may particularly benefit in terms of lowered risk of severe hypoglycemia. Why this risk factor had a lesser impact among reduced-awareness subjects is unclear. However, future research should be directed at enhancing BGAT further so that it explicitly focuses on reducing the number and magnitude of low BG events, as well as on improving detection of low BG events.

BGAT may have direct application to patients undergoing intensive insulin therapy. If patients undergoing intensive therapy could be taught to better recognize/anticipate their low BG levels, then they would be in a better position to prevent severe hypoglycemia. As recently pointed out (18), severe hypoglycemia is a major barrier to implementation of the Diabetes Control and Complications Trial Research Group's findings.

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