Biopsychobehavioral Model of Severe Hypoglycemia II

Understanding the risk of severe hypoglycemia

DANIEL J. COX, PHD
LINDA A. GONDER-FREDERICK, PHD
BORIS P. KOVATCHEV, PHD
DEBORAH L. YOUNG-HYMAN, PHD
THOMAS W. DONNER, MD
DIANA M. JULIAN, MS
WILLIAM L. CLARKE, MD

OBJECTIVE — To evaluate the clinical/research utility of the biopsychobehavioral model of severe hypoglycemia in differentiating patients with and without a history of severe hypoglycemia and in predicting occurrence of future severe hypoglycemia.

RESEARCH DESIGN AND METHODS — A total of 93 adults with type 1 diabetes (mean age 35.8 years, duration of diabetes 16 ± 10 years, HbA_1 8.6 ± 1.8%), 42 of whom had a recent history of recurrent severe hypoglycemia (SH) and 51 who did not (NoSH), used a handheld computer for 70 trials during 1 month recording cognitive-motor functioning, symptoms, blood glucose (BG) estimates, judgments concerning self-treatment of BG, actual BG readings, and actual treatment of low BG. For the next 6 months, patients recorded occurrence of severe hypoglycemia.

RESULTS — SH patients demonstrated significantly more frequent and extreme low BG readings (low BG index), greater cognitive-motor impairments during hypoglycemia, fewer perceived symptoms of hypoglycemia, and poorer detection of hypoglycemia. SH patients were also less likely to treat their hypoglycemia with glucose and more likely to treat with general foods. Low BG index, magnitude of hypoglycemia-impaired ability to do mental subtraction, and awareness of neuroglycopenia, neurogenic symptoms, and hypoglycemia correlated separately with number of SH episodes in the subsequent 6 months. However, only low BG index, hypoglycemia-impaired ability to do mental subtraction, and awareness of hypoglycemia entered into a regression model predicting future severe hypoglycemia ($R^2 = 0.25$, $P < 0.001$).

CONCLUSIONS — Patients with a history of severe hypoglycemia differed on five of the seven steps of the biopsychobehavioral model of severe hypoglycemia. Helping patients with a recent history of severe hypoglycemia to reduce the frequency of their low-BG events, become more sensitive to early signs of neuroglycopenia and neurogenic symptoms, better recognize occurrence of low BG, and use fast-acting glucose more frequently in the treatment of low BG, may reduce occurrence of future severe hypoglycemia.

Diabetes Care 22:2018–2025, 1999

Multiple episodes of hypoglycemic unconsciousness have been reported to be associated with brain dysfunction (1,2) and structural changes of the brain (3). While it is controversial that severe hypoglycemia causes permanent brain damage (4,5), it is not disputed that severe hypoglycemia can compromise cognitive and motor functioning, placing patients at high risk if performing dangerous activities, e.g., driving vehicles or operating heavy equipment (6). Because of this potential, severe hypoglycemia can be frightening to both patients (7–9) and their spouses (10,11), and is reported to be the major barrier to intensive insulin therapy (12).

Occurrence of severe hypoglycemia is not a random event. A German survey of 426 patients with type 1 diabetes found that 80% of the severe hypoglycemia episodes were accounted for by 14% of the patients (13). The Diabetes Control and Complications Trial (DCCT) (14) reported that both for conventional care and intensive therapy the best predictor of future severe hypoglycemia was a recent history of severe hypoglycemia. It has been reported that failure to hormonally counterregulate to low blood glucose (BG) during intensive insulin therapy increases the risk of severe hypoglycemia 25-fold (15). Presumably this is because counterregulatory hormones are not available either to raise the BG or to trigger symptoms to prompt self-treatment. However, this perspective does not explain why some people who do not counterregulate do not have severe hypoglycemia, or why some people who do counterregulate experience severe hypoglycemia (16). In the DCCT, 50% of the episodes of severe hypoglycemia were preceded by symptoms.

We have presented a biopsychobehavioral model (17) that proposes that the occurrence of severe hypoglycemia is a consequence of a complex interplay among physiological, psychological, and behavioral factors. In this model (Fig. 1) there are seven steps, each having a theoretical binary (yes/no) outcome. The steps are linked by paths that reflect conditional probabilities, which quantify (18) how the patient progresses to the next step (Fig. 1, arrows). Step 1 represents patient risk factors that can lead to low BG. More insulin and/or exercise than usual or less food than usual, increase the likelihood that step 2 will involve the occurrence of a low-BG event ("Yes" in Fig. 1) (19). If there is no low BG ("No"), there can be no severe hypoglycemia. Step 3 refers to the potential physiological consequences of low BG: neuroglycopenia and counterregulatory hormone release. With

From the University of Virginia Health Sciences Center (D.J.C., L.A.G.-F., B.P.K., D.M.J., W.L.C.), Charlottesville, Virginia; and the Department of Endocrinology (D.L.Y.-H., T.W.D.), University of Maryland, College Park, Maryland.

Address correspondence and reprint requests to Daniel J. Cox, Behavioral Medicine Center, Box 223, University of Virginia Health Sciences Center, Charlottesville, VA 22908. E-mail: djc4f@virginia.edu.

Received for publication 27 April 1999 and accepted in revised form 24 August 1999.

Abbreviations: BG, blood glucose; DCCT, Diabetes Control and Complications Trial; NoSH, no history of severe hypoglycemia; SH, history of severe hypoglycemia; SMBG, self-measurement of blood glucose.

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

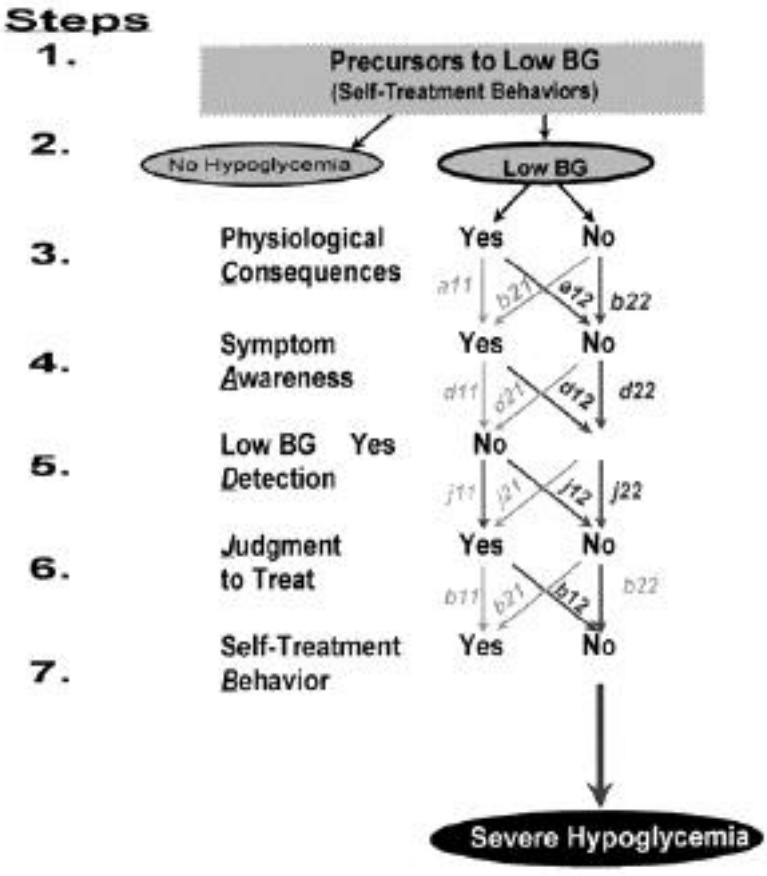

Figure 1—*Biopsychobehavioral model of severe hypoglycemia, its seven steps and its risky (1–2) and preventive (2–1) paths.*

physiological changes comes the potential for perception of either neuroglycopenic and/or neurogenic symptoms. It is assumed that hormonal counterregulation is necessary for the patient to be aware of neurogenic symptoms during hypoglycemia compared with other BG levels. If the patient is aware of hypoglycemic symptoms (step 4, "Yes"), then the patient is "symptom aware."

With symptom unawareness (step 4, "No"), there is less likelihood that the patient will recognize he or she is hypoglycemic (step 5, "Yes"), and therefore less likelihood of making the judgment to self-treat (step 6, "Yes") or of executing self-treatment appropriately (step 7, "Yes"). Detection of low BG (step 5, "Yes") can occur for a variety of reasons, even when there are no symptoms (step 4, "No"), e.g., being told by another, realizing that a snack was missed, and self-measurement of blood glucose (SMBG) results. Nonetheless, awareness of hypoglycemia symptoms is a major determinant of hypoglycemia detection (20). If a patient detects hypoglycemia, it does not necessarily follow that the person will judge that immediate treatment (step 6, "Yes") is necessary. A patient may decide not to treat (step 6, "No") for a variety of reasons, e.g., too embarrassed, too busy, or low risk appraisal. Whether a person adequately treats their low BG (step 7, "Yes") depends on a variety of factors, including making the judgment to treat, knowledge of how best to treat, availability of fast-acting glucose, assistance by others, and so on.

Figure 1 illustrates that there are several possible paths to reach the outcome of inadequate self-treatment (step 7, "No"), allowing low BG to proceed to severe hypoglycemia. Coming out of each step's "Yes" and "No" are two sets of paths (arrows). Vertical paths proceed in the expected direction (Yes to Yes or 1–1 and No to No or 2–2), while diagonal paths represent a reversal (Yes to No or No to Yes). All "1–2" paths represent increased risk and all "2–1" paths represent decreased risk or prevention of severe hypoglycemia (transitions from a "No" to a "Yes"). Theoretically, the more 1–1 and 2–1 paths a person takes, the more likely they should avoid severe hypoglycemia, and the more 1–2 and 2–2 paths a person takes, the more likely they should proceed to severe hypoglycemia.

By comparing patients with a recent history of multiple severe hypoglycemia (SH) episodes and patients with no such history (NoSH), the present study tested the biopsychobehavioral model in three ways. First, these two groups were compared at each of the seven steps of the model to determine whether SH patients engage in self-management behaviors that increase the risk of having low BG (step 1, "Yes") and that lead to more frequent low BG (step 2, "Yes") more neuroglycopenia during low BG (step 3, "Yes"), less awareness of hypoglycemic symptoms, (step 4, "No"), less detection of low BG (step 5, "No"), fewer judgments to treat when BG was low (step 6, "No"), and less adequate treatment of low BG (step 7, "No"). Second, the model implies several different paths that lead to either increased risk (1–2 paths) (Fig. 1) or decreased risk (2–1 paths). This study investigated whether SH patients engaged in more risky paths and fewer preventive paths than did NoSH patients. Third, the relative value of these steps and paths in predicting occurrence of severe hypoglycemia over the next 6 months was examined. These measurements were obtained with objective data collected in the patients' natural environment with the use of a handheld computer.

RESEARCH DESIGN AND METHODS

Patients

A total of 42 patients who reported at least two episodes of severe hypoglycemia in the past year (SH) and 51 who reported no episodes during the previous year (NoSH) were recruited from central Virginia (n = 60), Baltimore, Maryland (n = 18), and Nashville, Tennessee (n = 15). Consistent with the DCCT, severe hypoglycemia was defined as low BG leading to stupor or unconsciousness, precluding the ability to self-treat the low BG. Classification into groups was based on patients' responses to the question, "In the past year how many times have you had severe hypoglycemia episodes (episodes when someone else had to treat you because you were too severely confused, disoriented or unconscious and unable to treat yourself)?". Patients' significant others were randomly called to confirm these reports. Inclusion criteria were: diabetes for at least three years, insulin usage

since time of diagnosis, age between 25 and 55 years, and routine performance of SMBG (at least twice daily). Exclusion criteria included having a single episode of severe hypoglycemia in the past 12 months, and factors that might preclude participation in a 7-month study, i.e., pregnancy, significant depression, active substance abuse, or plans to relocate. No patients were excluded for the latter factors. Patients were paid $70 for completing the 1-month phase 1 and $60 for completing the 6-month phase II. Patients were also given a memory meter and SMBG supplies to complete phase I. Additionally, patients were given a free glycosylated hemoglobin assay.

Patients were recruited through newspaper and television advertisements, diabetes newsletters, and direct physician referrals. There were 38 males and 55 females, with a mean age of 35.8 ± 8 years, with a mean HbA_1 of 8.5 ± 1.8% (upper limit of normal = 6.9%), a mean duration of diabetes of 17 ± 11 years, and a mean insulin dosage of 0.58 ± 0.2 U · kg^{-1} · day^{-1}. Table 1 compares the SH and NoSH groups, revealing the SH patients were slightly older (37 vs. 34 years, $P = 0.02$), had diabetes slightly longer (18 vs. 14 years, $P = 0.05$), and took fewer insulin injections per day (2.4 vs. 2.8, $P = 0.04$). These two groups did not differ with regard to BMI, male/female distribution, insulin dosage, HbA_1, average SMBG, frequency of SMBG, or education level.

Table 1—*Demographic characteristics contrasting patients with and without a history of severe hypoglycemia*

Variables	SH patients	NoSH patients	*P* value
Number of retrospectively reported episodes of severe hypoglycemia in past 12 months	8.5 ± 6.6	0	<0.001
Number of prospectively reported episodes of severe hypoglycemia in future 6 months	5.2 ± 7.1	0.1 ± 0.4	<0.001
Age (years)	37.3 ± 8.9	33.5 ± 6.6	0.025
Duration of disease (years)	18.4 ± 10.0	14.3 ± 9.9	0.05
BMI (kg/m^2)	23.1 ± 2.8	24.1 ± 4.6	NS
M/F (%)	41/59	40/60	NS
Injections/day	2.4 ± 1.1	2.8 ± 0.8	0.04
Insulin dose (U · kg^{-1} · day^{-1})	0.6 ± 0.19	0.55 ± 0.18	NS
HbA_1	8.5 ± 1.7	8.5 ± 1.9	NS
Average SMBG (mmol/l)	8.1 ± 1.8	8.3 ± 1.6	NS
Frequency of SMBG/day	3.5 ± 1.2	3.8 ± 1.5	NS
Years of education	15.5 ± 1.5	16.2 ± 2.7	NS

Data are means ± SD unless otherwise indicated.

Procedure

Phase I involved a group meeting introducing patients to the study, obtaining signed informed consent, completion of questionnaires, and instruction in the use of the Psion 250 handheld computer and the LifeScan One Touch memory meter. At this meeting, participating patients turned in their own meters in order to ensure the memory meter would capture all SMBG data over the next month. After this meeting, patients used the computer and memory meter for 70 trials over the next four weeks. Patients were instructed to employ the computer immediately before their routine SMBG. Three procedures were taken to encourage and monitor whether computer entries preceded SMBG. First, the computer prompted patients with the message, "No blood sample yet," as soon as it was turned on. Second, the computer tracked elapsed time between when the computer instructed the patient to "Measure your BG" and the entry of this SMBG reading. At least 45 s are required for a patient to set the computer down, lance a finger, collect a blood sample, and analyze the BG level with the One Touch meter. Any readings entered in less than 45 s were considered unreliable. Third, computer BG readings were compared with memory meter data to ensure accurate entry of SMBG results.

The computer program was designed to collect data on steps 1–7 of the model. The computer prompted patients to rate four neuroglycopenic symptoms (difficulty concentrating, incoordination, visual disturbance, lightheaded/dizzy), four neurogenic symptoms (pounding heart, trembling, sweaty, jittery/tense/nervous), one generic symptom (something not right), and one personal symptom not included in the above list on a scale where 0 = none and 6 = extreme (step 4). Patients then performed three neuropsychological tests: *1*) a visual vigilance test in which patients moved the cursor across four rows of alphanumeric characters, pressing the "Delete" button whenever the cursor was beneath the randomly positioned numbers 2 or 7; *2*) 10 mental subtraction problems, randomly generated (three-digit numbers), for which the patient entered the answers on the number pad; and *3*) 15 choice reaction time trials where the number 1, 3, 7, or 9 was randomly presented on the screen and the patient had to press the corresponding number on the key pad as quickly as possible. The primary dependent variable was elapsed time to complete each of the three tests (21) (step 3, Fig. 1). To assess awareness of neuroglycopenia (step 4), patients rated on the 0–6 scale the extent to which they perceived impairment in their performance on the neuropsychological tests. Self-management behaviors (step 1) were quantified by having patients report whether their most recent insulin, food intake, and physical activity was more, less, or usual based on their typical routine. After this, patients entered an estimate of their current BG level (step 5). Based on this estimate, patients were asked whether they would make the judgment to treat themselves (step 6). Finally, patients performed and entered their SMBG reading. If the SMBG reading was <3.9 ml, then the next time the computer was turned on, it asked whether patients (step 7) had treated their low BG with fast-acting glucose such as glucose tablets, gel, or hard candy and/or with more general food.

Phase II began 1 month later with a second meeting in which patients turned in the computers, had the memory meters downloaded, had blood samples drawn for an HbA_1 assay, and were instructed on how to fill out monthly diaries to record the occurrence of any episodes of severe hypoglycemia using the same criteria as in the screening questionnaire. These diaries were mailed in monthly for the next 6 months. To insure accurate recording of severe hypoglycemia, patients were asked to telephone the research team whenever an episode occurred. This call triggered an in-depth interview to insure that patients

in fact did experience either stupor or unconsciousness that precluded self-treatment of low BG.

Data analysis

To address the questions of whether SH and NoSH patients differed at each step of the model, in terms of path frequencies and predictability of future severe hypoglycemia, several different variables were included in the analyses, which were quantified as detailed below.

Differences in steps. Because groups were compared across patients for between-group comparisons, each patient's data were quantified as a single data point (i.e., patient mean or frequency). This allowed us to compare SH and NoSH patients at all seven steps of the model.

Step 1 (risk factors for low BG) was defined as the frequency at which patients took more insulin than usual, ate less than usual, and/or engaged in more physical activity than usual.

Step 2 (occurrence of low BG) was defined by the low BG index, which was computed from memory meter data. The low BG index is a weighting of SMBG readings, such that readings >6.25 mmol/l receive a weighting of 0 and readings below 6.25 mmol/l receive a logarithmically increasing weight so that a reading of 1.1 mmol/l would get a weighted value of 100. The weightings for each of the individual's SMBG readings are then averaged, so that the low BG index increases with more frequent and more extreme low BG readings. The low BG index has been associated with the occurrence of future severe hypoglycemia in a nonlinear fashion, where a low BG index of 2.5–5.0 is associated with moderate risk of future severe hypoglycemia and a score >5 is associated with high risk (22–24).

Step 3 (physiological consequences of low BG) was quantified by calculating the relative slowing, in seconds, of cognitive-motor performance on all three neuropsychological tests during low BG (<3.9 mmol/l) relative to a patient's mean euglycemic performance (BG 4.7–10 mmol/l). Consequently, while we were unable to quantify counterregulation in the field, we were able to generate a measure reflecting neuroglycopenia.

Step 4 (symptom awareness) was defined as the average number of significant symptoms, i.e., symptom rating during hypoglycemia in the 95th percentile of that patient's euglycemic symptom ratings. In other words, based on that patient's rating of a particular symptom, a mean ± SD was calculated and the 95th percentile determined. If the euglycemia rating for a particular patient on a particular symptom was "0" or "1" 95% of the time, then a rating of >1 for that symptom by that patient during low BG would be considered significant. The average number of significant symptoms/hypoglycemic episode was then calculated.

Step 5 (low BG detection) was quantified as the percentage of times the patient estimated their BG to be <3.9 mmol/l when it actually was below 3.9 mmol/l.

Step 6 (judgment to treat low BG) was quantified by the percentage of times the patient said they would take action to raise BG when the actual BG was <3.9 mmol/l.

Step 7 (actual treatment of low BG) was quantified in terms of the percentage of times the patient reported using fast-acting glucose and/or general foods, after SMBG feedback indicating that their BG was <3.9 mmol/l.

Differences in paths. This analysis involved calculating the percentage of preventive paths (a21, d21, j21, b21) (Fig. 1), where the patient's data indicated a transition from the right to the left side of the model, and risky paths (a12, d12, j12, b12), where the patient moved from the left to the right side when BG was low. The analysis first required us to operationalize where the patient was at each step of the model on each trial. Step 2 was not considered because these are singular data points.

Step 1 was "Yes" when the amount of insulin or exercise was rated as usual or less than usual or when food was rated as usual or more than usual, each of which would decrease the likelihood of low BG.

Step 3 was "Yes" when the speed of performance for any neuropsychological test during hypoglycemia was ≥95th percentile of the patient's performance during euglycemia.

Step 4 was "Yes" if one of the 10 symptoms' 0–6 rating during hypoglycemia was ≥95th percentile of that patient's euglycemic symptom ratings.

Step 5 was "Yes" if estimated BG was <3.9 mmol/l during hypoglycemia.

Step 6 was "Yes" if a positive answer was given to the question "Would you treat now?" when actual BG was <3.9 mmol/l.

Step 7 was "Yes" if the patient reported having eaten fast-acting glucose when BG was low.

Once yes/no responses were quantified at each step, then the conditional probability that the patient proceeded to either yes/no at the next step was quantified. For example, on the condition that the patient had detected an actual low BG (step 5, "Yes"), what was the probability that the patient would either progress to the judgment to treat or not to treat (step 6, "Yes"/"No"). The percentage of time the patient pursued paths 1–1 and 1–2 was computed, where the sum of these percentages/probabilities equaled 100%. SH and NoSH patients were compared for each of the risky paths (a12, d12, j12, b12) and each of the preventive (a21, d21, j21, b21) paths. These paths could only be taken when the patient was hypoglycemic (step 2, "Yes").

Predicting occurrence of future severe hypoglycemia

The number of severe hypoglycemia episodes per patient, derived from monthly diaries from phase II, was correlated with the variables defining the steps of the model. Multiple regression analysis was used to predict the number of severe hypoglycemic episodes, using as predictors the patient's low BG index and path data.

RESULTS

Differences in steps

As illustrated in Table 2, the SH group differed in the expected direction from the NoSH groups at five steps of the model, and differed significantly in 9 of 14 comparisons. Specifically, while we have reported that taking more insulin, exercising more, and eating less than usual are each associated with increased risk of low BG, SH patients did not engage in these behaviors more than NoSH patients (step 1) (19,25). However, the SH group had more frequent and extreme low BG readings (step 2, low BG index, $P < 0.001$); demonstrated more cognitive-motor slowing during hypoglycemia (step 3) on mental subtractions ($P < 0.001$) and choice reaction time ($P = 0.02$); was less aware of hypoglycemic symptoms (step 4) in terms of neurogenic ($P < 0.001$) and neuroglycopenic ($P < 0.01$) symptoms and perceived cognitive-motor impairment ($P < 0.01$); were less likely to detect hypoglycemia (step 5, $P < 0.001$); were less likely to judge that they needed to eat when hypoglycemic (step 6, $P < 0.2$); and actually treated their hypoglycemia differently (step 7), being less likely to use fast-acting glucose ($P = 0.05$) and more likely to use general foods ($P < 0.002$). Table 3 illustrates the interrelationships among these variables.

Table 2—*Mean results for the SH versus NoSH groups for the seven steps of the biopsychobehavioral model and their correlation with future episodes of severe hypoglycemia*

	SH group	NoSH group	*P* value	Correlation
Step 1				
Risk factors for low BG (mean frequency) (%)				
Using more insulin than usual	12.9	17.1	0.17	−0.02
Exercising more than usual	8.1	8.1	0.99	−0.13
Eating less than usual	6.8	6.7	0.94	−0.07
Step 2				
Low BG index	5.4	3.0	<0.001	0.42*
Step 3				
Reduction in performance speed during hypoglycemia(s)				
Visual vigilance	2.8	1.5	0.11	0.11
Mental subtraction	11.4	4.3	<0.001	0.28†
Choice reaction time	1.1	0.5	0.02	0.13
Step 4				
Number of significant neuroglycopenic symptoms	1.1	1.7	0.005	−0.7
Number of significant neurogenic symptoms	1.1	1.7	<0.001	−0.21‡
Lower ratings of impairment	1.2	1.7	0.01	−0.17‡
Step 5				
Percentage of low SMBG events that were estimated to be <3.9 mmol/l	37	56	<0.001	−0.28†
Step 6				
Percentage of times patients reported they would raise their BG when their BG was low	52	60	0.20	−0.05
Step 7				
When SMBG was low, percentage of times patients reported treating with:				
Fast-acting glucose	14	25	0.05	−0.12
Food	92	82	0.002	0.08

Low BG index is based on memory meter data. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Differences in paths

The above comparisons demonstrate that the two groups differed at five steps of the model, but do not tell if and how patient behaviors might contribute to these differences. The following analysis of conditional probabilities evaluated the likelihood of SH patients taking preventive and risky paths. Preventive paths (a21, d21, j21, b21) represent transitions from a "No" to a "Yes," going from right to left in our model. For example, path d21 refers to the patient detecting low BG despite not being aware of hypoglycemic symptoms. Risky paths (a12, d12, j12, b12) involve going from a "Yes" to a "No," or from left to right (Fig. 1). For example, path a12 refers to when the patient experienced neuroglycopenia (step 3, "Yes") but was not aware of any symptoms of low BG (step 4, "No"). As predicted, Fig. 2 illustrates that SH patients were generally less likely to take preventive paths and more likely to take risky paths. However, there were only two risky paths that were significant: SH patients were more likely to experience neuroglycopenia but not recognize it (a12, 60% of the time) and less likely to treat themselves with fast-acting glucose when they had judged themselves in need of treatment (b12, 88% of the time).

Predicting occurrence of future severe hypoglycemia

As seen in Table 2 (last column), low BG index, and cognitive slowing during mental subtractions correlated positively with future severe hypoglycemia (*P* values <0.01), while awareness of cognitive motor impairments, number of neurogenic symptoms, and detection of hypoglycemia correlated negatively with future severe hypoglycemia (*P* values <0.05). As we have reported in other studies (22,24), glycosylated hemoglobin did not correlate with future severe hypoglycemia. Total number of risky paths ($r = 0.28$, $P < 0.01$) and number of times a patient reported no symptoms but still detected low BG (d21 $r = -0.26$, $P < 0.01$) correlated with future severe hypoglycemia.

Number of future occurrences of severe hypoglycemia episodes was predicted on the basis of this model ($R^2 = 0.25$, $P < 0.0001$), incorporating variables from steps 2, 4, and 5. The predictive variables, in order of significance, were low BG index (partial correlation = 0.44, $P < 0.001$), detection of low BG when there were no hypoglycemic symptoms (path d21, partial correlation = 0.25, $P = 0.03$) and not being aware of hypoglycemic symptoms when neuroglycopenic (path a12, partial correlation = −0.20, $P = 0.06$).

Post hoc analyses

Because the low BG index was such a potent discriminator between groups and predictor of future severe hypoglycemia, we investigated whether the low BG Index reflected some sampling bias, rather than a true difference in the BG profiles. As reported in Table 1, there was no difference in mean SMBG readings, as there was no difference in HbA_1, indicating that there was no systematic effort by SH patients to

Table 3—*Correlational matrix among the operational definitions of the steps in the biopsychobehavioral model*

	Operational definitions												
	2	3	4	5	6	7	8	9	10	11	12	13	14
Step 1. Risk factors for low BG													
1. Percent more insulin	0.27*	0.38†	NS	NS	NS	NS	NS	NS	NS	0.23*	NS	NS	0.20‡
2. Percent more exercising	—	0.43†	NS	NS	NS	NS	NS	NS	NS	0.36†	0.32†	NS	NS
3. Percent eating less	—	—	NS	NS	NS	NS	NS	NS	NS	0.24*	0.20‡	NS	0.17‡
Step 2													
4. Low BG index	—	—	—	NS	NS	NS	−0.19‡	−0.22‡	−0.21‡	−0.17‡	NS	NS	NS
Step 3													
5. Visual vigilance	—	—	—	—	0.25*	0.33†	NS	NS	NS	−0.16‡	NS	NS	NS
6. Mental subtraction	—	—	—	—	—	0.36	NS	0.22*	NS	−0.19‡	NS	NS	0.25*
7. Choice reaction time	—	—	—	—	—	—	NS	NS	NS	NS	NS	NS	NS
Step 4													
8. Number of neuroglycopenic symptoms	—	—	—	—	—	—	—	0.68†	0.62†	0.52†	0.29‡	NS	NS
9. Number of neurogenic symptoms	—	—	—	—	—	—	—	—	0.60†	0.61†	0.39†	NS	NS
10. Impairment ratings	—	—	—	—	—	—	—	—	—	0.47†	0.28*	0.24‡	NS
Step 5													
11. Percent detection of low BG	—	—	—	—	—	—	—	—	—	—	0.54*	NS	0.19‡
Step 6													
12. Percent making judgment to treat low BG	—	—	—	—	—	—	—	—	—	—	—	NS	NS
Step 7. Percent treating low BG with:													
13. Fast-acting glucose	—	—	—	—	—	—	—	—	—	—	—	—	0.35†
14. Food	—	—	—	—	—	—	—	—	—	—	—	—	—

*$P < 0.01$; †$P < 0.001$; ‡$P < 0.05$.

select lower BG readings. Also, as reflected in Table 1, these two groups did not perform SMBG at different frequencies. When we divide the day into four periods, there is no difference ($P = 0.80$) in terms of when the two groups of patients measure their BG (Table 4). Also consistent with the low BG index reflecting a biological rather than a behavioral phenomenon, Table 3 illustrates that the low BG index was unrelated to insulin, food, or exercise behaviors, but, as expected, negatively related to symptom and hypoglycemia awareness.

CONCLUSIONS — Application of the biopsychobehavioral model demonstrates that patients with a history of severe hypoglycemia, as a group, are clearly descriptively different at five steps of the model. Contrary to traditional approaches, severe hypoglycemia was not exclusively related to nonoccurrence of neurogenic symptoms (presumably reflecting less frequent/robust hormonal counterregulation) or hypoglycemia unawareness. Patients with recurrent severe hypoglycemia: have more frequent and extreme low-BG events; experience more cognitive-motor impairment during low BG; are less aware of these impairments; have fewer neurogenic and neuroglycopenic symptoms; are less likely to detect low BG when it does occur; and are less likely to self-treat with fast-acting glucose.

It is a commonly held clinical assumption that if patients perceive hypoglycemic

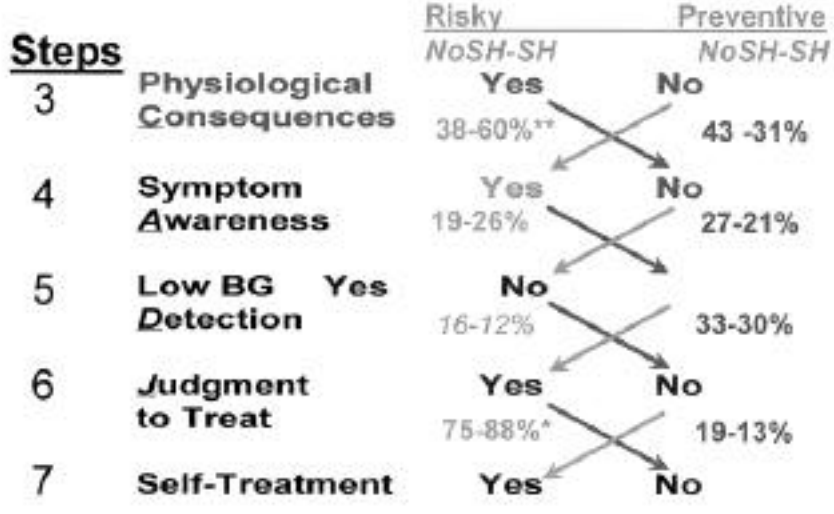

Figure 2—*Conditional probabilities for NoSH and SH patients taking risky and preventive paths. Boldface numbers indicate data in the expected direction.* *P < *0.05,* **P < *0.01.*

symptoms, they will recognize low BG and make a judgment to take appropriate action (d11, j11), or that if there are no detected symptoms they will not detect low BG and will not make a judgment to self-treat (d22, j22). Based on our findings, these are not the usual sequences in the natural environment. In fact, NoSH and SH patients took paths d11 and j11 46 and 32% of the time, and paths d22 and j22 15 and 27% of the time. This illustrates that preventive and risky paths are often being taken. Analysis of the preventive and risky conditional probabilities indicates that patients with a history of severe hypoglycemia engage in more risky and fewer preventive behaviors. Specifically, SH patients were less likely to recognize neuroglycopenia and to treat themselves with glucose when they knew their BG was low. Regardless of group assignment, future severe hypoglycemia was predicted in the regression analysis by the frequency and extent of low BG (low BG index) and high frequency of one risky behavior (failure to be aware of neuroglycopenia, a12) and low frequency of one preventive behavior (failure to detect hypoglycemia without symptoms, d21). Occurrences of frequent and extreme low BG (low BG index) were an independent and more robust predictor of future severe hypoglycemia. From a probability perspective, the more often BG becomes low, the more likely BG will become too low. However, it is probably not that simple. Low BG index was negatively correlated with symptom awareness (neurogenic symptoms $r = -0.19$, $P < 0.04$; neuroglycopenic symptoms $r = -0.22$, $P = 0.02$; and impairment ratings $r = -0.21$, $P = 0.04$); detection of low BG ($r = -0.17$, $P = 0.05$); and making a judgment to treat when low BG is detected (j12, $r = -0.25$, $P = 0.01$). This would suggest that frequent and extreme low BG readings are associated with fewer symptoms, poorer detection of hypoglycemia, and poorer judgment to treat low BG. While it would seem logical that low BG index would drive reduced awareness and thus poorer detection of low BG, making the judgment not to treat when BG is low may be driving the low BG index. This suggests diabetes education should focus on teaching patients to attend to possible signs of neuroglycopenia as heralding hypoglycemia, to actively consider the possibility of being hypoglycemic when warning signs are present, to treat hypoglycemia with fast-acting glucose rather than generic foods, and to avoid frequent low BG.

Table 4—*Distribution of SMBG averaged over a 24-h day*

Time of day	2400–0659	0700–1259	1300–1859	1900–2359
SH group	13.8	34.6	28.7	22.9
NoSH group	14.4	31.6	29.2	24.8

Data are %.

Future severe hypoglycemia

As reported by the DCCT and elsewhere (26,27), patients who did not have a history of severe hypoglycemia were not likely to have future severe hypoglycemia, while patients who did have such a history were much more likely to have future episodes. Only 4% of our NoSH patients, compared with 67% of our SH patients, prospectively recorded episodes of severe hypoglycemia during 6 months of diary-keeping. This is important to realize because it allows more precise focusing of efforts designed to prevent future severe hypoglycemia. These data also suggest that within this subgroup of at-risk patients, an elevated low BG index is a further selection criterion. While future experimental studies will have to be performed, the current data suggest that preventive efforts in such an at-risk group could involve a variety of behavioral interventions. These would include reducing the frequency and extent of low BG events (28), possibly by having patients prophylactically treat BG readings in the 4–5 mmol/l range. Teaching such patients to be more sensitive to early signs of neuroglycopenia might aid in improving detection of low BG. Additionally, encouraging at-risk patients to both carry and use fast-acting glucose sources may be beneficial.

What must be kept in mind, however, is that these are group data, and that individuals probably have very specific profiles of risk factors, which would require very specific interventions. For example, in this study one NoSH patient who experienced severe hypoglycemia had a low BG index of 6.7, but no other risk factors as defined by the model. One SH patient who did not experience any episodes in 6 months had no risk factors, but scored significantly high on the preventive factors a21 and b21. In other words, he was aware of hypoglycemia even with no obvious symptoms and would self-treat even when he did not estimate his BG to be <3.9 mmol/l. Another SH patient who had seven severe hypoglycemia episodes in the 6 months of follow-up reported a high j12; that is, for more than half the times that he estimated his BG to be low, he judged treatment was not necessary.

Use of a device like the handheld computer for individual patient assessment can provide an individualized profile to guide clinicians in focusing interventions to reduce risk of severe hypoglycemia. However, testing of the biopsychobehavioral model is neither limited to the use of the handheld computer nor to the variables we collected with it. The model could potentially be tested with psychometric instruments or with hospital-based insulin infusion studies. Testing this model with different measures and different methods could further confirm and extend its utility as well as enhance its comprehensiveness.

Acknowledgments — This research was supported by National Institutes of Health Grants DK28288 and RR00847 and a grant from LifeScan.

We would like to thank the staff of the General Clinical Research Center at the University of Virginia Health System and Ms. Cheralee VonAncken.

References

1. Deary IJ, Crawford JR, Hepburn DA, Langan SJ, Blackmore LM, Frier BM: Severe hypoglycemia and intelligence in adult patients with insulin-treated diabetes. *Diabetes* 42:341–344, 1993
2. Wredling R, Levander S, Adamson U, Lins PE: Permanent neuropsychological impairment after recurrent episodes of severe hypoglycemia in man. *Diabetologia* 33:152–157, 1990
3. Perros P, Deary IJ, Sellar RJ, Best JJ, Frier BM: Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. *Diabetes Care* 20:1013–1018, 1997
4. Gold AE, Deary IJ, Frier BM: Recurrent severe hypoglycaemia and cognitive function in type I diabetes. *Diabet Med* 10: 503–508, 1993
5. Lawson JS, Williams Wradahl DL, Monga TN, Bird CE, Donald MW, Surridge DHC, Letermendia FJJ: Neuropsychological function in diabetic patients with neuropathy. *Br*

J Psychiatry 145:263–268, 1984
6. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Julian DM, Clarke WL: Progressive hypoglycemia's impairment on driving simulation performance: occurrence, awareness and correction. *Diabetes Care*. In press
7. Cox DJ, Irvine A, Gonder-Frederick LA, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation and utilization. *Diabetes Care* 10:617–621, 1987
8. Irvine A, Cox DJ, Gonder-Frederick LA: The Fear of Hypoglycaemia scale. In *Handbook of Psychology and Diabetes*. Bradley C, Ed. London, Hardwood Academics, 1994, p. 133–155
9. Irvine AA, Cox DJ, Gonder-Frederick LA: Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin dependent diabetes mellitus. *Health Psychol* 11:135–138, 1992
10. Gonder-Frederick LA, Cox DJ, Kovatchev B, Julian D, Clarke W: The impact of severe hypoglycemic episodes in patients with IDDM on spouses' psychosocial status and marital relationships. *Diabetes Care* 20: 1543–1546, 1997
11. Stahl W, Hartmut S, Cox DJ: Spouse's worries concerning diabetic partner's possible hypoglycemia. *Diabet Med* 15:619–620, 1998
12. Cryer PE, Fisher JN, Shamoon H: Hypoglycemia. *Diabetes Care* 17:734–755, 1994
13. Dreyer M: Qualitatsmanagement im stationaren Bereich: Bemuhungen der ADDK um eine effektive und effiziente Diabetikerbetreung. *Diabetes und Stoffwechsel* 6:26–27, 1997
14. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450–459, 1991
15. Cryer PE: *Hypoglycemia: Pathology, Diagnosis, and Treatment*. Oxford, U.K., Oxford University Press, 1997
16. Cox DJ, Gonder-Frederick LA, Antoun BW, Clarke WL, Cryer PE: Psychobehavioral metabolic parameters of severe hypoglycemic episodes. *Diabetes Care* 13:458–459, 1990
17. Gonder-Frederick L, Cox D, Kovatchev B, Schlundt D, Clarke W: A bio-psychobehavioral model of risk of severe hypoglycemia. *Diabetes Care* 20:661–669, 1997
18. Kovatchev B, Cox D, Gonder-Frederick L, Clarke W: A stochastic model of decision making during hypoglycemia for individuals with insulin dependent diabetes mellitus. *Health Psych* 17:277–284, 1998
19. Clarke WL, Cox DJ, Gonder-Frederick L, Julian D, Kovatchev B, Schlundt D, Young-Hyman D: The biopsychobehavioral model of risk of severe hypoglycemia: self-management behaviors. *Diabetes Care* 22:580–584, 1999
20. Cox DJ, Gonder-Frederick LA, Antoun B, Cryer PE, Clarke WL: Perceived symptoms in the recognition of hypoglycemia. *Diabetes Care* 16:519–527, 1993
21. Gonder-Frederick LA, Cox DJ, Driesen NR, Ryan C, Clarke WL: Individual differences in the neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM. *Diabetes* 43:1407–1412, 1994
22. Cox DJ, Kovatchev B, Julian D, Gonder-Frederick LA, Polonsky WH, Schlundt DG, Clarke WL: Frequency of severe hypoglycemia in IDDM can be predicted from self-monitoring blood glucose data. *J Clin Endocrinol Metab* 79:1659–1662, 1994
23. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL: Symmetrization of the blood glucose measurement scale and its applications. *Diabetes Care* 20:1655–1658, 1997
24. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL: Assessment of risk for severe hypoglycemia among adults with IDDM. *Diabetes Care* 21:1870–1875, 1998
25. Clarke WL, Gonder-Frederick LA, Cox DJ: Nonroutine use of insulin, food and exercise predicts the occurrence of hypoglycemia in IDDM adults with varying degrees of hypoglycemic awareness and metabolic control. *Diabetes Educ* 23:55–58, 1997
26. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
27. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U: Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med* 230:101–108, 1991
28. Bolli GB: How to ameliorate the problem of hypoglycemia in intensive as well as non-intensive treatment of type 1 diabetes. *Diabetes Care* 22 (Suppl. 2):B43–B52, 1999