Hypoglycemia Unawareness in IDDM

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OBJECTIVE — To assess the characteristics of patients with hypoglycemia unawareness (development of neuroglycopenia without appropriate prior autonomic warning symptoms) and its predisposing factors.

RESEARCH DESIGN AND METHODS — We studied 43 insulin-dependent diabetes mellitus patients who were objectively categorized as having or not having hypoglycemia using the stepped hypoglycemic clamp technique in which plasma glucose was clamped at plateaus of 4.3, 3.6, 3.0, and 2.3 mmol/l and a statistical criterion (onset of autonomic warning symptoms at a plasma glucose concentration 2 SD below normal) and examined their clinical characteristics and hormonal, symptomatic, and cognitive responses.

RESULTS — Eleven (26%) of the patients were classified as having hypoglycemia unawareness. Compared with the other patients, unaware patients had a lower HbA_{1c} level ($P < 0.01$), a longer duration of diabetes ($P < 0.01$), and a history of more severe hypoglycemia ($P < 0.003$). During experimental hypoglycemia, counterregulatory hormone responses, neuroglycopenic symptoms, and cognitive dysfunction all began at lower plasma glucose concentrations in unaware patients ($P < 0.01, 0.03$, and 0.01, respectively). Moreover, although the magnitudes of their plasma catecholamine responses and autonomic symptoms were reduced (both, $P < 0.01$), the plasma catecholamine levels at which autonomic symptoms began was not altered. Finally, as seen from glucose infusion rates necessary to maintain identical plasma glucose levels, patients with hypoglycemia unawareness had increased sensitivity to insulin ($P < 0.001$).

CONCLUSIONS — Our results confirm an association between hypoglycemia unawareness and duration of diabetes, glycemic control, and occurrence of severe hypoglycemia, and in addition provide evidence that both autonomic and neuroglycopenic symptoms are affected and that insulin sensitivity is increased, but β-adrenergic sensitivity is not diminished.

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Decreases in plasma glucose concentration normally trigger a characteristic hierarchy of responses (1–3). At ~3.8 mmol/l, increased secretion of neurohumoral counterregulatory factors begins. If this response does not prevent a further decrease in plasma glucose, classic autonomic warning signals (e.g., sweating, hunger, anxiety, palpitations, or tremor) occur at ~3.3 mmol/l. A further decrease in plasma glucose to ~2.8 mmol/l initiates signs and symptoms of neuroglycopenia (e.g., confusion, dizziness, blurred vision, or weakness) and deterioration in cognitive function (2,3).

The lack of appropriate autonomic warning signals before development of neuroglycopenia, commonly referred to as hypoglycemia unawareness (4), occurs in patients with insulin-dependent diabetes mellitus (IDDM) (5) and has been associated with frequent episodes of severe hypoglycemia (6,7). Although this phenomenon was first reported shortly after the introduction of insulin therapy (8), both its pathogenesis and prevalence remain unclear.

Previous studies (5) have suggested that it may occur in anywhere from 7 to 70% of IDDM patients. Suspected predisposing factors include use-deficient counterregulation (5) of intermediate-acting insulin (9), human versus animal insulin (10), improvement in glycemic control with intensive insulin therapy (2,11,12), autonomic neuropathy (7,13–15), decreased β-adrenergic sensitivity (16), duration of diabetes (17), and hypoglycemia itself (18–20).

A major limitation of previous studies has been the reliance on questionnaires using recollection of hypoglycemic episodes to categorize subjects as having this condition. These studies were undertaken to better assess the characteristics of patients with this condition and its predisposing factors by evaluating IDDM patients whose awareness of hypoglycemia was objectively categorized using a statistical criterion and the stepped hypoglycemic clamp technique (1–3).

Table 1—*Clinical characteristics of subjects studied*

	Nondiabetic subjects	Diabetic subjects with unawareness	Diabetic subjects without unawareness	P value
n	19	11	32	
Gender (female/male)	7/12	5/6	12/20	NS
Age (years)	33 ± 2	31 ± 2	28 ± 2	NS
Duration of diabetes (years)	—	13 ± 2	7 ± 2	<0.01
HbA$_{1c}$ (%)	5.6 ± 0.2	8.6 ± 0.5	11.1 ± 0.5	<0.01
Body mass index (kg/m^2)	24.1 ± 1.0	24.0 ± 0.9	23.4 ± 0.6	NS
Subjects claiming to be always aware of hypoglycemia (%)	—	27	81	<0.001
Hypoglycemic episodes per week (% of group)				
<1	—	55	56	NS
1–2	—	18	34	NS
>3	—	27	10	NS
Severe hypoglycemia during last 3 months (%)	—	36	3	<0.003

Data are means ± SE. P value shows diabetic patients with unawareness versus diabetic patients without unawareness.

RESEARCH DESIGN AND METHODS

After the protocol had been approved by the University of Pittsburgh Biomedical Institutional Review Board, informed consent was obtained from 19 nondiabetic volunteers and 43 subjects with IDDM whose clinical characteristics are given in Table 1. Data for some of the nondiabetic volunteers have been used in previous publications (3,20). Diabetic subjects were recruited from volunteer lists, from advertisements, and at clinic visits without regard for their history of hypoglycemia, glycemic control, and duration of diabetes. No attempt was made to obtain a random sampling. Diabetic volunteers were excluded from study only if they had signs or symptoms of autonomic neuropathy or if they had abnormal autonomic cardiovascular reflexes. Volunteers with a beat-to-beat variation during deep breathing of <15 or with a decrease in systolic blood pressure of more than 15 mmHg upon standing were excluded from study (21).

Subjects were admitted to the Clinical Research Center the evening before experiments and were given a standard dinner between 5:30 and 6:30 P.M. (30 kcal/kg, 50% carbohydrate, 35% fat, and 15% protein) and a standard snack (~4 h later) at bedtime (10 kcal/kg, 50 carbohydrate, 35% fat, and 15% protein).

The diabetic subjects had been withdrawn from their depot insulin (NPH or Ultralente) for 48–72 h and had been managed by preprandial injections of regular insulin. Overnight before the study, the diabetic subjects were maintained near-normoglycemic (5–7 mmol/l) by an intravenous infusion of insulin. None of the diabetic subjects reported having a hypoglycemic reaction within 48 h of study, and all were documented not to have had a hypoglycemic reaction for at least 14 h before study. Between 7:00 and 7:30 A.M., a hand vein was cannulated retrogradely and maintained in a Plexiglas thermoregulated box (70°C) for sampling of arterialized venous blood. If not done so already, a deep antecubital vein of the same arm was cannulated for infusion of insulin and glucose. After a 60-min equilibration period, infusion of insulin was begun (1 mU · kg^{-1} · min^{-1} for 270 min followed by 2 mU · kg^{-1} · min^{-1} for an additional 60 min). The greater insulin infusion rate during the final 60 min was used because in previous studies (3), it was necessary to lower plasma glucose levels to the final glycemic plateau after counterregulation had been activated. Plasma glucose was clamped by variable glucose infusions at sequential target glucose concentrations of 4.3, 3.6, 3.0, and 2.3 mmol/l, as previously described (3).

The plasma glucose concentration was allowed to decrease 0.6–0.7 mmol/l over 45 min, and a plateau was maintained for 45 min before the next decrease. Arterialized venous blood samples were drawn every 30 min from 0 to 360 min for determination of plasma insulin (free insulin in the diabetic subjects), growth hormone, glucagon, cortisol, epinephrine, and norepinephrine.

A semiquantitative symptom questionnaire was administered every 15 min. Subjects scored from 0 (none) to 5 (severe) for each of the following symptoms: dizziness, tingling, blurred vision, difficulty in thinking, faintness, anxiety, palpitations, hunger, sweating, irritability, or tremor. Consistent with the categorization used by previous investigators (1–3,22), the first five symptoms were considered neuroglycopenic and the last six were considered autonomic (23). The sum of each of these constituted the symptom score.

In addition, at baseline and during each plateau the following standard cognitive tests were administered (3): trail-making part B (24), verbal fluency (25), interference subtest from the Stroop test (26), simple and choice visual reaction time (3), word and color subtests from the Stroop test (26), digit vigilance test (27), trail-making part A (3), verbal

Table 2—*Effect of duration of diabetes and glycemic control on frequency of hypoglycemia unawareness*

	Unaware (number of patients)	P values
Duration of diabetes		
<10 years	5/30 (17%)	
>10 years	6/13 (46%)	<0.04
HbA$_{1c}$		
<9%	8/13 (62%)	
>9%	3/30 (10%)	<0.001
Duration >10 years and HbA$_{1c}$ <9%	5/6 (83%)	
Duration <10 years or HbA$_{1c}$ >9%	6/37 (16%)	<0.001

memory test (3), and forward and backward digit span (3). The evening before the study, subjects were provided with extensive practice on each test. For the actual study, six alternate test forms were prepared. Subjects were not informed of their plasma glucose levels during experiments.

Subsequent to experiments, subjects were administered a questionnaire about previous hypoglycemia. They were asked: *1*) whether they almost always, sometimes, or never were aware of hypoglycemia; *2*) whether they had experienced a severe episode (defined as coma or requiring the help of another person for recovery) during the last 3 months; and *3*) how often they had any hypoglycemia during this period.

Analytical methods
Plasma glucose was measured using a Yellow Springs Instruments glucose analyzer (Yellow Springs, OH). Plasma insulin, free insulin, glucagon, growth hormone, cortisol, epinephrine, and norepinephrine were measured by assays described previously (3). HbA$_{1c}$ was determined by a high-performance liquid chromatography method (Bio-Rad Daimat, Richmond, CA, normal range 4.3–6.1%).

Statistical analysis
Glycemic thresholds were determined as described previously (1,3,22); namely, the glycemic threshold for a given param-

eter was defined as the measured plasma glucose concentration at which the parameter first exceeded the 95% confidence limit observed for changes in that parameter at the corresponding time point in euglycemic control experiments. Euglycemic control experiments were performed in 18 volunteers (13 nondiabetic subjects, some of whose results have been previously reported [3], and 5 IDDM subjects, whose results did not differ from those of the nondiabetic subjects). Data are given as means ± SE. Because of differences in units of measurement, results of cognitive tests were transformed to z scores (mean divided by SD) (28) to permit their summation to obtain one unitless value for evaluation (3). A commercially available software package (CSS, Statsoft, Tulsa, OK) was used for statistical analysis. The differences among groups were analyzed using either analysis of variance followed by the least significant difference test (28) or the χ^2 test (28).

RESULTS

Clinical characteristics
Of the 43 IDDM subjects, 11 (26%) developed autonomic symptoms at a plasma glucose level more than 2 SD below normal and were therefore classified as having hypoglycemia unawareness. Only 27% of these patients claimed to be always aware of hypoglycemia vs. 81% of

the other patients (P < 0.001) (Table 1). During the previous 3 months, proportionately more patients with unawareness had an episode of severe hypoglycemia (36% vs. 3%, P < 0.003). There was, however, no difference in the overall reported frequency of hypoglycemia.

The patients with unawareness had a significantly longer duration of diabetes and a significantly lower HbA$_{1c}$ level (Table 2). Only 17% of patients with a duration of diabetes <10 years had unawareness in contrast to 46% of those with a duration of diabetes >10 years (P < 0.04). Of patients with HbA$_{1c}$ levels <9%, 62% had unawareness in contrast to only 10% with HbA$_{1c}$ levels >9% (P < 0.001). Indeed, 83% of patients with both a duration of diabetes >10 years and a HbA$_{1c}$ level <9% had unawareness compared with 16% of the other patients (P < 0.001).

Autonomic and neuroglycopenic symptoms and cognitive function
During experimental hypoglycemia, the patients with unawareness not only had their autonomic symptoms begin at a lower plasma glucose level but also had significantly (P < 0.01) reduced autonomic symptom scores (Fig. 1. Using multiple linear regression, we found that the plasma glucose level at which autonomic symptoms began was inversely correlated with duration of diabetes ($r = -0.40, P < 0.01$) and was directly correlated with HbA$_{1c}$ levels ($r = 0.50, P < 0.001$). Although maximal neuroglycopenic symptoms and deterioration of cognitive function did not differ significantly among the groups, the plasma glucose concentrations at which neuroglycopenic symptoms and cognitive dysfunction began were both significantly lower in the patients with unawareness (P < 0.03 and 0.01, respectively) (Fig. 2, Table 3).

Counterregulatory hormone responses
Baseline plasma counterregulatory hormone concentrations did not differ significantly among the groups. Both groups of

Table 3—*Glycemic thresholds for initiation of counterregulation, symptoms, and cognitive dysfunction*

	Nondiabetic subjects	Diabetic subjects with unawareness	Diabetic subjects without unawareness
Epinephrine	3.80 ± 0.08	2.78 ± 0.10	3.89 ± 0.11
Norepinephrine	3.76 ± 0.09	2.67 ± 0.12	3.44 ± 0.15
Growth hormone	3.75 ± 0.08	3.28 ± 0.16	3.78 ± 0.15
Cortisol	3.29 ± 0.07	2.50 ± 0.13	3.28 ± 0.09
Autonomic symptoms	3.38 ± 0.06	2.33 ± 0.06	3.61 ± 0.11
Neuroglycopenic symptoms	2.86 ± 0.08	2.48 ± 0.11	2.83 ± 0.08
Cognitive dysfunction	2.65 ± 0.06	2.39 ± 0.07	2.69 ± 0.06

Data are means ± SE in mmol/l. $P < 0.05$ vs. nondiabetic subjects and IDDM subjects without awareness.
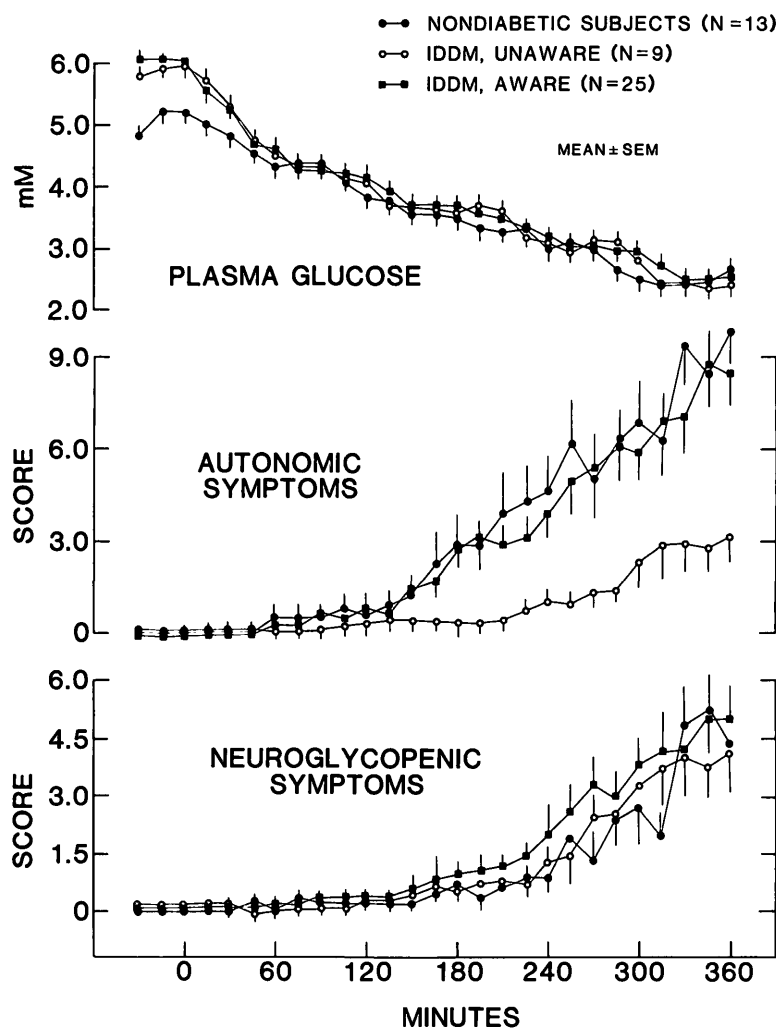

Figure 1—*Plasma glucose concentrations and scores for autonomic and neuroglycopenic symptoms during stepwise reductions of plasma glucose in nondiabetic volunteers and IDDM subjects with and without hypoglycemia unawareness.*

patients had negligible increases in plasma glucagon, and thus it was not possible to calculate their threshold for release of this hormone. Thresholds for epinephrine, norepinephrine, growth hormone, and cortisol responses occurred at significantly lower plasma glucose concentrations in the patients with unawareness than in both other groups of subjects (all $P < 0.01$) (Fig. 3, Table 3). The thresholds for epinephrine responses were positively correlated with HbA_{1c} levels ($r = 0.51$, $P < 0.001$) and were negatively correlated with duration of diabetes ($r = -0.43$, $P < 0.005$). Although maximal plasma epinephrine and norepinephrine responses were significantly reduced in the patients with unawareness, there were no significant differences between the plasma epinephrine and nor-
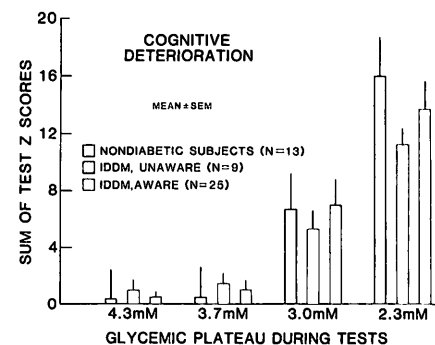

Figure 2—*Deterioration of cognitive function tests during stepwise reductions of plasma glucose in nondiabetic volunteers and IDDM subjects with and without hypoglycemia unawareness.*
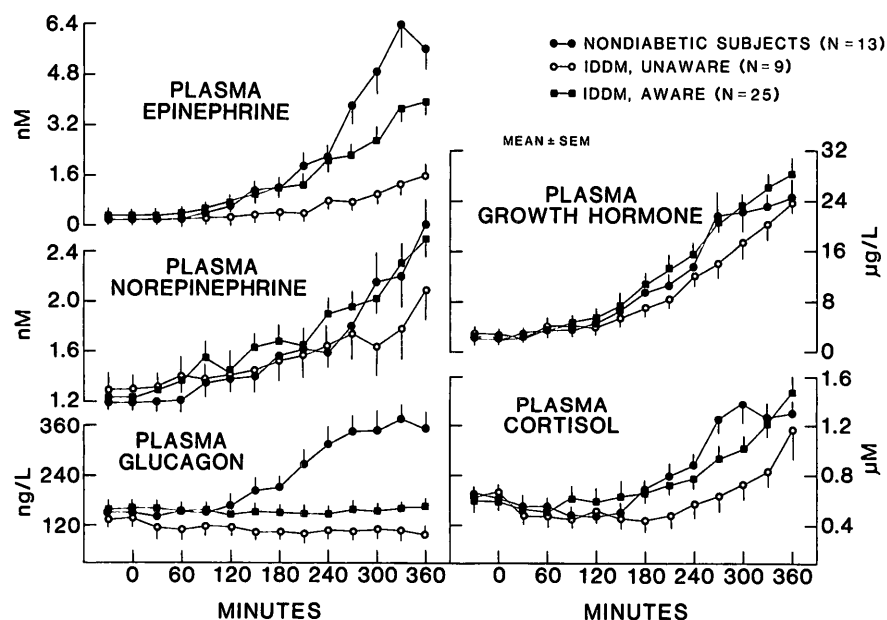
Figure 3—*Plasma counterregulation hormone concentrations during stepwise reductions of plasma glucose in nondiabetic volunteers and IDDM subjects with and without hypoglycemia unawareness.*

epinephrine concentrations at which autonomic symptoms began in patients with (251 ± 33 and 310 ± 37 pg/ml) and without unawareness (335 ± 38 and 301 ± 19 pg/ml) and the nondiabetic subjects (320 ± 46 and 311 ± 22 pg/ml).

Plasma insulin levels and glucose infusion rates

Plasma insulin levels, which have been reported to influence counterregulatory hormone responses to hypoglycemia (29), were comparable in all groups of subjects (Fig. 4). Despite this, glucose infusion rates necessary to maintain the targeted plasma glucose concentrations, an index of insulin sensitivity, differed significantly among the groups. Initially, before activation of counterregulation (up to 150 min), both IDDM groups had significantly lower glucose infusion rates than did the nondiabetic subjects ($P < 0.05$). After activation of counterregulation, glucose infusion rates decreased in nondiabetic subjects and in the IDDM patients without unawareness, eventually reaching virtually identical rates. In contrast, during this period, glucose infusion rates

in the IDDM patients with unawareness did not decrease and were significantly less than those in the other two groups ($P < 0.001$).

CONCLUSIONS — Previous studies of the hypoglycemia unawareness phenomenon in IDDM patients have generally categorized subjects as having or not having this condition on the basis of questionnaires relying on patients' recollection of hypoglycemic episodes. An obvious limitation of such an approach is that patients with hypoglycemia unawareness may not recognize mild hypoglycemia and may lead to their misclassification. To avoid this problem, these studies classified patients using a statistical criterion, based on their responses to a standardized hypoglycemia test. Those having the onset of autonomic warning symptoms (anxiety, palpitations, hunger, sweating, tremor, and irritability) (23) at a plasma glucose level >2 SD below that at which these occurred in normal volunteers were classified as having hypoglycemia unawareness.

Although this stringent criterion

might lead to some patients with small reductions in awareness being misclassified as having normal awareness, we were able to confirm previous observations of a relation of this syndrome with the duration of diabetes (7,17), the degree of glycemic control (2,11,12), and the occurrence of severe hypoglycemia (6,7). Moreover, although our subjects were not randomly selected for study, we found a prevalence of the phenomenon similar, i.e., ~25%, to that reported by Hepburn et al. (7), whose study was based on responses to a questionnaire from random selection of a clinic population. Interestingly, in both studies, patients classified as having hypoglycemia unawareness had an increased prevalence of severe hypoglycemia, but not the overall number of hypoglycemic episodes. This could be explained by the occurrence of asymptomatic nocturnal hypoglycemia (20), which is common in IDDM patients, and the fact that patients with hypoglycemia unawareness would, by definition, be less likely to recognize mild hypoglycemic episodes.
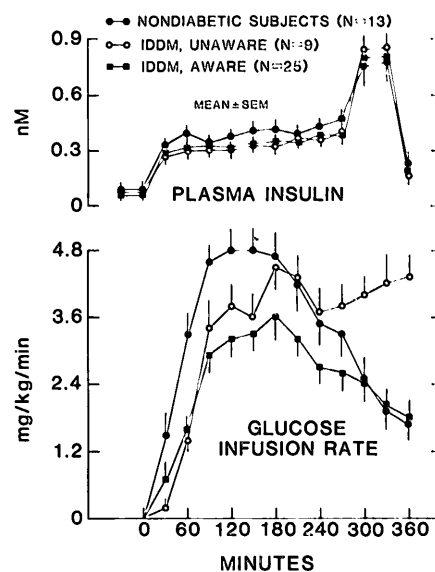

Figure 4—*Plasma insulin concentrations and glucose infusion rates during stepwise reductions of plasma glucose in nondiabetic volunteers and IDDM subjects with and without hypoglycemia unawareness.*

Three new observations emerge from this study. First, under our experimental conditions, patients with hypoglycemia unawareness are apparently more sensitive to insulin. This might be explained simply on the basis of their reduced counterregulatory hormone responses, but deserves further study under standardized euglycemic conditions. Another important observation in the present studies was that onset of both neuroglycopenic symptoms and cognitive dysfunction required greater hypoglycemia. This has been found to occur in insulinoma patients (30), but previous studies in diabetic patients have suggested that the threshold for neuroglycopenia might not be altered (2,31). The latter studies (2,31) had thus questioned the proposal (5,32) that the syndrome might be explained by an hypoglycemia-induced alteration in blood-brain glucose transport (33,34), because this theory predicts that autonomic warning symptoms and signs of neuroglycopenia should both be affected. Our results indicate that both are affected and therefore support this theory, but because the threshold for warning symptoms is more affected than that for development of neuroglycopenia, the net effect is that there is less time between onset of warning symptoms and development of neuroglycopenia, and the warning symptoms may not provide adequate warning for patients to take appropriate action (i.e., eat something) to prevent progression to greater hypoglycemia and deterioration in cognitive function.

Finally, the results of these studies indicate that, although the threshold and magnitude of plasma catecholamine responses are abnormal in patients with hypoglycemia unawareness, the plasma catecholamine levels at which autonomic warning symptoms occur are not altered. These observations cast doubt on the proposal (16) that altered β-adrenergic sensitivity plays a role in the pathogenesis of this phenomenon, because, if this were true, onset of autonomic warning symptoms would have been expected to be associated with greater plasma catecholamine levels.

In conclusion, the present studies indicate *1*) that reduced awareness of hypoglycemia is a common occurrence in patients with insulin-dependent diabetes, *2*) that reduced awareness is associated with an increased prevalence of severe hypoglycemia, *3*) that its occurrence is independently related to both duration of diabetes and degree of glycemic control and does not require the presence of autonomic neuropathy, *4*) that patients with this condition have increased sensitivity to insulin during hypoglycemia, *5*) that the thresholds for autonomic and neuroglycopenic symptoms are both affected, although to different degrees, and *6*) that because plasma catecholamine levels at which autonomic symptoms develop are not altered, it is unlikely that reduced β-adrenergic sensitivity plays an important role in the pathogenesis of this condition.

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