Evidence for Elevated Glucose Threshold in Patients With Impaired Glucose Tolerance and Symptoms of Hypoglycemia During OGTT

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We evaluated the relationship between hypoglycemic symptoms, glucose nadir levels, and hormone changes in patients with impaired glucose tolerance (IGT) after an oral glucose tolerance test (OGTT). The peak counterregulatory hormone response was determined at the glucose nadir identified by continuous glucose monitoring. Eight patients with IGT who had symptoms and signs typical of hypoglycemia at the glucose nadir were compared with completely asymptomatic subjects (5 IGT patients and 13 patients who had normal glucose tolerance [NGT]). The mean glucose nadir of symptomatic IGT patients was 3.50 ± 0.46 mM, which was not statistically different from the mean of asymptomatic NGT patients (4.10 ± 0.56 mM) but was significantly lower than that for asymptomatic IGT patients (5.10 ± 0.81 mM, $P < 0.001$). Seven of 8 symptomatic IGT patients had glucose levels that never fell below the range of glucose nadirs for asymptomatic NGT patients. However, the symptomatic IGT group had significantly higher levels of growth hormone, cortisol, epinephrine, and norepinephrine than the asymptomatic groups in response to the nadir. We conclude that patients with IGT are capable of experiencing signs and symptoms of hypoglycemia at physiological glucose levels during OGTT with reflex stimulation of counterregulatory hormone release. This may indicate that symptomatic IGT patients have a higher glucose threshold for eliciting characteristic hypoglycemic symptom episodes than individuals with NGT. *Diabetes Care* 13:507–12, 1990

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Signs and symptoms characteristic of insulin-induced hypoglycemia have been observed in some patients with impaired glucose tolerance (IGT) after an oral glucose tolerance test (OGTT) (1–6). Most subjects with normal glucose tolerance (NGT) do not have symptoms of insulin-induced hypoglycemia unless blood glucose drops to <2.8 mM (2,7). Although many previous studies have focused on symptom episodes in IGT patients who had glucose levels <2.8 mM (1–3,5,6), IGT patients have also been reported to have symptoms at glucose levels in the physiological range (4). The interpretation of symptom episodes at glucose levels of >2.8 mM in IGT patients has been difficult for several reasons. For example, intermittent blood sampling may have inadvertently missed a lower true glucose nadir. Also, patients were classified as symptomatic based on their subjective reports, their symptoms being frequently nonspecific in nature and not objectively confirmed. Finally, some symptomatic patients may have had personality disorders that led them to report symptoms during OGTT that were unrelated to hypoglycemia (4,8).

The measurement of hormonal changes can serve as an objective indicator of the stimulatory effect of hypoglycemia on the central nervous system (9,10). Concurrent measurement of counterregulatory hormones has been proposed as an objective criterion for assessing patients during OGTT rather than reliance on subjective symptom reports or glucose levels alone (3,8,11). However, measurement of counterregulatory hormones and glucose levels in symptomatic IGT patients has not been uniformly performed in the past.

The goal of this study was to evaluate the relationship between glucose levels, counterregulatory hormone secretion, symptoms, and signs during OGTT in IGT patients. Glucose levels were followed throughout each

procedure with a continuous glucose monitoring (CGM) system to identify the true glucose nadir. Measurement of counterregulatory hormones in response to the true nadir served as an objective assessment of the effect on the central nervous system.

RESEARCH DESIGN AND METHODS

With the exception of one individual, patients were referred to our diagnostic center for OGTT by their private physicians with a provisional diagnosis of postprandial hypoglycemia. In a pretest interview, these patients reported several symptoms of varying duration and timing in relation to their usual meals that were possibly compatible with symptoms of hypoglycemia. One patient was evaluated for suspected glucose intolerance. Many of the patients had a family history of diabetes. All patients were in otherwise general good health, ambulatory, and fully active. None had had gastrointestinal surgery or was taking medications known to alter glucose tolerance. None of the patients had previously been studied in our diagnostic unit.

OGTT protocol. For the 3 days before OGTT, patients were instructed to consume at least 300 g carbohydrate/day. The test began in the morning between 0730 and 0900 after a 12- to 14-h overnight fast. Blood glucose levels were monitored throughout the procedure in real time with a nonthrombogenic CGM system previously described (11,13,14). Blood from a cannulated peripheral vein is continuously drawn through a nonthrombogenic catheter to the monitor. In the monitor, the blood is automatically mixed with buffer and drawn past a glucose sensor. Glucose levels are presented on a digital display and recorded permanently on a paper tracing. The glucose display is positioned so that it is visible only to the attendant but not to the patient. Blood glucose levels by CGM correspond to plasma glucose levels measured by the glucose oxidase method (14). There is an ~3-min lag from the time blood leaves the vein until the glucose level is displayed.

Thirty minutes after the nonthrombogenic catheter for CGM was inserted into a large peripheral vein, baseline (time 0) blood samples were drawn for insulin, epinephrine, norepinephrine, cortisol, glucagon, and growth hormone. Glucose was then administered orally as dextrose (Glucola, Miles, Elkhart, IN) 1.75 g/kg body wt.

Before starting the procedure, patients were asked to report any change in their status during the test to the attending staff member. All subjectively reported symptoms during the test were carefully recorded in the patient's procedure flow sheet at the time of occurrence. In addition, any observed changes in the patient's physical status (signs) were noted on the flow sheet by the attendant.

Glucagon, growth hormone, cortisol, epinephrine, and norepinephrine levels were assayed from the samples taken at time 0, at the true glucose nadir identified during CGM, and at 10 and 20 min after the nadir. The maximum or peak hormone level attained within 20 min of the nadir is reported. Insulin levels at the time of the glucose nadir are also reported. An OGTT was concluded 40 min after the true glucose nadir when glucose levels were clearly stable or after a maximum duration of 360 min.

This protocol complied with the prevailing institutional standards for investigation with human subjects. Written informed consent for the procedure was obtained from all patients.

Inclusion and classification criteria. All patients had time 0 blood glucose <7.8 mM. Glucose tolerance was considered impaired if the blood glucose level at 0.5, 1, and/or 1.5 h is ≥11.1 mM and the blood glucose at 2 h is >7.8 mM (12).

Patients with IGT were included in the symptomatic IGT group if at the phase of falling glucose levels before and at the true glucose nadir they reported experiencing two or more subjective symptoms (anxiety, difficulty concentrating, confusion, irritability, palpitations, hunger, fatigue) and demonstrated at least one or more signs (sweating, pallor, shakiness).

Patients with IGT were included in the asymptomatic IGT group if there was no reported change in their sub-

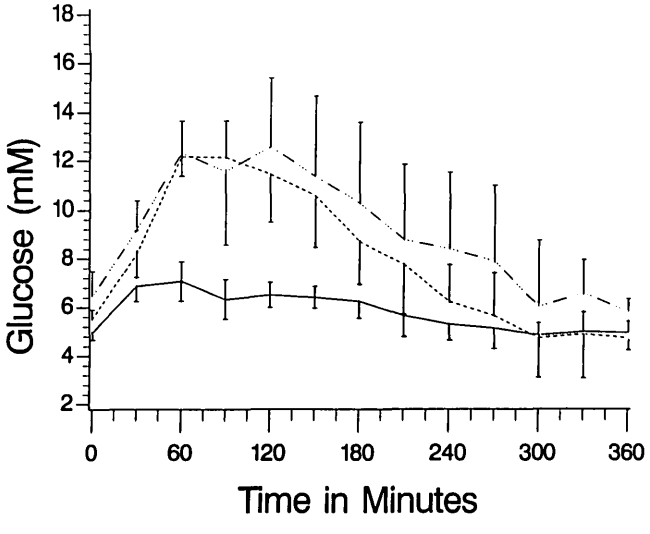

FIG. 1. Mean ± SE glucose levels for each group at 30-min intervals from time of glucose ingestion. *Solid line*, asymptomatic patients with normal glucose tolerance (NGT); *partly dotted line*, asymptomatic patients with impaired glucose tolerance (IGT); *dashed line*, symptomatic patients with IGT. Due to individual variation, true glucose nadirs are obscured by this type of plot, and data on true glucose nadir levels are shown in Fig. 2 and Table 1. Unless specified, number of patients at each time equals total number of patients for that group. Some patients concluded their studies before 360 min, as described in RESEARCH DESIGN AND METHODS; thus, *n* = 3 at 330 and 360 min, for asymptomatic IGT group; *n* = 7 at 330 min and *n* = 6 at 360 min for NGT; and *n* = 7 at 270 and 300 min, and *n* = 6 at 330 and *n* = 4 at 360 min, for symptomatic IGT.

TABLE 1
Features of oral glucose tolerance tests for study groups

	n	Age (yr)	Body mass index (kg/m²)	Weight (kg)	Glucose nadir (mM)	Time of glucose nadir (min)	Hypoglycemic index	Rate of glucose fall to nadir (mM/min)
Impaired glucose tolerance								
Symptomatic	8	48 ± 16	31 ± 7	83 ± 21	3.50 ± 0.45	296 ± 54	1.6 ± 0.4*	0.0610 ± 0.0112*
Asymptomatic	5	32 ± 17	32 ± 7	85 ± 22	5.10 ± 0.81	318 ± 63	0.7 ± 0.4	0.0390 ± 0.0224
Normal glucose tolerance								
Asymptomatic	13	33 ± 12	26 ± 7	67 ± 18	4.10 ± 0.56	268 ± 66	0.7 ± 0.3	0.0280 ± 0.0112

Values are means ± SD.
*$P < 0.05$ vs. asymptomatic patients in both groups.

jective condition or any observed signs during the period of the glucose nadir. A group of subjects with NGT studied under identical conditions who had no change in symptoms or observed signs during the glucose nadir of their OGTT were included for comparison (asymptomatic NGT).

Glucose. The hypoglycemic index (HI) for each patient was calculated as glucose level 90 min before nadir minus glucose level at nadir divided by glucose level at nadir (11,13,14). The rate of glucose fall (RF; $mg \cdot dl^{-1} \cdot min^{-1}$) was calculated as glucose level 90 min before nadir minus glucose nadir level divided by 90 min.

Hormone assays. Insulin (15) and growth hormone (16) concentrations were determined by radioimmunoassay. Plasma epinephrine and norepinephrine levels were measured by a radioenzymatic assay (17,18). The plasma cortisol level was measured by a protein-binding method (19). Glucagon was assayed by radioimmunoassay (20).

Results are means ± SD. Data were analyzed with the Statistical Analysis System program (21). The effect of patient group on the measured variables was evaluated by an analysis of variance technique via the general linear model procedure (21). When necessary, logarithmic transformation of data was performed to control heterogeneity of variances before performing statistical analysis. Multiple comparison of variables between diagnostic categories were performed according to the method of Tukey with a level of statistical significance set at $P < 0.05$ for these comparisons (21).

RESULTS

Eight patients (1 man, 7 women) with IGT reported a change in symptom status (onset of at least 2 symptoms suggestive of hypoglycemia, i.e., anxiety, difficulty concentrating, confusion, irritability, palpitation, hunger, or fatigue) and were also observed by the attendant to be either sweaty, pale, or shaky during the period of the glucose nadir (symptomatic IGT group). Symptom episodes occurred only during the phase of the OGTT as glucose levels were decreasing just before and during the true glucose nadir. All the symptomatic patients recovered spontaneously from their symptom episode. None of these patients had a severe adverse reaction during the test, i.e., loss of consciousness or convulsions. After the procedure, these patients stated that the symptom episodes resembled symptoms they were experiencing after their usual meals.

Five women patients who had IGT reported no change in subjective status and were without observable signs during the period of the glucose nadir (asymptomatic IGT). This group included the one patient who had been referred only for evaluation of glucose tolerance.

In addition, data from the OGTTs of 13 (5 men, 8 women) patients who had NGT was evaluated. These patients reported no change in subjective status or observed signs (asymptomatic NGT) during the nadir of their OGTT. Mean blood glucose levels at 30-min intervals during the testing for the 3 groups are shown in Fig. 1.

Age, body mass index, body weight, the true glucose nadir, time to the true glucose nadir, HI, and RF for symptomatic and asymptomatic patient groups are presented in Table 1. Although the mean age of symptomatic patients with IGT was slightly older than the other groups, this difference was nonsignificant ($F = 2.04$, $P < 0.13$). There was a trend for patients with IGT to be more obese, but this was nonsignificant ($F = 2.11$, $P < 0.15$). The asymptomatic NGT group had a higher percentage of men than the other two groups; however, there was no effect of sex on the results in this sample.

Blood glucose nadir levels. With the exception of one patient, symptomatic individuals had glucose nadir levels within the range of asymptomatic patients who had NGT (Fig. 2). The mean glucose nadir of the symptomatic IGT patients was significantly lower than asymptomatic IGT ($P < 0.001$) patients. Although the mean glucose nadir of symptomatic IGT patients was somewhat below the mean nadirs of asymptomatic patients with NGT, this difference was nonsignificant.

Although IGT patients tended to reach the glucose nadir after patients with NGT, these differences were nonsignificant ($F = 2.56$, $P < 0.07$).

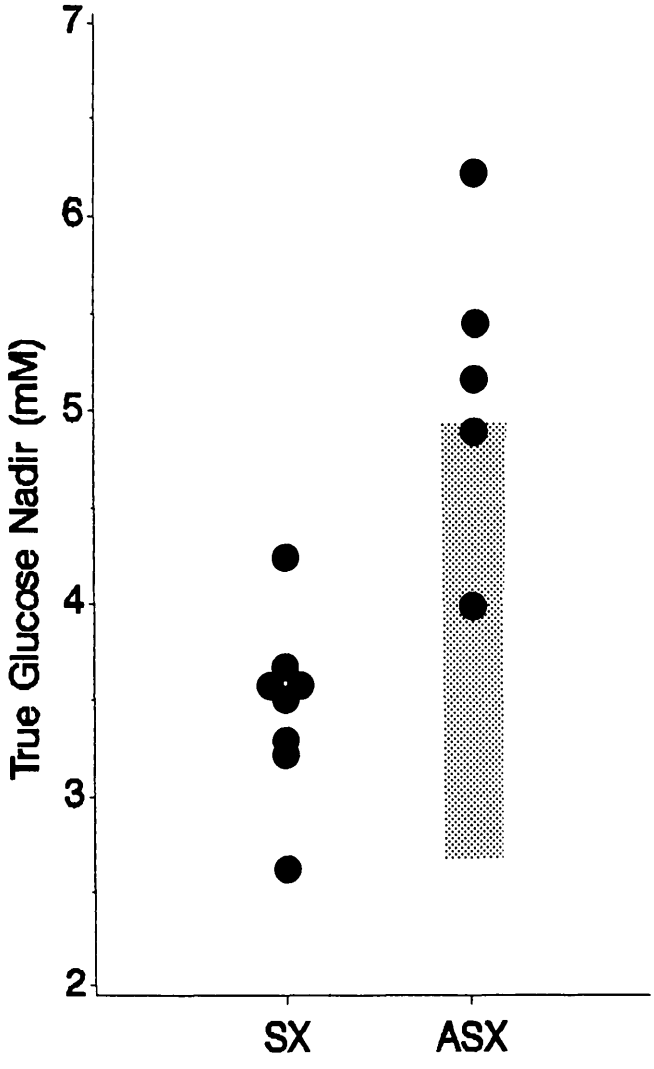

FIG. 2. Individual true glucose nadir levels by continuous glucose monitoring for symptomatic impaired glucose tolerance (SX) and asymptomatic impaired glucose tolerance (ASX) patients during oral glucose tolerance test. Mean glucose nadir of SX patients was significantly lower than that of ASX patients ($P < 0.001$). *Shaded box*, range for ASX patients with normal glucose tolerance (NGT). Seven SX patients had nadir levels within range of asymptomatic NGT patients.

HI and RF. The mean HI was higher in symptomatic patients compared with the asymptomatic patients ($P < 0.002$). There was no statistical difference in the mean RF before the nadir between symptomatic and asymptomatic patients with IGT. The mean RF in symptomatic patients with IGT was significantly faster than that of the asymptomatic subjects with NGT ($P < 0.05$).

Hormone responses. The mean hormone levels at baseline and in response to the glucose nadir are presented in Table 2 for epinephrine, norepinephrine, cortisol, growth hormone, glucagon, and insulin. In symptomatic patients with IGT, there was a significant increase in epinephrine, norepinephrine, growth hormone, and cortisol at the nadir compared with basal hormone levels. Only the rise in glucagon level was nonsignificant. Although there was a trend for the basal epinephrine and glucagon levels to be higher in symptomatic patients, these differences were nonsignificant. In asymptomatic IGT subjects, none of the counterregulatory hormone concentrations at the nadir was statistically different from baseline.

At the glucose nadir, all counterregulatory hormone levels with the exception of glucagon for symptomatic IGT patients were statistically higher than the nadir levels of the asymptomatic IGT group (Table 2). Interestingly, although obese, symptomatic IGT patients had a large increase in growth hormone at the nadir.

There was no difference in mean nadir insulin levels between symptomatic and asymptomatic groups with IGT. Only the difference of nadir insulin levels of patients with IGT compared with symptomatic NGT patients attained statistical significance ($P < 0.05$).

DISCUSSION

In asymptomatic patients with NGT, glucose nadirs during OGTT have been infrequently noted to drop to <2.8 mM (3,7,22,23). In addition, symptoms during acute insulin-induced hypoglycemia or associated with insulinomas have been reported to occur at glucose levels <2.8 mM (7). For these reasons, several previous studies of patients with IGT and hypoglycemic symptoms selected patients for study only if they had documented blood glucose levels <2.8 mM during OGTT (1–6). Because most of these studies used intermittently drawn glucose samples, the choice of a glucose cutoff also prevented inclusion of symptomatic patients with glucose levels >2.8 mM who may actually have had lower true nadirs that had been inadvertently missed by the sampling technique.

Johnson et al. (4) reviewed the records of 32 patients with early diabetes who had undergone OGTT and found that 37.5% had reported symptoms. Blood glucose samples were drawn at hourly intervals and additional samples at the time of symptoms. Only three of the patients in their study had glucose levels ≤2.8 mM. Counterregulatory hormones were not measured. Thus, most reviewed cases had symptoms associated with glucose levels >2.8 mM. Johnson et al. suggested that patients with symptoms of hypoglycemia at physiological glucose levels may have had emotional disturbances accounting for the occurrence of symptoms (4).

This study represents a further evaluation of this phenomenon via CGM and hormone measurement. CGM permits the identification of the true glucose nadir during the OGTT. We found that eight patients with IGT had symptoms and signs typical of hypoglycemia associated with falling glucose levels and the true glucose nadir during OGTT. These patients also had a significant concurrent stimulated rise in counterregulatory hormone levels. The release of counterregulatory hormones is an objective indication of central nervous system stimu-

TABLE 2
Hormone levels at baseline and peak response within 20 min of true glucose nadir

	Epinephrine (pM)		Norepinephrine (nM)		Cortisol (nM)		Growth hormone (μg/L)		Glucagon (ng/L)		Insulin (μU/mL)	
	Basal	Nadir	Basal	Nadir	Basal	Nadir	Basal	Nadir	Basal	Nadir	Basal	Nadir
IGT												
Symptomatic	169 ± 87	2108 ± 945*	1.94 ± 0.95	3.36 ± 2.01*	248 ± 82	635 ± 221*	6 ± 6	20 ± 20†	141 ± 74	173 ± 93	32 ± 19	44 ± 36‡
Asymptomatic	109 ± 60	240 ± 169	1.43 ± 0.84	1.36 ± 1.12	276 ± 138	166 ± 55	1 ± 1	2 ± 2‡	98 ± 25	104 ± 41	24 ± 8	36 ± 14‡
NGT												
Asymptomatic	115 ± 66	306 ± 218	1.69 ± 0.72	1.67 ± 0.75	359 ± 221	304 ± 248	6 ± 6	16 ± 14	79 ± 26	89 ± 27	20 ± 17	19 ± 17

Values are means ± SD. IGT, impaired glucose tolerance; NGT, normal glucose tolerance.
*$P < 0.05$ vs. asymptomatic IGT and NGT groups.
†$P < 0.05$ vs. asymptomatic IGT patients.
‡$P < 0.05$ vs. asymptomatic NGT group.

lation by a change in glucose levels (3,10). Seven of eight patients never had a blood glucose level by CGM <3 mM. The nadir levels of these seven patients were also within the range of glucose nadirs (2.8–5.0 mM) of asymptomatic patients who had NGT and physiological hormone changes. Although these seven symptomatic patients with IGT were not hypoglycemic by previous standards or in comparison with asymptomatic patients having NGT, they had a stereotypic hypoglycemic symptom episode and release of hormones that coincided with the glucose nadir. Thus, the timing and character of symptoms and signs, together with the stimulation of hormone secretion, are evidence for an effect on the central nervous system by changes in glucose levels at this phase of the OGTT. We suspect that this group of symptomatic patients with IGT may have an upward alteration in the glucose threshold at which they respond with characteristic hypoglycemic symptoms and hormone release. An upward shift in glucose threshold for eliciting a hypoglycemic response has been reported in other circumstances associated with hyperglycemia (24–27).

Symptomatic IGT patients had a rate of glucose lowering before the nadir nearly double that of asymptomatic patients with NGT. The RF or a combination of the RF and the glucose nadir level may be the trigger for symptom episodes in these particular patients. However, several previous studies suggest that the glucose threshold rather than the RF is a more important factor in eliciting symptoms and hormone release (28–31).

Asymptomatic individuals with IGT had glucose nadir levels well above most of the symptomatic IGT patients and above or in the upper limits for asymptomatic individuals with NGT. The RF in this group was similar to that in the asymptomatic patients with NGT. The asymptomatic patients with IGT may also potentially have hypoglycemic symptoms, signs, and stimulated hormone release, if their glucose concentrations were lowered to a level comparable to the symptomatic group. This possibility may be tested in the future with graded insulin-infusion techniques (29). However, the possibility that symptoms are due to factors specifically associated with the ingestion of glucose, i.e., secretion of hormones, cannot be ruled out at this time. Of interest is the lack of difference in stimulated glucagon levels between the groups. Glucagon has a primary role in glucose counterregulation and maintaining blood glucose homeostasis (10). Whether impaired glucagon secretion plays a causative role in symptom episodes in patients with IGT will need to be evaluated in more detail.

As we observed in the course of this study, hypoglycemialike symptom episodes in patients with IGT occurred predominantly at physiological glucose concentrations, were self-limited, and were followed by complete spontaneous recovery without apparent adverse effect. Although from a clinician's standpoint these symptomatic episodes are benign, they were quite distressing to the patient. On questioning after the procedure, the symptomatic patients reported having similar symptom episodes periodically at home or work on their regular diets. Varying the composition of a meal can influence the glycemic response (32–34). Thus, some but not all meals these patients prepare for themselves may replicate the glycemic load of the OGTT and provoke postprandial symptom episodes with hormone release. Because most of the patients had symptoms at glucose levels >2.8 mM during OGTT, it is unlikely that chemical hypoglycemia would be documented in these patients during a particular meal. In practice, it is not feasible to replicate the various permutations of diet composition that may provoke a symptom episode. In patients in whom further diagnostic evaluation is desired, the response to oral glucose loading with measurement of counterregulatory hormones at the true nadir may provide helpful objective data on the etiology of the patient's symptoms.

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