Relationship of Nocturnal Hypoglycemia to Daytime Glycemia in IDDM

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In view of the continuing debate about the clinical relevance of nocturnal hypoglycemia as an explanation for high blood glucose (BG) levels before breakfast, we prospectively analyzed 281 overnight BG profiles (blood samples obtained at 2100, 0200–0300, and 0700) in 66 consecutive patients with insulin-dependent diabetes mellitus. Nocturnal hypoglycemia (0200–0300 BG concentration ≤50 mg/dl) occurred in 27 patients (41%) and in 36 profiles (13%). All the patients with nocturnal hypoglycemia received two or more injections of insulin each day. When hypoglycemia occurred at 0200–0300, the preceding BG concentration at 2100 was significantly lower than when nocturnal BG was >100 mg/dl (108 ± 11 vs. 145 ± 12 mg/dl; $P < .05$; mean ± SE). A BG ≤120 mg/dl at 2100 preceded nocturnal hypoglycemia in 24 (67%) of 36 profiles. The mean BG at 0700 was significantly lower in the profiles associated with nocturnal hypoglycemia than in those with nocturnal BG levels >150 mg/dl (156 ± 10 vs. 201 ± 11 mg/dl; $P < .05$). BG values >180 mg/dl at 0700 were infrequently (11 of 143 or 8% of profiles) preceded by nocturnal hypoglycemia, and no instances of major hyperglycemia (BG >300 mg/dl) at 0700 were preceded by nocturnal hypoglycemia. Furthermore, BG at 0700, 1100, and 1500 on the day before the occurrence of nocturnal hypoglycemia were similar to those on the day after. Individuals with nocturnal hypoglycemia whose subsequent BG at 0700 exceeded 180 mg/dl consumed significantly more calories (181 ± 18 vs. 115 ± 12; $P < .001$) and carbohydrate (39 ± 4 vs. 26 ± 3 g; $P < .05$) than those with BG ≤120 mg/dl at 0700. Nocturnal hypoglycemia was not followed by major hyperglycemia at 0700 or higher daytime glycemia than on the previous day. Excessive food intake to treat nocturnal hypoglycemia appears to be an important factor contributing to unacceptably high BG levels before breakfast. ***Diabetes Care*** **11:636–42, 1988**

In clinical practice, when fasting hyperglycemia occurs in an individual with insulin-dependent diabetes mellitus (IDDM) receiving conventional insulin replacement therapy it is commonly attributed to the effects of undetected nocturnal hypoglycemia. This practice relates to a widely accepted concept proposed in 1938 by Somogyi, who believed that excess insulin was a major cause of unstable diabetes. He attributed posthypoglycemic hyperglycemia in diabetic patients to activation of the pituitary and adrenal systems by hypoglycemia (1–3).

Despite widespread acceptance of the Somogyi phenomenon and its inclusion in standard texts on diabetes (4–7), its clinical relevance continues to be controversial (8–17). Although individuals with IDDM frequently experience asymptomatic nocturnal hypoglycemia (18–23), the relevance of antecedent hypoglycemia to early-morning hyperglycemia has been questioned (12,13,15–17). Several authors have suggested that the assumption that fasting hyperglycemia occurs as a result of nocturnal hypoglycemia is likely to be erroneous (13,15–17). Indeed, clinical studies have shown that nocturnal hypoglycemia does not commonly result in major hyperglycemia in the morning or during the daytime. Furthermore, nocturnal hypoglycemia has been found to predict lower blood glucose (BG) levels before breakfast (16,17,19,20).

In view of the continuing debate about the clinical relevance of nocturnal hypoglycemia as an explanation for high BG levels before breakfast, we examined the relationship of nocturnal hypoglycemia to BG levels

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TABLE 1
Characteristics of patient population

	Patients with documented nocturnal hypoglycemia* (n = 27)	Patients with no documented nocturnal hypoglycemia† (n = 26)	All patients (n = 66)
n (F/M)	20/7	19/7	44/22
Age (yr)	25 ± 2 (9–53)	24 ± 3 (8–56)	24 ± 2 (8–56)
Duration of diabetes (yr)	9 ± 1 (2–27)	11 ± 2 (2–49)	10 ± 1 (2–49)
Total HbA_1 (%)‡	10.9 ± 0.4 (6.5–16.6)	12 ± 0.6 (7.7–16.7)	11.8 ± 0.3 (6.5–18)
Insulin therapy			
Total insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.8 ± 0.05 (0.5–1.5)	0.80 ± 0.04 (0.4–1.2)	0.81 ± 0.03 (0.4–1.5)
1 injection/day (n)	0	9	9
≥2 injections/day (n)	27	17	57
Incidents of symptomatic nocturnal hypoglycemia during month before hospitalization (n)	18 (67%)	15 (58%)	35 (53%)

Values are means ± SE (range).
*Blood glucose ≤50 mg/dl at 0200–0300.
†Blood glucose >70 mg/dl at 0200–0300.
‡Normal values 5.4–7.4% (6.4 ± 0.5 SD).

during the preceding evening and following day in individuals with IDDM.

MATERIALS AND METHODS

Subjects. We prospectively analyzed 281 overnight BG profiles (blood samples obtained at 2100, 0200–0300, and 0700) in 66 consecutive patients with IDDM (3–6 profiles/patient) during their admission to the Diabetes Treatment Unit of the New England Deaconess Hospital. Most patients were admitted because BG control was poor. Fifteen patients specifically complained about frequent episodes of symptomatic nocturnal hypoglycemia, and 4 patients had experienced ketoacidosis in the month before admission. There were 22 males and 44 females, and their clinical characteristics, mode of treatment, and level of metabolic control are shown in Table 1. Seventeen patients (26%) had evidence of background diabetic retinopathy and/or peripheral neuropathy; 5 patients had preproliferative or proliferative retinopathy. Seven patients had minimal or no awareness of hypoglycemic reactions.

Patients with diabetes for <2 yr were excluded because they were considered more likely to be secreting clinically significant amounts of insulin (24). Other exclusion criteria were any acute medical or surgical illness, severe painful neuropathy, use of β-blockers, clinical nephropathy (albuminuria ≥250 mg/day), and age >60 yr.

Methods. Total glycosylated hemoglobin (HbA_1) was measured by an electrophoretic method (25). The normal value in our laboratory is 6.4 ± 0.5% (mean ± SD). The capillary BG concentrations obtained at 0700, 1100, 1500, and 2100 were measured in the hospital clinical chemistry laboratory on a Kodak Ektachem analyzer (Eastman Kodak, Rochester, NY). The BG concentrations of capillary blood samples obtained at 0200–0300 were measured with an Accu-Chek II blood glucose meter (Boehringer Mannheim, Indianapolis, IN) by the staff nurses working on the diabetes treatment unit at night.

Before undertaking this study, we determined the accuracy of capillary BG measurements by the staff nurses who performed 186 capillary BG determinations on samples simultaneously analyzed in the clinical chemistry laboratory. There was a high degree of correlation between BG concentrations determined by the nurses and those determined by the clinical chemistry laboratory (r = .964). The relationship between laboratory measurements (x) of BG concentrations and those performed by the nurses using an Accu-Chek II glucose meter (y) was linear and was defined by the regression equation $y = 1.046x + 3.3$. For BG concentrations <100 mg/dl (n = 31), the correlation was 0.8, and the relationship was defined by the equation $y = 0.87x + 13.96$.

Nocturnal hypoglycemia was defined as a BG concentration ≤50 mg/dl at 0200–0300. The data were separately analyzed with the definition of nocturnal hypoglycemia as a BG level <70 mg/dl at 0200–0300, a level below which counterregulation is activated in normal and diabetic individuals (26,27). Overnight BG profiles (2100, 0200–0300, and 0700) were grouped by 50-mg/dl intervals (range 19–483 mg/dl), except values >300 mg/dl, based on the BG level at 0200–0300. BG levels at each 50-mg/dl interval at 0200–0300 were compared with the corresponding BG concentrations at 2100 and at 0700 in the same profiles. We also analyzed BG profiles on the day before and the day after an episode of nocturnal hypoglycemia.

Table 1 shows the clinical characteristics of the pa-

TABLE 2
Clinical characteristics of patients with nocturnal hypoglycemia (blood glucose ≤50 mg/dl at 0200–0300) grouped by early-morning (0700) blood glucose levels

	Blood glucose at 0700		
	≤120 mg/dl	121–180 mg/dl	181–285 mg/dl
Frequency (profiles/patients)	11/11	14/11	11/10
n (F/M)	7/4	9/5	10/1
Age (yr)	24 ± 4	22 ± 2	27 ± 4
Duration of diabetes (yr)	8 ± 2	9 ± 1	10 ± 2
Total HbA_1 (%)	11.1 ± 0.5	11.1 ± 0.5	10.5 ± 0.8
Total insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.76 ± 0.06	0.89 ± 0.08	0.91 ± 0.08
Carbohydrate intake after hypoglycemia (g)*	26 ± 3	31 ± 2	39 ± 4
Calorie intake after hypoglycemia (kcal)†	115 ± 12	142 ± 10	181 ± 18
Symptoms of hypoglycemia (yes/no)	7/4	9/5	8/3

*P NS for ≤120 vs. 121–180 and $P < .05$ for ≤120 vs. 181–185.
†P NS for ≤120 vs. 121–181 and $P < .001$ for ≤120 vs. 181–285.

tient population ($n = 66$). Also shown are the characteristics of patients whose BG levels at 0200–0300 were ≤50 mg/dl ($n = 27$) compared to those ($n = 26$) who did not develop hypoglycemia (BG level at 0200–0300 exceeded 70 mg/dl). Individuals who experienced nocturnal hypoglycemia were divided into three groups according to the subsequent BG levels at 0700: early-morning BG levels ≤120 mg/dl, early-morning mild hyperglycemia (values from 121 to 180 mg/dl), and early-morning moderate hyperglycemia (values from 181 to 304 mg/dl; Table 2).

Meals were served at 0800, 1200, and 1730 and snacks at 1000, 1500, and 2100. The nature and quantity of food used to treat nocturnal hypoglycemia were carefully recorded by the nurses. The precise amount and nature of the food given was at the discretion of the nurses, who followed certain guidelines used on the unit. However, note that the guidelines were not strictly adhered to, and certain patients refused to consume the full amount of food offered to them. When BG was ≤50 mg/dl between 0200 and 0300, even in the absence of symptoms, the patient was given 4 oz orange juice and crackers equivalent to a bread exchange, constituting a total of 30 g carbohydrate. If an individual had intense symptoms of hypoglycemia or had engaged in strenuous physical exercise during the preceding evening, hypoglycemia was treated with 6–8 oz orange or apple juice and a snack consisting of three peanut butter sandwich crackers or four Arrowroot cookies, i.e., 37.5–45 g carbohydrate, 3 g protein, and 5 g fat. Individuals whose BG levels at 0200–0300 were 51–80 mg/dl received 4 oz fruit juice with extra food only when symptoms of hypoglycemia were intense or the patient had engaged in strenuous physical exercise. Patients were also encouraged to take a snack consisting of 4 oz orange or apple juice and crackers equivalent to a bread exchange when their BG levels were ≤80 mg/dl at 2100.

Neither author was responsible for supervising the care of patients, and the collection of data occurred in the context of the routine clinical management of the patients. The presence or absence of symptoms of hypoglycemia (sweating, headache, tremor, nightmares, restless sleep, difficulty awaking, seizures, unconsciousness) was ascertained from a questionnaire administered the next morning by one of the authors (I.G.L.).

Statistics. The data were expressed as means ± SE. Overnight profiles (2100, 0200–0300, and 0700 BG levels) were analyzed by repeated-measures analysis of variance. The significance of differences was determined by Student's t test for paired and unpaired data and the χ^2-test where appropriate. Correlations were determined by the least-squares method of linear regression. Statistical significance was set at $P < .05$.

RESULTS

Prevalence of nocturnal hypoglycemia. Nocturnal hypoglycemia (BG ≤50 mg/dl) occurred in 27 patients (41%) and 36 profiles (13%). Forty patients (61%) had BG ≤70 mg/dl at 0200–0300, and this occurred in 58 profiles (21%). The number of insulin injections per day was the only variable that was found to be significantly different ($P < .05$) in patients who experienced nocturnal hypoglycemia compared with those who did not. All the patients who had a documented episode of nocturnal hypoglycemia received two or more injections per day (Table 1).

Overnight blood glucose profiles. Significant differences between 2100 and 0200–0300, and between 0700 and 0200–0300, were found only in those profiles with 0200–0300 BG levels ≤100 mg/dl (Fig. 1). When hypoglycemia (BG ≤50 and ≤70 mg/dl) occurred at 0200–0300, the preceding BG concentrations at 2100 (108 ± 11 and 117 ± 9 mg/dl) were significantly lower ($P < .05$) than when the nocturnal BG concentrations were >100 mg/dl (145 ± 12 mg/dl).

The mean fasting BG concentration was 184 ± 5 mg/dl ($n = 281$), and 143 (51%) of the profiles had BG

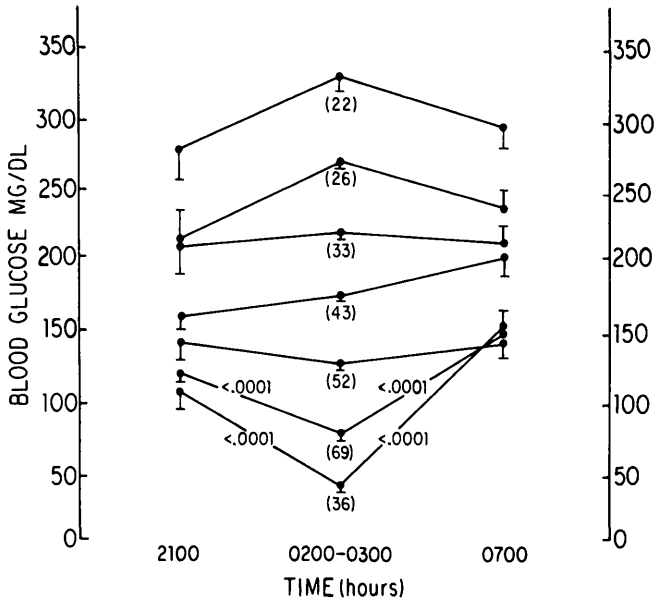

FIG. 1. Blood glucose concentrations (means ± SE) at 2100, 0200–0300, and 0700 in 66 patients (281 profiles) with insulin-dependent diabetes mellitus. Profiles are grouped by 50-mg/dl intervals based on blood glucose level at 0200–0300. Numbers in parentheses refer to number of profiles in each group.

values >180 mg/dl at 0700. The mean BG concentration at 0700 after BG levels of ≤50 mg/dl at 0200–0300 was 156 ± 10 (range 28–285 mg/dl), and when BG levels at 0200–0300 were ≤70 mg/dl, the BG concentration at 0700 was 160 ± 8 (range 28–304 mg/dl). The mean 0700 BG levels were significantly lower in the profiles associated with nocturnal hypoglycemia than in those with BG values >150 mg/dl at 0200–0300 (156 ± 10 vs. 201 ± 11 mg/dl; $P < .05$). There was a significant correlation between the 0200–0300 and the 0700 BG values ($r = .55$, $P < .0001$). BG concentrations >180 mg/dl at 0700 were preceded by nocturnal hypoglycemia in only 11 (7.7%) of 143 profiles, and nocturnal hypoglycemia followed by fasting morning BG values in the range of 181–285 mg/dl occurred in only 11 (30%) of 36 profiles. No instances of major hyperglycemia (BG >300 mg/dl) were preceded by nocturnal hypoglycemia.

When patients with nocturnal hypoglycemia were divided into groups based on their subsequent 0700 BG levels (≤120, 121–180, and 181–304 mg/dl; Table 2), the only variable that differed significantly among the groups was the quantity of food used to treat hypoglycemia. Individuals with fasting BG >180 mg/dl consumed significantly more calories (181 ± 18 vs. 115 ± 12 kcal; $P < .001$) and more carbohydrate (39 ± 4 vs. 26 ± 3 g; $P < .05$) than those whose BG at 0700 was ≤120 mg/dl. Statistically significant differences were also observed with respect to total calories and carbohydrate intake when the data were reanalyzed with BG levels ≤70 mg/dl at 0200–0300.

There was a significant relationship between the BG concentrations at 2100 and the BG levels at 0200–0300 ($r = 0.53$, $P < .001$; $y = 0.522x + 69$). Of the profiles in which the BG concentration was ≤120 mg/dl at 2100, 24 (21%) of 114 had nocturnal hypoglycemia. In contrast, when BG levels at 2100 were >180 mg/dl, nocturnal hypoglycemia occurred in only 5 (5%) of 102 overnight profiles. Nocturnal hypoglycemia was preceded by BG ≤120 mg/dl in 24 (67%) of 36 profiles.

Comparison between 24-h blood glucose profiles on the days preceding and following nocturnal hypoglycemia. Figure 2 shows that BG levels at 0700, 1100, and 1500 on the day before were similar to those on the day after an episode of nocturnal hypoglycemia. BG levels at 2100 preceding nocturnal hypoglycemia, however, were significantly lower than at 2100 on the next day (108 ± 11 vs. 159 ± 21 mg/dl; $P < .05$). Similar results were obtained when nocturnal hypoglycemia was defined as ≤70 mg/dl (data not shown).

When profiles with fasting (0700) BG >180 mg/dl were grouped according to whether there had been preceding nocturnal hypoglycemia, no significant differences were observed in the subsequent BG levels measured at 1100, 1500, and 2100 (Fig. 3).

DISCUSSION

Soon after insulin became available for clinical use a paradoxical diabetogenic effect was described in both diabetic (28) and nondiabetic (29,30) individuals. Somogyi was the first to suggest that counterregulatory hormones play an im-

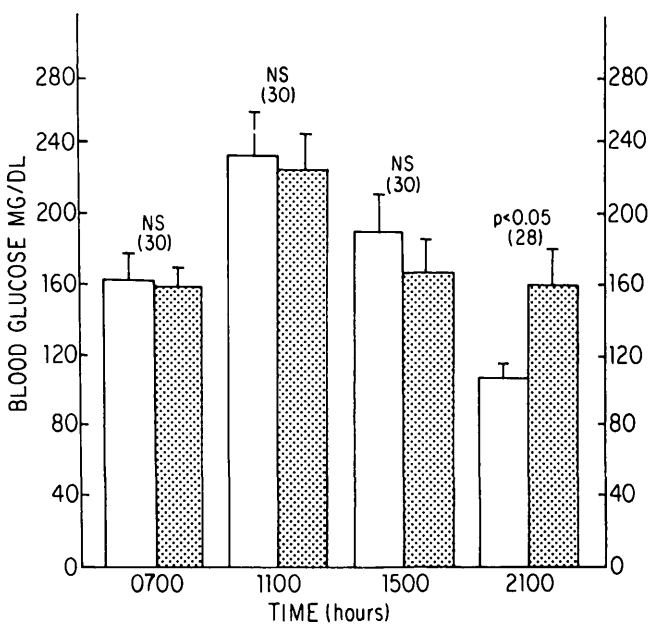

FIG. 2. Blood glucose concentration (means ± SE) on day before (*open bars*) compared to day after (*stippled bars*) nocturnal hypoglycemia. Number of profiles is shown in parentheses.

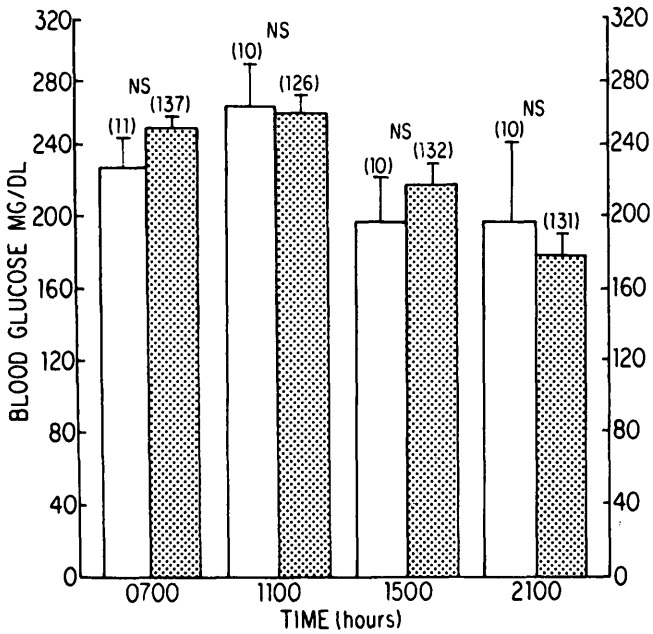

FIG. 3. Blood glucose concentration (means ± SE) on days with blood glucose >180 mg/dl at 0700 with (*open bars*) or without (*stippled bars*) preceding nocturnal hypoglycemia. Numbers in parentheses refer to number of profiles.

portant role in raising BG levels and that overinsulinization was an important cause of unstable diabetes (1–3). The Somogyi phenomenon (posthypoglycemic hyperglycemia or rebound hyperglycemia) is a concept that has become well entrenched in the medical literature.

The prevalence of nocturnal hypoglycemia differs according to the characteristics of the study population, the diagnostic criteria for hypoglycemia, the intensity of insulin treatment, and the frequency of BG measurements during the night. A single sample between 0200 and 0400 fails to detect approximately one-fourth to one-third of the episodes of nocturnal hypoglycemia (12,20). Nevertheless, with a single blood sample obtained at 0200–0300 in this study, which attempted to simulate routine clinical practice, it was confirmed that nocturnal hypoglycemia (defined as a BG concentration ≤50 mg/dl) is common in diabetic patients receiving conventional insulin replacement therapy. Hypoglycemia was detected in 27 (41%) of the patients and in 36 (13%) of the profiles. BG concentrations ≤70 mg/dl at 0200–0300 occurred in 40 (61%) of the patients and in 58 (21%) of the profiles. Note that our study population consisted of IDDM patients who were, for the most part, not tightly controlled as reflected by a mean total HbA_1 level of 11.8 ± 0.3% at the time of admission to the hospital. Only 8 of 66 patients were using more than two injections of insulin each day, and none was using continuous subcutaneous insulin infusion.

Of the various clinical characteristics examined, only the number of insulin injections used each day differed significantly in the patients with documented hypoglycemia compared with those without nocturnal hypoglycemia. All the patients with nocturnal hypoglycemia were using at least two insulin injections per day. A higher prevalence of nocturnal hypoglycemia has been documented in patients with very good metabolic control (19,20,22), in patients using intensive insulin regimens (20,22) or higher insulin doses, in children (11,23,31), and in patients with severely impaired counterregulatory responses (32,33).

We did not find major fasting hyperglycemia (BG >304 mg/dl) after an episode of nocturnal hypoglycemia, and the blood glucose values during the following day were no higher than on the previous day. Our observations are similar to those of other authors who found that early-morning major hyperglycemia following nocturnal hypoglycemia was an uncommon event (16,17,19,20). Although a high prevalence of prebreakfast BG values >180 mg/dl was found (143/281 or 51% of profiles), they were infrequently preceded by nocturnal hypoglycemia (11/143 or 8% of profiles).

In an effort to identify a subgroup of patients with rebound hyperglycemia, we separately examined the patients with nocturnal hypoglycemia on the basis of their subsequent fasting BG levels. Patients with BG levels >180 mg/dl at 0700 consumed a larger amount of food to treat nocturnal hypoglycemia (181 ± 18 vs. 115 ± 12 kcal). It has previously been suggested that marked hyperglycemia after hypoglycemia is usually related to the ingestion of a meal, often too large, in an attempt by the patient to relieve the symptoms of hypoglycemia (15). In this study, we did not attempt to strictly control the amount of food given to the patients who had nocturnal hypoglycemia. Rather, we intended to document the effects of the practices that have been employed for several years on the diabetes treatment unit and are adopted by patients in treating themselves at home. Although certain guidelines were followed, the precise amount of food was left to the discretion of the staff nurses and was influenced by the compliance of the patients.

Extensive literature has accumulated during the past few years concerning the counterregulatory responses to hypoglycemia and the mechanisms involved in raising BG levels during the early morning (34–43). The main factor predisposing to posthypoglycemic hyperglycemia seems to be the inability to increase insulin availability to compensate for the increased glucose production and insulin resistance that follows the counterregulatory response evoked by hypoglycemia (40,42). This study did not measure counterregulatory factors or insulin dynamics; however, it can be inferred from BG profiles that the magnitude of any posthypoglycemic hyperglycemia, if present, was mild. It can be argued that the low prevalence and minimal rebound hyperglycemia were due to greater insulin availability in the study population. Most patients were on an insulin regimen that included an intermediate-acting insulin either before supper or at bedtime. Therefore, an

appreciable insulin level 12–14 h later would be expected. Another possible explanation could be reduced counterregulatory hormone responses or effect. After 5 yr of diabetes, most IDDM individuals have a blunted glucagon response to hypoglycemia and depend on epinephrine-mediated β-adrenergic mechanisms that can also fail after several years (42). The possibility that early treatment of nocturnal hypoglycemia might have aborted or diminished the counterregulatory response cannot be excluded; however, food was given when the threshold for activating counterregulation had been exceeded. Furthermore, we found that higher early-morning BG values were associated with increased food consumption.

The data also showed that BG levels <120 mg/dl at 2100 were associated with nocturnal hypoglycemia in 24 (67%) of 36 profiles. The positive predictive value of BG levels ≤120 mg/dl at 2100 to be followed by nocturnal hypoglycemia was 21%. This finding is consistent with previous reports that normal or low BG concentrations before bedtime are more frequently associated with nocturnal hypoglycemia (20,21,23). The lower positive predictive value in this study is probably explained by the fact that patients whose BG level at 2100 was ≤80 mg/dl had an extra snack before retiring. This practice has been shown to diminish the risk of nocturnal hypoglycemia (21,23). The practical application of this observation is that patients receiving intermediate-acting insulin before their evening meal should receive an extra snack if their BG level is <120 mg/dl at bedtime.

In conclusion, we found that major fasting hyperglycemia did not commonly occur after nocturnal hypoglycemia. Furthermore, BG levels on the day after an episode of nocturnal hypoglycemia were no greater than on the previous day. Based on these findings, which are similar to those reported by Havlin and Cryer (16), we suggest that clinicians reconsider the role of nocturnal hypoglycemia as an explanation for major hyperglycemia before breakfast. An important factor associated with higher fasting BG levels after an episode of nocturnal hypoglycemia was the amount of food used to treat hypoglycemia. Excessive food consumption to treat nocturnal hypoglycemia is a common practice and may be an important factor contributing to unacceptably high fasting BG values. Other possible explanations for high fasting BG levels such as inadequate overnight insulinemia, waning insulin effect before breakfast, and increased early-morning insulin requirement should be given greater consideration.

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