Impact of Bedtime Snack Composition on Prevention of Nocturnal Hypoglycemia in Adults With Type 1 Diabetes Undergoing Intensive Insulin Management Using Lispro Insulin Before Meals

A randomized, placebo-controlled, crossover trial

MARIA KALERGIS, MSC, RD[1,2]
ALICIA SCHIFFRIN, MD[3]
RÉJEANNE GOUGEON, PHD[1]

PETER J.H. JONES, PHD[2]
JEAN-FRANÇOIS YALE, MD[1]

OBJECTIVE — To determine the impact of four bedtime (HS) snack compositions on nocturnal glycemic control, including frequency of hypoglycemia (<4 mmol/l) and morning hyperglycemia (>10 mmol/l), in adults with type 1 diabetes using lispro insulin before meals and NPH insulin at bedtime.

RESEARCH DESIGN AND METHODS — Substitutions of 15 g carbohydrate (one starch exchange) for an equivalent amount of uncooked cornstarch or pure protein were compared to a standard snack (control: two starch + one protein exchange) and to no snack (placebo) in 15 adults using a randomized, cross-over design. All snacks were equivalent in kcal, fat, and total available glucose. An intravenous facilitated hourly blood glucose sampling during the night (11:00 P.M. to 7:00 A.M.).

RESULTS — The glycemic level at bedtime (<7, $7–10$, and >10 mmol/l) mediated the effects observed. A total of 14 hypoglycemic episodes, in 60% of patients, and 23 morning hyperglycemic episodes occurred over 50 nights. Most hypoglycemic episodes (10 of 14, 71%) occurred with no snack compared to any snack ($P < 0.001$) and at HS levels of <7 mmol/l ($P = 0.05$). The standard and protein snacks resulted in no nocturnal hypoglycemia at all HS glucose levels ($P < 0.001$). Only HS glucose >10 mmol/l was protective against hypoglycemia, even in the absence of a snack ($P = 0.05$); 46% of morning hyperglycemic episodes were associated ($r = 0.37$, $P = 0.07$) with this HS glucose level.

CONCLUSIONS — The need for and composition of an HS snack depends on the HS glucose such that no snack is necessary at levels >10 mmol/l. At levels between 7 and 10 mmol/l, any snack is advised, and at <7 mmol/l, a standard or protein snack is recommended.

Diabetes Care **26:9–15, 2003**

Nocturnal hypoglycemia is a significant problem for both children and adults (1–5) with both conventional and intensive management regimens (6–8). The Diabetes Control and Complications Trial indicated that ~40% of episodes of severe hypoglycemia occurred primarily overnight between midnight and 8:00 A.M. in both conventional and intensive treatment arms (6–8). The etiology of nocturnal hypoglycemia is largely related to the inadequacy of current insulin preparations to mimic normal physiology, especially during the nocturnal period, during which insulin requirements often decrease at the same time that current basal insulin preparations (NPH insulin or Ultralente) peak (9,10). Furthermore, nocturnal hypoglycemia is often asymptomatic (4,5); up to 67% of episodes go unrecognized (4,5) and are implicated in the development of hypoglycemia unawareness (11–15) and deterioration of daytime glycemic control (9). Moreover, it has recently been shown that sleep itself impairs counter-regulatory hormone secretion in response to hypoglycemia (16). Therefore, prevention of nocturnal hypoglycemia is imperative.

Although it is recommended that individuals with type 1 diabetes consume a bedtime snack to prevent nocturnal hypoglycemia, the need for a snack and its composition have largely been based on tradition rather than scientific evidence. It was not until the late 1980s that a few studies demonstrated that a bedtime snack is beneficial in reducing the incidence of nocturnal hypoglycemia in children (2,17) and adults (4) with type 1 diabetes. More recently, the scientific community began to question the impact of bedtime snack composition on nocturnal glycemic control. Studies conducted in patients with glycogen storage disease have shown that raw cornstarch can reduce the incidence of nocturnal hypoglycemia by providing a source of continuous glucose for up to 7 h (18–20). With respect to type 1 diabetes, five studies to date have demonstrated that raw cornstarch can reduce the incidence of noctur-

nal hypoglycemia in children (21–24) and adults (25). Although protein is routinely recommended in the bedtime snack of individuals with type 1 diabetes, the validity of this recommendation remains to be established. Recent studies examining the role of protein at supper (26) and the efficacy of an amino acid infusion compared with a standard bedtime snack containing protein (27) also have demonstrated a lower incidence of nocturnal hypoglycemia in adults with type 1 diabetes. Although the underlying mechanisms by which protein exerts its effect on glycemic control have yet to be fully elucidated, there is evidence to suggest that protein increases late plasma glucose response in type 1 diabetes (26–29), including overnight (26,27,29). As new insulin preparations with more physiologic kinetic profiles have become available, clinicians are beginning to question whether a bedtime snack is even necessary. Currently, use of lispro (Humalog; Eli Lilly, Indianapolis, IN) instead of regular insulin is being advocated in the management of type 1 diabetes, because studies have shown less nocturnal hypoglycemia with lispro insulin compared with regular insulin, without deterioration of long-term glycemic control (30–32), independent of basal insulin regimen (30).

Therefore, the present study was undertaken to test the hypothesis that a bedtime snack is necessary to prevent nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management despite the use of lispro insulin at supper. This study also focused on determining whether a bedtime snack composition with the potential to either provide a continuous source of glucose (uncooked cornstarch) or a delayed source of glucose (protein), especially at the time of the basal insulin peak, would result in a more favorable nocturnal glycemic profile, including a reduced incidence of nocturnal hypoglycemia compared with a conventional or standard snack. The goal of our study was to assess, in adults with type 1 diabetes undergoing intensive insulin therapy with multiple daily injections of insulin consisting of lispro insulin before meals and NPH insulin at bedtime, the impact of four bedtime (HS) snacks: placebo or no snack; standard snack; cornstarch-containing snack; and protein-rich snack, on nocturnal glycemic control. Specific

Table 1—Bedtime snack compositions

Snack	Composition	CHO (g)	Pro (g)	Fat (g)	Kcal	*TAG (g)
Placebo	Aspartame	0	0	0	0	0
Standard (control)	2 starch + 1 Pro	30	11	3	191	37
Cornstarch	1 starch + 14 g CS + 1 Pro	29	11	3	187	36
Protein	1 starch + 15 g Pro + 1 Pro	15	24	3	192	30

*TAG (total available glucose) is based on the premise that 100% of the grams of carbohydrate, 60% of the grams of protein, and 10% of the grams of fat are converted to glucose after digestion (35). All three snack conditions included the placebo drink. Pro, 1 protein exchange; Placebo, aspartame-containing orange drink; CS, cornstarch; CHO, carbohydrate. One starch exchange of the standard snack was replaced with an equivalent amount of raw cornstarch in the cornstarch condition or an equivalent amount of protein in the protein snack.

objectives of our study were *1*) to determine the nadir blood glucose concentration during the night; *2*) to determine the mean blood glucose concentration during the night (excluding baseline or bedtime value); *3*) to determine the frequency of nocturnal hypoglycemia (blood glucose <4 mmol/l); and *4*) to determine the frequency of morning hyperglycemia (blood glucose >10 mmol/l) with all four conditions.

RESEARCH DESIGN AND METHODS

Subjects and methodology
The study, undertaken at the Clinical Investigation Unit of The Royal Victoria Hospital (Montreal, Quebec, Canada), was approved by the Department of Medicine's Ethics Committee of the Royal Victoria Hospital. Most participants were referred by the Metabolic Day Center of the Royal Victoria Hospital. Adults aged 18–65 years with endocrine diagnosis of type 1 diabetes of at least 3 years, who were treated intensively with three or more injections of insulin per day for at least 1 year (including lispro insulin at supper), and had a history (at least one known episode in the last month) of nocturnal hypoglycemia were considered for inclusion in the study. Patients were excluded if they had extreme obesity (BMI >35 kg/m^2), evidence of significant hepatic or renal disease, pregnancy, or concurrent participation in another study. Participants were hospitalized four times according to their order of randomization, which was accomplished using sealed envelopes with a manually derived randomization schedule. Participants were asked to complete all four hospital study conditions with a minimum of 3

days and a maximum of 3 weeks between hospitalizations. In an attempt to minimize interruption of their usual daily routines, participants were admitted to the Clinical Investigation Unit of the Royal Victoria Hospital at 9:00 P.M., where they stayed overnight until 7:00 A.M. Upon arrival at the hospital, participants were weighed and asked to complete a 24-h general recall questionnaire about the food they ate, the amount of insulin they used, their blood glucose readings, and the type of activity they had performed during the last 24 h. Participants were also asked to complete one descriptive questionnaire regarding their history and management of hypoglycemia and were asked to keep their activity level and supper composition consistent during each visit. Adherence to these recommendations was verified at each visit via administration of the 24-h general recall questionnaire. An intravenous catheter was inserted in an antecubital vein and kept open by 0.9% saline solution for hourly blood sampling during sleep. Blood glucose was measured at 10:00 P.M. (baseline or bedtime value) because the blood glucose value at this time point has been shown to be predictive of nocturnal hypoglycemia (5,33,34). Participants took their usual dose of bedtime insulin at 10:00 P.M. and were presented with one of the following four snacks: *1*) placebo snack (aspartame-containing orange-flavored drink); *2*) standard snack, defined as two starch + one protein exchange (two slices of white bread + one ounce of cheddar cheese + placebo drink); *3*) cornstarch-containing snack (similar to standard snack except one slice of white bread was replaced with 14 g raw cornstarch dissolved in the placebo drink); *4*) protein-rich snack (similar to

Table 2—*Baseline subject characteristics*

N	9 men, 6 women
Age (years)	41 ± 12 (23–65)
Duration of diabetes (years)	23 ± 11 (8–43)
HbA$_{1c}$ (%)	8.1 ± 1.2 (6.3–10.3)
BMI (kg/m^2)	25.6 ± 4.5 (18–35)
Evening basal insulin use	$n = 11$: NPH at bedtime
	$n = 2$: Ultralente at supper
	$n = 2$: Ultralente at bedtime
Bedtime snack composition (compared with recommended standard snack†)	$n = 10$: Less ($n = 5$, no snack)
	$n = 3$: Same
	$n = 2$: More

Data are means ± SD (range). HbA$_{1c}$ normal reference range at Royal Victoria Hospital = 4–6%. Standard snack according to our clinical practice: 20–30 g carbohydrate and 1 protein exchange. †Comparisons are based on amount of carbohydrate and/or protein, whereby less, same, and more signify a lower, similar, or higher amount, respectively, of carbohydrate and/or protein compared with that of the standard snack.

standard snack except one slice of white bread was replaced with 15 g pure protein in the form of an orange-flavored drink supplied by Bariatrix [Lachine, Quebec, Canada]). All snacks contained comparable amounts of energy (kcal), fat, and total available glucose (35), as shown in Table 1. All snacks were consumed within 10 min, and the midway time point was chosen as a marker of when to start hourly blood sampling. Participants and the study nurse were blinded regarding the exact composition of the snacks. This was accomplished using an aspartame-containing orange-flavored drink (Crystal Light; Kraft Canada, Don Mills, Ontario, Canada) with each snack. The raw cornstarch (Bensons; Best Foods Canada, Etubicoke, Ontario, Canada) and protein powder were dissolved with 1 teaspoon of Crystal Light drink mix with water during the cornstarch and protein snack conditions. The crystal light mix was dissolved in water only during the standard and placebo snack conditions. The snacks were, therefore, similar in appearance and taste. Verification of blinding was performed at each visit by asking participants if they could guess the composition of their snack. Blood samples were collected every hour to measure glucose, from 11:00 P.M. until 7:00 A.M. A registered nurse and the study coordinator were on site during the night, and an endocrinologist was on call for each study.

Our primary efficacy measures, on which sample size calculations were based, were nadir glucose (the lowest glucose level attained during the night) and nocturnal hypoglycemia (whole blood glucose concentration, as measured by the Elite Glucometer [Bayer, Tarrytown, NY] of <4 mmol/l, irrespective of symptoms). Secondary efficacy measures included overnight glucose (the mean glucose level from 11:00 P.M. until 7:00 A.M.) and morning hyperglycemia (blood glucose >10 mmol/l at 7:00 A.M.). Hypoglycemic episodes were treated with glucose tablets according to hospital protocol, as described elsewhere (36). All glucose values (including values recorded after treatment of hypoglycemia) were included in the overnight glucose calculation.

Statistical analyses and power calculation

Data were analyzed using the Statistical Program for Social Sciences (SPSS version 9; SPSS, Chicago, IL). All data obtained after randomization were included in the analyses. A one-way ANOVA with Bonferroni adjustment for multiple comparisons was used to assess differences among groups for the continuous variables (nadir and overnight glucose) according to three bedtime glucose categories as follows: *1*) <7 mmol/l; *2*) 7–10 mmol/l; and *3*) >10 mmol/l. Tukey's honestly significant difference was used to identify the differences. χ^2 analysis was used to assess frequency of nocturnal hypoglycemia and morning hyperglycemia according to the three categories of HS blood glucose. Pearson product moment correlations were used to assess relationships between bedtime glucose and nadir, mean, and morning glucose concentrations. The 95% CIs and *P* values were calculated for all continuous estimates. A *P* value <0.025 was used to assess statistical significance for nadir and overnight glucose. A *P* value <0.05 represented statistical significance for all other measures.

A difference in nadir glucose of 2 mmol/l and a reduction in the frequency of hypoglycemia by at least 50% were considered clinically significant and were used to determine the sample size required to achieve a power of 80%.

RESULTS

Baseline demographic data

A total of 15 adults (9 men and 6 women) aged 23–65 years with type 1 diabetes ranging from 8 to 43 years in duration participated in this randomized, crossover, placebo-controlled trial. We conducted preliminary analyses to confirm our power calculation when we reached 15 participants, at which point we concluded that we had enough subjects to terminate the study. Most participants (9 of 15, 60%) completed all four study conditions, whereas three participants completed three conditions, two participants completed two conditions, and one participant completed one condition. The size of the groups at the end of the study were as follows: standard ($n = 13$), cornstarch ($n = 14$), protein ($n = 12$), and placebo ($n = 11$). No significant differences existed between full and partial completers. Only one participant did not continue the study after completing two conditions (cornstarch and protein) because of a negative experience (i.e., difficulty sleeping). A detailed description of the baseline characteristics of participants is shown in Table 2. Participants were weight stable and had a mean BMI of 25.6 kg/m^2 and a mean HbA$_{1c}$ of 8.2% (reference range 4–6%) at baseline. All participants took lispro insulin before meals, and most subjects (11 of 15) took NPH insulin at bedtime. All subjects took their HS insulin in accordance with their usual routine, as recommended by their respective physicians. Most of the subjects (60%) adjusted their HS insulin dose according to their bedtime blood glucose results using a sliding scale, as recommended by their physicians. A total of 10 subjects always consumed a bedtime snack, whereas 5 subjects never did. Of those who had a snack, only three subjects consumed an amount of carbohydrate and protein similar to that of the recommended standard snack. Five subjects consumed less carbohydrate and protein than the recommended standard snack, and two subjects consumed more than the standard snack. On average, the

Table 3—*Mean nadir and overnight blood glucose concentrations by bedtime category per bedtime snack condition*

	<7 mmol/l	7–10 mmol/l	>10 mmol/l
Nadir glucose			
Placebo	3.2 ± 0.5 (2.6–3.7)[a]	4.6 ± 1.0 (3.1–6.1)	8.0 ± 2.9 (3.5–12.5)
Standard	6.8 ± 1.9 (5.0–8.6)[b]	9.4 ± 0.3 (6.9–11.9)	9.7 ± 3.2 (6.3–13.0)
Cornstarch	5.8 ± 2.5 (3.2–8.4)[ab]	8.2 ± 1.0 (−1.4 to 17.7)	9.2 ± 5.2 (2.7–16.0)
Protein	6.7 ± 2.8 (3.7–9.7)[b]	8.0 ± 2.9 (0.7–15.0)	14.0 ± 1.7 (11.2–16.8)
	$P < 0.025$	$P = 0.048$	$P = 0.13$
Overnight glucose			
Placebo	5.8 ± 2.2 (5.2–6.5)[a]	6.3 ± 1.8 (5.5–7.1)[a]	10.4 ± 3.2 (8.6–12.2)[a]
Standard	9.7 ± 3.0 (8.8–10.5)[b]	10.5 ± 0.9 (9.9–11.0)[b]	11.1 ± 3.7 (10.0–12.3)[a]
Cornstarch	8.8 ± 3.9 (7.7–9.9)[b]	9.1 ± 1.2 (8.4–9.8)[b]	12.7 ± 4.8 (11.2–14.2)[a]
Protein	8.8 ± 3.2 (7.8–8.6)[b]	11.1 ± 3.9 (9.4–12.8)[b]	15.4 ± 2.4 (14.5–16.2)[b]
	$P < 0.001$	$P < 0.001$	$P < 0.001$

Data are means ± SD (95% CI) for blood glucose values in mmol/l. Average overnight glucose: ab = $P < 0.001$; nadir glucose: ab = $P < 0.025$. Within each bedtime glucose category, conditions that share the same letter are not statistically significant.

carbohydrate content of the usual bedtime snacks was 14 ± 4.5 g (range 0–60). The mean ± SE protein content was 0.53 ± 0.2 exchanges (range 0–2). Of the 10 participants who consumed a bedtime snack, 4 participants never consumed any protein in that snack.

A total of 435 blood glucose values were recorded for comparison over 50 nights. Most results were presented according to three bedtime blood glucose categories: <7 mmol/l ($n = 209$), 7–10 mmol/l ($n = 83$), and >10 mmol/l ($n = 143$). These categories were established post priori secondary to the discovery of a significant mediating effect with the efficacy measures of interest. The mean blood glucose concentrations (± SE, range) associated with these categories were as follows: <7 mmol/l (5.1 ± 0.1, 3.6–6.8); 7–10 mmol/l (8.3 ± 0.1, 7.2–10); >10 mmol/l (12.5 ± 0.1, 10.4–16.3 mmol/l).

Nadir blood glucose
There was a significant correlation between HS blood glucose and the nadir glucose ($r = 0.56$, $P < 0.001$). There was also a significant ($P < 0.05$) relationship between HS snack composition and mean nadir glucose during the night, whereby having no snack resulted in a lower mean nadir glucose compared with any snack. The mean nadir blood glucose concentrations during the night, according to the three HS categories, are shown in Table 3. The absence of a snack resulted in a lower nadir glucose value such that at an HS glucose value <7 mmol/l, the mean nadir glucose value was in the hypoglycemic range: 3.2 mmol/l (95% CI 2.6–3.7, $P < 0.05$). At HS blood glucose concentrations between 7 and 10 mmol/l, having no snack was associated ($P = 0.048$) with lower nadir glucose than with the standard and protein snacks: 4.6 (95% CI 3.1–6.1) vs. 9.4 (6.9–11.9) and 8.0 mmol/l (0.7–15.0), respectively. At >10 mmol/l, there was a trend ($P = 0.13$) indicating a lower nadir glucose value with no snack than with any snack.

Mean overnight glucose
There was a significant correlation between the bedtime blood glucose and the mean glucose during the night ($r = 0.52$, $P < 0.001$). There was also a significant ($P < 0.025$) relationship between bedtime snack composition and mean blood glucose during the night, whereby having no snack resulted in a lower mean glucose compared with having any snack across all HS glucose levels. The mean blood glucose concentrations, according to the three categories described, are shown in Table 3. At bedtime blood glucose concentrations of <7 and 7–10 mmol/l, having no snack was associated with significantly ($P < 0.001$) lower mean glucose compared with having any snack. The protein snack was significantly ($P < 0.001$) associated with the highest mean glucose compared with all other conditions at a bedtime glucose concentration >10 mmol/l.

Frequency of nocturnal hypoglycemia
A total of 14 hypoglycemic episodes occurred over 50 nights in 60% of patients, 80% of whom were asymptomatic. The mean ± SE (range) associated with these episodes was 3.4 ± 0.1 mmol/l (2.6–3.9). There was a strong trend ($P = 0.05$) between HS blood glucose and frequency of nocturnal hypoglycemia, whereby most hypoglycemic episodes (11 of 14, 79%) occurred at <7 mmol/l. Two episodes occurred at HS glucose concentrations of 7–10 mmol/l, and one episode occurred at >10 mmol/l. There was a significant relationship ($P < 0.001$) between snack composition and the frequency of nocturnal hypoglycemia, whereby most episodes (10 of 14, 71%) occurred with no snack and four episodes were associated with the cornstarch snack. No hypoglycemic episodes were associated with the standard or protein snacks at any HS glucose level. At HS glucose concentrations <7 mmol/l, most hypoglycemic episodes (8 of 11, 73%) occurred with no snack and three episodes occurred with the cornstarch snack ($P < 0.001$). Two episodes occurred at concentrations of 7–10 mmol/l with no snack ($P = 0.19$) and one episode occurred at HS glucose level >10 mmol/l with cornstarch (NS, $P = 0.50$).

Frequency of morning hyperglycemia
There was a total of 23 hyperglycemic episodes at 7:00 A.M. over 50 nights in 73% of patients. The mean ± SE (range) associated with these episodes was 14.4 ± 0.6 mmol/l (10.3–19.4). There was a trend indicating a correlation ($r = 0.37$, $P = 0.07$) between HS blood glucose and morning hyperglycemia, whereby 46% occurred at blood glucose concentrations >10 mmol/l. At HS concentrations <7 mmol/l, there were nine morning hyperglycemic episodes (38%), only two of which were preceded by hypoglycemia. A trend ($P = 0.13$) indicated that the lowest incidence of morning hyperglycemia was associated with no snack (8%) versus any snack (29% with standard and cornstarch snacks, 33% with protein snack).

Nocturnal profiles
Nocturnal profiles (or nights) containing one or more episodes of hypoglycemia, morning hyperglycemia (without nocturnal hypoglycemia), and neither one, expressed as a percentage of total nights for each snack composition according to the
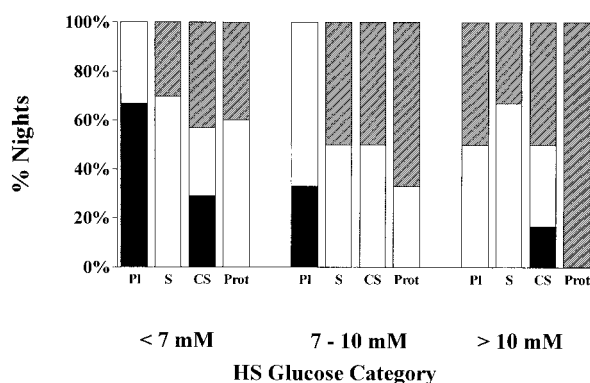
Figure 1—*Frequency of nights with hypoglycemia and morning hyperglycemia.* □, *no hypoglycemia and no morning hyperglycemia;* ■, *hypoglycemia;* ▨, *morning hyperglycemia only. Pl = placebo; S = standard snack; CS = cornstarch snack; Prot = protein snack. Data represent the percentage of nights whereby there was nocturnal hypoglycemia, morning hyperglycemia (with no nocturnal hypoglycemia), and neither one with all four snack conditions according to three categories of HS glucose.*

three categories of bedtime glucose, are shown in Fig. 1. At blood glucose concentrations <7 mmol/l, there was a strong trend ($P = 0.08$) indicating that having no snack results in 67% of nights with one or more episodes of hypoglycemia but no morning hyperglycemia. At this HS glucose concentration, both the standard and protein snacks resulted in no hypoglycemia (100% reduction) and an equivalent frequency of morning hyperglycemia (43 and 40%, respectively). At bedtime glucose concentrations of 7–10 mmol/l, having no snack resulted in 33% of nights with nocturnal hypoglycemia and no morning hyperglycemia.

All three snack compositions resulted in no nocturnal hypoglycemia at this HS glucose concentration; the standard and cornstarch snacks resulted in an equal frequency of morning hyperglycemia (50%), compared with 67% for the protein snack ($P = 0.60$). A bedtime glucose concentration >10 mmol/l resulted in no nocturnal hypoglycemia in the absence of a bedtime snack but a 50% frequency of morning hyperglycemia. The standard and cornstarch snacks resulted in morning hyperglycemia frequencies of 67 and 40%, respectively, whereas the protein snack was associated with a frequency of 100% ($P = 0.29$) at this HS glucose level.

CONCLUSIONS — Our study found that the need for a bedtime snack and the recommended composition are dependent on the blood glucose concentration at bedtime. This finding is extremely important because people living with type 1

diabetes have varying blood glucose values at bedtime, which must be taken into consideration when deciding whether, and what, bedtime snack is necessary. Despite the use of lispro insulin, only a bedtime glucose concentration >10 mmol/l was protective against nocturnal hypoglycemia in the absence of a bedtime snack. This level of 10 mmol/l is higher than that found to be protective in previous studies (5,33,34). One explanation may be the fact that other studies involved different populations, such as children (21–24, 33), or modalities of treatment, such as conventional management (34). In addition, all previous studies used regular insulin as the short-acting insulin. For bedtime blood glucose concentrations <10 mmol/l, a bedtime snack is necessary, especially when the blood glucose concentration is <7 mmol/l. A value of ~7 mmol/l has been reported as predictive of nocturnal hypoglycemia in previous studies (5,7,33,34). Both the standard and protein snacks were equally effective at this bedtime blood glucose concentration. The large, sustained increase in blood glucose that occurred with the protein snack (data not shown) was surprising and impressive. Although the mechanisms by which protein exerts its effect on glycemic response remain to be elucidated, this is likely due to the rise in plasma glucagon and/or other counterregulatory hormones as a result of feeding protein to people with type 1 diabetes (37). This is a very important observation, because there is current controversy regarding the impact and need for protein

in the bedtime snack composition of people with type 1 diabetes (38). We believe our findings, in addition to those of a previous studies (27,29), clearly demonstrate that protein is an appropriate alternative in the bedtime snack of individuals with type 1 diabetes because, for the equivalent amount of calories and less carbohydrate, the protein-rich snack was equally effective as the standard snack in preventing nocturnal hypoglycemia. Although this study was able to single out the effects of pure protein by keeping energy and nutrient composition consistent among groups, we cannot rule out the possibility of an additive or synergistic effect between protein and carbohydrate. Therefore, further research is encouraged to test the efficacy of a pure protein bedtime snack in the absence of carbohydrate. Unlike previous studies (21–25), we did not find that raw cornstarch was superior in the prevention of nocturnal hypoglycemia, especially at bedtime glucose concentrations <7 mmol/l, as evidenced by a 27% incidence of nocturnal hypoglycemia with the use of cornstarch at this HS glucose level. Cornstarch may release glucose too slowly to be effective at this level. However, at bedtime blood glucose concentrations of 7–10 mmol/l, we found that cornstarch was equally effective as the standard and protein snacks in preventing nocturnal hypoglycemia. A possible explanation for why the cornstarch snack was not more effective than the other conditions in the present study is that this is the first study to identify a mediating effect of bedtime blood glucose level and the first study in adults to compare raw cornstarch against a clearly defined "standard snack" representative of that recommended in clinical practice. For example, in two of the five previous studies (21,25), cornstarch was only compared with placebo.

Furthermore, the amount of carbohydrate contained in the standard snacks used in most previous studies (22–24) is much less than that used in the present study, which was 30 g carbohydrate for the standard snack.

In the present study, the standard snack was the only snack composition that was effective at preventing nocturnal hypoglycemia at all bedtime blood glucose levels without significantly impacting overall nighttime and morning glycemic control, especially at bedtime blood glucose concentrations <7 and

7–10 mmol/l. Because the aim of this study was to ensure minimal disruption of participants' usual routines, no attempt was made to further modify the usual insulin dose regimens, including bedtime insulin. Further research is encouraged to determine the efficacy of meticulous titration of insulin dose, in the absence of a bedtime snack, on nocturnal glycemic control.

Although the small sample size in this study limits generalizability of the findings, we feel confident, given that the results were both clinically and statistically significant, in making the following recommendations for the management of adults with type 1 diabetes treated with lispro insulin before meals, especially at supper, and NPH insulin at bedtime: no bedtime snack seems to be necessary at bedtime (10:00 P.M.) blood glucose concentrations >10 mmol/l. For bedtime blood glucose concentrations <10 mmol/l, a bedtime snack is necessary. For a bedtime blood glucose concentration of 7–10 mmol/l, a standard, cornstarch, or protein-rich snack is beneficial. For bedtime blood glucose concentrations <7 mmol/l, a standard or protein rich-snack is beneficial.

Although the addition of a small amount of protein to a bedtime snack has recently been questioned (29,38), the potential benefits for including protein far outweigh the risks of adding ~70 calories. However, applied research in an outpatient setting is encouraged to elucidate the implications of these findings with respect to energy balance and body composition. Titration of the bedtime insulin dose may be necessary at all bedtime blood glucose concentrations to minimize morning hyperglycemia; this also requires further research. Perhaps the ideal approach would be to aim for a bedtime blood glucose concentration between 7 and 10 mmol/l with inclusion of a standard snack. The application of these findings to pediatric or other populations, such as patients with type 2 diabetes, also warrants further research. Moreover, the application of these findings with the use of new insulin preparations such as Glargine and Aspart or continuous insulin infusion (CSII) also warrants further research to determine the efficacy of these recommendations under these conditions.

References
1. Gale EAM, Tattersall RB: Unrecognized nocturnal hypoglycemia in insulin-treated diabetics. *Lancet* 19:1049–1052, 1979
2. Yale JF: Hypoglycemia. In *Evidenced-Based Diabetes Care*. Gerstein HC, Haynes RB, Eds. Hamilton, Canada, BC Decker, 2001, p. 380–395
3. Bendtson I, Kverneland A, Parmming S, Binder C: Incidence of nocturnal hypoglycemia in insulin-dependent diabetic patients on intensive therapy. *Acta Med Scand* 223:543–548, 1988
4. Vervoort G, Goldschmidt HMG, Van Doorn LG: Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (≥4) daily insulin injection regimens. *Diabet Med* 3:794–799, 1996
5. Kalergis M, Aljaberi K, Schiffrin A, Meltzer S, Gougeon R, Yale JF: Frequency and duration of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive management as determined by continuous glucose monitoring (Abstract). *Can J Diabetes Care* 25:156A, 2001
6. DCCT Research Group: The effect of intensive treatment of diabetes on the development of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
7. DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 90:450–459, 1991
8. DCCT Research Group: Effect of intensive diabetes treatment in the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: diabetes control and complications trial. *J Pediatr* 125:177–187, 1994
9. Bolli GB, Fanelli CG, Perriello G, De Feo P: Nocturnal blood glucose control in type 1 diabetes mellitus. *Diabetes Care* 16:71–89, 1993
10. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142–2148, 2000
11. Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, Cryer P: Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. *Diabetes* 47:1920–1927, 1998
12. Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
13. Cryer PE: Iatrogenic hypoglycemia as a cause of hypoglycemia-associated autonomic failure in IDDM: a vicious cycle. *Diabetes* 40:255–260, 1992
14. Davis MR, Mellman M, Shamoon H: Further defects in counter-regulatory responses induced by recurrent hypoglycemia in IDDM. *Diabetes* 41:1335–1340, 1992
15. Ligenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UW, Zaiser-Kaschel H, Eggstein M, Jakober B: Compromised hormonal counter-regulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. *Diabetes* 42:610–618, 1993
16. Jones TW, Porter P, Sherwin R, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 338:1657–1662, 1998
17. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. *Diabetes Care* 12:239–244, 1989
18. Chen YT, Cornblath M, Sidbury JB: Cornstarch therapy in type I glycogen-storage disease. *N Engl J Med* 310:171–175, 1984
19. Smit GPA, Berger R, Potasnick P, Moses SW, Fernandes J: The dietary treatment of children with type 1 glycogen storage disease with slow release carbohydrate. *Pediatr Res* 18:879–881, 1984
20. Wolfsdorf JI, Crigler JF: Cornstarch regimens for nocturnal treatment of young adults with type 1 glycogen storage disease. *Am J Clin Nutr* 65:1507–1511, 1997
21. Ververs MTC, Rouwe C, Smit GPA: Complex carbohydrates in the prevention of nocturnal hypoglycemia in diabetic children. *Eur J Clin Nutr* 47:268–273, 1993
22. Kaufmann FR, Devgan S: Use of uncooked cornstarch to avert nocturnal hypoglycemia in children and adolescents with type I diabetes. *J Diabetes Complications* 10:84–87, 1996
23. Kaufmann FR, Halvorson M, Kaufmann N: A randomized, blinded trial of un-

cooked cornstarch to diminish nocturnal hypoglycemia at diabetes camp. *Diabetes Res Clin Pract* 30:205–209, 1995

24. Kaufmann F, Halvorson M, Kaufmann N: A snack bar containing uncooked cornstarch to diminish hypoglycemia (Abstract). *Diabetes* 45:200A, 1996

25. Axelsen M, Wesslau C, Lonnroth P, Arvidsonn Lenner R, Smith U: Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycemia in intensively treated type 1 diabetes subjects. *J Intern Med* 245:229–236, 1999

26. Winiger G, Keller W, Laager R, Girard J, Berger W: Protein content of the evening meal and nocturnal plasma glucose regulation in type I diabetic subjects. *Horm Res* 44:101–104, 1995

27. Saleh T, Cryer PE: Alanine and terbutaline in the prevention of nocturnal hypoglycemia in IDDM. *Diabetes* 20:1231–1236, 1997

28. Peters AL, Davidson MB: Protein and fat effects on glucose response and insulin requirements in subjects with insulin-dependent diabetes mellitus. *Am J Clin Nutr* 58:555–560, 1993

29. Hess A, Beebe CA: Glycemic effect of a small amount of protein added to an evening snack in type 1 diabetes (Abstract). *Diabetes Care* 22 (Suppl. 1):A306, 1999

30. Anderson JH, Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L, DiMarchi R, Multicentre Insulin Lispro Study Group: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 46:265–270, 1997

31. Koivisto VA: The human insulin analogue insulin lispro. *Ann Intern Med* 30:260–266, 1998

32. Heller SR, Amiel S, Mansell P, U.K. Lispro study Group: Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. *Diabetes Care* 22:1607–1611, 1999

33. Schiffrin A, Suissa S: Predicting nocturnal hypoglycemia in patients with type I diabetes treated with continuous subcutaneous insulin infusion. *Am J Med* 82:1127–1132, 1987

34. Pramming S, Thorsteinsson B, Bedtson I, Ram B, Binder C: Nocturnal hypoglycemia in patients receiving conventional treatment with insulin. *BMJ* 291:376–379, 1985

35. DCCT Research Group: Nutrition interventions for intensive therapy in the diabetes control and complications trial. *J Am Diet Assoc* 93:768–772, 1993

36. Esslinger K, Rochon G, Bonhomme S, Yale JF: Therapy of hypoglycemia by nurses on hospital wards: assessment of protocol knowledge. *Can J Diabetes Care* 25:14–21, 2001

37. Sherwin RS, Felig P: Effect of glucagon on amino acid metabolism and gluconeogenesis. In *Glucagon: Physiology, Pathophysiology, Morphology of Pancreatic A-Cells*. New York, Elsevier, 1981, p. 256–271

38. Franz MJ: Protein controversies in diabetes. *Diab Spect* 13:132–141, 2000