Original Article

OMITTING LATE-NIGHT EATING MAY CAUSE HYPOGLYCEMIA IN "WELL CONTROLLED" BASAL INSULIN-TREATED TYPE 2 DIABETES

Allen B. King, MD; Dawn Clark, ANP

ABSTRACT

Objective: To assess hypoglycemia caused by eating the last meal of the day earlier or its omission in "well controlled" type 2 diabetes mellitus patients treated with once-nightly basal insulin.

Methods: Previously basal insulin-titrated subjects (n = 20) (fasting plasma glucose, FPG, <110 mg/dL and no self-reported hypoglycemia) underwent continuous glucose monitoring (CGM) during 3 consecutive eating conditions of 3 days each; (*1*) usual eating, (*2*) the last meal restricted to 18:00, and (*3*) 1 sequential meal omitted/day thereby creating a fasting day after transposing the 4-hour period after a meal with that when the meal was omitted. One 24-hour (00:00 to 00:00) period within each eating condition was selected for comparison.

Results: The mean duration in all hypoglycemic ranges doubled (P = .0584 or greater) when the last meal was omitted or eaten at 18:09 ± 0:39 instead of 19:43 ± 1:01, the usual time for the subjects' undisturbed eating. The mean duration of hypoglycemia was greatest between 00:00 to 06:00 compared to the 3 other 6-hour periods of the day.

Conclusions: Increased hypoglycemia occurs when the subject's last meal is eaten earlier or omitted and may not be recognized because it occurs predominately during sleep. When titrating basal insulin from the morning FPG, considerations should be given to the effect of the last meal of the day and possible hypoglycemia between 00:00 and 06:00 to avoid excessive basal insulin treatment. **(Endocr Pract. 2015;21:280-285)**

Abbreviations:
A1c = glycated hemoglobin A1c; **BMI** = body mass index; **CGM** = continuous glucose monitoring; **CSII** = continuous subcutaneous insulin infusion; **FP** = fasting glucose; **FPG** = fasting plasma glucose; **Iso w/meals** = isocaloric diet with all meals consumed; **Iso w/o meals** = isocaloric diet with sequentially one meal per day omitted; **TTT** = treat-to-target trials; **Usual** = usual eating pattern

INTRODUCTION

The purpose of basal insulin is to control fasting plasma glucose (FPG) during the entire 24-hour day. In patients treated by continuous subcutaneous insulin infusion (CSII), basal FPG is assessed by frequent testing during sleep and by meal omissions during the waking day (1). Because of ease, the morning FPG is used as a surrogate for basal glucose in clinical practice and treat-to-target (TTT) trials (2). The American College of Endocrinology treatment goal for FPG is <110 mg/day yet avoiding significant hypoglycemia (3). In order to achieve this FPG goal, it has been estimated to require an average basal insulin dose >0.6 U/kg/day (4).

Late-night eating is common in type 2 diabetes, especially in insulin-treated obese subjects (5). Late and large meals increase the morning FPG (6-8) and may mislead the provider into increasing the nightly basal insulin dosage. If so, one would expect that if the late night eating was restricted, hypoglycemia would occur.

The purpose of this study was to determine the increase in hypoglycemia that may occur when the late night eating is curtailed in subjects with basal insulin-treated type 2 diabetes who appear "well controlled."

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From the Diabetes Care Center, Salinas, California.
Address correspondence to Dr. Allen King, 1260 South Main, Suite 202; Salinas, CA 93901. E-mail: aking@diabetescarecenter.com
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METHODS

In type 2 diabetes subjects previously titrated to FPG goal with once-nightly basal analog insulin, we measured the minutes that the CGM glucose was <70 mg/24 hours while on their usual undisturbed diet, an isocaloric diet with the last meal restricted to 18:00, and an isocaloric diet with sequentially 1 meal omission each day. The study was conducted according to the Declaration of Helsinki and all subjects enrolled in the study provided informed consent prior to treatment. Prior treatment with antihyperglycemic medications was permitted.

Subjects were consecutively recruited from our center if they met the inclusion criteria of age >17 years, body mass index (BMI) ≤45 kg/m^2, glycated hemoglobin A1c (A1c) ≤10%, diagnosed with type 2 diabetes, having been previously titrated on once-nightly basal analog treatment, and a mean 3-day FPG value <110 mg/dL with no self-reported hypoglycemia. Subjects were excluded if they showed evidence of urinary ketosis, expected to have an alteration in insulin sensitivity (e.g., major surgery, infection, or glucocorticoid treatment). In addition, they were excluded for renal failure (serum creatinine >1.5 mg/dL), currently participating in another clinical trial, using bolus insulin, pregnant or nursing or intending to become pregnant during the trial period, had significant liver or heart failure, or had a recent (within 2 weeks) serious hypoglycemic episode that required another person's assistance.

CGM levels were monitored using a sensor (Guardian CGM®, Medtronic, Northridge, CA) inserted into the subcutaneous tissue of the abdomen. Sensor calibration was performed by the patient with 4 self-monitored glucose meter readings (One Touch® Ultra®, LifeScan, Inc, Milpitas, CA) spaced throughout the day. Once each weekday, the sensor data was uploaded, the diet was reviewed, and hypoglycemia episodes were recorded by a nurse practitioner and certified diabetes educator during a 30-minute visit. A hypoglycemic episode was defined as a self-measured plasma glucose <70 mg/dL and typical hypoglycemic symptoms. The basal insulin analog was injected once nightly at 21:00.

Each subject was studied under 3 consecutive 3-day eating conditions (9 days total): (*1*) their usual diet in which there was no interference with meal content or timing (usual), (*2*) an isocaloric diet (50% carbohydrate, 30% fat and 20% protein) in which the last meal of the day was eaten at 18:00 and at least 4 hours after lunch (iso w/meals), and (*3*) the same but 1 meal per day omitted (dinner, lunch, and then breakfast; (iso w/o meals). The first day (00:00 to 00:00) during each of the 3 eating periods that the CGM tracing was <5% absent, the correlation coefficient between the self-monitored plasma glucose and CGM glucose was >0.79, and the subject complied with the dietary directions was selected for comparison. A fasting day (iso w/o meals) was created with the "selected" day by discarding the 4-hour postmeal CGM recording when a meal was eaten and substituting that when a meal was omitted during the other 2 iso w/o meal days. The mean number of minutes per 24 hours spent in each hypoglycemic category, (i.e., <70, <60, <50, and 40 mg/dL), was determined for each eating condition. The primary endpoint of this study was the mean number of minutes spent <70 mg/dL during each eating condition. Additional variables, including the comparison between the subject's insulin dose, U/kg, and the time of the last meal, were evaluated using a 1-tailed paired *t* test with a significance level of $P<.05$.

RESULTS

Of 21 subjects who enrolled, 1 withdrew consent, and 20 (12 females) completed the study. The baseline characteristics (mean ± SD) of the subjects were age of 58 ± 13 years, BMI of 36.6 ± 7.3 kg/m^2, HbA1C of 7.37 ± 1.16%, and diabetes duration of 9.3 ± 6.1 years. Eight subjects were on insulin glargine, and 12 were on insulin detemir, with both drugs administered once nightly. The mean basal insulin dosage was 0.52 ± 0.24 U/kg/day, and the mean of the 3-day prestudy FPG was 95 ± 10 mg/dL. The noninsulin antiglycemic therapies were metformin (13/20), sulfonylurea (12/20), dipeptidyl peptidase-4 inhibitor (4/20), thiazolidinedione (1/20), and glucagon-like peptide 1 receptor agonist (3/20).

The mean hourly CGM glucose for a 24-hour period during the usual, iso w/meals, and iso w/o meals periods are shown in Figure 1. On the usual diet, the mean CGM glucose remained higher (~40 mg/dL) than the mean of iso w/o meals during the period from 20:00 to the following morning ($P<.05$ at the mean CGM glucose at 02:00 and 04:00). The mean time for the last meal of the day was 19:43 ± 1:01 for the usual diet and 18:09 ± 0:39 for the iso w/meals. The postprandial glucose values were similar between usual undisturbed eating and iso w/ meals.

No self-reported hypoglycemic episodes occurred during monitoring while on the usual diet despite a mean of 51.8 ± 17.3 minutes spent <70 mg/dL by CGM. Seven reports of symptomatic hypoglycemia were documented while on the iso w/meals, and there were 30 reports while on the iso w/o meals. Figure 2 shows the mean number of minutes the subjects spent in each hypoglycemic category on each diet. Except for the category of <70 mg/dL, both iso w/ and w/o meals resulted in a similar number of minutes spent in each category of hypoglycemia, and these values were twice that for the usual diet in those same categories. The differences were not statistically significant ($P = .0584$, for the usual versus the iso w/o meals in the <70 mg/dL hypoglycemic category).

Dividing the 24-hour period in 6-hour intervals, the mean number of minutes spent in each interval at <70 mg/dL while the subjects were on the iso w/o meals is depicted in Figure 3. The hours between 00:00 and 06:00 had the

highest mean duration of hypoglycemia. Nearly 46% of the 24-hour period of hypoglycemia occurred during this 6-hour period.

The dose of insulin in U/kg was significantly correlated to the time the subject began their last meal while on their usual diet (r = 0.475, *P* = .0172).

DISCUSSION

Our once-nightly basal analog insulin treated subjects were "well-controlled" as evidenced by the mean morning FPG <110 mg/dL and no self-reported hypoglycemia. Their baseline characteristics were similar to other clinical

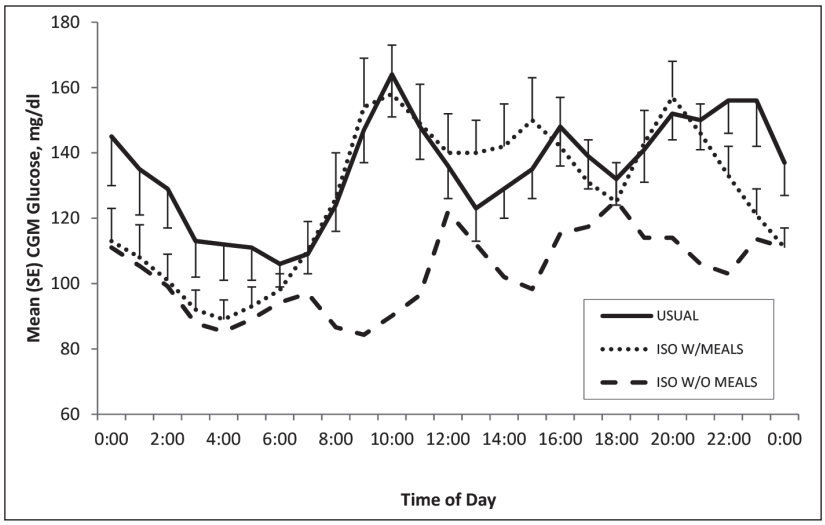

Fig. 1. The mean (± SE) hourly continuously monitored glucose over 24 hours in 20 "well-controlled" subjects with type 2 diabetes treated with once-nightly basal analog insulin at 21:00 h while on their usual diet (USUAL), isocaloric diet with the last meal at 18:00 h (ISO W/MEALS), or isocaloric diet with meals sequentially omitted (ISO W/O MEALS). For each patient, a 24-hour interval of CGM measurements was selected to represent each of two eating patterns, "usual" and "iso w/meals," and was not modified. Although a 24-hour interval was selected to represent the "iso w/o meals" eating pattern, the tracing was modified by cutting 4 hours, after each meal that was eaten, and replacing with a corresponding interval of CGM measurements from a day when that meal was omitted. By this process, an artificial 24-hour basal glucose day was created for each patient. *CGM* = continuous glucose monitoring.

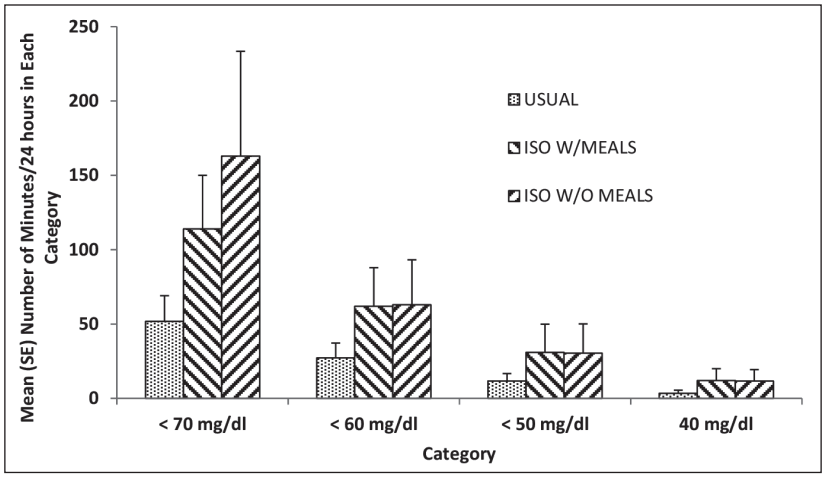

Fig. 2. The mean (± SE) number of minutes per 24-hour period spent in hypoglycemic categories in 20 "well-controlled" subjects with type 2 diabetes treated with once-nightly basal analog insulin at 21:00 h while on their usual diet (USUAL), isocaloric diet with the last meal of the day eaten at 18:00 h (ISO WITH MEALS), or the isocaloric diet with meals sequentially omitted (ISO W/O MEALS). The 4-hour period of CGM following the omitted meal was cut and pasted to create a 24-hour basal glucose day. *CGM* = continuous glucose monitoring.

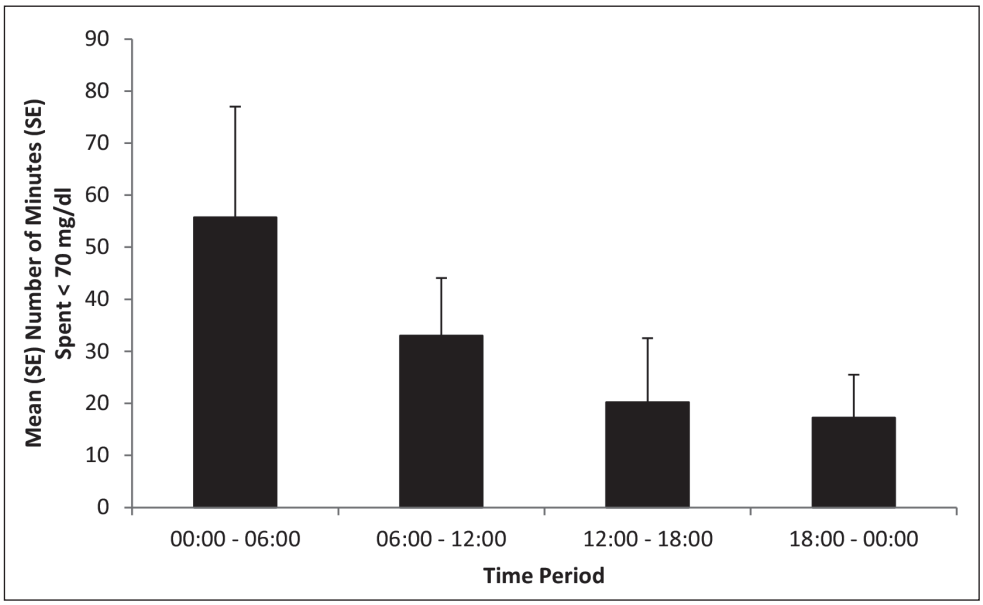

Fig. 3. The mean (± SE) number of minutes per 6-hour time period in which the CGM glucose was <70 mg/dL following injection at 21:00 h of once-nightly basal analog insulin in 20 subjects with type 2 diabetes. The subjects were on an isocaloric diet with sequential single meal per day omitted. The 4-hour period of CGM following the omitted meal was cut and pasted to create a 24-hour basal glucose day. *CGM* = continuous glucose monitoring.

basal insulin trials with regard to mean age, A1C, diabetes duration, and mean dose of insulin (9-11). Despite being "well-controlled" and not self-reporting hypoglycemia, the mean CGM glucose was <70 mg/dL for nearly 1 hour a day while on their usual undisturbed eating pattern. In a multicenter study of type 2 diabetes treated with insulin, Zick et al reported that CGM frequently detected hypoglycemia that was unrecognized by the subject (12).

The finding of the peak incidence of hypoglycemia between the hours of 00:00 and 06:00 has been previously demonstrated. In titrating once-nightly insulin glargine in a large TTT trial and achieving a mean FPG of 117 mg/dL, Riddle et al demonstrated a higher frequency of hypoglycemia during the early morning hours (9). One may assume the hypoglycemia may have been even more common than they reported since their subjects were asleep. This timing of the peak incidence may be related to the slightly higher basal analog insulin effect during its first 12 hours of action (13) and to the reduced insulin sensitivity just before the dawn phenomenon period (14). If, on the other hand, the basal insulin glargine was given in the morning and the morning FPG was still targeted, Haman et al demonstrated that in type 1 diabetes subjects, less nocturnal hypoglycemia was reported but more basal insulin was needed than when given at bedtime (15). The latter may be due to the waning basal analog insulin action on the FPG.

In a prior study in which the last meal of the day was eaten prior to 18:00, we titrated once-nightly basal insulin glargine and detemir in type 2 diabetic subjects by CGM to a mean FPG of ~100 mg/dL (16). The average basal dose was 0.27 U/kg (unpublished observation). Four of the 36 subjects entering the trial were titrated off of insulin when the last meal of the day was restricted to before 18:00. In another study, type 2 subjects were initiated on insulin pump therapy (17). Their basal rate was adjusted to achieve a basal CGM glucose of 100 mg/dL while on a controlled diet and serial meal omissions as with our current study. The mean total basal dose was 0.23 U/kg. Since the average basal insulin dose was less than half of the dose administered in TTT trials (0.6 U/kg), we would conclude that the extra insulin is for the treatment of late-meal postmeal hyperglycemia. This is further supported by our current finding of a significant association between time of the last meal of the day and the insulin dose (U/kg).

Since our subjects' insulin dose was twice that used in our diet-controlled studies, why didn't we observe more hypoglycemia when the evening meal was eaten earlier or omitted? One explanation may be that the subjects developed progressively greater insulin resistance during the prestudy upward titration of basal insulin. Shanik et al has reviewed the evidence supporting excessive insulin treatment as the cause of insulin resistance rather than the result (18). In a small study, we demonstrated that starting basal insulin titration with a larger dose (0.4 vs. 0.1 U/kg/day) resulted in about twice the amount of insulin in the former group to achieve the same FPG target but no difference in hypoglycemia (19).

In our experience, late-night eating is common in obese insulin-treated type 2 diabetes. Shereen et al (20) reported 9.7% of type 1 and 2 diabetic attendees to their clinic reported eating >25% of their calories after the evening meal and/or waking at night to eat at least 3 times a week. These same individuals had higher A1C values. In a survey of patients with type 2 diabetes from several clinics, Reutrakul et al reported that obesity, insulin use, and high A1C values were associated with the "chronotype" quartile that had a late-eating pattern (5). The average dinnertime in this study was 19:19 ± 1.30 h, which is similar to the time of the last meal in our subjects, 19:43 ± 1.01 h.

Late-night eating can be intermittent or constant. In the latter case, one would expect that the basal dose would be high in an effort to lower the "basal" FPG. If the eating is intermittent, one would expect a variable FPG. In TTT trials, we (21,22) and others (23) have reported that after the initial FPG goal is reached, FPG variability is significantly correlated with the insulin dosage increase during the time basal insulin is initiated but before upward titration begins. It is also correlated to a higher incidence of hypoglycemia and greater weight gain. These observations suggest that those individuals with highly variable FPG, perhaps due to intermittent late-night eating, have a consistent trait that is recognizable in the beginning of insulin therapy. If so, it would offer a chance to address the variability and avoid excessive insulin dosing.

Because of intense monitoring, frequent clinic visits, and diet restrictions, our study was short in duration. The subject sample size was small and from a single clinic. Despite these limitations, the subjects' baseline characteristics were similar to those of TTT clinical trials.

CONCLUSION

We conclude that without late-meal control and only targeting the morning FPG, the mean dosage in TTT trials has been excessively high. We propose that periodically restricting the last meal to 18:00 h and checking for hypoglycemia during the early morning (e.g., 00:00 to 06:00 h), might result in smaller insulin doses. The resulting lower doses in type 2 diabetic patients could reduce the weight gain and hypoglycemia associated with basal insulin therapy. This would be especially true when large basal insulin doses are given to control late-night postmeal hyperglycemia and then the evening meal is missed as in the case of fasting before a surgical procedure.

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DISCLOSURE

Dr. Allen B. King has received speaker fees, been a consultant and received research funds from Lilly, Sanofi, NovoNordisk, Medtronic, Animas, and Lifescan. Dawn Clark has no multiplicity of interest to disclose.

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