# Premeal Injection of Rapid-Acting Insulin Reduces Postprandial Glycemic Excursions in Type 1 Diabetes

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**OBJECTIVE** — To assess the effect of three premeal timings of rapid-acting insulin on postprandial glucose excursions in type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Ten subjects participated in a three-way randomized crossover trial. Mean ± SD age was 45.5 ± 12.1 years, A1C was 8.55 ± 1.50%, duration of diabetes was 23.8 ± 7.8 years, and duration of continuous subcutaneous insulin infusion therapy was 8.5 ± 6.1 years. Insulin aspart was administered at 30, 15, or 0 min before mealtime.

**RESULTS** — Area under the curve was lower in the −15 stratum (0.41 ± 0.51 mmol/l/min) than that in the −30 stratum (1.89 ± 0.72 mmol/l/min, $P = 0.029$) and 0 stratum (2.11 ± 0.66 mmol/l/min, $P = 0.030$). Maximum glucose excursion was lower in the −15 stratum (4.77 ± 0.52 mmol/l) than that in the −30 (6.48 ± 0.76 mmol/l, $P = 0.025$) and 0 stratum (6.93 ± 0.76 mmol/l, $P = 0.022$). Peak glucose level was lower in the −15 stratum (9.26 ± 0.72 mmol/l) than that in the −30 stratum (11.74 ± 0.80 mmol/l, $P = 0.007$) and the 0 stratum (12.29 ± 0.93, $P = 0.009$). Time spent in the 3.5–10 mmol/l range was higher in the −15 stratum (224.5 ± 25.0 min) than that in the 0 stratum (90.5 ± 23.2 min, $P = 0.001$). There was no significant difference in occurrence of glucose levels <3.5 mmol/l between strata ($P = 0.901$).

**CONCLUSIONS** — Administration of rapid-acting insulin analogs 15 min before mealtime results in lower postprandial glucose excursions and more time spent in the 3.5–10.0 mmol/l range, without increased risk of hypoglycemia.

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One of the most challenging aspects of attaining adequate glycemic control is limiting the postprandial raise of glucose. Current American Diabetes Association guidelines recommend aiming for postprandial blood glucose levels <10 mmol/l (1,2). With the advent of rapid-acting insulin analogs (insulin lispro, aspart, and glulisine), individuals with diabetes can attain lower postprandial glucose excursions (3–5). Therefore, because of the possibility of giving the dose of insulin at mealtime rather than 15–30 min before the meal, as was recommended for human insulin (6), rapid-acting insulin analogs have become the preferred mealtime insulin for people with type 1 diabetes (7,8).

After a meal, the postprandial glucose peak mostly occurs between 1 and 2 h with a mean peak time of 75 min (9). Rapid-acting insulin analogs display a maximum effect at ~100 min after subcutaneous injection (10). Thus, the question arises whether perhaps it would be better to inject the mealtime insulin 15 or even 30 min before the start of a meal. In this way the insulin peak action is better synchronized with the glycemic excursions after a meal, thereby potentially minimizing the height of the postprandial glucose excursions. Limited data address this topic. The aim of this study was to measure the effect of different premeal timing of rapid-acting insulin on postprandial excursions.

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## RESEARCH DESIGN AND METHODS

— Subjects were recruited from a cohort of patients willing to participate in scientific research at the Department of Internal Medicine at the Academic Medical Centre in Amsterdam, the Netherlands. The protocol was approved by the medical ethics committee, and all subjects signed a consent form. The study was performed in concordance with the Declaration of Helsinki.

Ten people with type 1 diabetes were included in this study. All patients met the inclusion criteria, treatment with continuous subcutaneous insulin infusion (CSII) therapy for at least 6 months, duration of diabetes of at least 2 years, and a BMI ≤35 kg/m$^2$. All patients were treated with insulin aspart, and four patients who were treated with insulin lispro switched to insulin aspart for the duration of this trial.

The study consisted of three visits for each subject. On the day before the 1st study day, patients were provided with a subcutaneous continuous glucose monitoring (CGM) sensor (Sof-Sensor, Medtronic Diabetes, Northridge, CA) and were instructed to calibrate the sensor at home according to the manufacturer's specifications. Patients received a telephone number with 24-h availability for assistance on problems with the sensor (e.g., alarms or help with calibration) and returned home for the night.

At each visit, insulin to cover breakfast was administered using the patient's insulin pump. The size of the insulin bolus was determined by the patient with their usual carbohydrate-to-insulin ratio. Patients were randomly assigned each day by means of sequentially numbered opaque, sealed envelopes to insulin bolus administration at 30, 15, or 0 min before the meal using a cross-over design. On each study day patients reported fasting to the clinical research unit and received an intravenous catheter in the antecubital vein for blood collection. Before the start of the study protocol blood glucose was measured by finger prick (OneTouch Ultra; Lifescan, Milpitas, CA). If blood glucose was between 3.5 and 7.8 mmol/l, the

study protocol would commence immediately. If blood glucose was higher, insulin aspart was administered intravenously according to the following formula (11): insulin aspart intravenous dose = (measured blood glucose − target blood glucose)/(100/daily insulin dose in international units).

If blood glucose had been corrected to range and remained stable (excursions <0.6 mmol/l over 1 h), the study protocol commenced. If blood glucose was too low, patients would not start the study protocol and were asked to return another day.

Each patient was provided with a breakfast comparable to their regular breakfast. The meal for an individual patient was identical for all study days. Blood was sampled every 15 min during 1 h before the meal, every 10 min during the first 2 h after the meal, and every 20 min during the 3rd and 4th h after the meal. Blood samples were collected in 2-ml sodium fluoride tubes for determination of blood glucose. Patients would go home 4 h after the test meal while continuing to wear the CGM sensor and reported back to the clinical research unit the following days to complete the study. At the end of the 3rd study day, the CGM sensor was removed, and the sensor data were plotted against the venous blood glucose.

The area under the curve (AUC) was calculated (trapezoid method) using as a baseline the mean values of the first three blood glucose values before insulin administration. The primary outcome measure was the AUC for the blood glucose values from the start of the meal until 4 h afterward. Secondary outcome measures were the AUC for the sensor glucose values, the maximum glucose excursion from baseline, the peak glucose value, the number of hypoglycemic episodes defined as glucose values <3.5 mmol/l, and total time spent in euglycemia, defined as the time spent in the glucose range between 3.5 and 10.0 mmol/l.

Outcome measures were analyzed for significance ($P < 0.05$) using SPSS 17.0 (SPSS, Chicago, IL). A repeated-measures ANOVA was performed for all outcome measures. When the repeated-measures ANOVA indicated an overall significant difference among treatment arms, a paired samples *t* test was performed between treatment arms. Categorical variables were analyzed using the $\chi^2$ test or Fisher exact test. Data are presented as means ± SEM, means ± SD, and frequency.

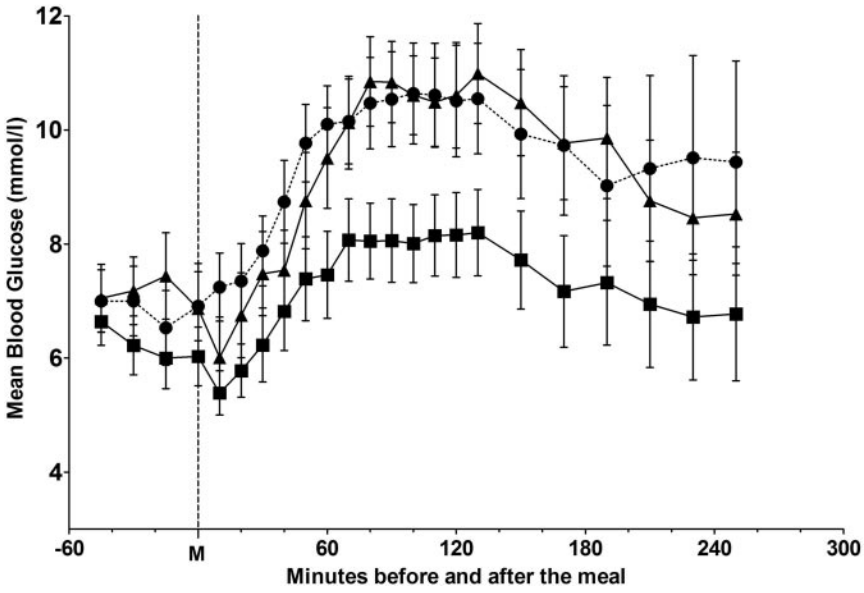


**Figure 1**—*Blood glucose during mealtime with different timing of insulin bolus. The figure shows mean ± SEM blood glucose values before and after a meal (M). The timing of the insulin bolus was 30 min before the meal (▲), 15 min before the meal (■), and directly at the start of the meal (●). The AUC, maximum excursion, and maximum blood glucose values are all significantly lower in the −15 treatment arm. The number of minutes in the 3.5–10 mmol/l glucose range is also significantly increased in the −15 treatment arm.*

**RESULTS** — All participants, three females and seven males, completed the three study visits. Mean ± SEM age was 45.5 ± 12.1 years. A1C was 8.55 ± 1.50%, duration of diabetes was 23.8 ± 7.8 years, and duration of CSII therapy was 8.5 ± 6.10 years. The mean carbohydrate content of the meal was 48.02 ± 6.23 g. The mean size of the insulin bolus was 6.03 ± 0.60 IU. There was no significant difference in blood glucose levels (mean ± SEM) at the start of the study among treatment arms (7.00 ± 0.55 mmol/l for the 0 treatment arm, 6.64 ± 0.41 mmol/l for the −15 treatment arm, and 7.05 ± 0.59 mmol/l for the −30 treatment arm, $P = 0.749$), nor was there any difference among treatment arms for the need for an intravenous insulin infusion to get glucose within the predefined range upon admittance (three times in the 0 treatment arm, three times in the −15 treatment arm, and three times in the −30 treatment arm, $P = 1.000$). Patients reported with a blood glucose value >3.5 mmol/l on all study days. According to CGM values, no patient experienced nocturnal hypoglycemia on the night before an experiment. Figure 1 shows the averaged blood glucose values from the start of the study protocol until the end of the study day per treatment arm. Primary and secondary outcome measures are summarized in Table 1 for both blood glucose and CGM data. The −15 treatment arm had a significantly lower AUC of 0.41 ± 0.51 mmol/l/min than the 0 treatment arm at an AUC of 2.11 ± 0.66 mmol/l/min ($P = 0.030$) and the −30 treatment arm, which had a AUC of 1.89 ± 0.72 mmol/l/min ($P = 0.029$). There was no significant difference in AUC between the −30 and 0 treatment arm ($P = 0.785$). In a post hoc analysis for differences in AUC among treatment arms in subgroups according to A1C level above or below the median and fasting blood glucose above or below the mean, no significant overall differences among treatment arms could be detected; however, the AUC of the −15 treatment arm remained the smallest among the three treatment arms (data not shown).

The −15 treatment arm had a significantly lower glucose excursion (4.77 ± 0.52 mmol/l) than the 0 treatment arm (6.93 ± 0.76 mmol/l, $P = 0.022$) and −30 treatment arm (6.48 ± 0.76 mmol/l, $P = 0.025$). The −15 treatment arm had significantly lower maximum blood glucose values (9.26 ± 0.72 mmol/l) than the −30 treatment arm (11.74 ± 0.80 mmol/l, $P = 0.007$) and the 0 treatment arm (12.29 ± 0.93 mmol/l, $P = 0.009$). There was no significant difference be-

**Table 1—*Summary of results for blood glucose and CGM data***

| | Treatment arm −30 | Treatment arm −15 | Treatment arm 0 | Overall *P* value (repeated-measures ANOVA)* |
|---|---|---|---|---|
| Blood glucose–derived outcomes | | | | |
| AUC (mmol/l/min) | 1.89 ± 0.72 | 0.41 ± 0.51 | 2.11 ± 0.66 | 0.043† |
| Maximum glucose excursion (mmol/l) | 6.48 ± 0.76 | 4.77 ± 0.52 | 6.93 ± 0.76 | 0.038† |
| Peak glucose level (mmol/l) | 11.74 ± 0.80 | 9.26 ± 0.72 | 12.29 ± 0.93 | 0.003† |
| Time spent in euglycemia (min)‡ | 182.5 ± 28.2 | 224.5 ± 25.0 | 90.5 ± 23.2 | 0.000† |
| Hypoglycemic events (no. of measurements)§ | 6 of 220 | 7 of 220 | 4 of 220 | 0.901 |
| CGM–derived outcomes | | | | |
| AUC (mmol/l/min) | 2.32 ± 0.59 | 1.10 ± 0.11 | 1.89 ± 0.34 | 0.088 |
| Maximum glucose (mmol/l) | 11.48 ± 1.08 | 10.11 ± 0.59 | 11.31 ± 0.82 | 0.174 |
| Maximum glucose excursion (mmol/l) | 5.24 ± 1.01 | 4.37 ± 0.64 | 5.41 ± 0.67 | 0.537 |

Data are means ± SEM. *Significance between treatment arms when repeated-measures ANOVA indicated an overall significant difference among treatment arms is given in RESULTS. †Results are significantly different among groups. ‡Defined as blood glucose values between 3.5 and 10 mmol/l. §Defined as blood glucose values <3.5 mmol/l.

tween treatment arms 0 and −30 ($P$ = 0.456).

Time spent in euglycemia was highest in the −15 treatment arm (224.5 ± 25.0 min), not significantly different from that for the −30 treatment arm (182.5 ± 28.2 min, $P$ = 0.212) but significantly higher than that for the 0 treatment arm (90.5 ± 23.2 min, $P$ = 0.000). Compared with the 0 treatment arm, the −15 treatment arm had a 80.6% lower AUC, 31.2% lower maximum blood glucose excursion, 24.7% lower maximum blood glucose value, and 148.1% more time spent in euglycemia. There was no significant difference between the occurrence of hypoglycemia defined as a blood glucose value <3.5 mmol/l among treatment arms. All hypoglycemic values were noted afterward in the laboratory report, not from the finger prick measurements during the study. None of the hypoglycemic values occurred before the start of the meal, and no rescue carbohydrates were administered during the entire duration of the study.

When we looked at the outcome measures using the data from the CGM device, no significant differences among treatment arms could be found in AUC (−30 treatment arm 2.32 ± 0.59 mmol/l/min, −15 treatment arm 1.10 ± 0.11 mmol/l/min, and 0 treatment arm 1.89 ± 0.34 mmol/l; $P$ = 0.088), maximum glucose values ($P$ = 0.174), and maximum blood glucose excursions ($P$ = 0.537). The overall mean absolute difference (MAD) from sensor values relative to the blood glucose values was 23.5 ± 1.0%. When MAD was divided into baseline MAD (the hour before administration of insulin) and postprandial MAD (the first 4 h after the meal), there was a trend toward increased MAD postprandially from 18.6 ± 1.6% in the baseline period to 22.8 ± 1.1% in the postprandial period ($P$ = 0.088). It should be noted that for this subanalysis data from study days on which patients had received an intravenous insulin correction bolus were discarded (9 of 30 study days).

**CONCLUSIONS** — This study tested the hypothesis that earlier administration of a mealtime bolus of rapid-acting insulin would lower postprandial glucose excursions. We found administration of insulin 15 min before a meal to be optimal; it significantly lowered the AUC, the postprandial maximum blood glucose value, and the maximal blood glucose excursion by 80.6, 24.7, and 31.2%, respectively. The administration of insulin 15 min before the meal led to significantly more time spent in euglycemia (3.5–10 mmol/l) than administration at the start of a meal. In addition, these beneficial effects were not accompanied by an increase in the occurrence of hypoglycemia. As can be seen in Fig. 1, however, the blood glucose declines slightly before mealtime when insulin is administered at −15 min. This finding implies that it might be prudent to administer insulin at this time only when preprandial glucose levels are >5.0 mmol/l. This study did not show any significant difference in AUC, maximum blood glucose swing, and postprandial maximum blood glucose between the −30 and 0 treatment arms, although an initial decline was noticeable in the −30 min treatment arm.

An earlier study by Cobry et al. (12), which tested the effect of insulin given 20 min before the meal, at the start of the meal, and 20 min after the meal, also found significantly better postprandial glucose control with insulin injection 20 min before the meal. In addition, a study in a pediatric population by Scaramuzza et al. (13) tested the effect of timing of mealtime insulin. Thus study also demonstrated a significant difference in 1-h postprandial glucose levels, which were significantly higher when the insulin bolus was administered after the meal and lowest when insulin was administered 15 min before the meal. However, there was no significant difference in AUC among treatment arms. Thus, three studies argue for insulin injection 15–20 min before the meal, with our study arguing against even earlier administration at 30 min before the meal.

We can only speculate on the reason that, in this study, insulin administration at −30 min did not improve postprandial glycemic control compared with that in the 0 treatment arm. One could argue that if insulin administration at 15 min before the meal is the optimum, then both −30 and 0 treatment arms had an equal 15 min mismatch with the optimum, resulting in almost equal postprandial glycemic control. Further research is needed, however, to support this hypothesis.

During this study we fitted every patient with a CGM sensor. With use of sensor data alone, we could not demonstrate any significant changes among insulin administration times. We hypothesize that this result is due to the fact that sensor accuracy is worse with rapid increases and decreases in blood glucose and therefore tends to underreport the changes in glucose levels. This hypothesis is supported by analyses of CGM accuracy by Breton et al. (14), who concluded that there is a correlation between rate of

change and CGM accuracy. This study also found that at a positive rate of change of blood glucose, the CGM sensor tends to read lower glucose values. In contrast, at a negative rate of change, the CGM sensor tends to read higher glucose values. Thus, the CGM sensor has a tendency to report flattened out postprandial excursions. The MAD of the sensor during our study was relatively high at 23.5 ± 1.0% compared with other published MAD values, with a trend toward the highest MADs in the postprandial period, confirming compromised sensor accuracy during the postprandial rapid rise and fall in glucose (15).

The data from this study could also prove valuable for use in closed-loop systems, in which dealing with the postprandial glucose excursions is one of the main challenges (16). According to our data regarding the effect of timing of insulin administration, an argument can be made for mealtime announcement by patients wearing future closed-loop devices, should these devices use current rapid-acting insulin analogs administered via CSII.

Administration of rapid acting insulin analogs 15–20 min before the meal improves postprandial glucose control but will require added vigilance of patients. Thus, larger trials outside the clinical research center are needed before this recommendation is incorporated in clinical guidelines.

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No other potential conflicts of interest relevant to this article were reported.

Y.M.L. researched data and wrote the manuscript. A.C.V.B. wrote the study protocol and reviewed/edited the manuscript. J.B.H. contributed to discussion and reviewed/edited the manuscript. J.H.D.V. supervised the protocol development and the research, contributed to discussions, and reviewed/edited the manuscript.

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