

Dietary Fat Acutely Increases Glucose Concentrations and Insulin Requirements in Patients With Type 1 Diabetes

Implications for carbohydrate-based bolus dose calculation and intensive diabetes management

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OBJECTIVE—Current guidelines for intensive treatment of type 1 diabetes base the mealtime insulin bolus calculation exclusively on carbohydrate counting. There is strong evidence that free fatty acids impair insulin sensitivity. We hypothesized that patients with type 1 diabetes would require more insulin coverage for higher-fat meals than lower-fat meals with identical carbohydrate content.

RESEARCH DESIGN AND METHODS—We used a crossover design comparing two 18-h periods of closed-loop glucose control after high-fat (HF) dinner compared with low-fat (LF) dinner. Each dinner had identical carbohydrate and protein content, but different fat content (60 vs. 10 g).

RESULTS—Seven patients with type 1 diabetes (age, 55 ± 12 years; A1C $7.2 \pm 0.8\%$) successfully completed the protocol. HF dinner required more insulin than LF dinner (12.6 ± 1.9 units vs. 9.0 ± 1.3 units; $P = 0.01$) and, despite the additional insulin, caused more hyperglycemia (area under the curve >120 mg/dL = $16,967 \pm 2,778$ vs. $8,350 \pm 1,907$ mg/dL·min; $P < 0.001$). Carbohydrate-to-insulin ratio for HF dinner was significantly lower (9 ± 2 vs. 13 ± 3 g/unit; $P = 0.01$). There were marked interindividual differences in the effect of dietary fat on insulin requirements (percent increase significantly correlated with daily insulin requirement; $R^2 = 0.64$; $P = 0.03$).

CONCLUSIONS—This evidence that dietary fat increases glucose levels and insulin requirements highlights the limitations of the current carbohydrate-based approach to bolus dose calculation. These findings point to the need for alternative insulin dosing algorithms for higher-fat meals and suggest that dietary fat intake is an important nutritional consideration for glycemic control in individuals with type 1 diabetes.

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Current guidelines for the intensive treatment of type 1 diabetes focus exclusively on carbohydrate counting for mealtime bolus calculation (1,2). This carbohydrate-based approach to insulin dose calculation assumes that carbohydrate is the only dietary macronutrient that affects glucose levels and insulin requirements.

Dietary fat and free fatty acids (FFAs) are known to impair insulin sensitivity and to enhance hepatic glucose production (3,4). Furthermore, pharmacologic interventions that lower FFA levels in nondiabetic and type 2 diabetic individuals lead to both improved insulin sensitivity and glucose tolerance (5,6). Studies in

patients with type 1 and type 2 diabetes have shown that dietary fat delays gastric emptying, leading to a lag in glucose absorption (7,8). Although there has been considerable interest in the role of dietary fat and circulating FFAs in the pathogenesis of type 2 diabetes (9,10), relatively little attention has been given to the possible implications of FFA-induced insulin resistance for the treatment of type 1 diabetes. Review of continuous glucose monitoring and food log data from our adult patients with type 1 diabetes led to the observation that, contrary to the current treatment recommendations, higher-fat meals usually require more insulin coverage than lower-fat meals with similar carbohydrate content.

Pizza is widely recognized to cause marked late postprandial hyperglycemia in patients with type 1 diabetes (11). Some studies have shown that use of an extended bolus with (12) or without (13–15) an increase in total dose is needed to attenuate hyperglycemia after higher-fat pizza meals. To our knowledge, a controlled study to determine whether changes in dietary fat intake, independent of other macronutrients, leads to alterations in glucose control and insulin requirements in type 1 diabetes has not been undertaken. In this study, we carefully regulated the macronutrient intake of patients with type 1 diabetes undergoing closed-loop glucose control to test the hypothesis that high-fat (HF) meals require more insulin coverage than low-fat (LF) meals with identical carbohydrate content.

RESEARCH DESIGN AND METHODS

Adult subjects with type 1 diabetes followed-up at the Joslin Clinic were recruited. Eligibility criteria were age 21–70 years, type 1 diabetes for >5 years, A1C $<9\%$, and insulin pump therapy for >6 months. Exclusion criteria were celiac

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disease, dietary restrictions, and gastric motility disorders. The protocol was approved by the Institutional Review Boards of the Joslin Diabetes Center and Beth Israel Deaconess Medical Center.

Study design and procedures

Each subject was admitted to the Clinical Research Center (CRC) at the Beth Israel Deaconess Medical Center for a 48-h period. The study had a cross-over design comparing two 18-h periods of closed-loop control after either an HF dinner or an LF dinner containing identical carbohydrate and protein content (Fig. 1).

Late morning the day before admission, two Abbott Freestyle Navigator (Alameda, CA) continuous glucose monitoring devices were inserted. During the morning of the admission day, subjects inserted a new pump infusion catheter. They were instructed to avoid vigorous physical activity that morning. The subjects were admitted to the CRC in the late morning, and an intravenous catheter for frequent blood sampling was inserted. The subject's pump was changed to an Animas Ping pump (West Chester, PA), and an insulin bolus was delivered with lunch. Subjects were encouraged to engage in mild to moderate physical activity during the afternoon and wore a pedometer to document activity. At 5:45 P.M. the insulin pump was changed from open-loop to closed-loop control, and at 6:00 P.M. dinner was served. Subjects were randomly assigned to have the HF dinner on day 1, followed by the LF dinner on day 2, or vice versa (Fig. 1). At 8:00 A.M. the next morning, subjects were given breakfast. Closed-loop control was continued until

12:00 P.M., when open-loop control was resumed and the subjects were provided lunch. Subjects were encouraged to have activity similar to that of the previous afternoon. As on day 1, at 5:45 P.M. closed-loop control was resumed and at 6:00 P.M. dinner was provided. At 8:00 A.M. the next morning, subjects received the identical breakfast as that served the previous day. Closed-loop control was continued until 12:00 P.M. Venous glucose levels were sampled every 20–30 min during the two periods of closed-loop control from 5:45 P.M. until 12:00 P.M. Plasma insulin levels were obtained every 20–60 min during closed-loop control.

Closed-loop control system

The closed-loop system consisted of an Abbott Navigator continuous glucose monitor, Animas Ping pump, and a physiologic insulin delivery algorithm. During the meals (breakfast, 7:45 A.M.–12:00 P.M.; dinner, 5:45 P.M.–11:00 P.M.), the physiologic insulin delivery algorithm was configured with a proportional integral component in parallel with a proportional derivative component. The proportional integral component was used to adjust basal insulin delivery up or down in proportion ($K_{P(CORR)}$) to sensor glucose (SG) above or below target (110 mg/dL) and not approaching target at a desired rate ($[SG - target]/T_I$; integration time T_I equals 60 min). The proportional derivative component was used to calculate corrective insulin in proportion (K_P) to SG above or below target, and the rate of change of SG ($K_{P(CORR)} \times T_D$; T_D equals 120 min). Proportional constants were set relative to the subject's daily insulin

requirement (DIR) ($K_{P(CORR)} = DIR/1,300$; $K_{P(BASAL)} = 0.25 \times DIR/1,300$), where DIR was set to 15, 30, or 45 units/day for subjects using <15 units/day, between 15 and 45 units/day, and >45 units/day, respectively. Approximately 15 min before the start of each meal, a meal priming bolus was administered (1, 2, or 3 units corresponding to the different DIR ranges). The basal (proportional integral) component was constrained by a piecewise continuous function to be not more than three-times the subject's maximum basal rate for $SG \geq 80$ mg/dL, and not greater than $K_{P(CORR)} \times target - 60$ for $SG < 60$ mg/dL. Insulin feedback was effected assuming an insulin pharmacokinetic/pharmacodynamic profile characterized by a three-compartment model with time constants 50, 70, and 55 min. Insulin feedback gains were chosen to reduce the affect of these delays to apparent values of 29, 41, and 32 min (16). During the night (11:00 P.M.–7:45 A.M.), the algorithm was configured with the proportional integral component in series with the proportional derivative component (T_D set to 60 min; T_I set to 30 min). Postmeal changes in insulin delivery were effected with the aid of an Excel spreadsheet (Microsoft Excel version 2010), with SG values entered into the spreadsheet each minute; changes in insulin delivery from 11:00 P.M. to 7:30 A.M. were effected using paper-based instructions with blood glucose values used to adjust the delivery rate every 30 min.

Navigator sensors were calibrated according to the prescribed device schedule. The sensor insertion time (at 12:00 P.M. the day before admission) was chosen to optimize the likelihood that the glucose level would be stable during the prescribed calibrations at 10 h and 24 h post-insertion. Plasma glucoses were measured using a YSI 2300 glucose analyzer (YSI Life Sciences, Yellow Springs, OH). Plasma insulin was measured using a chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA).

Diet intervention

Meals were prepared in the CRC metabolic kitchen and had carefully controlled macronutrient content. Total caloric content of the six meals (two breakfasts, two lunches, and two dinners) during the 48 h of the CRC admission was adjusted to meet each subject's energy requirement calculated using the Harris-Benedict equation (17). The two dinners received

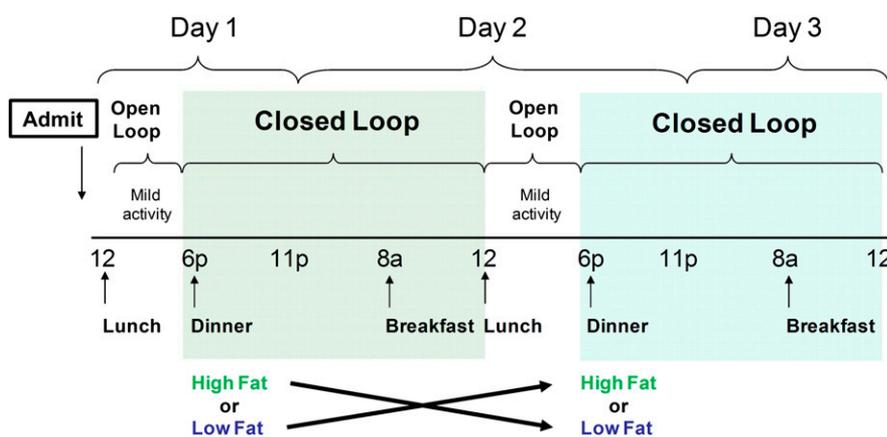


Figure 1—Closed-loop glucose control periods (shaded) starting with LF and HF dinners (10 vs. 60 g) with identical carbohydrate and protein content, and ending after identical breakfast meals. Each closed-loop period was preceded by an open-loop period with identical lunch meals and similar activity.

by each subject had identical carbohydrate and protein quantities, but they differed in fat content (10 g vs. 60 g). All subjects had the same foods for the LF dinner (grilled chicken breast, rice, broccoli, carrots, green salad, and grapes) and for the HF dinner (grilled cheese sandwich, green salad with added cheese, croutons, and grilled chicken, and orange slices). By design, the carbohydrates in the LF dinner and HF dinner had similar glycemic indexes. The lunch meals received by each subject on days 1 and 2 were identical and LF to minimize any possible carry-over effect that an HF lunch could have on the insulin requirements of the subsequent dinner. The breakfast received by each subject on days 2 and 3 were identical and LF, with high-carbohydrate load. The caloric content for breakfast and lunch was calculated to compensate for the 450-kcal difference in the two dinner meals and to keep total calories consumed during the 48-h admission equal to the subject's estimated 48-h energy requirement (Table 1). After calculating the total caloric content of the two dinner meals, the remaining calories for the admission were equally apportioned to the four remaining meals (two breakfasts and two lunches). Subjects were under direct observation during dinner and breakfast and were encouraged to have similar eating times for the matched meals. Subjects were not allowed to consume any interprandial or bedtime snacks apart from carbohydrate needed to prevent hypoglycemia and to cover the afternoon activity.

Study design considerations

The protocol was designed specifically to minimize confounding factors that could diminish the power to detect a difference in insulin requirements during the two 18-h periods of closed-loop glucose control after the HF and LF dinner meals. In addition to the identical breakfast and lunch meals, subjects were encouraged to have similar mild to moderate activity during the two afternoons of open-loop control. To minimize the potential confounding effect on insulin sensitivity of hormonal counter-regulation from hypoglycemia, the protocol included rigorous measures to minimize hypoglycemia. During the 24-h preceding admission, the two afternoon periods of open-loop control and the nocturnal period, the low alarm threshold of the continuous glucose monitoring devices were set at ≥ 90 mg/dL. In addition, during the entire CRC stay including the closed-loop

Table 1—Estimated daily energy requirements and nutritional intake

Study subject	Harris Benedict estimated daily energy requirement (Kcal)	Breakfast meal (Kcal)	Lunch meal (Kcal)	HF dinner meal (Kcal)	Total HF day (B+L+D) (Kcal)	Total HF day:		Total LF day (B+L+D) (Kcal)	Total LF day:	
						grams fat/energy (grams/%)	grams fat/energy (grams/%)		grams fat/energy (grams/%)	grams fat/energy (grams/%)
2	2,128	605	603	1,145	2,353	80/31	695	1,903	30/14	
4	2,427	765	749	1,135	2,649	80/27	690	2,204	30/12	
5	2,027	635	617	999	2,251	80/32	550	1,802	30/15	
6	1,886	562	549	999	2,110	80/34	550	1,661	30/16	
7	2,660	871	876	1,136	2,883	80/25	690	2,437	30/11	
8	1,892	568	549	999	2,116	80/34	550	1,667	30/16	
11	2,517	813	790	1,140	2,743	80/26	688	2,291	30/12	
Mean	2,220	688	676	1,079	2,444	80/30	630	1,995	30/14	
SEM	118	48	49	28	118	0/1	28	119	0/1	

The total caloric content of the diet given to each study subject during the 48-h CRC admission was 2X the Harris Benedict estimated daily energy requirement (column 2). For each study subject, the total caloric content of both the HF dinner (column 5) and LF dinner (column 8) was subtracted from the calculated total energy requirements for the 48-h admission, and the remaining calories were equally apportioned to the four remaining meals (two breakfasts and two lunches). Breakfast and lunch received by each study subject on the HF day and LF day were identical. Caloric content for the HF day (column 6) was the calories consumed from the HF dinner (column 5), breakfast (column 3), and lunch (column 4). Caloric content for the LF day (column 9) was the calories consumed from the LF dinner (column 8), breakfast (column 3), and lunch (column 4). B, breakfast; L, lunch; D, dinner.

control, carbohydrate was administered in advance of any incipient hypoglycemia.

Statistical analysis

Insulin requirements for the paired LF and HF dinner meals were calculated by summing the predinner bolus (5:45 P.M.) with closed-loop insulin delivered between 6:00 P.M. and 11:00 P.M. Insulin requirements for the two identical breakfast meals were calculated by summing the prebreakfast bolus (7:45 A.M.) with closed-loop insulin delivered between 8:00 A.M. and 12:00 P.M. Night insulin requirements after the LF and HF dinner meals were separately calculated for the period from 11:00 P.M. to 4:00 A.M. and the period from 4:00 A.M. to 8:00 A.M. (excluding 7:45 A.M. meal bolus). Changes in insulin requirement were assessed with two-way repeated-measures ANOVA, with the dinner meal fat content (low compared with high) and interval (6:00 P.M.–11:00 P.M., 11:00 P.M.–4:00 A.M., 4:00 A.M.–8 A.M., and 8:00 A.M.–12:00 P.M.) as factors. Post hoc analysis, with Bonferroni correction, was used to assess the difference in the insulin requirement for the LF dinner compared with HF dinner per se (predefined primary outcome) and insulin requirements during the subsequent night, morning, and breakfast. Other outcome measures, glucose area above target (area under the curve [AUC]_{G>120}) and insulin total AUC (AUC_{INS}), were similarly evaluated with separate two-way repeated-measures ANOVA. Regions where individual time points in the responses to HF dinner and LF dinner had 95% confidence intervals of the paired (HF – LF) responses different from zero were identified. Data are reported as mean ± SEM unless otherwise noted. Statistical analysis was performed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla CA).

RESULTS—A total of 11 studies were performed. In studies 1, 3, 9, and 10, the two successive periods of open-loop and closed-loop control were not appropriately matched because of the following: in study 1, there was an accidental interruption of basal insulin delivery in one of the afternoon open-loop periods, resulting in markedly different glucose levels at the start of the matched closed-loop periods (185 mg/dL vs. 74 mg/dL); in study 3, the subject exercised vigorously one afternoon, resulting in unmatched activity; in study 9, nausea prevented the subject from finishing dinner, resulting

in unmatched carbohydrate intake; and in study 10, a vasovagal reaction triggered by difficulties inserting an intravenous catheter resulted in incomplete data collection. Data from these subjects were excluded, with the remaining seven studies (including five men and two women) presented in this report. The demographics (mean ± SD) of these subjects are as follows: age 55 ± 12 years; diabetes duration 42 ± 6 (range, 15–60) years; A1C 7.2 ± 0.8%; total daily insulin dose 0.50 ± 0.14 (range, 0.28–0.73) units/kg; and BMI 26.3 ± 3.6 (21.5–30.6) kg/m².

By design, total calories consumed during the 2-day admission were equal to twice the per-day energy requirement, but with more calories on the HF dinner day than on the LF dinner day (2,444 ± 118 vs. 1,995 ± 119) and a higher percentage of energy derived from fat on the HF dinner day than on the LF dinner day (30 ± 1% vs. 14 ± 1%; Table 1). Each subject consumed the same amount of carbohydrates for the LF dinner and HF dinner (96 ± 8 g), and for the two identical breakfast meals (106 ± 14 g).

Glucose levels at initiation of the two 18-h periods of closed-loop control were closely matched (117.3 ± 15.2 mg/dL vs. 116.5 ± 17.4 mg/dL; Fig. 2, top panel). There were no instances of blood glucose ≤70 mg/dL in any subject at any time. HF dinner required more insulin than LF dinner (12.6 ± 1.9 vs. 9.0 ± 1.3 units; *P* = 0.01; Figs. 2, and 3, bottom panels) and, despite the additional insulin, caused more hyperglycemia (AUC >120 mg/dL = 16,967 ± 2,778 vs. 8,350 ± 1,907 mg/dL·min; *P* < 0001; Figs. 2 and 3, top panels). This resulted in elevated insulin levels 5 to 10 h after the meal (insulin AUC elevated from 11:00 P.M. to 4:00 A.M. were 9,345 ± 2,482 vs. 7,215 ± 1,802 μU/mL·min; *P* < 0.05), with levels not different in the periods 6:00 P.M.–11:00 P.M., 4:00 A.M.–8:00 A.M., and 8:00 A.M.–12:00 P.M. Calculated carbohydrate-to-insulin ratios were significantly lower for the HF meals (9 ± 2 g/unit vs. 13 ± 3 g/unit, HF dinner vs. LF dinner, respectively; *P* = 0.01). In contrast, the two breakfast meals, which had identical carbohydrate and fat content, required similar insulin coverage (Fig. 3).

HF dinner increased mean insulin requirement 42%, with marked individual differences (43, 33, 62, 28, 108, –17, and 36% for subjects 2, 4, 5, 6, 7, 8, and 11, respectively). The increase was significantly correlated with individual daily insulin requirements (*R*² = 0.64, *P* = 0.03).

No correlation was observed between the increased insulin requirement and BMI (*P* = 0.25).

CONCLUSIONS—This study suggests that adults with type 1 diabetes require more insulin coverage for higher-fat meals than for lower-fat meals with identical carbohydrate content. These findings highlight the limitations of the carbohydrate-based method for calculating meal-time insulin dosage widely used in the intensive management of type 1 diabetes. The evidence that dietary fat increases glucose concentrations suggests that dietary fat intake is an important nutritional consideration in individuals with type 1 diabetes striving for tight glycemic control.

Our findings are consistent with those of previous studies indicating that higher-fat pizza meals cause late postprandial hyperglycemia necessitating increased insulin doses (11). The time course of the increase in the glucose concentrations after the higher-fat dinner meal is in keeping with clamp studies in nondiabetic humans indicating that physiological FFA elevations lead to insulin resistance within several hours (18). The finding that the glucose and insulin profiles after the identical breakfast meals on the two successive study days were indistinguishable provides additional supporting evidence suggesting that the different profiles after the two dinners was attributable to the fat content of the meal. Differential susceptibility to fat-induced impairment of insulin sensitivity has been noted in nondiabetic individuals (19,20). Other factors, such as differences in FFA concentrations, gastric emptying rates, glucagon, or incretins, could possibly underlie the interindividual variation in the glycemic effect of dietary fat noted in our study subjects.

This evidence that dietary fat affects glycemic control has important implications for patient education and counseling. In our clinic, practical approaches to translate these findings into actionable steps to improve glycemic control are still evolving. Because of the marked interindividual differences in response to dietary fat, patient food and glucose records need to be evaluated on a case-by-case basis to determine if glucose excursions are (in part) related to consumption of higher-fat foods. This review of patient records also can help identify alternative favorite foods that have less glycemic effect. In the

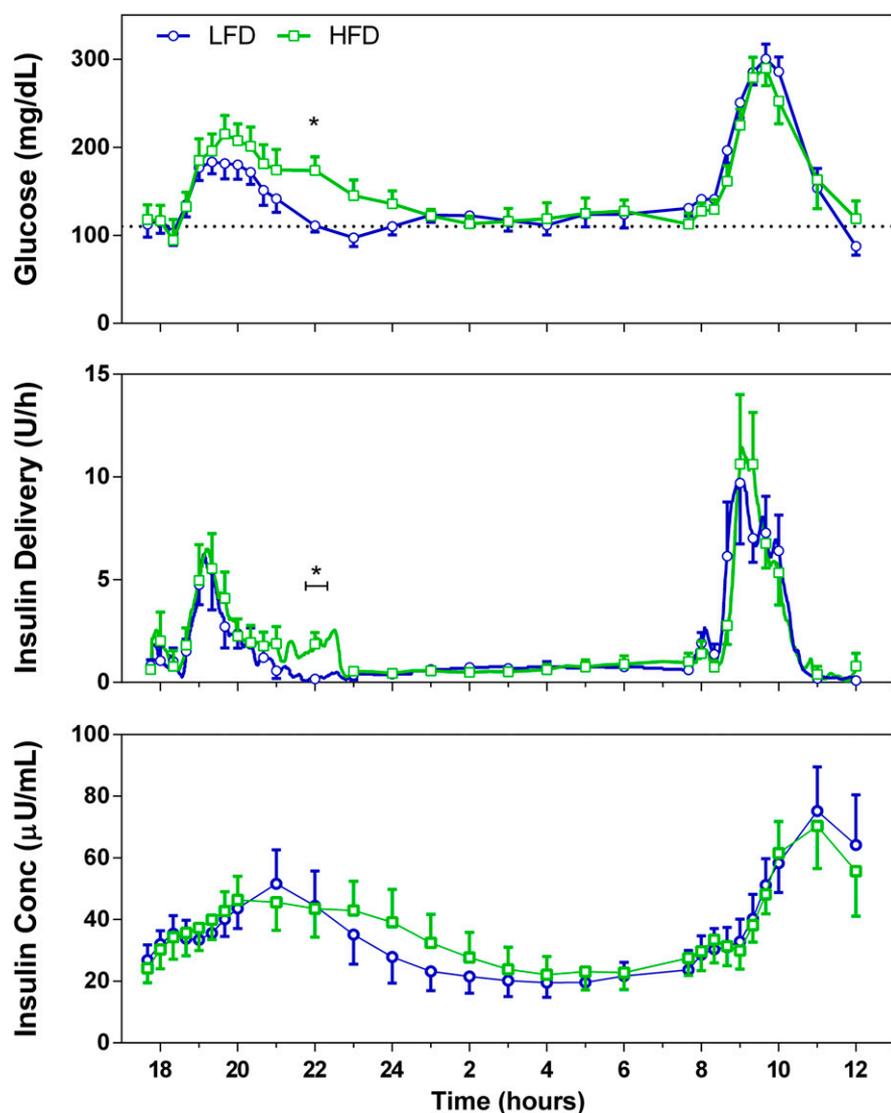


Figure 2—Top: Venous plasma glucose levels during the two 18-h periods of closed-loop insulin delivery (from 6:00 P.M. until 12:00 P.M.) after the LF diet (LFD) dinner compared with HF diet (HFD) dinner. Middle: Insulin delivery during the closed-loop control. Bottom: Insulin concentration (Conc) during the closed-loop control. *Significant ($P < 0.05$) difference in paired data.

motivated patient with type 1 diabetes, these insights, together with nutritional coaching about substituting lower-fat choices for problem foods, can lead to improved eating behavior.

Modeling the data from this study will facilitate the development of insulin dosing algorithms to adjust for the glycemic effect of dietary fat. A formula for increasing meal-time insulin doses based on the fat and protein, in addition to the carbohydrate, content of the food recently has been reported (12,21). However, this empiric formula using the patient's established carbohydrate-to-insulin ratio to calculate the additional insulin coverage for dietary fat has not been validated in a crossover study. Moreover, our data

showed no relationship between the carbohydrate-to-insulin ratio and the need for more insulin to cover the HF meal. An alternative approach for dosing meal-time insulin in type 1 diabetes, the food insulin index (FII), recently has been shown to be better than carbohydrate counting in estimating the optimal doses required to cover high-carbohydrate meals (22). The utility of the FII as a tool to calculate insulin doses for higher-fat meals has not been examined. Because FII-based dosing is calculated from insulin requirements during the initial 2-h postprandial period (23), HF foods have low calculated FII scores (i.e., low predicted insulin requirements) (24). Our findings suggest that this system therefore may

underestimate the insulin doses needed for higher-fat meals.

Although we examined a relatively small sample of individuals with type 1 diabetes, the crossover design of our study with careful control of diet and activity allowed us to readily detect the effect of dietary fat on insulin requirements. However, the small study group was heterogeneous, and further studies will be needed to determine whether age, BMI, diabetes duration, or sex underlies the differential susceptibility of individuals to dietary fat. It is noteworthy that sex-related differences in the effect of FFAs on insulin sensitivity have been noted in some (25), but not all (26), studies. Studies also will be required to determine if fat has similar effects in other patient groups including younger individuals with type 1 diabetes, individuals with type 2 diabetes, or athletes.

Several additional limitations and caveats regarding the study design and results need to be mentioned. The marked hyperglycemia after the HF dinner and large breakfast carbohydrate loads occurred despite the administration of a small priming bolus before the meals. These glucose excursions reflect the limitations of the closed-loop system, particularly delayed activation of insulin delivery attributable to sensor lag (27). Although the diet received by each study subject during the 48-h CRC admission was isocaloric, the HF dinner was more caloric than the LF dinner. Making these two dinners isocaloric while keeping carbohydrate content identical would have necessitated addition of considerable protein to the LF meal, confounding evaluation of the study hypothesis that changes in dietary fat intake, independent of other macronutrients, alter insulin requirements. Also, our study design did not allow us to determine whether the increase in insulin required to cover an HF meal is dependent on the amount of fat per se.

Studies in nondiabetic individuals indicate that saturated fats cause more profound insulin resistance than monounsaturated and polyunsaturated fats (28,29). By design, the HF dinner meal in the current study was predominantly saturated fat. Further investigations will be needed to determine the impact of foods enriched in monounsaturated and polyunsaturated fat on glycemic control in individuals with type 1 diabetes. It is noteworthy that patients with type 1 diabetes placed on an isocaloric LF diet for 3 months show improved insulin

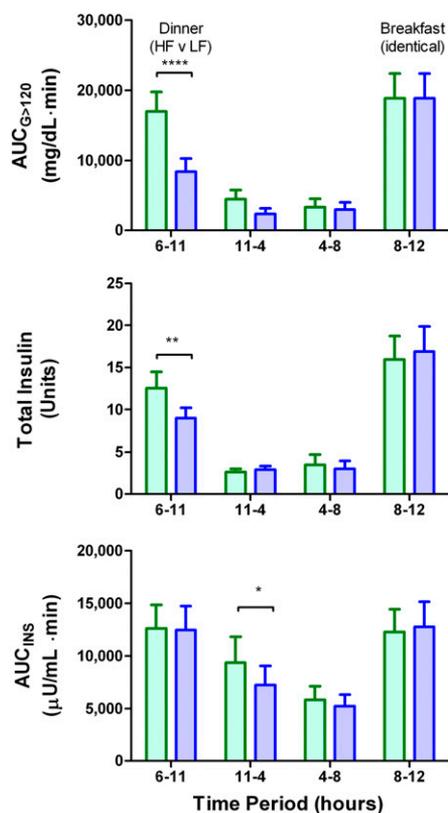


Figure 3—Top: Glucose AUC >120 mg/dL ($AUC_{G>120}$). Middle: Total insulin delivered. Bottom: Insulin AUC. Time Period, indicates clock time. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.0001$.

sensitivity (30). Furthermore, a strong association between long-term dietary fat intake and glycemic control (independent of BMI) has been noted in the intensively treated cohort followed in the Diabetes Control and Complications Trial; patients whose fat intake was in the lowest quintile (62 g fat per day) had a mean A1C 7.14% compared with A1C 7.47% in the highest quintile (120 g fat per day) (31).

To date, the major focus of closed-loop research has been on proof-of-concept studies to examine the efficacy and safety of this new technology in achieving tight glucose control in type 1 diabetes (32). In these studies there was no systematic attempt to control the macronutrient content of the diet, and meals were determined by patient choice (27,33). The current study demonstrates an additional potential application of closed-loop technology as a tool in nutrition research.

The accumulating evidence pointing to the risks associated with postprandial hyperglycemia (34) underscores the importance of targeting postprandial glucose levels. However, preventing postprandial

hyperglycemia remains one of the most challenging aspects of diabetes management. The evidence from this study that dietary fat can cause postprandial hyperglycemia in some individuals with type 1 diabetes highlights the limitations of the current carbohydrate-based approach to bolus dose calculation that is widely used in intensive diabetes management. Further studies are needed to develop and validate alternative insulin dosing algorithms for higher-fat meals, and to define new nutritional approaches for minimizing hyperglycemia induced by dietary fat.

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H.A.W. wrote the first draft of the manuscript. H.A.W., A.A.-C., S.A.S., and G.M.S. analyzed the data. A.A.-C. recruited the subjects. A.A.-C. and S.A.S. conducted the study, collected the data, and reviewed and edited the manuscript. H.A.W. and G.M.S. conceived and designed the study and supervised the closed-loop. G.M.S. set up the closed-loop and contributed to the writing of the manuscript. H.A.W. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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