Amount and Type of Dietary Fat, Postprandial Glycemia, and Insulin Requirements in Type 1 Diabetes: A Randomized Within-Subject Trial

Kirstine J. Bell,[1] Chantelle Z. Fio,[1] Stephen Twigg,[1,2] Sally-Anne Duke,[3] Gregory Fulcher,[3] Kylie Alexander,[3] Margaret McGill,[2] Jencia Wong,[2] Jennie Brand-Miller,[1] and Garry M. Steil[4,5]

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OBJECTIVE

The American Diabetes Association recommends individuals with type 1 diabetes (T1D) adjust insulin for dietary fat; however, optimal adjustments are not known. This study aimed to determine *1*) the relationship between the amount and type of dietary fat and glycemia and *2*) the optimal insulin adjustments for dietary fat.

RESEARCH DESIGN AND METHODS

Adults with T1D using insulin pump therapy attended the research clinic on 9–12 occasions. On the first six visits, participants consumed meals containing 45 g carbohydrate with 0 g, 20 g, 40 g, or 60 g fat and either saturated, monounsaturated, or polyunsaturated fat. Insulin was dosed using individual insulin/carbohydrate ratio as a dual-wave 50/50% over 2 h. On subsequent visits, participants repeated the 20–60-g fat meals with the insulin dose estimated using a model predictive bolus, up to twice per meal, until glycemic control was achieved.

RESULTS

With the same insulin dose, increasing the amount of fat resulted in a significant dose-dependent reduction in incremental area under the curve for glucose ($iAUC_{glucose}$) in the early postprandial period (0–2 h; $P = 0.008$) and increase in $iAUC_{glucose}$ in the late postprandial period (2–5 h; $P = 0.004$). The type of fat made no significant difference to the 5-h $iAUC_{glucose}$. To achieve glycemic control, on average participants required dual-wave insulin bolus: for 20 g fat, +6% insulin, 74/26% over 73 min; 40 g fat, +6% insulin, 63/37% over 75 min; and 60 g fat, +21% insulin, 49/51% over 105 min.

CONCLUSIONS

This study provides clinical guidance for mealtime insulin dosing recommendations for dietary fat in T1D.

The impact of dietary fat on glycemia has been highlighted by those living with type 1 diabetes (T1D) who, despite accurate carbohydrate counting, have found glycemic control difficult to achieve when consuming high-fat meals. Clinical research supports their experience, with dietary fat having been shown to modulate the postprandial glucose response in all seven studies included in a recent systematic review (1). We have previously shown that in adults with T1D, the addition of both fat and protein to a

[1]Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia
[2]Royal Prince Alfred Hospital Diabetes Centre, Sydney, New South Wales, Australia
[3]Royal North Shore Hospital Diabetes Centre, Sydney, New South Wales, Australia
[4]Harvard Medical School, Boston, MA
[5]Boston Children's Hospital, Boston, MA

Corresponding author: Kirstine J. Bell, kirstine.bell@sydney.edu.au

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See accompanying article, p. 13.

carbohydrate meal doubled the glycemic response over 6 h and that insulin doses need to be increased by an average of 65% to maintain glycemic control (2). Given the diabetes complications arising from poor glycemic control, improving the insulin-dosing algorithm is an important clinical priority.

The American Diabetes Association recommends that fat and protein be incorporated into mealtime insulin dosing (3); however, the optimal insulin dose adjustments for dietary fat are unclear. Important clinical questions highlighted by our international collaborative review group (1) remain unanswered and are the focus of the current study in which we aimed to *1*) determine the effect of amount and type of dietary fat on the postprandial glucose response in adults with T1D and *2*) determine the insulin dose adjustments needed to achieve postprandial glycemic control following meals of varying fat content.

We hypothesize that increasing the amount of fat in a meal will cause significantly more hyperglycemia when meals are controlled with the same insulin dose (aim 1 hypothesis) or equivalently that a meal containing more fat will require more insulin to achieve postprandial glycemic control (aim 2 hypothesis).

RESEARCH DESIGN AND METHODS

This randomized, within-subject trial compared capillary postprandial glycemia and insulin requirements for varying types and amounts of dietary fat over 5 h in adults with T1D using insulin pump therapy.

Participants were included if they were aged 18–65 years, had been diagnosed with T1D for ≥1 year, used insulin pump therapy ≥6 months, had HbA_{1c} ≤8.5% (69 mmol/mol), performed an average of four or more blood glucose checks per day, and were fluent in English. Participants were excluded if they were diagnosed with concurrent medical issues including celiac disease or gastroparesis; had food allergies, intolerances, or eating disorders; were using medication(s), other than insulin, known to influence blood glucose level (BGL); or were pregnant or lactating. Participants were recruited through Royal North Shore Hospital, Royal Prince Alfred Hospital, and advertisements at The University of Sydney, local T1D events, and through social media. The trial was approved by the Sydney Local Health District (Royal Prince Alfred Hospital zone), and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000828325).

In the 2 weeks prior to the first test meal, participants' glucose data were reviewed by the clinical team and their insulin pump rates adjusted as needed. Participants also underwent a venous blood test to determine baseline HbA_{1c}, C-peptide, cholesterol and triglycerides, and C-reactive protein to assess glycemic control, endogenous insulin secretion, baseline lipids, and inflammation, respectively. Thereafter, participants were admitted to the Charles Perkins Centre clinical research center on 9–12 occasions to complete study sessions (number of sessions was dependent on the number of attempts required to optimize glycemia). The order of test meals was randomized using a computer-generated random sequence prior to subjects beginning the study (with meals being repeated in aim 2 if target glucose control was not achieved). Test meals and target glucose control are defined below.

In the 24 h prior to each test session, participants were instructed to avoid alcohol and exercise. On the day of each session, participants were instructed to avoid, or minimize, insulin adjustments overnight to minimize differences among study days and not make any manual insulin adjustments within 3 h of commencing their session. In the case of overnight hypoglycemia, they were instructed to treat their glucose levels according to their usual practice, and their test session was rescheduled.

Participants arrived at the Charles Perkins Centre clinical research center at The University of Sydney between 7:00 and 9:00 A.M. after an overnight fast. On arrival, a baseline capillary blood glucose test was performed to confirm eligibility to commence the testing session (fasting glucose level: 4.0–10.0 mmol/L). If eligible, capillary blood samples were taken 30, 15, and 0 min prior to consumption of the test meal, with the insulin dose administered 15 min prior to consuming the meal. Participants were given 12 min to consume the test meal. Plain water was permitted ad libitum from 1 h following the test meal. No other food or drink was provided for the remainder of the test session. In the case of hypoglycemia (≤3.5 mmol/L), the test session was terminated and the participant treated appropriately. Capillary BGLs were obtained at 0 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, and 5 h using a HemoCue Glucose 201 Analyzer.

Test Meals

Test meals consisted of equal amounts of carbohydrate (pane di casa bread; 45 g carbohydrate) and varying types or amounts of dietary fat (Supplementary Table 1). Four amounts of fat (0 g, 20 g, 40 g, and 60 g fat provided as avocado) and three types of fat, which were rich in monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), or saturated fat (SFA) (all meals contained 20 g of total fat as avocado, margarine, or butter), were studied. Meals were all consumed with 250 mL of plain water.

Insulin Dosing

In aim 1, insulin doses for each participant were calculated from their insulin/carbohydrate ratio (ICR) (i.e., same dose for each meal as the amount of carbohydrate was identical). Doses were delivered 15 min prior to consuming the meal using a dual wave with a 50/50% split over 2 h in order to reduce the risk of early hypoglycemia (and thus session termination) known to occur with high-fat meals (1). For aim 2, insulin doses, including dual-wave split and duration, were estimated using a Model Predicted Bolus (MPB) estimator, as described below.

MPB

Optimal bolus amount, split, and duration for the high-fat meals was obtained with the iterative model-predictive dosing algorithm previously described (2). Briefly, a two-step approach was used. In step 1, parameters defining a metabolic model were identified from the blood glucose response obtained in aim 1 to assess the response to meals containing varying amounts of fat, obtained using the patient's ICR. In step 2, an optimal dose and dual-wave split and duration were obtained by minimizing the sum square difference between the model's predicted response for that meal and the patient's target glucose value, subject to five constraints: *1*) that hypoglycemia not be predicted at any time (i.e., nadir model predicted glucose value be >4 mmol/L), *2*) that the model predicted glucose be between −0.6 and +4.4 mmol/L from the fasting glucose

level within the first 3 h, *3*) that the model predicted glucose be between −0.6 and +2.2 mmol/L from the fasting glucose level at 4 h, *4*) that the model predicted glucose be within ±1.1 mmol/L from the fasting glucose level at 5 h, and *5*) that the model predicted insulin dose not be >1.75 times the dose used in the previous nonoptimal meal used for identification. Instances in which the MPB was thought to be too aggressive could be adjusted by the study team, provided the alternate bolus satisfied the same constraints above. If the postprandial glycemic response obtained during the test session with the MPB was not within these parameters on the first attempt, the subject returned to the clinic for a repeat meal, with dose based on model parameters estimated using all available data.

Statistical Analysis

The primary outcome was 5-h incremental area under the curve for blood glucose ($iAUC_{glucose}$). Secondary outcomes included differences in insulin dose, split, and duration needed to achieve acceptable postprandial control (aim 2), together with differences in *1*) risk of hypoglycemia (<3.5 mmol/L); *2*) absolute mean BGL; *3*) SD around mean incremental BGL; *4*) coefficient of variation (CV); *5*) J-index; and *6*) mean incremental glycemic amplitude (peak minus nadir BGL level). Based on our previous study (2), we estimated 14 participants would provide 80% power to detect a difference in 5-h $iAUC_{glucose}$ of 150 mmol/L·min. To allow a 25% margin for dropouts, a total of 20 subjects were recruited.

A general linear model with preprandial BGL as a covariate was used to analyze the parameters for the test conditions. If a session was stopped due to hypoglycemia, the incident was included in the total number of episodes of hypoglycemia and totals for fat amounts or types were compared by χ^2 test; the relative risk of hypoglycemia was expressed as a proportion of all test sessions (intention-to-treat) and was visualized using a Kaplan-Meier survival plot. A separate per-protocol analysis was performed to estimate the effect of fat amount and type on insulin requirement. Differences were considered statistically significant if P was <0.05 (two-tailed) and highly significant if P was <0.001 (two-tailed). Data are presented as mean ± SD for participant characteristics and mean ± SE for trial outcome measures.

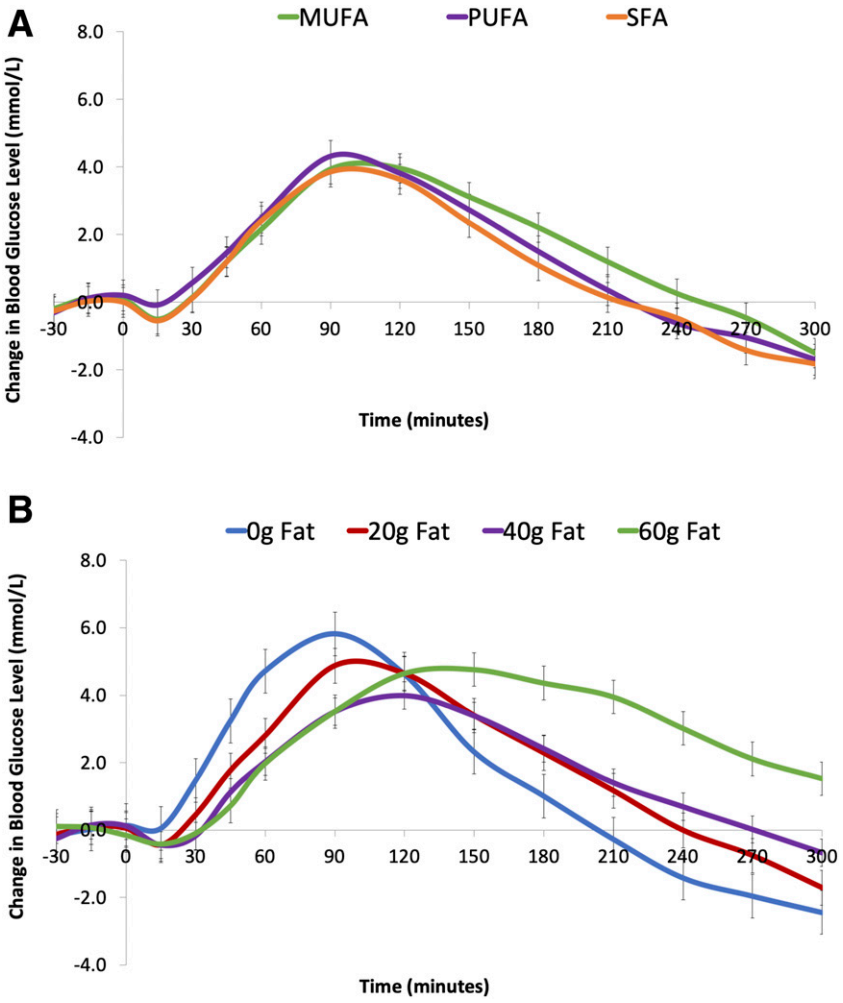

Figure 1—Postprandial glucose profiles for varying types (*A*) (n = 16) and amounts (*B*) (n = 15) of fat in adults with T1D using insulin pump therapy with insulin dosed according to individualized ICR as dual-wave 50/50% over 2 h.

RESULTS

Twenty-one adults with T1D were recruited, with two participants withdrawing prior to completing baseline measures. Of these, 14 were female and 5 were male; mean ± SD age was 37.7 ± 17.6 years, BMI 27.7 ± 5.1 kg/m^2, T1D diagnosis duration 20.7 ± 16.0 years, and insulin pump usage duration 6.0 ± 4.0 years. All participants were C-peptide negative (<0.10 nmol/L) except for 1 participant with fasting C-peptide of 0.25 nmol/L. HbA_{1c} was 7.3 ± 0.6% (57 ± 6 mmol/mol), total daily insulin dose 42.7 ± 13.5 units/day, percentage of the total daily dose as basal 52 ± 7%, ICR 8.3 ± 2.8 units/g carbohydrates, total cholesterol 5.0 ± 0.9 mmol/L, LDL cholesterol 2.9 ± 0.7 mmol/L, HDL cholesterol 1.6 ± 0.3 mmol/L, triglycerides 1.0 ± 0.9 mmol/L, and C-reactive protein 1.9 ± 2.3 mg/L. Three additional participants withdrew after completing one to two sessions (all completed a 0-g fat meal; one participant also completed the MUFA meal). All available data were included for estimating risk of hypoglycemia (intention-to-treat analysis; all subjects, all meals included). Estimates for the effect of dose and type of fat on the postprandial glucose profile (aim 1) and amount and timing of insulin required to achieve target glucose with different amount and type of fat (aim 2) were limited to subjects completing all meals (per-protocol analysis; number of subjects completing all meals reported).

Table 1—Mean postprandial glycemic responses to three types and four amounts of dietary fat in adults with T1D using insulin pump therapy with insulin dosed using individualized ICR as a dual wave

	Type of fat (n = 16)				Amount of fat (n = 15)				
	MUFA	PUFA	SFA	P value	0 g fat	20 g fat	40 g fat	60 g fat	P value
Dosing approach	ICR	ICR	ICR	—	ICR	ICR	ICR	ICR	—
Mean insulin dose (units)	6.1 ± 0.4	6.1 ± 0.4	6.1 ± 0.4	—	6.2 ± 0.4	6.2 ± 0.4	6.2 ± 0.4	6.2 ± 0.4	—
Mean insulin dual-wave split (%/%)	50/50	50/50	50/50	—	50/50	50/50	50/50	50/50	—
Mean insulin dual-wave duration (min)	120	120	120	—	120	120	120	120	—
5-h iAUC (mmol/L·min)	570 ± 115	556 ± 108	473 ± 101	0.595	613 ± 73	644 ± 115	551 ± 79	930 ± 159	0.059
0–120-min iAUC (mmol/L·min)	252 ± 54	278 ± 47	243 ± 42	0.761	409 ± 35	312 ± 59	227 ± 37	254 ± 54	0.004*
120–300-min iAUC (mmol/L·min)	435 ± 93	399 ± 87	340 ± 83	0.491	356 ± 57	473 ± 90	434 ± 66	803 ± 136	0.008*
Incremental mean BGL (mmol/L)	1.2 ± 0.4	1.1 ± 0.5	0.8 ± 0.4	0.636	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	2.3 ± 0.5	0.110
Incremental SD (mmol/L)	2.2 ± 0.3	2.3 ± 0.2	2.1 ± 0.2	0.797	2.8 ± 0.2	2.4 ± 0.3	1.9 ± 0.2	2.2 ± 0.3	0.014*
Incremental peak BGL (mmol/L)	4.6 ± 0.7	4.9 ± 0.7	4.2 ± 0.6	0.606	5.9 ± 0.4	5.3 ± 0.8	4.5 ± 0.5	5.6 ± 0.8	0.239
Time to peak (min)	118 ± 13	99 ± 7	101 ± 5	0.086	83 ± 5	104 ± 8	130 ± 6	152 ± 10	<0.001*
Nadir (mmol/L)	−1.8 ± 0.4	−1.9 ± 0.4	−2.3 ± 0.5	0.482	−2.5 ± 0.5	−1.9 ± 0.4	−1.4 ± 0.5	−0.9 ± 0.2	0.018*
Time to nadir (min)	192 ± 37	201 ± 34	180 ± 37	0.825	242 ± 22	200 ± 35	165 ± 35	78 ± 30	0.009*
CV (%)	25 ± 0	38 ± 0	36 ± 0	<0.001*	40 ± 0	38 ± 0	35 ± 0	38 ± 0	0.070
J-index	5.2 ± 1.4	5.0 ± 1.2	4.0 ± 1.3	0.530	6.6 ± 1.6	5.0 ± 1.2	4.2 ± 1.0	9.0 ± 2.5	0.130
Incremental amplitude (mmol/L)	6.5 ± 0.7	6.8 ± 0.6	6.5 ± 0.6	0.835	7.2 ± 0.8	6.8 ± 0.6	5.9 ± 0.6	6.5 ± 0.8	0.010*
Incidence of hypoglycemia [n (%)]	5 (29)	3 (18)	3 (18)	0.624⊥	7 (47)	3 (20)	1 (7)	0 (0)	<0.001*⊥

Data are mean ± SE unless otherwise indicated. *Statistically significant, $P < 0.05$. ⊥Tested by χ^2.

Type of Fat

No significant differences in 5-h $iAUC_{glucose}$ were observed for different fat types (570 ± 115, 556 ± 108, and 473 ± 101 mmol/L·min, for MUFA, PUFA, and SFA, respectively; n = 16; P = 0.595) (Fig. 1*A* and Table 1). There were no significant differences in any other blood glucose metrics except for CV ($P > 0.05$) (Table 1).

Amount of Fat

Increasing the amount of fat did not significantly alter the overall 5-h $iAUC_{glucose}$ (n = 15; P = 0.059) (Fig. 1*B* and Table 1); however, there were significant dose-response relationships when comparing the early (0–2 h; P = 0.004) and late (2–5 h; P = 0.008) response (Supplementary Fig. 1), with a significant trend for increasing dietary fat lowering the early postprandial glucose response ($P < 0.001$) and raising the late postprandial response (P = 0.001).

Adding dietary fat to carbohydrate significantly reduced the nadir BGL (P = 0.018) and brought the nadir glucose level increasingly earlier (P = 0.009). In contrast, there was no significant difference in the incremental peak BGL, but the time to peak glycemia was progressively lengthened with increasing amounts of fat ($P < 0.001$) (Table 1). The impact of increasing dietary fat on glycemic variability was less clear, with significant differences in the SD around the mean BGL (P = 0.014) and amplitude of glucose excursion (P = 0.010) but not in the CV or J-index ($P > 0.05$) (Table 1).

With increasing amounts of fat, the incidence of hypoglycemia was significantly decreased. Meal-related hypoglycemia (≤3.5 mmol/L) occurred in 47%, 20%, 7%, and 0% of participants for the 0-g, 20-g, 40-g, and 60-g fat meals, respectively (χ^2 = 11.78; $P < 0.001$).

Insulin Dosing for Fat

With the optimal insulin dose, the 5-h $iAUC_{glucose}$ was significantly reduced by 50%, 35%, and 58% for the 20-g, 40-g, and 60-g fat meals, respectively ($P < 0.001$; n = 12) (Table 2 and Fig. 2). The mean peak BGL was reduced by 24–42% ($P < 0.001$). There was also significantly less glycemic variability with the optimized insulin dose. The mean incremental amplitude was reduced by 0.9–1.6 mmol/L for the three meals (P = 0.005), the J-index was reduced by 45–75% (P = 0.003), the CV was approximately halved for all meals ($P < 0.001$), and the SD around the mean glucose level was reduced by 17–32% (P = 0.002).

To achieve these results, 2 out of 12 participants were able to achieve target glycemia following the 20-g fat meal using their usual ICR and a 50/50% dual-wave split over 2 h, 6 with the 40-g fat meal, and 2 with the 60-g fat meal. Insulin doses to achieve target glycemic control were similar for the 20-g and 40-g fat meals, with only the dual-wave proportions varying (20 g fat: +6% dose [range −64% to +29%], dual-wave 74/26% over 73 min, vs. 40 g fat: +6% dose [range −16% to +18%], dual-wave 63/37% over 75 min; n = 12). For the 60-g fat meal, the mean optimal insulin dose needed to be increased by 21% on average (range −28% to +34%; dual-wave 49/50%, 105 min).

Two participants experienced hypoglycemia (≤3.5 mmol/L) following the 20-g fat meal when using their usual ICR dual-wave bolus. Two different participants experienced mild hypoglycemia (≤3.5 mmol/L) following the 20-g fat meal after their insulin dose was adjusted. In both instances, hypoglycemia was mild and occurred in the final 30 min. No hypoglycemia occurred for the 40-g and 60-g fat meals with the optimized insulin dose. There was no statistical difference in the risk of hypoglycemia between the ICR with a dual wave and the optimized insulin dose (relative

Table 2—Mean insulin doses and postprandial glycemic responses to three amounts of dietary fat added to a carbohydrate meal in 12 adults with T1D using insulin pump therapy with insulin dosed either using individualized ICR (as a dual wave) or an MPB

	20 g fat (n = 12)		40 g fat (n = 12)		60 g fat (n = 12)		Fat amount P value	Dosing algorithm P value	P value for interaction
Dosing approach	ICR	MPB	ICR	MPB	ICR	MPB	—	—	—
Mean insulin dose (units)	6.5 ± 0.4	7.0 ± 0.8 (+6%)	6.5 ± 0.4	6.9 ± 0.5 (+6%)	6.5 ± 0.4	7.9 ± 0.8 (+21%)	0.093	0.014*	0.093
Mean insulin dual-wave split (%/%)	50/50	74/26	50/50	63/37	50/50	49/51	0.019*	0.060	0.019*
Mean insulin dual-wave duration (min)	120	73	120	75	120	105	0.088	0.019*	0.088
5-h iAUC (mmol/L·min)	664 ± 126	326 ± 80	487 ± 64	315 ± 62	867 ± 178	361 ± 81	0.044*	<0.001*	0.281
0–120-min iAUC (mmol/L·min)	305 ± 59	160 ± 38	210 ± 39	123 ± 27	229 ± 56	126 ± 36	0.078	<0.001*	0.596
120–300-min iAUC (mmol/L·min)	499 ± 103	248 ± 64	378 ± 51	271 ± 51	755 ± 156	306 ± 67	0.012*	0.002*	0.206
Incremental mean BGL (mmol/L)	1.5 ± 0.4	0.5 ± 0.3	1.1 ± 0.2	0.6 ± 0.2	2.1 ± 0.5	0.7 ± 0.3	0.089	0.001*	0.404
Incremental SD (mmol/L)	2.3 ± 0.3	1.7 ± 0.2	1.8 ± 0.2	1.5 ± 0.2	2.2 ± 0.3	1.5 ± 0.2	0.072	0.002*	0.582
Incremental peak BGL (mmol/L)	5.3 ± 0.8	3.6 ± 0.5	4.2 ± 0.5	3.2 ± 0.5	5.3 ± 0.9	3.1 ± 0.6	0.216	<0.001*	0.529
Time to peak (min)	105 ± 9	113 ± 8	130 ± 8	132 ± 8	155 ± 12	147 ± 13	0.013*	0.795	0.348
Nadir (mmol/L)	−1.7 ± 0.5	−2.0 ± 0.4	−1.4 ± 0.3	−1.5 ± 0.2	−0.9 ± 0.2	−1.6 ± 0.4	0.081	0.226	0.662
Time to nadir (min)	180 ± 41	186 ± 37	174 ± 40	177 ± 40	93 ± 36	147 ± 13	0.378	0.332	0.515
CV (%)	38 ± 0	20 ± 0	35 ± 0	16 ± 0	37 ± 0	20 ± 0	0.066	<0.001*	0.772
J-index	6.4 ± 1.6	2.2 ± 0.7	3.3 ± 0.7	1.7 ± 0.4	8.3 ± 2.9	2.1 ± 0.6	0.082	0.003*	0.168
Incremental amplitude (mmol/L)	7.0 ± 0.9	5.6 ± 0.6	5.6 ± 0.6	4.7 ± 0.5	6.3 ± 0.9	4.7 ± 0.6	0.055	0.005*	0.819
Incidence of hypoglycemia [n (%)]	2 (17)	2 (17)	1 (8)	0 (0)	0 (0)	0 (0)	—	>0.999⊥	—

Data are mean ± SE unless otherwise indicated. *Statistically significant, $P < 0.05$. ⊥Relative risk of hypoglycemia (intention-to-treat for all meals).

risk 0.941 [95% CI 0.437–1.963; $P > 0.999$]). There were no other significant adverse events.

CONCLUSIONS

The current study has two important outcomes. First, the type of fat has no statistically or clinically significant impact on postprandial glycemia, but the amount of fat has a significant, dose-dependent effect. Second, the insulin delivery pattern, and in some cases total dose, needs to be adjusted based on the amount of fat in order to minimize the risk of early postprandial hypoglycemia and late postprandial hyperglycemia. This study suggests a 75/25% split over 1 1/4 h is appropriate for a 20-g fat meal, changing to a 65/35% split over the same time period for a 40-g fat meal, and finally a 50/50% split over 1 3/4 h for a 60-g fat meal. The results suggest a threshold for dietary fat, with ~20% more insulin dose required for 60 g fat with carbohydrate. These guidelines were appropriate for a majority of participants but the interindividual variability highlights that it will be important to individualize dosing advice in clinical practice. Additional research is needed for meals of varying protein and carbohydrate contents.

These results confirm, and expand on, the literature on the impact of dietary fat in T1D. For example, Smart et al. (4) showed the addition of 35 g of dietary fat to 30 g of carbohydrate significantly increased postprandial BGL from 3 h onward. Studies investigating insulin dosing for high-fat, high-protein meals (+40 to 50 g fat) report ~40–65% more insulin is needed despite identical carbohydrate contents (2,5,6). Fat and protein have also been shown to have additive effects on glycemia (4), which may help explain why the percentage increase in insulin dose was smaller in the current study than in these previous studies. Furthermore, the dose-response relationship observed between dietary fat and glycemia but not insulin dose could be explained by the fact that exogenous insulin is not under exquisite physiological regulation, and thus the relationship is less clear in practice. As a result, exogenous insulin is able to cover a specific range of dietary fat (i.e., similar total insulin doses for 20 g and 40 g fat but not 60 g fat). The same has been shown for carbohydrate, with the same insulin dose being appropriate for a 20-g range of carbohydrate but not for a 40-g range (7,8).

In contrast to our trial, Bozzetto et al. (9) have shown that olive oil significantly reduced the early postprandial response compared with butter for a high glycemic index (GI) but not low GI meal, although both the insulin dose and meal ingredients varied among the test meals. Differences in glycemia were attributed to differences in gastric emptying and glucagon-like peptide 1 secretion (10).

Two alternate insulin-dosing algorithms have been proposed: the Food

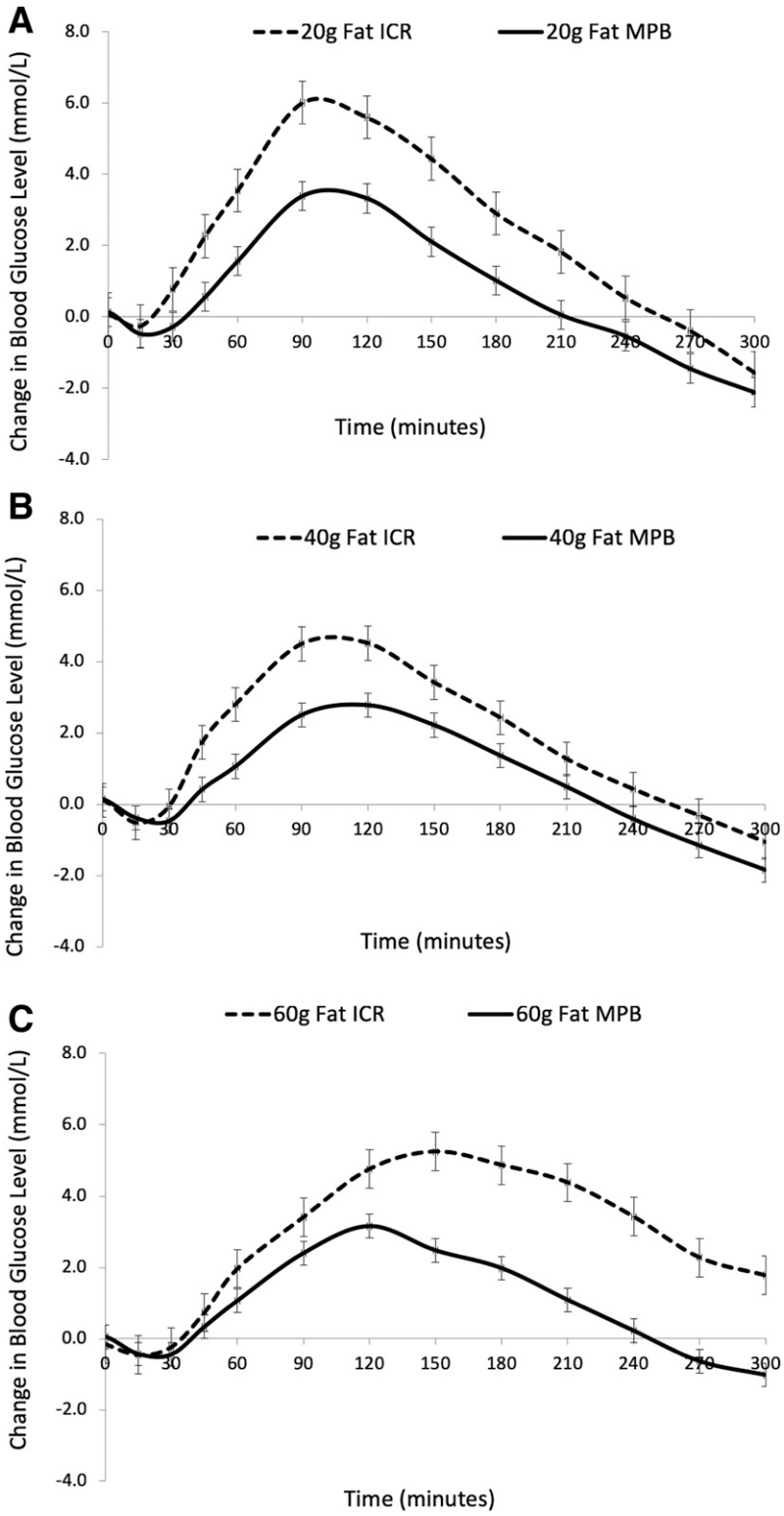

Figure 2—Postprandial glucose profiles for 20 g (*A*), 40 g (*B*), and 60 g (*C*) fat with 45 g carbohydrate in 12 adults with T1D using insulin pump therapy when insulin bolus was dosed according to their individualized ICR or with MPB.

Insulin Index (FII) (11) and the method of Pańkowska et al. (12); however, high rates of hypoglycemia are common. Comparing our individualized, meal-specific, optimized insulin dose with these algorithms, the FII underestimated the dose by 0.5 units, while the Pańkowska equation overestimated the dose by 3.7 units on average. The FII does not provide guidance on bolus type, but the Pańkowska equation recommends a dual wave over 4–8 h, a substantially longer duration than the 1 to 2 h suggested by our study.

In the current study, it was necessary to use a dual-wave bolus for all meals when assessing glycemic impact of the amount and type of fat; however, this likely underestimated the risk of early hypoglycemia and decreased the risk of late postprandial hyperglycemia for high-fat meals compared with a standard bolus. In contrast, the dual-wave likely overestimated the early postprandial response and increased risk of late postprandial hypoglycemia in the no- and low-fat meals. This latter effect may have contributed to the high risk of hypoglycemia (47%) seen with the 0-g fat meal, despite using their ICR, as insulin was still being delivered in the late postprandial period when the carbohydrate had likely already been absorbed. The reduced postprandial glycemic response seen in the first 3 h with higher-fat meals has important implications for clinical practice, as patients are often advised to self-monitor their BGL ~2 h after the meal.

Our study has strengths and limitations. One strength is the use of metabolic models to individualize the insulin doses to both the patient and the meal. Model-derived optimization allows the desired (optimal) postprandial response to be prespecified, simulated, and optimized prior to intervention in the participant. The metabolic models used are well-established models describing insulin pharmacokinetic/pharmacodynamics (13) (Bergman minimal model [14] and a two-compartment model describing rate of glucose appearance following a meal [15]), with the identification and optimization performed using readily available routines (in this study, a nonlinear generalized reduced gradient algorithm available in Microsoft Excel). The current study confirms that the approach is safe and effective, with the area under the glucose response over 5 h reduced by ~35–60% with no increased risk of hypoglycemia.

Additional strengths of this study include the within-subject trial design, 30-min glucose monitoring period prior to meal to establish glycemic stability, and the 5-h postprandial glucose monitoring period to capture the delayed

effects of fat, and the scope of dietary fat assessed reflects the range realistically consumed in a single meal (e.g., 60 g fat = 1 medium pepperoni pizza). Test meals were served with carbohydrate because fat is not usually consumed in isolation (unlike carbohydrate and protein), and the literature shows free fatty acids do not directly stimulate insulin secretion in healthy subjects; rather, they amplify glucose-stimulated insulin secretion (16). Conducting all sessions at breakfast minimized the impact of previous meals, physical activity, recent insulin boluses, stress, etc., and allowed relative differences between meals and insulin doses to be interrogated (17). However, testing meals at other times of the day may elicit different glycemic responses due to changes in circadian rhythm and insulin sensitivity.

This study was limited to participants using insulin pump therapy to allow for more precise insulin-dosing increments and for the use of the dual-wave bolus option. The results therefore need to be translated into individuals using multiple daily injections. Preliminary evidence and expert opinion have suggested giving an additional 30% insulin 3 h after the meal (18) or using a short-acting rather than rapid-acting insulin (1).

Future research should also investigate dietary protein as well as for low-carbohydrate and high- versus low-GI meals. Paterson et al. (19) have previously investigated the dose-response relationship between protein and glycemia, but the glycemic impact of varying the type of protein and the corresponding optimal insulin adjustments for protein remain unknown. Furthermore, while the available evidence suggests that the effect of fat and protein is also seen in children and adolescents and that insulin doses need to be increased by a similar proportion (4,5), current findings need to be verified in this population.

To translate these findings into clinical practice, user-friendly decision support tools are needed in order to ensure that improvements in glycemic control do not come at the expense of increased burden of disease. Given the difficulties and burden already associated with counting carbohydrate, we propose a novel bolus calculator with an integrated nutrition database would negate the need for any in-depth nutrition knowledge, counting multiple macronutrients, or complex calculations. Alternatively, optimized bolus algorithms for dietary fat could be preprogramed into insulin pumps. This research also has the potential to enhance the effectiveness of future control-to-range closed-loop or hybrid glucose control platforms as part of artificial pancreas systems. Almost all artificial pancreas systems include a premeal bolus; however, mealtime glucose control remains challenging, and little research has been conducted on how to optimize the premeal bolus. This project provides mathematical modeling of postprandial glucose responses to meals of varying macronutrient composition, including model analysis of the effect of the meal per se to alter metabolic parameters such as insulin sensitivity. Incorporation of this information into future hybrid artificial pancreas systems has the potential to enhance their effectiveness and improve diabetes health outcomes.

In conclusion, this study shows that while the type of fat has no demonstrated impact on the glycemic response, the amount of fat has a dose-response relationship with postprandial glycemia and that mealtime insulin doses need to be increased by up to 20% for high-fat meals and dosed as a dual wave to optimize the glycemic response. These clinically significant enhancements in glucose control and reduced glycemic variability may offer people greater well-being through a reduced burden of disease and decreased risk of long-term diabetes complications.

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References

1. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015
2. Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized mealtime insulin dosing for fat and protein in type 1 diabetes: application of a model-based approach to derive insulin doses for open-loop diabetes management. Diabetes Care 2016;39:1631–1634
3. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S90–S102
4. Smart CEM, Evans M, O'Connell SM, et al. Both dietary protein and fat increase postprandial glucose excursions in children with type 1 diabetes, and the effect is additive. Diabetes Care 2013;36:3897–3902
5. Smith T, Fuery M, Knight B, et al. In young people using insulin pump therapy an additional sixty percent of the mealtime insulin dose improves postprandial glycaemia following a high fat, high protein meal (Abstract). Pediatr Diabetes 2018;19:131–132
6. Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM. 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. Diabetes Care 2013;36:810–816
7. Smart CE, King BR, McElduff P, Collins CE. In children using intensive insulin therapy, a 20-g variation in carbohydrate amount significantly impacts on postprandial glycaemia. Diabet Med 2012;29:e21–e24
8. Smart CE, Ross K, Edge JA, Collins CE, Colyvas K, King BR. Children and adolescents on intensive insulin therapy maintain postprandial glycaemic control without precise carbohydrate counting. Diabet Med 2009;26:279–285
9. Bozzetto L, Alderisio A, Giorgini M, et al. Extra-virgin olive oil reduces glycemic response to a high-glycemic index meal in patients with type 1 diabetes: a randomized controlled trial. Diabetes Care 2016;39:518–524
10. Bozzetto L, Alderisio A, Clemente G, et al. Gastrointestinal effects of extra-virgin olive oil associated with lower postprandial glycemia in type 1 diabetes. Clin Nutr 2019;38:2645–2651
11. Bell KJ, Gray R, Munns D, et al. Estimating insulin demand for protein-containing foods using the food insulin index. Eur J Clin Nutr 2014;68:1055–1059
12. Pańkowska E, Błazik M, Groele L. Does the fat-protein meal increase postprandial glucose level in type 1 diabetes patients on insulin pump: the conclusion of a randomized study. Diabetes Technol Ther 2012;14:16–22
13. Sherwin RS, Kramer KJ, Tobin JD, et al. A model of the kinetics of insulin in man. J Clin Invest 1974;53:1481–1492
14. Caumo A, Bergman RN, Cobelli C. Insulin sensitivity from meal tolerance tests in normal

subjects: a minimal model index. J Clin Endocrinol Metab 2000;85:4396–4402
15. Wilinska ME, Chassin LJ, Acerini CL, Allen JM, Dunger DB, Hovorka R. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. J Diabetes Sci Technol 2010;4:132–144
16. Haber EP, Procópio J, Carvalho CR, Carpinelli AR, Newsholme P, Curi R. New insights into fatty acid modulation of pancreatic beta-cell function. Int Rev Cytol 2006;248:1–41
17. Leung GKW, Huggins CE, Bonham MP. Effect of meal timing on postprandial glucose responses to a low glycemic index meal: a crossover trial in healthy volunteers. Clin Nutr 2019;38:465–471
18. Campbell MD, Walker M, King D, et al. Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate, high-fat meal in type 1 diabetes. Diabetes Care 2016;39:e141–e142
19. Paterson MA, Smart CE, Lopez PE, et al. Influence of dietary protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus using intensive insulin therapy. Diabet Med 2016;33:592–598