Beyond Insulin to Carb Ratio- The Impact of Dietary Fat and Protein on Postprandial Glycemia and Implications for Mealtime dosing in Patients with Type 1 Diabetes

By

Julie Alexandra Hooper

The University of North Carolina at Chapel Hill
Gillings School of Global Public Health

A paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Department of Nutrition

December 5, 2019

Approved by: Elizabeth Mayer-Davis

Date: December 4, 2019

Abstract

Despite a growing understanding of the impact of fat and protein on post-prandial blood glucose levels, current medical nutrition therapy for treatment of type 1 diabetes continues to focus primarily on carbohydrate counting for mealtime bolus calculation. Standards of care practice guidelines suggest increasing mealtime dose for meals high in fat and/or protein, but do not provide specific guidelines on adjustment of insulin dose and timing for high fat and/or protein meals. There is no recommended macronutrient breakdown for patients with type 1 diabetes, who may follow a variety of diets and dietary patterns. Both low carbohydrate diets and higher carbohydrate plant-based diets have increased in popularity over recent years, revealing variability in individual response to diet composition and the role of various dietary components beyond solely carbohydrate content on glycemic control. Variability in response to various dietary components suggests the need for individually tailored dietary education to develop effective mealtime dosing strategies that improve glycemic control within the context of each individual's dietary preferences and responses. Therefore, this review examines recent research on the impact of dietary fat and protein on post-prandial blood glucose, discusses the current evidence for different mealtime dosing strategies that account for dietary fat and protein, and suggests critical areas for future work with the goal of improving postprandial blood glucose in patients with type 1 diabetes.

Keywords: *Type 1 diabetes, fat, protein, insulin dose, carbohydrate counting, mealtime*

Introduction

Despite a growing consensus that dietary fat and protein impact post-prandial blood glucose levels, current medical nutrition therapy for treatment of type 1 diabetes continues to focus solely on carbohydrate-counting for mealtime bolus calculation. A 2015 systematic review on the impact of fat and protein on postprandial blood glucose control in patients with type 1 diabetes concluded that both fat and protein significantly modified postprandial glycemia in all studies included in the review, and recommended that mealtime insulin doses be adjusted based on the complete composition of meals rather than solely on carbohydrate content.(1)

Since 2015, CGM use has increased by 23% and an automated insulin system has been approved in the United States, allowing for increased insight into dose adjustment for dietary fat and protein.(2) As continuous glucose monitoring becomes standard of care for type 1 diabetes management, and hybrid closed-loop systems become increasingly available, in-range postprandial blood glucose levels may become more feasible.

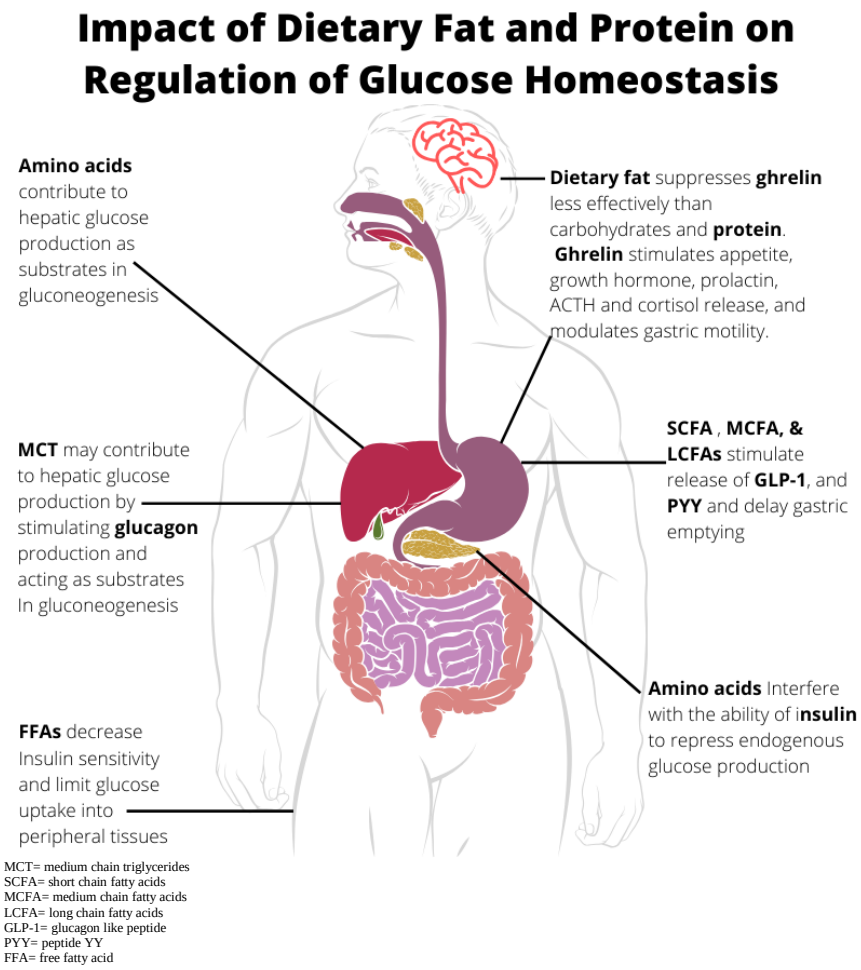
Recent standards of care practice guidelines have suggested increasing mealtime dose for meals high in fat and/or protein, but do not provide specific guidelines on dose adjustment and dose timing for high fat or protein meals.(3) The 2019 ADA consensus report on nutrition therapy for adults with diabetes or prediabetes states that, "When consuming a mixed meal that contains carbohydrate and is high in fat and/or protein, insulin dosing should not be based solely on carbohydrate counting. A cautious approach to increasing mealtime insulin doses is suggested; continuous glucose monitoring (CGM) or self-monitoring of blood glucose (SMBG) should guide decision-making for administration of additional insulin."(4) However, adjusting mealtime insulin dose to account for complete meal composition is complex, highly variable based on individual response, and therefore rarely incorporated into clinical practice.

The availability of new technology has allowed for the development and testing of different strategies for mealtime insulin dosing that account for macronutrient composition; however, to our knowledge, no studies have considered the potential translation of these dosing models within the context of what is currently understood about the glycemic response to dietary fat and protein, individual variability, and various commercially available insulin delivery systems. While glycemic index (GI) and glycemic load (GL) have also been indicated in postprandial glycemic response, this review focuses on the effects of fat and protein, and does not specifically address the impact of different types of carbohydrate on postprandial glycemia. Therefore, the purpose of this review is to address the following questions: what is known about how fat and protein impact blood glucose; what effects do fat, protein, and mixed meals have on postprandial blood glucose levels in people with type 1 diabetes; what new dosing models have been proposed; and what are critical areas for future work and implications for clinical practice.

Current Status of Knowledge

I. Proposed Mechanisms of Dietary Fat and Protein Impact on Blood Glucose

Figure 1-



Dietary fat and protein impact blood glucose through a variety of complex interconnected mechanisms. Postprandial glycemia is determined primarily by several interrelated factors: digestion and absorption of simple sugars by salivary enzymes, rate of gastric emptying, preprandial glycemic levels, macronutrient composition of meal, intestinal absorption, hepatic glucose production, degree of insulin resistance, and insulin secretion or provision of exogenous insulin. Dietary fat has been shown to impair insulin sensitivity and enhance hepatic glucose production in addition to delaying gastric emptying, while dietary protein is primarily thought to influence blood glucose via modulation of hepatic glucose production.

Amino acids are thought to impact blood glucose in people with type 1 diabetes by modulating hepatic glucose production both directly and indirectly. In healthy subjects, dietary proteins and amino acids are known to have an insulinotropic effect, promoting secretion of insulin from pancreatic beta cells; however, in animal models and patients with type 2 diabetes, high protein diets have been shown to increase hepatic glucose production.(5) Some amino acids can contribute to gluconeogenesis as substrates, have the ability to stimulate glucagon and, among those with remaining beta cell function, insulin secretion. Furthermore, amino acids can interfere with the ability of insulin to repress endogenous glucose production. High protein intake may increase hepatic glucose production; however, further studies are needed to address

the impact of type of protein/amino acid composition on blood glucose.(5, 6)

Dietary studies on both type 1 diabetes and type 2 diabetes have shown that fat delays gastric emptying.(7, 8) Rate of gastric emptying occurs in a biphasic pattern and is determined by the integration of motor activity and electrical signaling, and regulated by a complex system of metabolic, neuronal, and endocrine signals.(7) After ingestion of a meal, a gastric pacemaker located in the upper part of the stomach generates a slow-wave basal rhythm, and tonic contraction redistributes solids to the distal stomach. The lag phase consists of redistribution and breakdown of solids from the gastric fundus, which pass through the pylorus during the second phase known as the lineal emptying phase. Remnants are then delivered more slowly to the duodenum, which is regulated by a negative feedback mechanism mediated by the incretin hormones: cholescystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY).(9)

Dietary triglycerides stimulate intestinal release of incretin hormones via binding to G-protein-coupled receptors (GPCR) on intestinal mucosal L cells. Studies suggest that 2-monoacylglycerol, short-chain fatty acids (SCFAs), and medium and long chain fatty acids stimulate GLP-1 secretion via this mechanism.(10, 11) Products of protein breakdown may also stimulate GLP-1 secretion; however, the mechanism is poorly understood.(11) PYY, which is also released from L cells of the intestinal mucosa, exerts a similarly inhibitory effect on gut motility via inhibition of gastric acid secretion. Studies in animal models and in individuals with obesity suggest that a high fat diet stimulates PYY secretion to a greater extent than protein and carbohydrates.(12, 13)

Dietary fat may also modulate other gastrointestinal hormones involved in gastric emptying like ghrelin, a peptide hormone that originates primarily from the stomach, and stimulates growth hormone release, prolactin, adrenocorticotropic hormone (ACTH), and cortisol. Ghrelin has been shown to stimulate appetite in humans, but also modulates gastric motility, and studies have shown an increase in gastric emptying after ghrelin administration in normal weight non-diabetic individuals.(14) Ghrelin also directly stimulates glucagon secretion from pancreatic alpha-cells, reducing insulin sensitivity and increasing hepatic glucose production.(15) Feeding studies in both animal models and normal weight individuals without diabetes suggest that ghrelin is suppressed less effectively and more slowly by dietary fat than by carbohydrates and protein, suggesting that ghrelin may play a role in the modulation of gastric emptying by dietary fat.(16-18)

While it is well established that dietary fat increases post-prandial blood glucose levels, the impact of type of dietary fat on blood glucose and insulin sensitivity remains somewhat controversial. A number of studies have linked insulin resistance and hepatic glucose production with free fatty acids.(19) (20) On the other hand some studies have suggested that a diet rich in unsaturated fat, specifically polyunsaturated fat (PUFAs) is beneficial for blood sugar regulation.(21) Consumption of meals high in saturated fats is associated with increased insulin resistance when compared with meals high in monounsaturated and polyunsaturated fats, and monounsaturated fats have been shown to delay gastric emptying to a greater extent when compared with saturated fat.(22)

An additional factor involved in rate of gastric emptying and postprandial blood glucose is preprandial blood glucose level. Acute and chronic hyperglycemia has been shown to decrease rate of gastric emptying. Additionally, many people with diabetes (both type 1 and type 2) may experience delayed gastric emptying; however, reported estimates from the T1D Exchange clinic registry suggest that only approximately 4.8% of registry participants have a clinical diagnosis of gastroparesis.(23) Both individual and inter-individual variability in glycemic response to dietary fat and protein are important considerations when establishing mealtime dosing guidelines.

II. Effects of Fat, Protein, and Mixed Meals on postprandial blood glucose levels in people with type 1 diabetes

Research on Fat

Multiple studies published within the last ten years in patients with type 1 diabetes using continuous glucose monitors (CGMs) have concluded that dietary fat increases post-prandial blood glucose levels and/or insulin requirements.(24-29) This trend persists in some studies utilizing hybrid closed loop systems, suggesting the need to consider dietary fat content in mealtime dosing strategies regardless of technology utilized by patients with type 1 diabetes.(27)

High fat meals appear to cause sustained delayed postprandial glycemia. Bell et. al found that increasing dietary fat by 20 g significantly reduced early (0-2 hour) postprandial glucose response and significantly raised late (2-5 hour) post-prandial glycemic response when compared with the low fat (0 g fat) meal. Response was dose-dependent.(24) Wolpert et. al. similarly found that a high fat meal (60 g) significantly increased insulin needs by 42% 5-10 hours after a meal with use of a closed loop algorithm when compared with a low fat (10 g) meal. Noted individual differences were significantly correlated with individual daily insulin requirements.(27) While there is a trend across studies that addition of dietary fat results in delayed post-prandial hyperglycemia, both studies noted a high amount of variability in individual response to dietary fat in meals.(24, 27) Variability in response to dietary components is relevant when considering dose-adjustment for dietary fat.

Consideration of dietary fat in mealtime dose may also be relevant within the context of emerging technology for people with type 1 diabetes. In fact, it appears that not all hybrid closed loop algorithms are able to account for increased insulin needs post consumption of a high fat meal. A recent study in 7 participants with type 1 diabetes used a crossover design to examine 18-hour periods on a closed loop system post a high fat (60 g predominantly saturated fat) versus a low fat (10 g) meal. Within the context of this closed loop system, the high fat dinner increased mean insulin requirement by 42% with noted individual differences. Post-prandial plasma glucose and area under curve (AUC) despite additional insulin were significantly higher for participants after consuming the high fat meal compared with the low fat meal.(27) This suggests that not all algorithms may effectively account for increased insulin needs from high fat meals, and dosing strategies may need to be adjusted for high fat meals even with hybrid closed loop algorithms.

While a number of studies have examined the impact of high fat versus low fat meals on post-prandial hyperglycemia, only a handful of studies have examined the impact of different types or

sources of dietary fat on postprandial blood glucose. Bell et. al. examined response to test meals containing the same carbohydrate content but differing foods containing various fat types. The foods were: avocado which is high in monounsaturated fat, margarine which contains polyunsaturated fatty acids, or butter a source of mostly saturated fat. Bell et. al. found no significant difference in five hour incremental area under curve (iAUC) for the different fat sources.(24) Another study comparing the addition of extra-virgin olive oil (EVOO), butter, or a low fat meal found that iAUC was lower after the EVOO test meal than the low fat or butter test meals. Bozzetto et. al. also reported gastric antrum volume significantly larger 60-90 min (1-1.5 hrs.) post-prandially, and significantly smaller 330-360 min (5.5-6 hrs.) after consumption of the EVOO meal when compared to the butter meal. Postprandial GLP-1 iAUC was also significantly higher after the EVOO meal when compared with the other meals. Finally, triglyceride iAUC was significantly higher after the EVOO meal when compared with the butter meal.(25) These results suggest that type of fat may differentially affect rate of gastric emptying, time to peak glucose, and post-prandial blood glucose level; however, currently there is insufficient evidence to inform dosing recommendations based on fat source/type. More research is needed to assess glycemic response to both types of fat and specifically to various food sources of fat.

Research on Protein

The impact of protein on postprandial glycemia is less consistent, and appears to be dependent in part on quantity and macronutrient content of meal. While most studies report significant differences in glycemia with the addition of protein to a standard meal, protein appears to have different effects when consumed with and without carbohydrates.(1)

Glycemic response to protein may depend on quantity consumed. A recent within subject randomized crossover trial in 25 children and adults utilizing CGM data compared consumption of whey isolate protein drinks (varying g protein, 0 g carbohydrate, 0 g fat) to two 150 ml (10 g and 20 g glucose) glucose drinks. Authors found that consumption of greater than or equal to 75 g of protein significantly increased postprandial glycemia 3-5 hours after onset of the meal in comparison with the control 0 g protein drink. Compared with the 20 g glucose drink, glycemic excursion following consumption of greater than or equal to 75 g protein did not commence until 90 minutes and reached the same level as the 20 g glucose at 180 minutes (3 hours) compared to 60 minutes (1 hour).(30) This suggests that consumption of protein alone (unaccompanied by carbohydrates or fat) may only significantly impact blood glucose when consumed in large quantities (>75g).

Another study compared two similar test meals one with an additional 21.5 g of protein from non-fat fromage fraiche in 28 patients with type 1 diabetes. Control meal included 40 g protein, 37 g fat, and 90 g carbohydrate. Insulin doses were maintained across the two evening meals consumed on consecutive days. Capillary glucose was measured before, and 2 hrs. post-meal, along with continuous glucose monitoring. Authors found no difference in mean interstitial glucose or in capillary glucose for the 12 hours following the meal with added protein compared to the standard meal. The AUC was also similar across meals.(31) It may be that 21.5 g of protein was insufficient to significantly impact blood glucose. Effects may only be evident with multiple servings of protein (for example 75 g is equivalent to approximately 10 oz. of red meat).

Research on Mixed Meals

Given that many foods containing fat also contain protein, a number of studies examined the impact of sources of both fat and protein on post-prandial glycemia. Meals that are high in fat and protein require significantly more insulin than low fat low protein meals with the same amount of carbohydrates. In a study of 10 adults with type 1 diabetes, Bell et. al. found that a high fat high protein meal (44 g fat, 36 g protein) increased glucose iAUC over twofold and required an additional 65% more insulin when compared with a low fat low protein (4 g fat, 9 g protein) test meal.(32) Another study in 15 adolescents with type 1 diabetes compared a standard meal to a high fat high protein meal (36 g fat, 34 g protein) over two consecutive days. Insulin was dosed using insulin to carb ratios, and blood glucose was measured for 12 hours after consumption of the meals. Gingras et. al. found a significant difference in AUC between 4-12 hours post-meal. Maximum AUC difference occurred at 6 hours after the meal, and glucose concentration 12 hours after the meal remained higher after the high fat high protein meal than after the standard meal.(33) This shows that a high fat high protein meal requires significantly more insulin than a low carbohydrate meal, and that the effect may be most notable at least 4 hours after eating.

While some closed loop systems may be able to address increased insulin needs after a high fat high protein meal, they help highlight differences in time to glycemic peak and give insight into optimized insulin dosing. Gingras et. al examined fat and protein added to standard meals using a closed loop insulin delivery system in 15 adults with type 1 diabetes. The meals were as follows: (1) carbohydrate-only (standard 75 g CHO, 1 g fat, 7 g protein), (2) high protein (HP 1 g fat, 35 g protein), (3) high fat (HF 10 g protein, 33 g fat) and (4) high fat high protein (HFHP 36 g fat, 34 g protein). Addition of fat and/or protein to test meal with fixed carbohydrate content significantly increased time to glycemic peak by 40 minutes and increased post-meal insulin delivery. Five-hour post-meal basal insulin required 39% more insulin after the high fat high protein meal when compared to the standard meal; however, 5-hour post-meal sensor glucose area under curve was not significantly impacted by the addition of fat and protein.(33) While the algorithm appeared able to adjust for fat and protein in the test meal, insulin requirements were significantly increased for multiple hours post meal, important considerations when determining dosing and delivering medical nutrition therapy to patients with type 1 diabetes.

Another important consideration is that high fat high protein meals may include different foods with varying nutrient compositions, which may in turn impact blood glucose apart from simple macronutrient composition. One study looked at 2-hour blood glucose (BG), area under curve (AUC), and BG range after various takeout meals in 9 individuals with type 1 diabetes. The meals were as follows: high fat pasta meal, Thai meal, a hamburger meal, and a cheese sandwich. Authors found that BG range and AUC was lower after the HF pasta meal when compared with the other meals, but found no significant differences between sandwich, Thai, and a hamburger meal.(34) It is important to point out that, given the results from previous studies on fat and protein, significant differences may not have been noted within 2 hours post-meal. While this paper focuses on the impact of fat and protein on blood glucose, more research on various meal compositions is warranted, with blood glucose measured for at least 5 hours post-meal.

III. Mealtime Dosing Models

Table 1 Description of Dosing Models

Model Name	Description of Dose Model	Comparison of Model with Insulin to Carb Ratio	
Model Predicted Bolus (MPB) Estimator Bell et. Al.(24, 32)	**2-step individualized model:** Step 1: metabolic model comprising of insulin pharmacokinetic/pharmacodynamics model Bergman minimal model, and piecewise linear approximation of 2nd order meal absorption. Step 2 optimal insulin dose, split, and duration obtained by minimizing model-predicted glucose area below target 0-120 minutes and above target 120-360 minutes post-meal **Optimal pattern and Timing**: Varies based on individual and amount of fat in meal. Delivery patterns range from 10%/90% to 50%/50% split, with the extended bolus lasting from 2 to 3 h Average was a dual-wave bolus with a 30%/70% split over 2.4 hrs.(32) 20-g fat meal: 75/25% split over 11/ 4 h 40-g fat meal: 65/35% split over the same time period 60-g fat meal: 50/50% split over 13/4 hrs.(24)	Study 1(32): Compared with Insulin to Carb Ratio delivered as a 50%/50% combination bolus over 2 hours: **Meals:** LFLP v. HFHP (+ 40 g fat, + 27 g protein) **Insulin Dose: +** 65% ± 10% **iAUC difference:** MPB decreased the glucose iAUC from 27,092 ± 1,709 mg/dL · min to 11,712 ± 3,172 mg/dL · min (P = 0.0013) **Incremental change in blood glucose:** 73 ± 4 mg/dL to 24 ± 11 mg/dL (P = 0.001) **Inter-individual Variability**: insulin needs +17%–+124%; 8 of the 10 subjects requiring 75% or more insulin **Hypoglycemia:** MPB initially too high in 2/10 subjects	Study 2 (24): Compared with Insulin to Carb Ratio delivered as a 50%/50% combination bolus over 2 hours 15 min prior to meal: Meal types: 0g v. 20 g v. 40 g fat (MUFA v. PUFA v. SFA) **Mean Insulin Dose:** +6% (20 g fat), + 6% (40 g fat), +21% (60 g fat) **iAUC difference:** -50% (20 g fat), -35% (40 g fat), -58% (60 g fat) (<.001) **Inter-individual Variability:** Difference in insulin needs ranged from -64% to +29% (20 g fat), -16% to +18% (40 g fat) -28% to +34% (60 g fat) **Hypoglycemia:** Not significant, Relative risk between ICR and MPB dose 0.941 (95% CI 0.437–1.963; P > 0.999)
Food Insulin Index (FII)(35, 38)	Algorithm that ranks foods based on insulin demand in healthy subjects.(35) FID = FII x KJ per serving and dividing by 1000 KJ (FII x KJ per serving/1000)	**Study 1:** Triple-blinded randomized w/in subject crossover (36) **Meals:** Six foods: steak, battered fish, poached eggs, low-fat yoghurt, baked beans and salted peanuts **Time to peak glucose:** 34±5 min (FII) 56±7 min (ICR) P=0.007 **Peak BG Excursion:** 1.3±0.2mmol/L (FII) 1.8±0.3 mmol/L (ICR) (P=0.13) **Mean Change in BG**: -12% / 3 hours −0.7±0.2 mmol/L (FII) 0.1±0.2 mmol/L (ICR) (P=0.001) **Hypoglycemia**: Mild hypoglycemia occurred in 48% (FII) vs. 33% (ICR) of all test sessions (P=0.155)	**Study 2:** Compared Carbohydrate counting to FII algorithm.(37) **Meals:** 2 breakfast equal kcal, and FII (FII=60), but different Carbohydrates (75 g v. 41 g) **TIR:** +31% (p= 0.001) **iAUC difference:** -52%, (p= 0.013) **Time to peak glucose:** 59 min (FII) 97 min (ICR) (P=0.002) **Peak BG excursion:** -41% 2.4 ± 1.9 mmol/L (FII) 4.1 ± 3.1 mmol/L (ICR) (P =0.01) **Hypoglycemia:** No significant difference in occurrence of hypoglycemia for either meal. 11 episodes (ICR) 6 episodes (FII) (Meal A: P= 0.57) (Meal B: P= 0.31)

Warsaw Pump Therapy School (Warsaw formula/ Pankowska Equation)	Extended bolus comprised of number of Fat protein units (1 FPU = 100 kcal of fat and/or protein) multiplied by the insulin ratio (IR), which is defined as the dose of insulin that covers 10 g CHO or 100 kcal of fat and protein.(39) Timing of bolus determined based on the number of FPU, beginning with 3 hours for a meal containing 1 FPU (100 kcal from fat or protein) to 8 hours for a meal containing more that 3 FPU (300 kcal from fat or protein)	**Study 1:** Randomized controlled cross-over (40) **Meals:** SM (70 g CHO, 24 g protein, 17 g fat) v. 3 test meals HPM (70 g CHO, 36 g protein, 17 g fat), HPFM using ICR, HPFM using FPU (both 70 g CHO, 36 g protein, 30 g fat) **Total AUC:** ICR 53 275 mg/dLxdk FPU 45 253 mg/dL x dk (P=0.085) **Early AUC (0-120 min):** 27 289 mg/dl x dk (ICR) 24 644 mg/dlx dk (FPU) (p= 0.405) **Late AUC (120-240 min):** 25 986 mg/dl x dk (ICR) 20 609 mg/dlx dk (FPU) (p= 0.032) **Time to Peak Glucose:** 90 min for both ICR & FPU **Peak Glucose:** 251.93 (ICR) 225.00 (FPU) (p= 0.227)	

Currently, mealtime insulin dose is typically calculated by dividing amount of carbohydrate in a meal by an individual's insulin to carbohydrate ratio (ICR). Multiple mealtime dosing models for dietary fat and protein have been proposed (table 1), but only a few studies have evaluated the efficacy of these models in accounting for delayed post-prandial glycemic response, and only one study has compared these dosing models in patients with type 1 diabetes.

One proposed dosing model utilizes a dual wave bolus based on predicted individual response where a percentage of the dose is given immediately and the rest is given over time for high fat high protein meals. The adaptive Model Predictive Bolus (MPB) algorithm consists of a 2-step individualized model**.** Step 1 includes a metabolic model comprising of an insulin pharmacokinetic/pharmacodynamics model (the Bergman minimal model), and a piecewise linear approximation of 2nd order meal absorption. In step 2, optimal insulin dose, split and duration are obtained by minimizing model-predicted glucose area below target 0-120 minutes (0-2 hours) and above target 120-360 minutes (2-6 hours) post-meal. The MPB algorithm was evaluated in a study of 10 patients with type 1 diabetes. Bell et. al. found that a high fat high protein meal increased glucose iAUC over twofold and required an additional 65% more insulin, however, there was a large amount of variability with regards to insulin needs (+/- 10%). In two studies comparing MPB to dosing based on insulin to carb ratio, use of the MPB reduced iAUC significantly by at least 50%.(24, 32) In one study, hypoglycemia occurred in 2/10 participants, requiring adjustments to the model.(32) Bell et. al however found that when compared with dosing based on ICR, there was no significant difference in relative risk of hypoglycemia.(24) While the model accounts for individual differences in response to macronutrient composition

and utilizes modeling to predict insulin needs for high fat high protein meals, there may be challenges to implementing this dosing model in other settings.

Another dosing model is based on insulin response to specific foods in healthy individuals. The Food Insulin Index (FII) is a database containing more than 120 foods that ranks foods by relative insulin demand. It was developed in healthy subjects, and looked at relative dietary insulin demand generated by 1,000-KJ portions of foods. (35) Bell et. al compared carbohydrate counting for mealtime insulin dose to dose based on the estimated food insulin demand (FID), which is calculated by multiplying FII by KJ per serving and dividing by 1000 KJ (FII x KJ per serving/1000) in 15 adults with type 1 diabetes. For the purpose of the study, FID was scaled up by a factor of 100/59 (the FID of the reference food pure glucose) so that insulin to carb ratio in a pump could be utilized to calculate dose. Mean blood glucose levels after 180 minutes post meal were significantly lower when FII algorithm was used to calculate prandial dose when compared with carbohydrate counting (5.7 ± 0.2 vs. 6.5 ± 0.2 mmol/l, $P = 0.003$), and mean change in blood glucose level over 3 hours was also significantly lower (-0.7 ± 0.2 vs. 0.1 ± 0.2 mmol/l, $P = 0.001$).(36) The NIDDA (Normal Insulin Demand for Dose Adjustment) study also compared dose based on FII algorithm to insulin dose based on conventional carbohydrate counting in 28 adults with type 1 diabetes on insulin pump therapy. Bao et. al found that use of the FII algorithm improved time in range, and reduced post-prandial peak in blood glucose when compared with dose based on carbohydrate counting. No significant difference in hypoglycemia was noted between ICR and FII (Table 1).(37) One limitation of this model is that not all foods are available in the database, which limits the applicability of this model among patients that may consume foods not listed in the database. Additionally, due to the complexity of calculations required, patients may find it challenging and/or burdensome to implement.

The Warsaw Pump Therapy School or the Warsaw formula/Pankowska equation is another formula that accounts for fat and protein in mealtime dose calculation. The formula utilizes a standard insulin-carb ratio and an additional insulin-to-fat-protein ratio. Insulin is given for carbs immediately, and for fat and protein using an extended bolus comprised of number of fat protein units (1 FPU = 100 kcal of fat and/or protein) multiplied by the insulin ratio (IR). Dose timing is determined based on the number of FPU, beginning with 3 hours for a meal containing 1 FPU (100 kcal from fat or protein) up to 8 hours for a meal containing more that 3 FPU (300 kcal from fat or protein).(39) Utilizing this formula, Pankowska et. al described a bolus calculator that included a food database, and utilized the Warsaw Pump Therapy School formula to develop an algorithm for prandial insulin calculation.(41) A recent randomized controlled trial evaluated this algorithm compared to doses based on insulin to carb ratios in 30 adolescents with type 1 diabetes after consumption of test meals ranging in macronutrient composition. Kaya et. al found that blood glucose levels were significantly higher after consumption of the high fat high protein meal when only insulin to carb ratio was used for dose compared with the addition of the insulin-fat ratio at 120-240 minutes (2-4 hours) post meal.(40) The Warsaw formula allows for dosing based solely on macronutrient content without predictive modeling or a reference database; however, it may not adequately account for individual differences in response to different foods.

Only one study has compared these dosing models, and found that the Pankowska equation better reduced postprandial hyperglycemia after high fat and high protein meals. Lopez et. Al.

evaluated three prandial insulin-dosing algorithms in 33 children and adolescents with type 1 diabetes. Lopez et. al conducted a randomized, crossover trial at two pediatric diabetes centers. Two different test meals (high fat and high protein) were given containing equivalent carbohydrate and insulin was dosed according to carbohydrate counting, the Pankowska Equation, or the Food Insulin Index (FII). Postprandial glucose was measured for 300 minutes (5 hours) using continuous glucose monitoring. Mean insulin dose for carbohydrate counting was constant across test meals. Authors reported peak glucose excursion as significantly higher for carbohydrate counting and FII when compared to the Pankowska Equation (mean difference for carbohydrate counting vs. the Pankowska Equation =1.28 p <.02 for carbohydrate counting and FII) after adjusting for meal type. No significant difference was found between carbohydrate counting and FII. Percentage of time in target range was also lower using the Pankowska equation following both high fat and high protein meals [mean difference for carbohydrate counting vs. the Pankowska Equation = 13.6, p = 0.018) (mean difference FII vs. Pankowska Equation = 15.3 (p = 0.010)]; however, Lopez et al noted a significant increase in hypoglycemia.(42) While the Pankowska equation appeared to result in the greatest reduction in post-prandial hyperglycemia when compared with dosing based on the FII and ICR, it also resulted in a significant increase in hypoglycemia, suggesting the need to adjust dosing in some individuals with type 1 diabetes.

Table 2: Doses for Different meals using 15:1 Insulin to Carb Ratio

Meal	Nutrition Facts[1]	ICR (1u/15 g CHO)	MPB	FII	Warsaw Formula
1 cup Kraft Macaroni And Cheese (HFMPHC)	Kcal: 376 CHO: 47 g (50%) Total Fat: 16 g (39%) Protein: 9.7 g (10%)	3.13 u	Varies based on individual	5.4 u	5.87 u total: 3.13 u immediately + 2.74 u over 3.8 hrs.
6 oz. Beef Tenderloin (HFHPLC)	Kcal: 330 CHO: 0 g (0%) Total Fat: 15 g (38%) Protein: 54 g (58%)	0 u	Varies based on individual	5.5 u	5.55 u total: 0 u immediately 5.55 u over 8 hrs.
3 oz. Fish (ling) + 1/2 cup brown rice (LFHPHC)	Kcal: 345 CHO: 39 g (45%) Total Fat: 2.74 g (7%) Protein: 40.8 g (47%)	2.6 u	Varies based on individual	7.1 u	5.4 u total: 2.6 u immediately 2.8 u over 3.87 hrs.
100 g Mashed potatoes LFLPHC	Kcal: 364 CHO: 81.82 g (90%) Fat: 0 g (0%) Protein: 9.09 g (10%)	5.5 u	Varies based on individual	15.1 u	5.5 u total immediately

1 Nutrient Data Laboratory (U.S.), and Consumer and Food Economics Institute (U.S.). 1999. *USDA nutrient database for standard reference*. Riverdale, Md: USDA, Nutrient Data Laboratory, Agricultural Research Service.

TIR = Time in Range
iAUC= incremental Area under Curve
ICR= Insulin to carb ratio
IR = Insulin Ratio
FPU = Fat protein unit

IV. Future Research Needs and Implications for Practice

While there is significant evidence that dietary fat and protein impact blood glucose, specifically causing delayed post-prandial hyperglycemia in patients with type 1 diabetes, there are significant gaps in the literature that need be addressed to improve guidelines on mealtime insulin dosing to account for fat and protein.

First, more research is needed on the impact of various types and sources of fat and protein on postprandial glycemia. While Bell et. al found no significant differences across different fat-containing foods, Bozzetto et. al found that olive oil, a food high in monounsaturated fatty acids, improved post-prandial blood glucose when compared with butter.(24, 25) A large systematic review and meta-analysis that examined randomized controlled feeding trials in adults found differing glycemic responses to different types of fat overall and more specifically that polyunsaturated fatty acids consistently improved glycemia.(21) This suggests that more research is warranted on the differing effects of different sources of fat on blood glucose, and future research on dosing may consider type of fat in addition to quantity.

Similarly, more research is warranted on the impact of different protein sources and protein types. Most studies that have exclusively examined the impact of protein on postprandial glycemia have utilized whey protein (a protein in milk) in test meals.(30, 31) There is, however, less information on the impact of other protein types and sources. Not all amino acids are glucogenic, meaning that not all amino acids may be converted into glucose. More research is needed on how different protein sources and amino acid compositions impact blood glucose in patients with type 1 diabetes to improve mealtime dosing recommendations.

One challenge to improving dosing methods is the amount of individual variability observed in many studies (table 1). While these dosing models appear effective for some participants with type 1 diabetes, studies suggest a range of insulin needs that varies based on the participant, with some dosing models resulting in post-prandial hypoglycemia in some individuals and hyperglycemia in others.(24, 36, 39, 41, 43) Dosing models may need to be adjusted to the individual's response to fat and protein, suggesting the need for both guidance from a registered dietitian or other clinician, and potentially the future role of individualized or precision nutrition in diabetes management.

Another consideration is the challenge of translating a complicated dosing regimen, and teaching a dosing method in the clinic setting. While carbohydrate counting is currently standard of practice, adherence and accuracy are both concerns with carbohydrate counting. A number of studies have suggested that accuracy of estimating carbohydrates tends to be low in patients with type 1 diabetes. One study found that adults with type 1 diabetes estimated carbohydrates with 59% accuracy, and it has been suggested that accuracy and adherence may be even lower in adolescents and young adults with type 1 diabetes.(44) Any proposed dosing model would need to be simple enough to be translated effectively to the clinic setting, but currently many proposed models involve complex predictive modeling based on individual profile (MPB) or complicated calculations based on observed insulin response to specific foods (FII).

The complexity of dosing models suggests the possible role of technology in determining mealtime dosing based on macronutrient content. Mobile apps and newer hybrid closed loop

algorithms may be employed to optimize and even possibly individualize dosing. Currently, only unofficial DIY Loop systems allow for the input of high fat or high protein meals. Future algorithms may also consider similar mealtime dosing systems to better account for the delayed hyperglycemia experienced by many after a high fat high protein meal.

Finally, future research may consider the long-term impact of specific dietary patterns on insulin sensitivity and risk of complications. A recent qualitative paper suggested that use of a closed-loop system may promote less restraint with regard to dietary choices and may lead to increased consumption of higher fat, and more energy-dense foods. (45) While this review did not consider the long-term impact of diet composition, professionals delivering medical nutritional therapy and/or providing dosing education for patients with type 1 diabetes may consider risk of weight gain, increased insulin resistance, and risk for complications.

Conclusions

Dietary fat and protein cause delayed post-prandial hyperglycemia in patients with type 1 diabetes via a variety of complex interconnected mechanisms, and there is considerable individual variability in glycemic response to dietary fat and protein. Recent research in patients with type 1 diabetes supports the need for improved dosing models that account for fat and protein content in meals; however, only a handful of models have been proposed and studied, typically within a small and homogenous population. More research on these dosing models is needed in larger representative samples within various settings to better assess the feasibility and efficacy of these different models.

Technology, such as continuous glucose monitoring and automated insulin systems may be useful in addressing individual difference in response to meal composition. According to data from the T1D Exchange Registry, continuous glucose monitoring has increased from 7% in 2010-2012 to 30% in 2016-2018.(2) Automated insulin systems are also becoming increasingly available with one commercially available hybrid closed loop system and multiple others currently under FDA review. Reviewing CGM trends and dose history when available and asking patients about meal composition may be helpful in adjusting mealtime insulin dose to suit individual needs. The rapid development and increasing availability of these new technologies such as automated insulin delivery systems in combination with continuous glucose monitoring will allow for development and refinement of algorithms and dosing models accounting for fat and protein composition that will meet individual needs.

Acknowledgments

'All authors have read and approved the final manuscript.'

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(6):1008-15.
2. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019;21(2):66-72.
3. American Diabetes A. 4. Lifestyle Management: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S38-S50.
4. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019;42(5):731-54.
5. Azzout-Marniche D, Gaudichon C, Tome D. Dietary protein and blood glucose control. Curr Opin Clin Nutr Metab Care. 2014;17(4):349-54.
6. Krebs M, Brehm A, Krssak M, Anderwald C, Bernroider E, Nowotny P, et al. Direct and indirect effects of amino acids on hepatic glucose metabolism in humans. Diabetologia. 2003;46(7):917-25.
7. Lupoli R, Pisano F, Capaldo B. Postprandial Glucose Control in Type 1 Diabetes: Importance of the Gastric Emptying Rate. Nutrients. 2019;11(7).
8. Lupoli R, Creanza A, Griffo E, Nardone G, Rocco A, Bozzetto L, et al. Gastric Emptying Impacts the Timing of Meal Glucose Peak in Subjects With Uncomplicated Type 1 Diabetes. J Clin Endocrinol Metab. 2018;103(6):2269-76.
9. Hellstrom PM, Gryback P, Jacobsson H. The physiology of gastric emptying. Best Pract Res Clin Anaesthesiol. 2006;20(3):397-407.
10. Mandoe MJ, Hansen KB, Hartmann B, Rehfeld JF, Holst JJ, Hansen HS. The 2-monoacylglycerol moiety of dietary fat appears to be responsible for the fat-induced release of GLP-1 in humans. Am J Clin Nutr. 2015;102(3):548-55.
11. Bodnaruc AM, Prud'homme D, Blanchet R, Giroux I. Nutritional modulation of endogenous glucagon-like peptide-1 secretion: a review. Nutr Metab (Lond). 2016;13:92.
12. Essah PA, Levy JR, Sistrun SN, Kelly SM, Nestler JE. Effect of macronutrient composition on postprandial peptide YY levels. J Clin Endocrinol Metab. 2007;92(10):4052-5.
13. Onaga T, Zabielski R, Kato S. Multiple regulation of peptide YY secretion in the digestive tract. Peptides. 2002;23(2):279-90.
14. Levin F, Edholm T, Schmidt PT, Gryback P, Jacobsson H, Degerblad M, et al. Ghrelin stimulates gastric emptying and hunger in normal-weight humans. J Clin Endocrinol Metab. 2006;91(9):3296-302.
15. Chuang JC, Sakata I, Kohno D, Perello M, Osborne-Lawrence S, Repa JJ, et al. Ghrelin directly stimulates glucagon secretion from pancreatic alpha-cells. Mol Endocrinol. 2011;25(9):1600-11.
16. Sanchez J, Oliver P, Palou A, Pico C. The inhibition of gastric ghrelin production by food intake in rats is dependent on the type of macronutrient. Endocrinology. 2004;145(11):5049-55.

17. Overduin J, Frayo RS, Grill HJ, Kaplan JM, Cummings DE. Role of the duodenum and macronutrient type in ghrelin regulation. Endocrinology. 2005;146(2):845-50.
18. Koliaki C, Kokkinos A, Tentolouris N, Katsilambros N. The effect of ingested macronutrients on postprandial ghrelin response: a critical review of existing literature data. Int J Pept. 2010;2010.
19. Bajaj M, Suraamornkul S, Kashyap S, Cusi K, Mandarino L, DeFronzo RA. Sustained reduction in plasma free fatty acid concentration improves insulin action without altering plasma adipocytokine levels in subjects with strong family history of type 2 diabetes. J Clin Endocrinol Metab. 2004;89(9):4649-55.
20. Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. Physiol Rev. 2007;87(2):507-20.
21. Imamura F, Micha R, Wu JH, de Oliveira Otto MC, Otite FO, Abioye AI, et al. Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomised Controlled Feeding Trials. PLoS Med. 2016;13(7):e1002087.
22. Rocca AS, LaGreca J, Kalitsky J, Brubaker PL. Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. Endocrinology. 2001;142(3):1148-55.
23. Aleppo G, Calhoun P, Foster NC, Maahs DM, Shah VN, Miller KM, et al. Reported gastroparesis in adults with type 1 diabetes (T1D) from the T1D Exchange clinic registry. J Diabetes Complications. 2017;31(12):1669-73.
24. Bell KJ, Fio CZ, Twigg S, Duke SA, Fulcher G, Alexander K, et al. Amount and Type of Dietary Fat, Postprandial Glycemia, and Insulin Requirements in Type 1 Diabetes: A Randomized Within-Subject Trial. Diabetes Care. 2019.
25. Bozzetto L, Alderisio A, Giorgini M, Barone F, Giacco A, Riccardi G, 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(4):518-24.
26. Garcia-Lopez JM, Gonzalez-Rodriguez M, Pazos-Couselo M, Gude F, Prieto-Tenreiro A, Casanueva F. Should the amounts of fat and protein be taken into consideration to calculate the lunch prandial insulin bolus? Results from a randomized crossover trial. Diabetes Technol Ther. 2013;15(2):166-71.
27. 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(4):810-6.
28. Lodefalk M, Aman J, Bang P. Effects of fat supplementation on glycaemic response and gastric emptying in adolescents with Type 1 diabetes. Diabet Med. 2008;25(9):1030-5.
29. Papakonstantinou E, Papavasiliou K, Maouri C, Magriplis E, Pappas S, Bousboulas S, et al. Postprandial glucose response after the consumption of three mixed meals based on the carbohydrate counting method in adults with type 1 diabetes. A randomized crossover trial. Clin Nutr ESPEN. 2019;31:48-55.
30. Paterson MA, Smart CE, Lopez PE, McElduff P, Attia J, Morbey C, 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(5):592-8.

31. Borie-Swinburne C, Sola-Gazagnes A, Gonfroy-Leymarie C, Boillot J, Boitard C, Larger E. Effect of dietary protein on post-prandial glucose in patients with type 1 diabetes. J Hum Nutr Diet. 2013;26(6):606-11.
32. 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(9):1631-4.
33. Gingras V, Bonato L, Messier V, Roy-Fleming A, Smaoui MR, Ladouceur M, et al. Impact of macronutrient content of meals on postprandial glucose control in the context of closed-loop insulin delivery: A randomized cross-over study. Diabetes Obes Metab. 2018;20(11):2695-9.
34. MacDonald K, Lowe JM, Barker D, Mensch M, Attia J. Effect of popular takeaway foods on blood glucose levels in type 1 diabetes mellitus patients on intensive insulin therapy. Int J Clin Pract. 2009;63(2):189-94.
35. Holt SH, Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr. 1997;66(5):1264-76.
36. Bell KJ, Gray R, Munns D, Petocz P, Howard G, Colagiuri S, et al. Estimating insulin demand for protein-containing foods using the food insulin index. Eur J Clin Nutr. 2014;68(9):1055-9.
37. Bao J, Gilbertson HR, Gray R, Munns D, Howard G, Petocz P, et al. Improving the estimation of mealtime insulin dose in adults with type 1 diabetes: the Normal Insulin Demand for Dose Adjustment (NIDDA) study. Diabetes Care. 2011;34(10):2146-51.
38. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011;93(5):984-96.
39. Pankowska E, Szypowska A, Lipka M, Szpotanska M, Blazik M, Groele L. Application of novel dual wave meal bolus and its impact on glycated hemoglobin A1c level in children with type 1 diabetes. Pediatr Diabetes. 2009;10(5):298-303.
40. Kaya N, Gokmen Ozel H, Kurtoglu S. Does meal-time insulin dosing based on fat-protein counting give positive results in postprandial glycaemic profile after a high protein-fat meal in adolescents with type 1 diabetes: a randomised controlled trial. J Hum Nutr Diet. 2019.
41. Pankowska E, Blazik M. Bolus calculator with nutrition database software, a new concept of prandial insulin programming for pump users. J Diabetes Sci Technol. 2010;4(3):571-6.
42. Lopez PE, Evans M, King BR, Jones TW, Bell K, McElduff P, et al. A randomized comparison of three prandial insulin dosing algorithms for children and adolescents with Type 1 diabetes. Diabet Med. 2018;35(10):1440-7.
43. Pankowska E, Blazik 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(1):16-22.
44. Meade LT, Rushton WE. Accuracy of Carbohydrate Counting in Adults. Clin Diabetes. 2016;34(3):142-7.
45. Lawton J, Blackburn M, Rankin D, Allen J, Campbell F, Leelarathna L, et al. The impact of using a closed-loop system on food choices and eating practices among

people with Type 1 diabetes: a qualitative study involving adults, teenagers and parents. Diabet Med. 2019;36(6):753-60.