Factors Beyond Carbohydrate to Consider When Determining Meantime Insulin Doses: Protein, Fat, Timing, and Technology

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For many years, carbohydrate counting has been a popular strategy for determining mealtime insulin doses for people with diabetes who are on a multiple daily injection regimen or continuous subcutaneous insulin infusion. This approach assumes that only carbohydrate-containing foods and beverages affect postprandial glucose levels. However, many studies have indicated that the fat and protein content of a meal can play an important role in delaying postprandial hyperglycemia and should be considered when trying to optimize postprandial glucose levels. This article reviews research on making insulin dose adjustments for high-fat and high-protein meals, as well as the timing of mealtime insulin doses.

In people without diabetes, insulin is secreted continuously between meals and overnight, as well as in response to glucose excursions after ingestion of meals, snacks, or carbohydrate-containing beverages. Individuals with type 1 diabetes have a near-absolute deficiency of this endogenous insulin secretion because of destruction of their pancreatic β-cells. Administration of exogenous insulin (basal and prandial) is necessary to mimic normal physiologic insulin secretion. Because type 2 diabetes is associated with progressive β-cell loss, many people with longstanding type 2 diabetes may require exogenous insulin as their β-cell production declines to levels insufficient to optimally manage glucose.

It has been well established in people with diabetes that the amount of carbohydrate consumed and the available endogenous insulin may be the most important factors influencing glycemic responses after eating and should be considered when developing a prandial insulin dose prescription (1). It has also been suggested that ~90% of dietary carbohydrate is converted to glucose within 1–2 hours after eating (2). The American Diabetes Association's (ADA's) *Standards of Medical Care in Diabetes—2020* (3) recommend that most people on insulin therapy delivered in a multiple daily injection (MDI) regimen or via continuous subcutaneous insulin infusion (CSII) should be encouraged to assess their glucose levels before meals, snacks, and bedtime. Measuring postprandial glucose 1–2 hours after the start of a meal—generally when glucose levels peak in people using treatments aimed at reducing postprandial glucose values to <180 mg/dL—may also help lower A1C (3).

In the 1990s, the Diabetes Control and Complications Trial (DCCT) showed unequivocally that intensive glucose lowering reduced the risk of diabetes complications when compared with conventional treatment (4). Improved glycemic management was achieved through an intensive insulin therapy delivered in an MDI regimen or via CSII. Participants in the intensive insulin treatment arm performed self-monitoring of blood glucose (SMBG) four times per day and were taught how to adjust their prandial insulin using treatment algorithms based on their blood glucose test results, the amount of carbohydrate to be consumed, and their physical activity. Carbohydrate counting was found to be effective in helping participants achieve their blood glucose goals (4). Outside of the United States, flexible intensive insulin therapy (FIIT) for the management of type 1 diabetes was developed in Düsseldorf, Germany, in the late 1970s (5). FIIT is now taught in many structured diabetes education programs such as the Dose Adjustment for Normal Eating (DAFNE) course in the United Kingdom and Australia. It should be noted that both the DCCT and DAFNE research trials involved frequent follow-up with members of the diabetes team, including registered dietitian nutritionists and nurses, who assisted participants on an ongoing basis with adjusting their insulin doses (4,6).

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A recent systematic review supported earlier findings of the effectiveness of the carbohydrate-counting meal-planning approach (7). However, challenges in accurately quantifying the carbohydrate content of meals have also been reported (8–10). The degree to which other macronutrients (i.e., protein and fat) and nutritional factors (e.g., glycemic index) affect daily glycemic control remains a critical gap in knowledge (11,12).

Glycemic Impact of Dietary Protein and Fat

Our patients and clients who use SMBG and continuous glucose monitoring (CGM) data have observed that meals containing higher levels of protein, fat, or both, with or without accompanying carbohydrate intake, can result in postprandial hyperglycemia and prolonged glycemic excursions. As a result, many of these patients are requesting assistance with insulin-dosing strategies for these types of meals.

The impact of higher-protein and higher-fat meals in people with type 1 diabetes has been an evolving area of research. Two systematic reviews have been published in the past 5 years evaluating research related to mealtime insulin-dosing strategies for dietary protein and fat to minimize postprandial hyperglycemia in youth and adults with type 1 diabetes (11,12). Studies conducted to date have been small, typically involving fewer than 30 participants, frequently using a randomized crossover clinical trial design. Results from these recent high-fat and/or high-protein mixed-meal studies prompted the writing group for the ADA's 2019 consensus report in nutrition therapy in adults with diabetes or prediabetes to suggest checking glucose level 3 hours or more after eating to determine whether additional mealtime insulin adjustments are required (13). The International Society for Pediatric and Adolescent Diabetes made a similar recommendation in its 2018 consensus guidelines for nutritional management in children and adolescents with diabetes (14).

Insulin Dosing for Protein?

Proteins have been shown to stimulate increases in insulin and glucagon in people with and without type 2 diabetes, but responses to various proteins differ (15,16); for people with type 1 diabetes, who have near-absolute insulin deficiency, ingesting protein contributes to postprandial hyperglycemia and accompanying increased insulin requirements (17–19). In those with type 1 diabetes, protein consumption is thought to contribute to postprandial hyperglycemia via conversion of amino acids likely caused by enhancement of gluconeogenic pathways (20) and also by increasing plasma glucagon secretion (21,22).

More recently, protein has been observed to have different effects when consumed with or without carbohydrate (11). Protein-only meals (e.g., ≥230 g lean steak with salad) may require a different insulin-dosing strategy than meals that contain both protein and carbohydrate. Paterson et al. (18,19) have studied the impact of various amounts of protein when consumed in the form of a protein drink with or without carbohydrate. The study involving a protein-only drink showed that protein loads ≥75–100 g resulted in lower glycemic excursions than with two glucose test drinks (10 or 20 g) given for comparison in the period 60–120 minutes after ingestion, whereas a significant increase in postprandial glucose was observed in the period 180–300 minutes after ingestion (18). A more recent study by Paterson et al. (19) revealed that increasing the amount of protein in a low-fat drink that contained 30 g carbohydrate decreased postprandial glucose excursions initially (0–60 minutes after ingestion) but resulted in dose-dependent changes in glycemia in the later postprandial period (150–300 minutes after ingestion).

Piechowiak et al. (23) demonstrated that consuming a high-protein mixed meal (36 g protein, 30 g carbohydrate, and 5 g fat) with the insulin dose based solely on the carbohydrate content of the meal led to higher late postprandial glucose levels. They reported that adding an additional amount of insulin (66% more) as calculated using a protein-fat insulin-dosing algorithm and delivered in a combination (dual-wave) bolus over 3 hours improved postprandial glucose levels. It was also observed that, in a meal that is high in both protein and fat, the impacts of protein and fat were additive on postprandial glucose level (17).

However, other researchers have shown that a pure protein meal equivalent to a "usual" amount of protein (0.3 g/kg of body mass, based on 15–20% of total daily energy intake) without the addition of carbohydrate or fat had very little effect on glycemia (24). Another study (25) concluded that a difference of ~20 g in the protein content of two mixed meals (40 vs. 61.5 g protein) had no effect on postprandial or overnight glucose levels. However, the authors of this study described two limitations. Despite having a standardized protocol for correction of preprandial hyperglycemia, glucose levels differed among participants before consumption of the test meals, and there was also significant inter-individual variability in responses to the test meals. These results highlight the importance of individualizing insulin dosing for high-protein meals.

The previously mentioned 2019 systematic review by Paterson et al. (12) of the impact of dietary protein on postprandial glucose and insulin requirements in type 1 diabetes reached the following conclusions:

- Consumption of dietary protein has been shown to lead to increased insulin demand as well as delayed and sustained postprandial hyperglycemia in people with type 1 diabetes. The timing of the glycemic effect from dietary protein ranged from 90 to 240 minutes.
- The insulin demand and glycemic impact of dietary protein are different when protein is consumed with carbohydrate versus alone. In a carbohydrate-containing meal, ≥12.5 g of protein affected postprandial glucose.
- When dietary protein is consumed in isolation from carbohydrate and fat, a larger amount of protein (≥75 g) is needed to have an effect than when protein is consumed in the context of a mixed meal.
- Although mealtime insulin-dosing algorithms for protein and fat exist, this review of current evidence suggests that further research is needed.

Insulin Dosing for Fat?

High fat intakes have also been shown to elevate and prolong postprandial glucose excursions. Research has been conducted to assess the mechanisms underlying the higher insulin requirements observed with high-fat meals. In people without diabetes, dietary fat and free fatty acids are known to impair insulin sensitivity and enhance hepatic glucose production (26). Studies conducted in participants with type 1 or type 2 diabetes have reported that dietary fat delays gastric emptying, leading to a lag in glucose absorption (27,28). Wolpert et al. (29), using a closed-loop glucose control study design, observed that high-fat meals were not only associated with delayed gastric emptying, but also caused a statistically significant decrease in insulin sensitivity. However, participants in this particular study did not respond to high-fat meals in a uniform manner, highlighting once again the degree of inter-individual difference in the impacts of macronutrients on postprandial glucose control. Research findings suggest that a very cautious approach should be taken when increasing insulin doses for meals that are high in fat, protein, or both.

Since the publication of the previously mentioned 2015 systematic review by Bell et al. (11), which suggested increasing the insulin dose for higher-fat meals, three additional studies have been published (30–32). The objective of a study by Laxminarayan et al. (30) was to assess the mechanisms underlying the higher insulin requirement observed in previous studies to develop an improved method of adjusting insulin doses for high-fat meals. The research group used a predictive model–based approach derived for subjects using a closed-loop insulin pump while consuming two meals with varying fat content (10 vs. 60 g) and consistent amounts of carbohydrate (96 g). The model analysis confirmed results from the 2013 study by Wolpert et al. (29) that high-fat meals require more insulin than low-fat meals with identical carbohydrate content. The high-fat meal was associated with delayed gastric emptying (estimated to be ~30 minutes) but also revealed a statistically significant decrease in insulin sensitivity (of ~17%). The observed increase in insulin requirement was 42% for the high-fat meal.

Campbell et al. (31) conducted a study to investigate the influence of rapid-acting insulin dose and timing in subjects using MDI who consumed a high-fat, high-carbohydrate meal versus a low-fat, high-carbohydrate meal. The meals were matched for carbohydrate (68 g) and protein (26 g) content but differed in fat content (high-fat 55 g; low-fat 5 g). Carbohydrate counting was used to determine bolus doses. An additional insulin dose of 30% was delivered either with or 3 hours after the meal. The authors reported that 60% of the subjects experienced hypoglycemia if 30% additional insulin was delivered at the start of the meal compared with no incidences of hypoglycemia when the additional insulin was delivered 3 hours postmeal.

Bozzetto et al. (32) conducted a study to determine whether the type of fat (saturated, polyunsaturated, or monounsaturated) had an impact on postprandial hyperglycemia when consumed with a high–glycemic index meal. The researchers concluded that the addition of 37 g extra-virgin olive oil (EVOO) to a high–glycemic index meal blunts early postprandial glucose by ~50% compared with 43 g butter or very little fat added to the same meal. There is evidence that monounsaturated fatty acids can stimulate glucagon-like peptide 1 secretion more than saturated fatty acids, possibly influencing the rate of gastric emptying (33). The authors concluded that the mechanisms behind the effects of EVOO on postprandial glucose metabolism, as well as the separate impact of fat quality and other functional molecules present in EVOO (i.e., polyphenols), should be investigated.

The 2015 systematic review of the impact of dietary fat on postprandial glucose and insulin requirements in type 1 diabetes by Bell et al. (11) made the following conclusions:

- Increases in mealtime insulin doses for high-fat meals need to be individualized. More insulin may be needed to prevent late postprandial hyperglycemia, but that need should be balanced with risk of early hypoglycemia.
- For high-fat meals (≥40 g), consider additional mealtime insulin equivalent to 30–35% of the premeal dose.
  - With CSII, consider using a combination (dual-wave) bolus with 50% of the dose delivered before eating and the remaining 50% delivered over 2–2.5 hours.

  - With MDI, if using a rapid-acting analog insulin, administer additional insulin 1 hour after the meal.
- Use SMBG or CGM to guide individual responses and adjust as indicated.

Insulin Dosing Algorithms for Protein and Fat

The 2015 systematic review by Bell et al. (11) revealed that high-fat, high-protein meals mixed with carbohydrate do require more insulin compared with lower-fat, lower-protein meals with the same carbohydrate content. Five studies have been published on the impact of high-fat, high-protein meals on glycemia since the Bell review was published (34–38).

Three of these studies used participants' insulin-to-carbohydrate ratio (ICR) to determine the dose of insulin delivered by CSII or MDI for high-fat, high-protein meals (34–36). The test meals in these three studies included 15–40 g fat and 25–40 g protein. The carbohydrate content in test and control meals ranged from 30 to 50 g. In addition to carbohydrate counting, different strategies were employed to avoid postprandial hyperglycemia in response to the high-fat, high-protein test meals. These included use of a combination bolus (dual-wave) (34) or a correction dose of insulin delivered after 2 hours and as needed at 2-hour intervals (35). Bell et al. (36) used carbohydrate counting in addition to a predictive model–based approach to derive insulin doses for high-fat, high-protein meals.

All three studies reported that the high-fat, high-protein meals required significantly more insulin over a longer period of time compared with low-fat, low-protein meals with identical carbohydrate content. Lopez et al. (34) observed that high-fat, high-protein meals required ≥60% ICR as a standard bolus with an additional ICR of up to 70% in an extended bolus from 90 to 300 minutes after the meal to prevent delayed hyperglycemia. van der Hoogt et al. (35) found that high-fat, high-protein meals required 30% more insulin over a mean of 6 hours compared with the low-fat, low-protein meal with identical carbohydrate content. Bell et al. (36) found that 65% more insulin was required (range 17–124%) for high-fat, high-protein meals. The authors suggested that, for meals containing >40 g fat and 25 g protein, people should increase the insulin dose calculated based on their ICR by 25–30% using a combination (dual-wave) bolus, initially administering 30–50% of the dose and then extending the remainder over 2–2.5 hours. If review of blood glucose levels reveals late hyperglycemia (>3 hours after the meal), the extension of the bolus period should be increased. For individuals using MDI, the additional insulin should be injected 60–90 minutes after the meal.

A study conducted by Lopez et al. (38) compared two novel insulin-dosing algorithms—the Pankowska Equation (39) and the Food Insulin Index (FII) (40) (Table 1)—in addition to carbohydrate counting. The authors reported that, regardless of the algorithm or method used, participants experienced a significant amount of postprandial hyperglycemia after consumption of the identical test meals (38). Although the Pankowska Equation decreased postprandial hyperglycemia, there was a significant increase in the occurrence of hypoglycemia that was not observed with the FII or with carbohydrate counting. Other researchers have reported similar findings when the dose of insulin was increased for high-fat, high-protein meals using the Pankowska Equation (41,42).

It should be noted these insulin-dosing algorithms, in addition to the carbohydrate-counting method, require a person to look up nutrition facts for foods and beverages to be consumed or to access a database for predetermined nutrient values. That information is then used to perform mathematical calculations to derive mealtime doses. Thus, ideal candidates for these methods need to have higher levels of health literacy and numeracy. The use of bolus calculators embedded in insulin pumps, smart pens, smartphone apps, and blood glucose meters is becoming increasingly common and may be an option for many people, especially those who have deficiencies in health literacy or numeracy. However, the currently available bolus calculators only calculate mealtime insulin doses based on the carbohydrate content of the meal and do not take into consideration the amount of protein or fat to be eaten.

Jabłońska et al. (37) conducted a 3-day study to evaluate the impact of regular insulin, with its slower onset and longer duration of action, compared to a rapid-acting insulin analog on postprandial glucose in people using an MDI regimen. The three test breakfasts in the study contained the same carbohydrate content (30 g) and glycemic index. On day 1, the amounts of fat and protein were low (2.5 and 5.7 g, respectively) and subjects received rapid-acting analog. On days 2 and 3, the amounts of fat and protein were high (37 and 30 g, respectively), and subjects received consecutively rapid-acting (day 2 test meal) or regular insulin (day 3 test meal). The study revealed there was no benefit to covering such meals with regular insulin compared with rapid-acting insulin; however, they did find that 24% of participants who consumed the 30-g carbohydrate meal with low amounts of fat or protein (day 1 test meal) experienced early postprandial hypoglycemia. Observations of early postprandial hypoglycemia have also been reported by other researchers when subjects consumed high-fat, high-protein meals (17). A confounding variable in

TABLE 1 The Pankowska Equation and Food Insulin Index Insulin-Dosing Algorithms (39,40)

Pankowska Equation. With this algorithm, an individual's ICR is used to calculate the insulin dose for the carbohydrate component of the meal, which is administered before the start of the meal. Additional insulin is calculated using a fat/protein unit (FPU) calculation, in which 1 unit of insulin is given for every 100 calories in the meal from fat and protein. The additional insulin is given over 3–6 hours via CSII using the extended bolus feature. The time length was established to be 3 hours for a meal containing 1 FPU, 4 hours for 2 FPUs, 5 hours for 3 FPUs, and, 8 hours for >3 FPUs (300 kcal from fat and protein).

Example: Using the Pankowska Equation to calculate insulin needed for two slices of pizza in a person whose ICR is 1:10:

- 2 slices cheese pizza = 578 kcal: 69 g carbohydrate (276 kcal), 26 g protein (104 kcal), 22 g fat (198 kcal)
- Calories from fat and protein: 302
- Insulin for 69 g carbohydrate: 7 units delivered using normal bolus before meal
- Insulin for fat and protein = 3 FPU delivered over 5 hours using combination (dual-wave) bolus
- Total dose: 7 units + 3 units = 10 units

Food Insulin Index (FII). This index is a measure of postprandial insulin responses in people without diabetes based on the glycemic response to 1,000-kJ (239-kcal) portions of food for approximately 200 foods. In this method, insulin doses for meals are calculated using both the FII and the serving size of the meal and are adjusted according to a person's ICR. Use of this method is limited by the size of the FII database and the specificity of the foods tested. Further trials are required to assess how practical its use is in real-world situations.

the study by Jabłońska et al. may have been that 36% of subjects received basal insulin as a single evening dose of NPH insulin. Findings from all of these studies continue to support the need for additional insulin for high-fat, high-protein meals because of sustained late postprandial hyperglycemia.

Timing of Insulin Administration

Appropriately timing prandial insulin doses delivered via injection or insulin pump bolus to reduce the risk of either hyper- or hypoglycemia is also important to achieve optimal glycemic control. Although manufacturers of rapid-acting insulin analogs recommend injecting within 15 minutes of a meal or immediately after (to more precisely bolus based on the actual amount of carbohydrate consumed), health care professionals and researchers report better outcomes when boluses are given 15–20 minutes before meals (36). A recent literature review provided evidence for the superiority and safety of injecting 15–20 minutes before meals, which resulted in nearly 30% lower glucose levels, a lower area under the curve for hyperglycemia, and less postmeal hypoglycemia when premeal glucose levels were in range (43,44).

Future Research Directions as Hybrid Closed-Loop Pump Technology Continues to Evolve

With the recent U.S. Food and Drug Administration approval of a hybrid closed loop (HCL) insulin pump system, meal-induced glycemic variability and postprandial hyperglycemia compensation remain challenges for the widespread adoption of this technology (45). Currently, administering mealtime boluses before consumption of food or beverages appears to be one of the easiest ways to improve postprandial glucose control in HCL systems (46). Training in or thoroughly reviewing carbohydrate counting before transitioning to an HCL system is recommended (47,48). More accurate assessment of the carbohydrate content of meals should enhance HCL algorithm performance and reduce the likelihood of being "kicked out" of the HCL auto-mode feature when glucose levels are too far out of range. Long-term studies are needed to assess the safety and performance of this evolving technology under free living conditions, as well as the impact of high-fat and high-protein meals and varied levels of physical activity on these factors.

Summary

Because of inter-individual differences in glycemic responses to dietary fat and protein, research to date suggests the need for a very cautious approach to increasing insulin doses for both high-fat and high-protein meals. For people

on a CSII regimen, using an insulin pump's combination (dual-wave) bolus feature for prandial bolus may provide better insulin coverage to match slower glucose absorption after meals that are high in fat, protein, or both (35,36). Checking glucose 3 hours after meals may help to determine whether additional insulin adjustments are required. For those using an MDI regimen, combining a premeal injection and an additional injection delivered 60–180 minutes after such a meal may be a helpful strategy to reduce postprandial hyperglycemia (31,36). The effectiveness of the insulin-dosing approach used should be confirmed with CGM or structured SMBG to evaluate individual responses and the need for further insulin adjustments. Unfortunately, the ideal algorithm or method has yet to be determined for calculating mealtime insulin doses for high-fat, high-protein meals.

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

A.B.E. is the sole author and guarantor of this article and, as such, had full access to all the data presented and takes responsibility for the integrity of the review.

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