Insulin Dosing for Fat and Protein: Is it Time?

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Diabetes Care 2020;43:13–15 | https://doi.org/10.2337/dci19-0039

The impact of dietary fat and protein on postprandial glycemia in type 1 diabetes (T1D) and the need to adjust for them in the mealtime insulin dose have been controversial (1,2). Recently, carefully designed randomized trials in individuals living with T1D have shown protein and fat consumed in meals with carbohydrate reduce the early postprandial rise (1–2 h) and contribute to postprandial hyperglycemia in the late (3–6 h) postprandial period (3–5). In clinical practice, continuous glucose monitoring highlights the glycemic effects of different meal types demonstrating that mealtime insulin dosing strategies based on carbohydrate counting alone have limitations. There is a need for an evidence-based, safe, and practical method to guide insulin adjustments for high-fat, high-protein meals. In this issue of *Diabetes Care*, Bell et al. (6) address the pressing clinical question of optimal insulin adjustments for meals containing differing amounts of dietary fat. This is important because postprandial hyperglycemia has been identified as a risk factor for the development of long-term complications of diabetes (7), and higher fat diets have increased in popularity in recent years.

The mechanisms by which all three macronutrients impact blood glucose levels in people with T1D is shown in Fig. 1. Dietary carbohydrate is absorbed and rapidly increases the blood glucose concentration (8). Dietary protein results in a delayed and more prolonged increase in blood glucose levels by conversion of amino acids to glucose through gluconeogenesis, as well as an influence on multiple hormones including glucagon, cortisol, growth hormone, insulin-like growth factor 1, and ghrelin, thus increasing insulin resistance (9). Dietary fat also results in a delayed glycemic response by a number of mechanisms. Free fatty acids act via peroxisome proliferator–activated receptors and free fatty acid receptors to impact cellular responses to insulin, leading to increased insulin resistance (10). Fat also affects other hormones impacting glycemic regulation including glucagon, glucagon-like peptide 1, gastric inhibitory polypeptide, and ghrelin (10). Triacylglycerols in fat are metabolized to glycerol, which can be used for gluconeogenesis, although this accounts for only a small amount of triacylglycerol metabolism. Addition of fat to a meal will delay the rate of gastric emptying as the stomach empties at a constant energy rate (9).

Alternative algorithms such as the model predictive algorithm presented in this issue (6) are more complex than those for carbohydrate alone. Additional factors need to be considered in calculating insulin for fat and protein. In mixed meals, an adjustment based on the insulin-to-carbohydrate ratio (ICR) is needed because of the interactions between carbohydrate, fat, and protein on insulin resistance. When protein or fat are eaten alone or as part of a mixed meal, independent factors, proportional to the quantity of fat and protein, are needed to account for mechanisms such as gluconeogenesis (Fig. 1).

In order to provide clinical guidance for insulin adjustments, it is necessary to first consider the following: What is the impact of varying amounts of fat and protein on postprandial glycemia?

Previous studies in individuals with T1D have demonstrated the impact of a defined amount of fat in a meal (3,11,12). Bell et al. (6) add to these findings by demonstrating a dose response of fat in a carbohydrate-containing meal, showing dose-dependent reductions in the early postprandial period followed by increases in the late postprandial period. Data from preliminary results presented at the European Society for Paediatric Endocrinology also found that fat, when consumed alone, increases glucose levels in a dose-dependent manner (13).

The glycemic effect of protein alone (independent of carbohydrate and fat) and when consumed in a mixed meal has also been examined. When protein is consumed in isolation of carbohydrate, 75–100 g of protein needs to be consumed (equivalent to a 300-g lean steak with salad) before it has a significant

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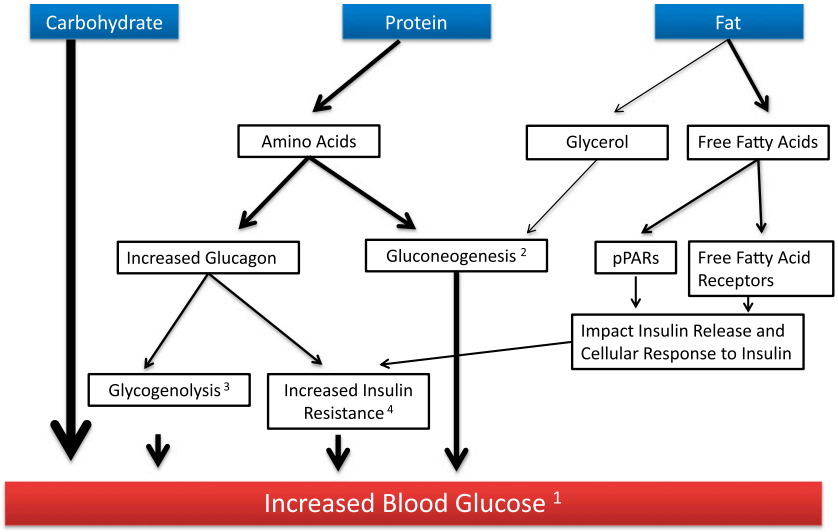

Figure 1—Mechanisms by which carbohydrate, protein, and fat contribute to increasing blood glucose levels and insulin requirements in type 1 diabetes. Numbers indicate points of insulin requirement. 1, insulin is required to metabolize glucose; 2, insulin is required to stop gluconeogenesis; 3, insulin is required to stop conversion of glycogen to glucose; 4, insulin is required to counteract insulin resistance. Width of arrows indicates relative contribution to increase in blood glucose. pPARs, peroxisome proliferator–activated receptors.

impact on postprandial glycemia (5). This large protein meal produced a late (3–5 h) glycemic response similar to that of 20 g of glucose consumed without insulin (5). In comparison, when protein was consumed with 30 g of carbohydrate (no fat), amounts as low as 12.5 g contributed to a significant glycemic response in both the early and late postprandial periods (14). Paterson et al. (14) demonstrated a dose response from protein similar to that from fat reported in this issue, with dose-dependent decreases in the early postprandial period that inverted later in the postprandial period.

The question then remains, how much additional insulin is needed for fat and protein and how should it be delivered?

A number of studies have previously investigated the additional insulin required for fat and protein (4,12,15,16,17), with all reporting marked interindividual differences. In their initial study using the same model predictive algorithm, Bell et al. (6) found that for a pizza meal a dose increase of 65% was needed to prevent hyperglycemia, with the majority of participants requiring an extra 75–124% of their usual dose (4). Wolpert et al. (12) found that a high-fat meal required on average 42% more insulin than a low-fat meal, with some participants requiring more than twice as much insulin while others required no extra insulin (−17% to 108%). Gingras et al. (15) found that a high-fat, high-protein meal required on average 32% more insulin than a low-fat, low-protein meal, with some participants needing twice as much insulin while others required almost none (5–120%) (15). Recent data in children and adolescents using pump therapy found a mean additional 30% of the dose for a very high-protein meal (16) and up to 60% more for a high-fat, high-protein meal (17) may be required.

In the present study, Bell et al. (6) undertook a randomized, within-subject trial to examine the insulin requirements for incremental doses of fat. Their main finding is that the mean additional insulin required for a meal increased from 6% for both an extra 20 g and 40 g of fat to 21% for an extra 60 g of fat. Interindividual variation was high, in support of earlier studies, with half of the participants who consumed the meal with 40 g added fat requiring only their usual dose. The model predictive control algorithm holds promise as it improves postprandial area under the glucose curve following high-fat meals, without an increase in hypoglycemia (4). However, the interindividual differences highlight the challenges in clinical translation and recommendations. Habitual diet and the amounts of fat and protein typically covered by an individualized ICR may have an important influence on individual sensitivity to different macronutrients. In the present study, almost half of participants (47%) experienced hypoglycemia following the meal that contained no fat, suggesting the ICR may have been optimized for meals containing moderate fat amounts.

Very few studies have addressed the duration and split of the combination bolus. New data reported in this issue (6) show the optimal duration of the combination bolus increases with fat amount, from 73 min for 20 g of fat (75%/25%) to 105 min for 60 g of fat (50%/50%). The findings provide support for recommendations (18,19) that a greater proportion of the total insulin dose needs to be given up front (≥50%) over a shorter duration (<2 h) than previously thought. Different strategies will be required for different foods (20), and dosing algorithms will need to incorporate multiple strategies for meals of varying macronutrient compositions (21).

In conclusion, optimal postprandial glycemia depends on matching insulin to the entire meal composition. The findings presented here have implications for clinical practice: insulin is required for dietary fat, with the dose adjustment dependent on the quantity of fat and individual sensitivity. A starting point for adjusting insulin based on differing amounts of fat is recommended, which requires tailoring to the individual. It will be important for future meal algorithms to adapt over a period of time to improve performance with respect to each individual's glycemic response. Ongoing research is needed to elucidate the implementation of routine fat and protein dosing into clinical practice.

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

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