COMMENTARY

Insulin:Carbohydrate Ratio—Part of the Story

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IN THIS ISSUE OF *DIABETES TECHNOLOGY & Therapeutics*, Laxminarayan et al.¹ present a secondary analysis of a previously published study on the effects of varying meal macronutrient composition (viz., varying fat contents while maintaining comparable carbohydrate content) on metabolic model parameters (insulin sensitivity, meal glucose appearance) in a cohort of individuals with type 1 diabetes. They demonstrate, not surprisingly, that a high-fat meal delayed a surrogate index of time to peak meal glucose appearance and lowered insulin sensitivity when compared with a low-fat meal. They rightly acknowledge the limitations of their methods as to the robustness of the models applied (because more sophisticated meal models are currently available)^{2–5} and the critical fact that they did not use glucose tracers and isotope dilution methods that could have enabled accurate assessment of meal glucose turnover and appropriate partitioning of postprandial glucose metabolism. However, the strength of this article lies in the use of data from patients with type 1 diabetes, highlighting the significant impact of high fat-containing meals on glucose parameters.

As has been previously shown,^{6–8} the plasma glucose concentration after a mixed meal reflects the net ultimate effects of multiple physiological processes that run concurrently after one eats.⁹ These processes include but are not limited to (a) rates of carbohydrate absorption from the gastrointestinal tract,¹⁰ which in turn depend on rates of gastric emptying¹¹; (b) insulin and glucagon concentrations in the portal vein^{12–15}; (c) net postprandial hepatic glucose uptake (storing meal-derived glucose as glycogen)¹⁶; (d) rates of hepatic glucose production¹⁷; and (e) net peripheral glucose uptake.⁶

From the carbohydrate absorption standpoint, an important and often neglected factor that has profound effects on postprandial plasma glucose concentrations is the meal macronutrient content. Simple versus complex carbohydrate ingestion results in widely divergent postprandial glucose, insulin, and glucagon concentrations even in the presence of similar meal macronutrient composition.¹⁸ Likewise, it is well established that high fat-containing meals delay rates of gastric emptying,¹⁹ hence significantly altering the temporal pattern of postprandial glucose concentrations as supported by the current article.¹

The insulin:glucagon ratio and glucose concentrations in the portal vein are important modulators of hepatic glucose

metabolism (glucose uptake and release),^{20–23} which in turn influences the rate at which glucose appears in the systemic circulation. A lower insulin:glucagon ratio would stimulate hepatic glucose production, thus increasing plasma glucose concentrations. This effect is compounded in those with type 1 diabetes because the peripherally administered insulin is unable to restore the normal portal vein insulin:glucagon ratio in the presence of the well-characterized α -cell defect that occurs in these individuals, which in turn leads to postprandial hyperglucagonemia^{24,25} with resultant hyperglycemia. This is because of two possible reasons: (1) delay in subcutaneously administered insulin reaching adequate concentrations in the portal vein and (2) a large insulin dose needs to be injected subcutaneously to counter the portal hyperglucagonemia, and this would increase the risk for late postprandial hypoglycemia.

Although the effects of a high-fat meal on glucagon secretion or on hepatic glucose uptake have not been extensively studied in type 1 diabetes,²⁶ it is well established that an elevated level of circulating free fatty acids, which could result after a high-fat meal, worsens hepatic insulin sensitivity, thus increasing hepatic glucose production and hence plasma glucose concentrations.^{27–29} Moreover, the extent to which systemic appearance of meal carbohydrates is a function of the grams of carbohydrates ingested minus the grams of ingested carbohydrates stored in the liver as glycogen, abnormalities in hepatic glycogen synthesis due to deficiencies in hepatic glucokinase activity,^{16,17,30} and/or reduced glucose transport into the hepatocytes could also influence postprandial glucose concentrations by increasing the net release of meal carbohydrates into the systemic circulation. Although hepatic glycogen content in individuals with poorly controlled type 1 diabetes has been shown to be reduced, putatively because of a defect in functional hepatic glucokinase activity,³¹ the role of a high-fat meal on glucokinase activity and/or hepatic glucose uptake is as yet unexplored in type 1 diabetes, although in individuals without diabetes elevated levels of free fatty acids did not alter hepatic glucose uptake.³²

As suggested by Laxminarayan et al.¹ in this issue of the journal and as is fairly well established by elegant physiological investigations,²⁸ high-fat meals and elevated levels of circulating free fatty acids lower whole-body glucose

utilization, thus worsening whole-body insulin sensitivity^{33,34} with resultant hyperglycemia.

Taken together, it is physiologically plausible, and indeed is routinely observed clinically in individuals with type 1 diabetes, high fat-containing meals greatly alter the temporal profile of postprandial glucose. This leads to varying prandial insulin requirements and patterns of insulin delivery. At present, there are no rigorously tested algorithms to guide our patients through their process of understanding how to deliver the correct dose and timing of prandial meal boluses with meals of varying composition. The tactics used by patients and their medical care providers to manage mealtime insulin dosing for high-fat meals are not evidence or scientifically based and are mostly handled as “trial and error” approaches. These include, among others, altering patterns of insulin delivery (viz., dual-wave or square-wave premeal boluses in varying proportions), additional correction boluses, changing insulin:carbohydrate ratios for high-fat meals, adjusting to a temporary higher basal insulin infusion rates after high fat meals. Patients on multiple daily injection programs find it even more difficult to manage such situations and often apply postprandial correction boluses with a resultant risk of hypoglycemia.

Few short-term closed-loop control studies³⁵ in type 1 diabetes have shown reasonable postprandial glucose control during free living while consuming high-fat meals.^{36,37} However, more work needs to be done both at the physiological level and at the clinical trial level to determine the contribution of noncarbohydrate nutrients on prandial insulin requirements. Evidently, the insulin:carbohydrate ratio alone is not enough. Undoubtedly, the time is ripe for rigorous physiological assessments of changing meal compositions on prandial hormonal balance and multiple hormone (islet cell peptides [viz., insulin, amylin, and glucagon]) pump therapy such that the data derived could then inform both open-loop and closed-loop control algorithms for better management of type 1 diabetes.

Author Disclosure Statement

No competing financial interests exist.

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