Comment on Russell-Jones et al. Diabetes Care 2017;40:943–950. Comment on Bowering et al. Diabetes Care 2017;40:951–957

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Diabetes Care 2018;41:e27–e28 | https://doi.org/10.2337/dc17-1916

We read with interest the recent papers relating to the onset 1 and onset 2 trials (1,2), which compared the clinical efficacy and safety profiles of fast-acting insulin aspart (faster aspart) with insulin aspart (IAsp) in patients with type 1 and type 2 diabetes who concurrently received basal insulin. The authors recognize the importance of lowering postprandial glycemia to achieve HbA_{1c} goals, particularly when fasting glucose is adequately controlled or only modestly elevated.

The central hypothesis underlying the trials is that mealtime insulin with a faster action will provide better control of postprandial glycemia and, potentially, HbA_{1c} when used with basal insulin. However, postprandial blood glucose concentrations are determined by glucose disposal and both exogenous and endogenous glucose production, i.e., interrelated mechanisms that are not dependent exclusively on, and often outweigh, the actions of insulin. In particular, gastric emptying (GE), which controls the rate of entry of carbohydrates into the small intestine, is a major determinant of the glycemic response to carbohydrate ingestion in health and diabetes (3). It is not well appreciated that GE exhibits a substantial interindividual variation, with the overall rate in the range of 1–4 kcal/min in health. In long-standing diabetes, this range is even wider; approximately 30–50% of patients have abnormally delayed GE, while in others GE is more rapid (3). By contrast, GE remains stable over many years within individuals (4). In noninsulin-treated patients with type 2 diabetes, interventions that slow GE result in decreased postprandial glycemic excursions, whereas acceleration of GE does the opposite. Moreover, slowing of GE is recognized as a key mechanism by which exogenous glucagon-like peptide 1 (GLP-1) and short-acting GLP-1 receptor agonists lower postprandial glycemia. Although GLP-1 is an incretin hormone, it often leads to a reduction in postprandial insulin secretion, reflecting delayed nutrient absorption (3). Likewise, insulin-treated patients with type 1 diabetes who have gastroparesis have been shown to require substantially less insulin to maintain euglycemia over 2 h postprandially when compared with those with normal GE (5). In this context, it is not surprising that faster aspart, while apparently more effective than IAsp for reducing the initial rise in blood glucose after a meal, was associated with a greater risk of hypoglycemia (2). Although both trials claimed noninferiority of faster aspart against IAsp, superiority of the former is likely to depend on whether GE is normal or rapid. A faster-acting insulin may be advantageous when GE is more rapid. In contrast, in gastroparesis a rapid onset of insulin action may be undesirable and increase the risk of hypoglycemia.

These considerations indicate that faster-acting insulin may not be a "universal" option for the management of postprandial glycemia. The fundamental concept is that effective control of postprandial hyperglycemia by insulin treatment is dependent on the precise coordination of insulin delivery with the rate of carbohydrate absorption, which is primarily dependent on GE. We believe that, particularly with the advent of noninvasive breath tests, GE should be measured more widely in diabetes and will allow insulin therapy to be targeted more effectively and safely.

Duality of Interest. T.W. has received travel support from Novartis. M.H. has participated in advisory boards and/or symposia for Novo Nordisk, Sanofi, Novartis, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, and AstraZeneca and has received honoraria for this activity. K.L.J. has received research funding from Sanofi and drug supplies from Merck Sharp & Dohme. C.K.R. has received research funding from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, Novartis, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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