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Diabetes Improvement Following Roux-en-Y Gastric Bypass: Understanding Dynamic Changes in Insulin Secretion and Action

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COMMENTARY

Roux-en-Y gastric bypass (RYGB) surgery leads to substantial and sustained weight loss and improved cardiometabolic parameters in obese people (1). Approximately 80% of patients with type 2 diabetes (T2D) experience complete remission, defined as normoglycemia without medication, and another 15% have improvement, albeit remaining on medication (2). These rates are superior to those seen with conventional medical management (3–5). Several lines of evidence suggest such glycemic improvements are beyond those anticipated by weight loss alone. For many, remission of diabetes occurs within days, before significant weight loss (6,7). Moreover, diabetes remission does not occur with similar degrees of caloric reduction following other surgical procedures, nor with liposuction or surgical resection of omental fat (8). These observations suggest potential mechanisms beyond weight loss by which RYGB leads to diabetes improvements, but the relative contribution of insulin sensitivity, β-cell function, and other potentially novel mechanisms to improved metabolism following RYGB remain incompletely understood.

In this issue, Bojsen-Møller et al. (9) report comprehensive longitudinal assessments of insulin secretion and action at 1 week, 3 months, and 1 year following RYGB in two cohorts of 10 obese patients with and without T2D (Fig. 1). At 1 week, the earliest time point comprehensively assessed to date, fasting glucose has already declined in patients with T2D. Such early improvements are likely mediated by the improvements observed in fasting hepatic insulin sensitivity, reduced basal endogenous glucose production, and increased hepatic insulin clearance. Together, these data point to the liver as a key mediator of early effects of RYGB on glycemia.

Insulin-mediated stimulation of peripheral glucose disposal and suppression of endogenous glucose production and of free fatty acids measured during hyperinsulinemic-euglycemic clamp were unchanged 1-week postoperatively, but improved over the year, at which time improved glucose utilization correlated with weight loss. Insulin secretion to intravenous glucose-glucagon stimulation was unchanged in T2D, such that the gradual improvement in the intravenous disposition index was largely due to parallel improvements in insulin sensitivity. In contrast, insulin secretion in response to oral glucose was improved by 3 months in T2D and was associated with exaggerated secretion of glucagon-like peptide 1 (GLP-1).

While there were substantial improvements in fasting and postload glycemia, insulin sensitivity, oral insulinogenic index, and disposition index to oral or intravenous stimuli, patients with prior T2D remained abnormal compared with control subjects, and patients with diabetes experienced a lower percent total weight loss over the year.

The findings of Bojsen-Møller et al. support a growing body of evidence demonstrating the importance of caloric deficit and improved hepatic metabolism to early improvements following RYGB. Rapid improvement in hepatic insulin sensitivity without immediate change in peripheral insulin sensitivity occurs in obese people subjected to caloric restriction (10). In the post-RYGB setting, reductions in endogenous glucose production are both immediate, as demonstrated by the current study at 1 week (even before marked weight loss), and sustained, as demonstrated by Nannipieri et al. (11) at 45 days after RYGB. After 45 days, little additional change in endogenous glucose production occurs over the first postoperative year. Similarly,

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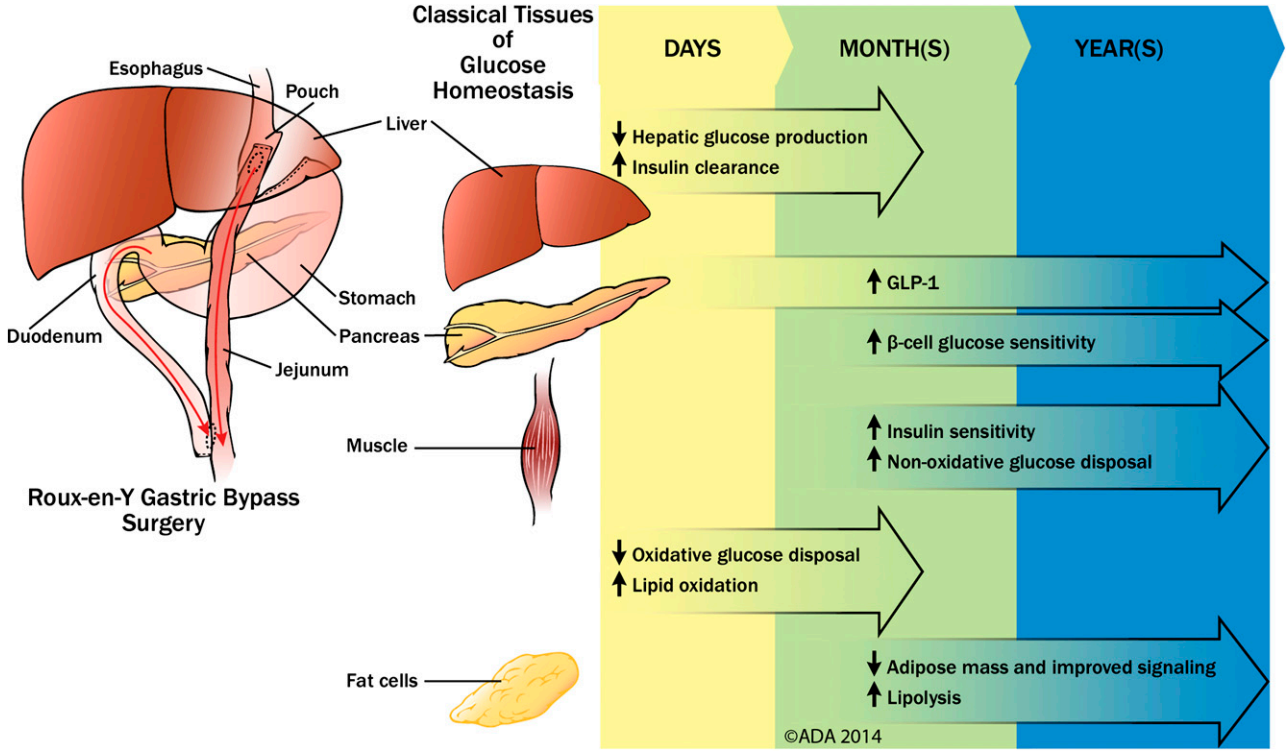

Figure 1—Physiologic effects of RYGB on classical pathways of glucose metabolism. Longitudinal physiologic studies of insulin secretion and action and glucose metabolism reveal the acute and evolving adaptations to RYGB procedure (9,11,12). Additional gastrointestinal, neuronal, and endocrine processes contribute to sustained weight loss and metabolic improvement.

increased lipid oxidation, consistent with energy deficit and shift of substrate utilization to lipids, is present at 2 weeks, but is attenuated by 1 year following RYGB (12). By contrast, peripheral insulin sensitivity improves in parallel with and in proportion to weight loss (11,12). However, at any BMI, those with T2D prior to surgery continue to have greater insulin resistance compared with those without diabetes preoperatively (11).

Enhanced insulin secretory responses also contribute to early improvements in metabolism following RYGB. β-Cell glucose sensitivity (the relationship between plasma glucose and the insulin secretory rate) increases independent of weight lost following RYGB in patients with and without T2D (11,13). Early β-cell functional improvements present within the first month are sustained over the first year (9,11,13). Like insulin sensitivity, β-cell function at any glucose concentration is lower prior to and following surgery in patients with T2D compared with those without (11). Improved β-cell responses may be attributed largely to dramatic increases in GLP-1 secretion (13), as supported by reduced β-cell secretion in the presence of the GLP-1 receptor inhibitor exendin(9–39) (14). Improvement in β-cell glucose sensitivity is not seen at similar weight loss following gastric band surgery (15), and gastric band surgery has not been associated with increased incretin response. Differences in incretin response coupled with greater weight loss likely contribute to higher rates of diabetes remission following RYGB compared with band.

There were limitations to Bojsen-Møller et al. Although physiologic characterization was thorough and longitudinal, cohorts were small. Participants had lost an average of 9.2 kg prior to surgery, which could attenuate effects attributable to surgery, especially at early assessment. There was no comparison group treated solely with caloric restriction, which is important as much of the early metabolic change may be directly related to caloric deficit. β-Cell function was assessed in response to oral glucose and intravenous glucose-glucagon, without glucose matching, limiting direct comparison of the route of stimulation.

Despite these limitations, Bojsen-Møller et al. (9) demonstrate that early RYGB effects on systemic metabolism can be linked to both caloric reduction and changes in hepatic metabolism. Subsequent metabolic effects, including improved peripheral insulin sensitivity, are likely to be more directly related to sustained weight loss. It remains to be determined the extent to which diabetes remission following RYGB is based on gastrointestinal, neuronal, and endocrine mechanisms promoting decreased appetite, increased satiety, and weight loss or traditional mechanisms related to insulin secretion and action. Additional novel mechanisms may include exclusion of inhibitory factors from the proximal intestine (16), morphological changes of the Roux limb with increased cellular size and

mass resulting in reprogramming of intestinal glucose metabolism (17), increased energy expenditure (18), changes in branched-chain amino acids (19), bile acid composition (20), gut microbiota (21), or other factors. Understanding the physiologic processes and sequence of change may help inform optimal selection of candidates most likely to benefit from different surgical interventions for diabetes and weight management and less invasive, safer alternative therapeutic approaches to manage obesity and T2D.

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