

# Does Caloric Restriction Alone Explain the Effects of Roux-en-Y Gastric Bypass on Glucose Metabolism? Not by a Long Limb

Adrian Vella

**A**mong patients with type 2 diabetes, bariatric surgery has been the subject of considerable interest because of its favorable effects on glucose metabolism. Indeed, various procedures have been associated with high rates of diabetes remission (1), although the outcomes of these studies have been assessed in a heterogeneous manner (2). Despite the favorable results overall, there has been divergence among procedures regarding improvement of diabetes (1). This observation raises the possibility of identifying underlying mechanisms leading to improved glucose metabolism as a means to identify new diabetes treatments. The pathophysiology underlying development of type 2 diabetes includes defects in insulin secretion, disordered postprandial suppression of glucagon secretion, and defects in insulin action and glucose effectiveness (the ability of insulin and glucose to stimulate glucose uptake and suppress glucose release) (3). The heterogeneous effects of various forms of bariatric surgery on these parameters remain a topic of intense interest.

Roux-en-Y gastric bypass (RYGB) is currently the most common bariatric procedure. This surgical approach results in both gastric restriction and malabsorption. Increased delivery of calories to the jejunum/ileum increases enteroendocrine secretion, most notably that of glucagon-like peptide-1 (GLP-1) (4). Whether the increase in postprandial concentrations of GLP-1 is relevant to insulin secretion or gastrointestinal motility in ways that benefit glucose metabolism after gastric bypass is uncertain. GLP-1 increases insulin secretion and suppresses glucagon secretion. In an intact upper gastrointestinal tract, GLP-1 also delays gastric emptying (5) and increases gastric accommodation (6). However, it is uncertain if these actions are present after RYGB due to the alterations in upper gastrointestinal tract anatomy. Some studies have suggested that increased GLP-1 concentrations after RYGB contribute to insulin secretion, although the experimental conditions do not relate directly to actual postprandial conditions (7).

Bariatric surgery is associated with a rapid improvement in fasting glucose concentrations and insulin action (8). These changes occur early in the postoperative course and

are independent of a significant change in weight (8). The same improvements are also observed in response to significant caloric restriction (600–800 kcal daily), suggesting that these benefits are not unique to bariatric surgery (9,10). Therefore, caloric restriction per se likely plays an important role in the favorable metabolic changes observed after bariatric surgery.

In this issue, Jackness et al. (11) compare the effect of a very low-calorie diet (VLCD) (500 kcal/day) and RYGB on  $\beta$ -cell function in type 2 diabetic patients during the first 3 weeks after intervention. Previously, the same group demonstrated that an 800 kcal/day diet produced less improvement in  $\beta$ -cell function compared with a matched cohort of subjects post-RYGB with equivalent weight reduction (12). The new study was undertaken to better control for differences in caloric consumption between the surgically treated and calorically restricted groups. Subjects with a history of type 2 diabetes scheduled to undergo RYGB and control subjects willing to maintain a VLCD were studied before and approximately 21 days after intervention using an insulin-modified, frequently sampled intravenous glucose tolerance test (fsIVGTT). The investigators reported that both groups achieved similar degrees of weight loss and that there were no significant differences in  $\beta$ -cell function between the groups. The authors concluded that caloric restriction was primarily responsible for the early effects of RYGB on glucose metabolism.

The investigators acknowledge that a significant limitation of their study was the use of an fsIVGTT to measure  $\beta$ -cell function. This approach does not account for potential influences of the incretin system on glucose metabolism (13). This is a significant weakness given the known effects of RYGB on incretin hormone concentrations. Another weakness is the potential carryover effects associated with glucose-lowering medications, which were stopped 2–3 days prior to the study. Furthermore, there is a dearth of information regarding how medication dosing changed over the duration of the study and whether any differences in treatment between the groups might have accounted for the end result.

Despite these limitations, there is some important information to be gleaned from this study as it creates conditions of controlled caloric intake and activity that mimic those in the immediate RYGB postoperative period. The authors suggest that none of the baseline function testing predicted the response to intervention as measured by changes in disposition indices and weight. This may be because the population under study had type 2 diabetes for a relatively short period of time (<6 years, self-reported) and their diabetes was controlled by relatively few agents and <60 units of insulin daily. While this limits generalizing the study's conclusions to a broader population, the data imply that it is reasonable to expect improvement in

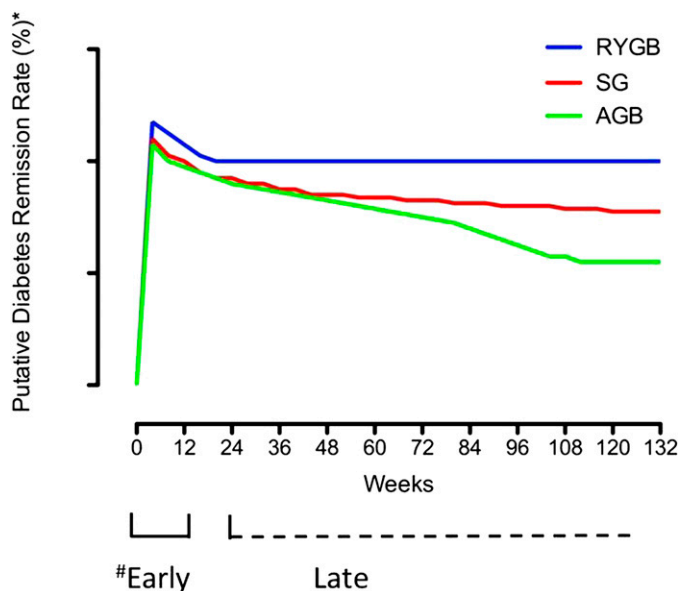
From the Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota.

Corresponding author: Adrian Vella, vella.adrian@mayo.edu.

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**FIG. 1.** Schematic representation of the time course for putative diabetes remission after various types of bariatric surgery. While it is probable that most of the “early” effects of bariatric surgery are produced by caloric restriction, it is possible/likely that other intestinal factors such as altered incretin secretion, bile acid malabsorption, and the degree of and durability of the surgically induced restriction may explain the durability of diabetes remission after surgery. \*The definition of remission after surgery is arbitrary, and it is important to emphasize that the data represented here are partially gleaned from the literature and partly from clinical experience. They are intended to illustrate the suggestion that differing surgeries may have differing success in maintaining a durable diabetes remission. #Arbitrarily defined as 12 weeks. SG, sleeve gastrectomy; AGB, adjustable gastric banding.

$\beta$ -cell function after a similar intervention in subjects with similar characteristics as those studied here. The study also reinforces the clinical suspicion that caloric restriction is a significant contributor to the rapid improvement in glucose metabolism observed after RYGB.

While two recent prospective, randomized, non-blinded studies concluded that bariatric surgery was superior to medical therapy alone in achieving glycemic control (14,15), there was significant heterogeneity in response. In the study by Schauer et al. (14), 12% of patients receiving medical therapy achieved an  $HbA_{1c} < 6\%$  in contrast to 42% undergoing RYGB. While this is a significant difference in favor of RYGB compared with intensive therapy, less than half of the RYGB group achieved the (admittedly arbitrary) definition of remission from type 2 diabetes. The reasons for this heterogeneity in response to surgery and how to better predict an optimal response to bariatric procedures remain elusive. Intriguingly, while sleeve gastrectomy had similar rates of resolution to RYGB 1 year after intervention, at 24 months subjects with RYGB exhibited greater reduction in truncal fat and improvement in  $\beta$ -cell function compared with sleeve gastrectomy or medical therapy (16). Whether these differences are attributable to

intestinal factors or merely reflect differing degrees and durability of restriction remain to be determined and warrant further study (Fig. 1).

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