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Mechanisms of surgical control of type 2 diabetes: GLP-1 is the key factor—Maybe

Marzieh Salehi, M.D., M.S.[a,*], David A. D'Alessio, M.D.[b]

[a]Department of Biomedical Science, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California
[b]Department of Medicine, Duke University, Durham, North Carolina

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Abstract Bariatric surgery is the most effective treatment for obesity and diabetes. The 2 most commonly performed weight-loss procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy, improve glycemic control in patients with type 2 diabetes independent of weight loss. One of the early hypotheses raised to explain the immediate antidiabetic effect of RYGB was that rapid delivery of nutrients from the stomach pouch into the distal small intestine enhances enteroinsular signaling to promote insulin signaling. Given the tenfold increase in postmeal glucagon-like peptide-1 (GLP-1) response compared to unchanged integrated levels of postprandial glucose-dependent insulinotropic peptide after RYGB, enhanced meal-induced insulin secretion after this procedure was thought to be the result of elevated glucose and GLP-1 levels. In this contribution to the larger point–counterpoint debate about the role of GLP-1 after bariatric surgery, most of the focus will be on RYGB. (Surg Obes Relat Dis 2016;12:1230–1235.)

Keywords: Gastric bypass surgery; GLP-1; Hyperinsulinemia; Diabetes; Hypoglycemia

The long-awaited reports of randomly assigned clinical trials have provided definitive evidence that weight-loss procedures induce diabetes remission [1–5]. This glycemic-reducing effect of bariatric surgery is indeed due to better fasting insulin sensitivity as a result of surgically induced weight loss [6–8]. However, there is also clear evidence that some of the glycemic improvement after Roux-en-Y gastric bypass (RYGB) [9] and, to a lesser degree, sleeve gastrectomy (SG) [10] is immediate and therefore weight-loss independent.

As early as 1 week after RYGB, meal-induced insulin secretion is increased both in individuals with or without type 2 diabetes (T2D) [11]. This postprandial hyperinsulinemia is associated with earlier and higher peaks of glucose as well as earlier and greater glucagon-like peptide-1 (GLP-1) secretion [11–16]. As a result, patients with RYGB have rapid clearance of glucose from the circulation and lower nadir glucose levels 60–90 minutes after eating.

The glycemic profile of RYGB is exaggerated in a subgroup of individuals who develop postprandial hypoglycemia years after the procedure [17], in whom meal-induced hyper- and hypoglycemia are associated with greater insulin and GLP-1 secretion compared to those without symptomatic low glucose [18] (Fig. 1). Similar to RYGB, although to a lesser degree, SG increases GLP-1 responses to meal ingestion [15,19] whereas other gastric bariatric procedures such as banding have no effect on postprandial glucose excursion or insulin and gut hormone responses [20]. Altogether, these findings are suggestive of a continuum in altered islet function mediated by changes in enteroinsular axis activity as a result of RYGB or SG.

*Correspondence: Marzieh Salehi, M.D., M.S., Cedars-Sinai Medical Center, Department of Biomedical Science, 8700 Beverly Blvd, Thalians E104, Los Angeles, CA 90048.
E-mail: marzieh.salehi@cshs.org

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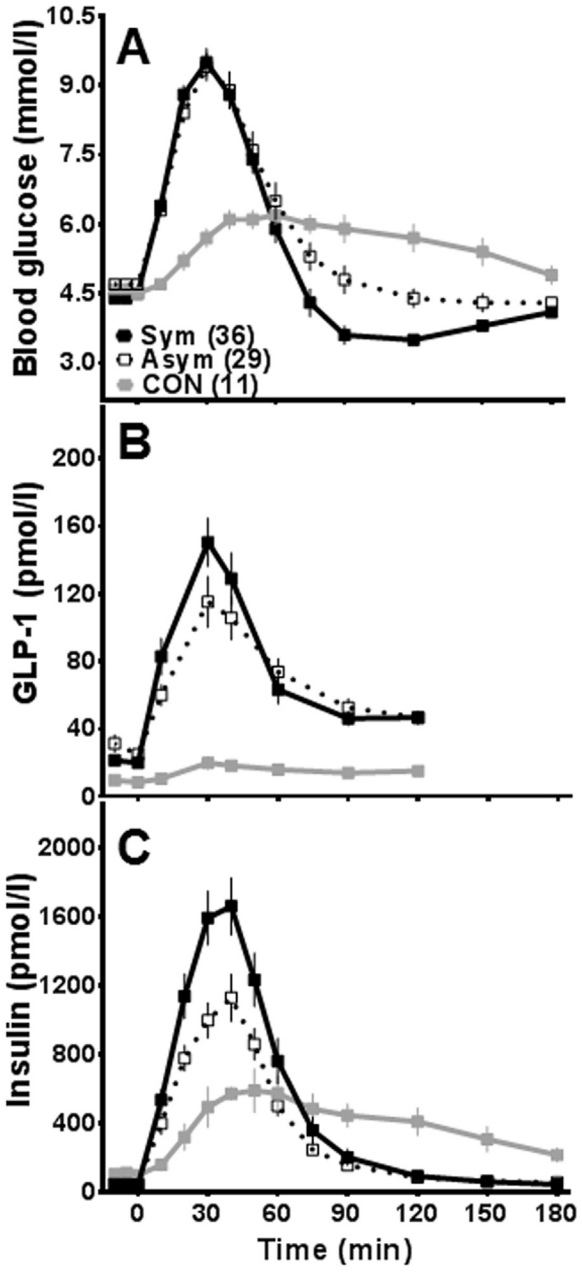

Fig. 1. (A) Blood glucose, (B) glucagon-like peptide-1, and (C) insulin responses to meal ingestion in individuals after Roux-en-Y gastric bypass with (Sym, solid black line and closed square) and without (Asym, dashed line and open square) previous history of postprandial hypoglycemia, and nonsurgical healthy controls (CON, grey solid line and closed square) [42].

In individuals with a normal gastrointestinal tract, postprandial glucose homeostasis is tightly regulated by glucose-dependent gut hormones, mainly GLP-1 and glucose-dependent insulinotropic peptide, secreted in response to nutrient ingestion [21–24]. In addition, it is recognized that the postmeal glycemic excursion is determined by the rate of carbohydrate entrance into the small intestine and splanchnic glucose uptake. Gastric emptying per se accounts for about one third of the variance of glycemic response to 75 g glucose ingestion in both normal individuals and those with T2D [25,26]. Direct infusion of glucose into the duodenum at varying rates within the normal range of gastric emptying (1–4 kcal/min) alters the glycemic response as well as insulin and gut hormone secretion dose-dependently [27]. Therefore, a major factor in the distinct postprandial glycemic pattern after RYGB can be attributed to faster transit of nutrients from the small gastric pouch into the small intestine [28], likely causing the augmented secretion of incretins, mainly GLP-1. Increased rates of carbohydrate appearance in the small intestine result in a larger flux of splanchnic and systemic glucose [16,29,30]. Consequently, increased meal-induced insulin secretion after RYGB is partly due to augmented β-cell sensitivity to glucose, while insulin secretion to intravenous glucose infusion does not differ among individuals with or without RYGB [31–33]. Taken together, the combined effects of elevated glucose [29,30,34] and a larger incretin effect [13,14,32] appear to account for enhanced meal-induced insulin secretion after RYGB, while the role of the incretin effect after SG is yet to be defined.

The physiologic effects of endogenous GLP-1 on postprandial glucose metabolism in humans have been investigated using intravenous infusions of the potent GLP-1 receptor (GLP-1r) antagonist, exendin-(9-39) (Ex-9), during meal tolerance test. However, elimination of GLP-1 action during meal ingestion results in relative hyperglycemia, which confounds the interpretation of the insulinotropic effects of endogenous GLP-1. To circumvent this problem, we have infused Ex-9 during meal studies when glucose levels were maintained fixed with a hyperglycemic clamp. In this setting, we have shown that GLP-1r blockade suppresses postprandial insulin secretion and increased glucagon levels in both healthy individuals [22] and patients with well-controlled diabetes [21]. Extending these experiments to address the direct effect of endogenous GLP-1 on postprandial insulin secretion after RYGB, we found that the contribution of endogenous GLP-1 to meal-induced insulin secretion is twice as large in nondiabetic individuals with RYGB as in the body mass index–matched healthy controls [32] (Fig. 2). While patients with RYGB had postprandial hyperglucagonemia compared to the nonsurgical cohort, Ex-9 infusion suppressed glucagon secretion similarly in both groups, demonstrating that the glucagonostatic effects of GLP-1 are not affected by RYGB [32]. This was the first evidence to confirm that elevated plasma GLP-1 concentrations in people with RYGB are associated with increased GLP-1 action, (e.g., meal-stimulated insulin release). Moreover, these results do not seem to be the result of changes in gastric emptying since the effect of Ex-9 infusion on the rate of nutrient passage from the gastric pouch to the small intestine was negligible [21,22,35].

Separate studies using Ex-9 infusion during meals without glucose clamps supported the initial experiments with GLP-1 blockade. Thus, blocking the GLP-1r had a larger

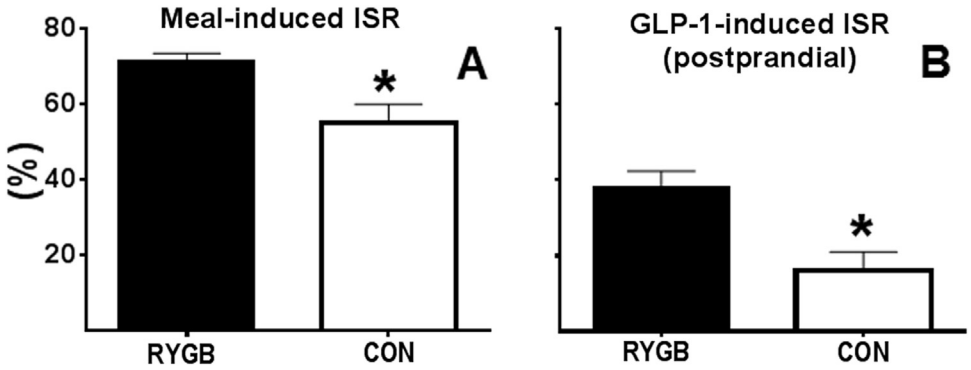

Fig. 2. Relative increase in (A) meal-induced insulin secretion rate (ISR) and (B) endogenous glucagon-like peptide-1contribution to ISR in individuals after Roux-en-Y gastric bypass (black bar) and body mass index–matched healthy controls (white bar). *$P < .05$ compared to gastric bypass [32].

incremental effect on the postprandial glycemic response in nondiabetic RYGB patients compared to weight-matched controls without surgery (37 ± 12% in gastric bypass versus 14 ± 12% in controls); this was associated with a similar reduction of insulin secretion (13%–14%) and β-cell glucose sensitivity (15%–20%) in the 2 groups [18]. Using a comparable study design, another group of investigators observed similar findings, with Ex-9 infusion having a disproportionate effect on raising blood glucose in RYGB relative to control patients (45% versus 24%) [36]. Again, the authors noted a relative reduction in β-cell glucose sensitivity in nondiabetic individuals after RYGB compared to the nonsurgical cohort.

As the number of bariatric surgeries performed over the last decade has increased, it has become more apparent that a subgroup of individuals develops postprandial hypoglycemia several years after RYGB [37–39]. Hypoglycemia in affected individuals is exclusively postprandial, progressive, often associated with loss of consciousness or seizures, and only partially responsive to diet modification or available therapeutic options [40]. While the histologic correlate of this syndrome remains under debate [38,41], it is recognized that this often-debilitating complication is associated with greater insulin and GLP-1 responses to meal ingestion compared to asymptomatic individuals after RYGB [37,42] (Fig. 1), raising the possibility of a pathogenic role for GLP-1 in this syndrome. Using Ex-9 infusion, we have shown that blocking GLP-1r corrects hypoglycemia by suppressing insulin secretion in these patients [18] (Fig. 3). However, we also have found that systemic meal-derived glucose appearance is larger in patients with the hypoglycemia syndrome than in asymptomatic individuals and is not affected by blocking GLP-1r [18], suggestive that other pathogenic factors beyond GLP-1 contribute to hypoglycemia.

Together, these findings indicate that elimination of GLP-1 has a greater postprandial glycemic effect in nondiabetic individuals after RYGB and, to larger degree, in those with hyperinsulinemic hypoglycemia syndrome. However, the question remains as to whether improved postmeal glucose homeostasis in patients with T2D is attributable to augmented GLP-1 action.

Several preclinical studies using mouse models with GLP-1 receptor deletions raised questions as to the necessity of GLP-1 signaling in glycemic improvement after bariatric surgery. GLP-1 receptor knockout mice had similar weight loss and improved glucose tolerance compared to control animals after RYGB [43] and SG [44]. While these models provide a powerful and specific approach to eliminating GLP-1 action, a caveat in the interpretation of these studies is that animals with developmental gene deletions may develop compensatory mechanisms to accommodate their lifelong absence of GLP-1 r signaling. Nonetheless, these findings do raise some question as to the role of GLP-1 after surgery.

The relevance of GLP-1 action in glucose-reducing effects of RYGB was investigated by 3 independent investigators using different methods. In the first study [45], 9 patients with T2D (average HbA1C of 6.5%) were studied with a meal tolerance test with and without GLP-1r blockade before RYGB, and 1 week and 3 months after surgery. A total 8 of 9 patients who were treated with antidiabetic medications before RYGB (metformin alone or in combination with insulin secretagogues or insulin) required no medications after surgery, with an average HbA1C reduction to 5.7% at 3 months. RYGB altered the glycemic response to meal ingestion, leading to an earlier peak and larger glucose excursion but no significant changes in the incremental area under the glucose response curve for 4 hours ($AUC_{Glucose[4\ hr]}$). In parallel to glycemic changes, postmeal insulin secretion was shifted to the left with greater β-cell glucose sensitivity after surgery. Blocking GLP-1r signaling resulted in a larger $AUC_{Glucose(4\ hr)}$ throughout the experiment. This glycemic effect of Ex-9 was associated with suppression of insulin secretion and β-cell glucose sensitivity to levels similar to preoperative at 1 week and 3 months, suggesting that the glycemic-reducing effect of RYGB is partly due to an enhanced GLP-1-stimulated insulin response. Ex-9 increased glucagon and had no effect on gastric emptying as previously reported.

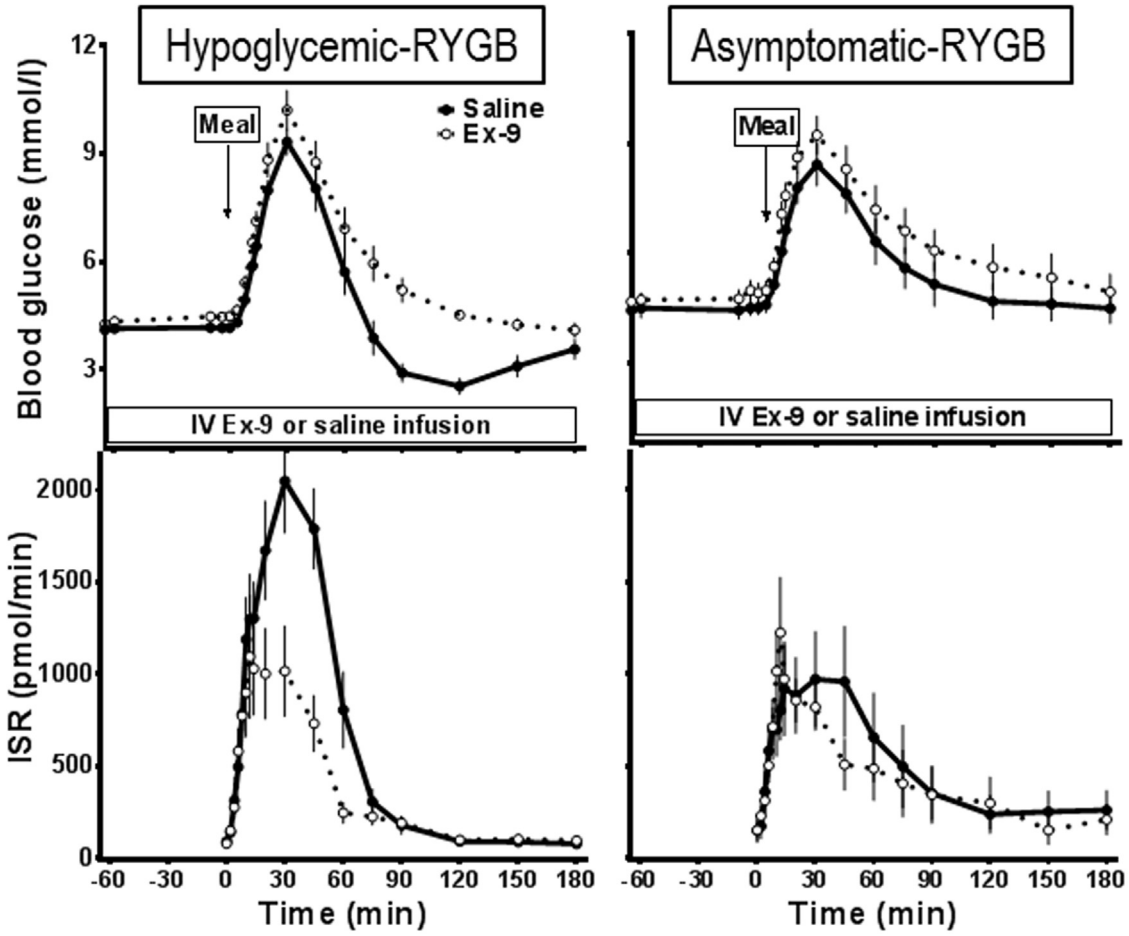

Fig. 3. Blood glucose and insulin secretion responses to meal ingestion in individuals with post–Roux-en-Y gastric bypass (RYGB) hyperinsulinemic hypoglycemia syndrome (left panels) and asymptomatic individuals after RYGB (right panels) during meal studies with (dashed line and open circle) and without (solid line and open circle) Ex-9 infusion [18].

The second study [46] evaluated glucose and insulin response to meal ingestion with and without infusion of Ex-9 in 8 patients with resolved diabetes after RYGB (average HbA1C of 6.6% before RYGB) compared to 7 leaner nondiabetic healthy controls (average body mass index: 31 kg/m^2 in RYGB versus 21 kg/m^2 in controls). Individuals with history of RYGB had larger $AUC_{Glucose(2\ hr)}$ values compared to the leaner controls. The relative enhancement in the integrated glucose levels measured for 2 hours as a result of Ex-9 infusion was similar in both groups (10%). The relative reduction in insulin secretion, on the other hand, was significantly larger in surgical patients compared to nonsurgical (decrease in $AUC_{Insulin(2\ hr)}$: 54% versus 4%), indicating that RYGB enhances GLP-1-induced insulin secretion.

In a more recent study [47], patients with T2D (average HbA1C of 7.5%) were studied with liquid mixed meals with and without infusion of Ex-9 after 10% weight loss achieved by RYGB (N = 8) or lifestyle modification (N = 8). The target weight loss was achieved in 2 months after RYGB and in 3 months in nonsurgical groups, leading to improved glucose levels in both groups estimated by HbA1C (average of 6.4%). Despite similar HbA1C reduction, weight loss led to a larger reduction in the incremental $AUC_{Glucose(3\ hr)}$ in the nonsurgical cohort compared to those after RYGB (35% versus 15%), likely due to an earlier and larger glycemic excursion after RYGB as a result of increased nutrient flux.

Cross-sectional comparison of Ex-9 effect on postprandial glucose levels after weight loss, however, revealed an identical relative enhancement in $AUC_{Glucose(3\ hr)}$ among surgical and nonsurgical individuals (41% in RYGB versus 44% in nonsurgical). Despite similar changes in glycemia, the insulinotropic effects of endogenous GLP-1 were significantly greater after RYGB than the lifestyle interventions (reduction in $AUC_{C\text{-}peptide(3\ hr)}$: 37% in RYGB versus 5% in nonsurgical), consistent with findings from the previous studies. The absence of glycemic-reducing effects of GLP-1r antagonist beyond the effect of weight loss in this study is considered to be evidence against the beneficial effects of enhanced GLP-1 action in diabetes remission after RYGB despite the enhanced insulinotropic effects.

The enteroinsular axis in postprandial glucose homeostasis after SG is much less characterized, but SG seems to have similar effects on glucose, insulin, and GLP-1 responses to meal ingestion as RYGB [15], only smaller [19]. Only one cross-sectional study has compared the integrated glucose and insulin responses to meal ingestion with and without Ex-9 infusion among 8 patients with resolved diabetes after SG, 6 nondiabetic individuals after SG, and 8 leaner nonoperated controls. Glycemic response to meal ingestion among groups was not similar, as those with SG and history of diabetes had a larger $AUC_{Glucose(2\ hr)}$ at the time of evaluation compared to those nondiabetic patients with SG or nonsurgical individuals. The glycemic effect of GLP-1r antagonist was similar in both lean control and SG patients with history of T2D, whereas the nondiabetic SG individuals had minimal glycemic effect as a result of Ex-9 infusion. Along with glycemic data, β-cell glucose sensitivity was suppressed equally in both lean control and SG patients with history of T2D (∼35%) with no changes in SG nondiabetic patients as a result of elimination of GLP-1 action. While the findings are not consistent with increased GLP-1 action after SG, further studies with alternative designs are needed to address this issue.

In summary, findings from clinical studies in humans support a significant role for enhanced contribution of endogenous GLP-1 to postprandial β-cell function and glycemic pattern after RYGB [32,36,45], especially in individuals with the hypoglycemia syndrome [18]. However, based on current data, the enhanced GLP-1 action on insulin response after RYGB has no further beneficial effect on glucose improvement in patients with diabetes remission after RYGB [47]. It is important to note that there are no data in favor of or against a role for increased GLP-1 action in relation to other components of the enteroinsular axis (i.e., nutrient and neural stimulation). Also, little is known about the interindividual variability in sensitivity to GLP-1 among individuals undergoing weight-loss operations. Such information will likely be critical for the development of novel approaches to treatment of diabetes as well as improvement of the glycemic effects of RYGB and SG in patients with partial diabetes remission or relapse after complete remission [1,48].

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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