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Commentary

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Bariatric Surgery: It's Not Just Incretins!

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Abbreviations: FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide-1; GOP, GLP1, OXM, and PYY; OXM, oxyntomodulin; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; T2D, type 2 diabetes; VLCD, very low-calorie diet.

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Metabolic/bariatric surgery is a highly effective approach for the treatment of type 2 diabetes (T2D). Several randomized clinical trials have demonstrated that surgery promotes both weight loss (beyond lifestyle measures and pharmacotherapy) and improved glycemic control and/or diabetes remission, allowing reduction or elimination in medication use, compared with nonsurgical medical management (1,2). Surgical management also reduces risk for macrovascular and microvascular complications of diabetes (3). Given these important endpoints for clinical care, the search for mechanisms mediating improved metabolic control and their translation into nonsurgical treatments remains an important scientific goal.

While sleeve gastrectomy is currently the most common bariatric procedure, Roux-en-Y gastric bypass (RYGB) is often still considered the "gold standard" procedure for T2D. RYGB creates a small gastric pouch, allowing rapid delivery of undigested food into the Roux limb (derived from the jejunum) and bypass of the duodenum. These anatomical changes result in both rapid weight loss and improved glucose metabolism potentially via acute reduction in appetite and food intake and improved hepatic, muscle, and adipose tissue insulin sensitivity (4). Sustained effects on weight loss and improved glycemic control are likely related to chronic remodeling of the gut–brain–liver axis. Increases in secretion of intestinally derived hormones, such as glucagon-like peptide-1 (GLP1), gastric inhibitory polypeptide (GIP), oxyntomodulin (OXM), peptide YY (PYY), ghrelin, and others, have been proposed as a dominant mediator of these effects, given their potent effects to increase glucose-stimulated insulin secretion, reduce gastric emptying, increase energy expenditure, and increase satiety (5). Additional contributors to postprandial metabolic changes after RYGB include alterations in the bile acid–farnesoid X receptor (FXR)–fibroblast growth factor 19 (FGF19) axis and the composition of the intestinal microbiota.

Jones et al. (6) have investigated whether a strategy designed to mimic the increased intestinal hormone secretion after RYGB could also induce similar changes in whole-body metabolism. The authors randomized participants with obesity and T2D or prediabetes, treated with either diet or a single oral agent, to infusion of a combination of GLP1, OXM, and PYY ("GOP", n = 14) or saline (control, n = 11) subcutaneously for 12 hours per day for 4 weeks, and analyzed both whole-body and fasting metabolomic effects, compared with individuals undergoing RYGB (n = 22) or caloric restriction with very low–calorie diet

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(VLCD) (800 kcal/day, n = 22). The authors previously reported that the GOP infusion led to reduction in fasting glucose and improved glycemia during meal tolerance testing compared with saline, but this may have reflected in part the higher baseline glucose levels in the GOP group (7). Weight loss was greater for GOP infusion than for saline, but less than that observed for RYGB or VLCD groups.

Despite these favorable effects of GOP infusion on glucose metabolism and weight loss, no significant changes were observed in the fasting plasma or urinary metabolome, and effects of GOP were similar to the placebo group. On the other hand, the metabolomic impact of RYGB and VLCD were robust and quite similar to each other, with up to one-third of metabolites changed. This included substantial decreases in acylglycerols (especially those containing shorter-chain and saturated lipid species), increases in fatty acids and acylcarnitines, decreases in phospholipids, and increases in ketones, a pattern consistent with known shifts toward fatty acid oxidation in the setting of caloric restriction. Relatively modest changes in amino acid metabolism were observed in RYGB, greater than for VLCD, but were not observed in response to GOP infusion. The majority of these changes correlated with weight loss.

While the methodology employed for the metabolomics assay and analysis was robust, the study design and results have some important limitations. Firstly, despite dosing to achieve concentrations similar to peak levels after RYGB, the constant infusion of GLP1, OXM, and PYY does not really mimic the physiological prandial surges in these hormones after RYGB, which may contribute to observed differences in postprandial glycemic variability and insulin secretion, and effects on the postprandial metabolome were not assessed. In addition, the study design did not test the impact of additional gut-derived incretin hormones such as GIP, and did not mimic surgery-induced alterations in bile acid metabolism, FXR activation and FGF19 secretion, key factors previously implicated in efficacy of bariatric surgery (5). Moreover, despite the reported impact of the GOP peptides on satiety and energy expenditure, the current therapy induced less weight loss than either RYGB or VLCD. Even potent incretin agonist drugs require substantial duration of therapy to achieve weight loss and diabetes control (8). Thus, the short-term duration of infusion of the candidate peptides in the current study may not have been adequate to achieve the maximal potential effect of GOP peptides. Chronic infusion of GOP did not reduce fasting insulin levels or modulate postprandial insulin dynamics, both of which may be important contributors to additional metabolomic responses under both conditions. Moreover, the impact of GOP infusion on visceral fat composition and adipocytokines, which could mediate metabolic benefits beyond weight loss, were not examined in the protocol. Finally, dietary macronutrient composition was not controlled, and differences between groups could modulate the measured metabolome.

Taken together, however, these data suggest that additional factors beyond sustained increases in plasma levels of GLP1, OXM, and PYY are required to produce the full impact of RYGB. While the tripeptide GOP infusion yielded improvements in glucose metabolism superior to RYGB or VLCD, there was little effect on the plasma metabolome. This suggests that the more robust and acute caloric restriction and weight loss observed with both RYGB and VLCD, together with additional intestinal and microbiome adaptations, changes in feeding behavior, and alterations in amino acid and bile acid metabolism over time, provide additional and sustained benefits for systemic metabolism and weight loss not observed with incretin infusion alone. Additional studies will be required to understand the unique and potent mediators of bariatric/metabolic surgery, and to identify those combinations of "bariatric mimetics" which can lead us 1 step closer to more effective nonsurgical solutions for obesity and T2D.

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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