■ BENCH TO BEDSIDE

Metabolic insights from cutting the gut

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Bariatric surgery is currently the most effective treatment option for obesity, resulting in substantial and durable weight loss with reduction in mortality and obesity-related comorbidites[1]. Obesity is the primary risk factor for type 2 diabetes mellitus (T2DM), which is characterized by insufficient insulin secretion and insulin resistance of peripheral tissues[2]. Proximal gastric bypass surgery (PGBP) is considered the 'gold standard' bariatric procedure, reducing excess body weight by up to 80%. Additionally, the majority of individuals with T2DM that undergo PGBP show immediate improved glycemic control after surgery, before significant weight loss. Although many therapeutic regimens aim to modulate glucose concentrations to prevent end-organ damage, bariatric surgery seems to be the only treatment modality with the potential to induce complete resolution of T2DM.

The mechanisms underlying this process, however, remain elusive. Recently, a technically less complex operation, sleeve gastrectomy, has been shown to result in weight loss and enhanced glycemic control comparable to PGBP[3]. Understanding how these surgical procedures induce sustained weight loss and resolution of T2DM holds the key to development of more directed, less invasive therapies. In a recent study, Chambers *et al.*[4] investigated bariatric procedures in rodent models of human obesity, highlighting the comparable effectiveness of sleeve gastrectomy with PGBP and the importance of gut-derived hormones in mediating improved glucose homeostasis after surgery.

PGBP restricts stomach volume by creation of a gastric pouch of approximately 20 ml along the lesser curvature that is anastomosed with mid-jejunum; hence, nutrient flow is rerouted from the upper stomach rapidly into the mid-jejunum and, subsequently, the unaltered distal gastrointestinal tract. Accordingly, most of the stomach, the entire duodenum and the proximal jejunum are bypassed but remain *in situ*. PGBP was designed to restrict gastric volume, limiting food intake and reducing nutrient absorption to induce weight loss. Sleeve gastrectomy was intended to be a solely restrictive procedure; it involves partitioning and removal of 80–90% of the stomach, parallel with the lesser curvature without altering the anatomy of the small intestine (**Fig. 1**). Sleeve gastrectomy therefore leads to rapid emptying of gastric contents into the small bowel[5]. Data from patient populations concerning long-term outcomes of sleeve gastrectomy are limited, but findings to date illustrate comparable efficacy with PGBP, with excess weight loss of up to 75% and resolution in T2DM in up to 84% of cases[6,7]. In a recent position paper, the International Diabetes Federation supported the selective use of various bariatric procedures for obese individuals with medically resistant T2DM[2].

The means by which these procedures achieve such impressive outcomes seems to involve alterations in several gut-derived hormones including ghrelin, peptide YY (PYY) and glucagon-like peptide 1 (GLP-1)[6]. Ghrelin is the only orexigenic hormone identified to date; it is mainly produced by the endocrine X/A secretory cells within the stomach fundus and duodenum. Diet-mediated weight loss results in increased circulating ghrelin concentrations[8]; in contrast, several studies report low circulating ghrelin concentrations after PGBP[6]. Although the gastric fundus remains *in situ*, nutrient contact with ghrelin-secreting cells is interrupted. Sleeve gastrectomy, which involves complete removal of the majority of the gastric fundus and hence the major population of ghrelin-secreting cells, also leads to substantial and sustained reductions in ghrelin concentrations[9]. Together, these observations indicate that disruption of nutrient stimulation of endocrine cells within the stomach contributes to the beneficial effects of these modes of bariatric surgery.

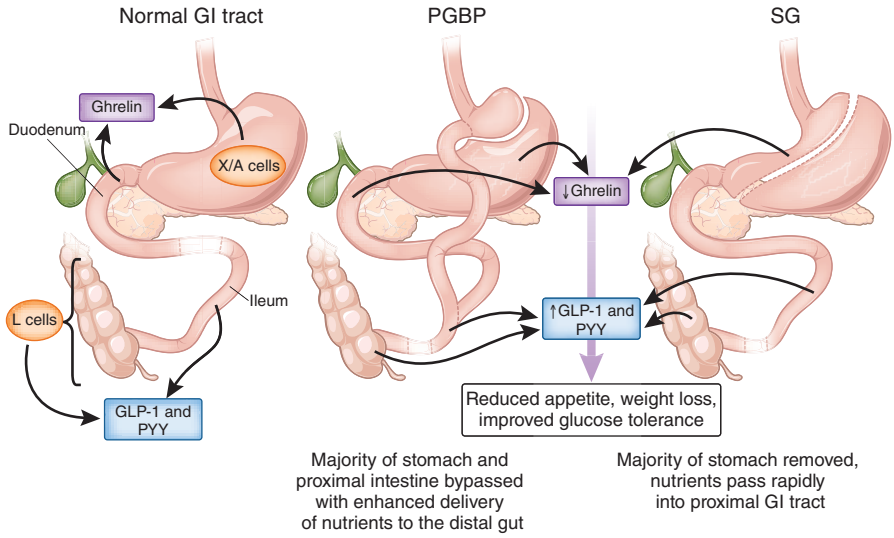

Figure 1 Hormonal insights from bariatric surgery. Several hormones are released from the gastrointestinal (GI) tract into the circulation (left); the 'hunger hormone' ghrelin is secreted from X/A cells, whereas PYY and GLP-1 are secreted from L cells, with the greatest concentration of L cells in the ileum and colon. In proximal gastric bypass (PGBP) (middle), a small gastric pouch is created and anastomosed with the mid-jejunum. Anastomosis of biliopancreatic limb with the jejunum allows drainage of biliary and pancreatic secretions. Nutrients flow through the gastric pouch and directly into the mid-jejunum, therefore bypassing the majority of the stomach, the duodenum and the proximal jejunum. In sleeve gastrectomy (SG) (right), the stomach is transected along the greater curve and the entire gastric fundus and body are removed without manipulation of small bowel. Nutrients enter the gastric sleeve and subsequently the small intestine with normal secretion of biliary and pancreatic products. Both PGBP and sleeve gastrectomy seem to result in reduction of circulating ghrelin and increased levels of GLP-1 and PYY, despite distinct anatomical differences. This combination of changes in the hormonal milieu might account for the improved glucose control and reduced appetite with subsequent weight loss observed after both procedures.

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PYY is an anorectic hormone that is secreted from enteroendocrine L cells, which are located throughout the gastrointestinal tract but mostly concentrated in the ileum and colon. After a meal, plasma PYY concentrations rise proportionally to caloric intake—although this response is blunted in obese subjects[10].The L cells also produce the incretin hormone GLP-1, which stimulates insulin secretion. Additionally, GLP-1 is thought to promote insulin sensitivity and may contribute to appetite suppression after eating. Several pharmacological agents targeted at the GLP-1 axis are being used to treat T2DM, including GLP-1 receptor agonists and dipeptidyl peptidase IV (DPP4) inhibitors, which extend the half life of biologically active endogenous GLP-1 (ref. 11). Several studies in humans show that PGBP leads to concomitant increases in both PYY and GLP-1 after a meal, with rises in these hormones occurring early after surgery[12] and independently of weight loss[13]. Early studies investigating gut hormone changes after sleeve gastrectomy suggest similar increases in post-operative nutrient-stimulated plasma PYY and GLP-1 concentrations[12].

It is thought that increased circulating PYY levels after surgery contribute to appetite reduction and hence drive weight loss, whereas increased circulating GLP-1 levels account for the marked changes in glucose control. Interestingly, the use of pharmaceutical GLP-1 agonists and DPP4 inhibitors alone does not result in the same glycemic benefits or T2DM resolution seen after bariatric surgery. Moreover, the changes in circulating levels of ghrelin, PYY and GLP-1 occur in synchrony post-operatively, indicating that the distinct roles of each hormone require delicate investigation using appropriate models. To account for the hormonal alterations induced by bariatric surgery, the 'foregut theory' was proposed, suggesting that bypassing the duodenum and proximal jejunum removes an anti-incretin factor, leading to improved glucose control[14]. However, the observed similarity in weight loss and glycemic control after sleeve gastrectomy, which does not entail bypass of the duodenum and proximal jejunum, brings this theory into question. The alternative 'hindgut theory' suggests that increased flux of unabsorbed, incompletely digested nutrients to the distal gastrointestinal tract causes greater L cell stimulation and therefore increased circulating GLP-1 and PYY concentrations.

To further understand the dynamic alterations in gut hormones engendered by surgery, animal models of PGBP and sleeve gastrectomy have been developed. In their recent study, Chambers *et al.*[4] performed these bariatric procedures on diet-induced obese rats to investigate putative mechanisms underlying altered glucose handling in the early post-operative period. The two procedures resulted in similar improvement in insulin sensitivity and glucose tolerance as well as similar concentrations of meal-stimulated GLP-1 secretion in the operated obese rats compared to sham-operated control rats. Moreover, the studies showed that blocking GLP-1 activity with an antagonist of its receptor (exendin9-39) blunted surgically induced improvements in glucose tolerance and insulin secretion[4]. Whereas previous studies have strongly alluded to the role of GLP-1 in the glycemic improvements after bariatric surgery, this study strongly supports that enhanced GLP-1 concentrations directly lead to increased insulin secretion and glucose control after both procedures.

This study provides further evidence negating the importance of proximal duodenal and jejunal bypass. Furthermore, it suggests that sleeve gastrectomy induces changes in the hormonal milieu akin to PGBP and may enhance nutrient delivery to the distal gastrointestinal tract without intestinal bypass. Modified gastric bypass procedures in diet-induced obese and *Pyy*-deficient obese mice have confirmed a key role of PYY in weight loss after surgery, as mice lacking PYY did not show the substantial weight loss observed in diet-induced obese mice early after surgery[15]. Current investigations in gut-derived cell lines from mouse models, employing electrophysiology studies, are providing further insights into L cell secretion mechanisms[16].

Bariatric surgery represents a safe treatment modality for sustained weight loss but involves procedural variability. Data from a large cohort of subjects suggest that 30-d mortality after bariatric procedures is low (less than 0.3%)[7,17]; however, a number of negative outcomes have been reported, including anastomotic leaks and macro- or micronutrient deficiencies[1]. Developing less invasive methods for weight loss, with efficient and durable outcomes, while minimizing complication rates, is a key focus of current investigations. Further studies are crucial to elucidate precise mechanisms underlying the metabolic benefits of bariatric procedures. Such studies will ensure the development of nonsurgical means to induce favorable hormonal profiles and sustainable weight loss to reduce obesity-related morbidity and mortality.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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