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Review article

Mechanisms in bariatric surgery: Gut hormones, diabetes resolution, and weight loss

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Abstract Gastric bypass surgery leads to profound changes in the secretion of gut hormones with effects on metabolism, appetite, and food intake. Here, we discuss their contributions to the improvement in glucose tolerance and the weight loss that results from the operations. We find that the improved glucose tolerance is due the following events: a negative energy balance and resulting weight loss, which improve first hepatic and later peripheral insulin sensitivity, in combination with increased postprandial insulin secretion elicited particularly by exaggerated glucagon-like peptide-1 responses. The weight loss is due to loss of appetite resulting in reduced energy intake, and we find it probable that this process is driven by exaggerated secretion of appetite-regulating gut hormones including, but probably not limited to, glucagon-like peptide-1 and peptide-YY. The increased secretion is due to an accelerated exposure to and absorption of nutrients in the small intestine. This places the weight loss and the gut hormones in key positions with respect to the metabolic improvements after bypass surgery. (Surg Obes Relat Dis 2018;▮:00–00.) © 2018 American Society for Metabolic and Bariatric Surgery. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The interest in the hormonal changes after bariatric surgery derives from 2 fundamental observations: (1) the weight loss appears to result from reductions in appetite and food intake, which suggests that the operation interferes with the normal regulation of appetite and food intake, and (2) the resolution of type 2 diabetes that occurs already a few days after surgery before any major weight loss has occurred [1,2], suggesting that mechanisms independent of weight loss are involved.

In our laboratory, the interest in the hormonal changes after bariatric surgery began with the observation that jejuno-ileal bypass in humans causes grossly elevated postprandial responses of "enteroglucagon." Enteroglucagon is a collective designation for glicentin and oxyntomodulin, products of the glucagon precursor, proglucagon, which is also expressed in the L-cells of the gut and here is processed to these 2 peptides [3]. A few years later we discovered that proglucagon in the gut gives rise to 2 additional glucagon-like peptides (GLPs), GLP-1 and GLP-2 [4], with important effects on insulin secretion [5], food intake [6], and intestinal growth [7]. Consistent with our findings after jejuno-ileal bypass, we found that

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GLP-2 secretion is greatly upregulated by ileal transposition in rats [8]. The potential importance of these changes in hormone secretion for the weight changes was supported by studies by Näslund et al. [9,10]. However, because of the powerful insulinotropic effects of GLP-1, it was relevant to examine secretion of this hormone in a group of patients undergoing Roux-en-Y gastric bypass (RYGB), who suffered from severe postoperative hypoglycemia [11]. Indeed, in these patients, we measured dramatically elevated postprandial levels of GLP-1, reaching between 300 and >500 pmol (i.e., 10–20 times higher normally observed except in people undergoing gastrectomies and those with postoperative dumping) [12]. Soon after, Le Roux et al. [13] published more comprehensive data from both human and animal studies showing exaggerated release of not only GLP-1 but also the additional L-cell product peptide-YY (PYY), which is also considered an appetite-regulating hormone [14]. In further studies, we observed that increases did not involve the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), and that similar changes were not observed in patients undergoing gastric banding operations [15]. We also observed that hypoglycemia occurring after RYGB was clearly hyperinsulinemic and was associated with even higher GLP-1 responses and that glucagon responses were paradoxically increased (in spite of the hyperglycemia and the exaggerated GLP-1 responses, which would be expected to inhibit glucagon secretion) [16]. These findings suggested that the surgical rearrangement after RYGB, similar to that after jejuno-ileal bypass, was responsible for the dramatic change in gut hormone secretion and that diabetes resolution and perhaps also loss of appetite/weight loss might be consequences of these changes. Indeed, in a patient with insulin-treated type 2 diabetes who had a gastrostomy catheter inserted after the operation, we were able to study metabolite and hormone secretion on 2 consecutive days 5 weeks postoperatively, when the patient was completely well and was given identical meals either orally (via the bypass) or via the gastrostomy catheter (i.e., via the "original" pathway: stomach, duodenum, and upper small intestine) [17]. On the day of gastrostomy feeding, he had diabetes and "normal" GLP-1 and insulin values; on the oral day, he had normal glucose tolerance and large GLP-1 and insulin responses. On the background of these and other studies we formulated a hypothesis [18] regarding diabetes resolution and weight loss after RYGB, shown diagrammatically in F1 Fig. 1 [19].

Mechanisms explaining diabetes resolution after RYGB

Early improvements in insulin sensitivity

The most important early event is probably the dramatic change in hepatic insulin resistance, which occurs within a few days and reaches approximately 50% of preoperative values after just 1 week [2]. At this time, the values are equivalent to those obtained in matched, glucose-tolerant individuals. The decrease is evident whether determined by calculation of the HOMA-IR value from basal glucose and Q6 insulin levels or measured using clamp and glucose tracer methodology [20]. Concomitantly with the changes in hepatic insulin sensitivity, insulin clearance increases immediately after RYGB, which importantly influences peripheral insulin concentrations (i.e., evaluation of changes in insulin secretion must be based on C-peptide measurements). These improvements are likely due to the postoperative calorie restriction and the ensuing loss of liver fat as elegantly demonstrated using magnetic resonance imaging for liver fat [21], although the improvement in insulin sensitivity after surgery was actually larger than that observed after a very low calorie intervention [22]. As recently demonstrated, liver fat is an important determinant of HOMA-IR/hepatic insulin sensitivity as well as insulin clearance [23,24].

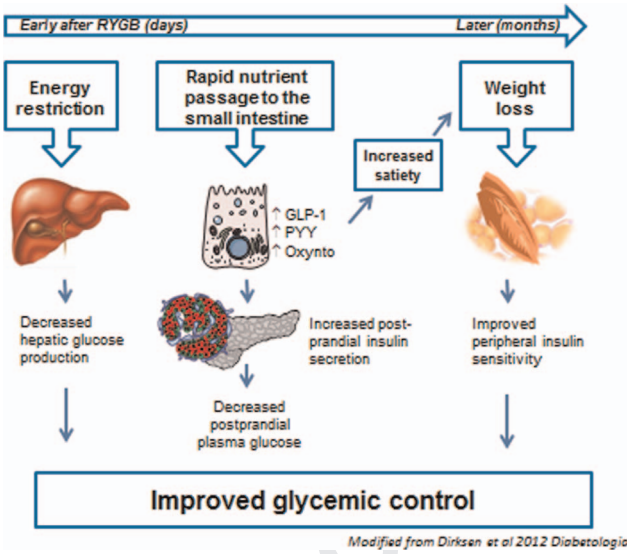

Fig. 1. . Q10

The early changes in hepatic insulin sensitivity lead to a rapid lowering of basal glucose concentrations, which may contribute to removal of glucotoxic effect on pancreatic beta cells as illustrated by the rapid enhancement of first phase insulin secretion in patients with type 2 diabetes [25]. With time and the accompanying weight loss, glucose disposal in peripheral tissues (muscle and fat) shows continued improvement (in fact near-normalization), which is explained by an enhanced insulin sensitivity and signaling [20,26], whereas glucose effectiveness seems to be unchanged after RYGB [25] This undoubtedly contributes importantly to the improved glucose tolerance after RYGB.

Digestion and absorption of nutrients

As soon as the newly operated patient begins to ingest nutrients, another mechanism sets in. As is clear today, the