



# From Entero-Endocrine Cell Biology to Surgical Interventional Therapies for Type 2 Diabetes

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## Abstract

The physiological roles of the enteroendocrine system in relation to energy and glucose

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homeostasis regulation have been extensively studied in the past few decades. Considerable advances were made that enabled to disclose the potential use of gastro-intestinal (GI) hormones to target obesity and type 2 diabetes (T2D). The recognition of the clinical relevance of these discoveries has led the pharmaceutical industry to design several hormone analogues to either to mitigate physiological defects or target pharmacologically T2D.

Amongst several advances, a major breakthrough in the field was the unexpected observation that enteroendocrine system modulation to T2D target could be achieved by surgically induced anatomical rearrangement of the GI tract. These findings resulted from the widespread use of bariatric surgery procedures for obesity treatment, which despite initially devised to induce weight loss by limiting the systemic availability of nutrients, are now well recognized to influence GI hormone dynamics in a manner that is highly dependent on the type of anatomical rearrangement produced.

This chapter will focus on enteroendocrine system related mechanisms leading to improved glycemic control in T2D after bariatric surgery interventions.

## Keywords

Bariatric surgery · Endoscopic interventions · Enteroendocrine system · Gastrointestinal

hormones · GIP · GLP-1 · Obesity ·  
Oxyntomodulin · Peptide YY · Type 2 diabetes

## Abbreviations

ADA	American Diabetes Association
BMI	Body mass index
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion with duodenal switch
CCK	Cholecystokinin
DJBL	Duodenal-jejunal Bypass Liner
DMR	Duodenal mucosal resurfacing
DSS-II	Second Diabetes Surgery Summit
EEC	Enteroendocrine cells
ESG	Endoscopic Sleeve Gastroplasty
EWL	Excess weight-loss
Gcg	Preproglucagon gene
GcGR	Glucagon receptor
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GJB	Gastrojejunal bypass
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
HbA1c	Hemoglobin A1c
IFSO	International Federation for the Surgery of Obesity
LSG	Laparoscopic sleeve gastrectomy
MNU	Neuromedin U
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
OHS	Obesity-hypoventilation syndrome
OSA	Obstructive sleep apnea
OXM	Oxyntomodulin
PYY	Peptide YY
RCTs	Randomized clinical trials
RYGB	Roux-en-Y Gastric Bypass
SADI-S	Single Anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy
T2D	Type 2 Diabetes

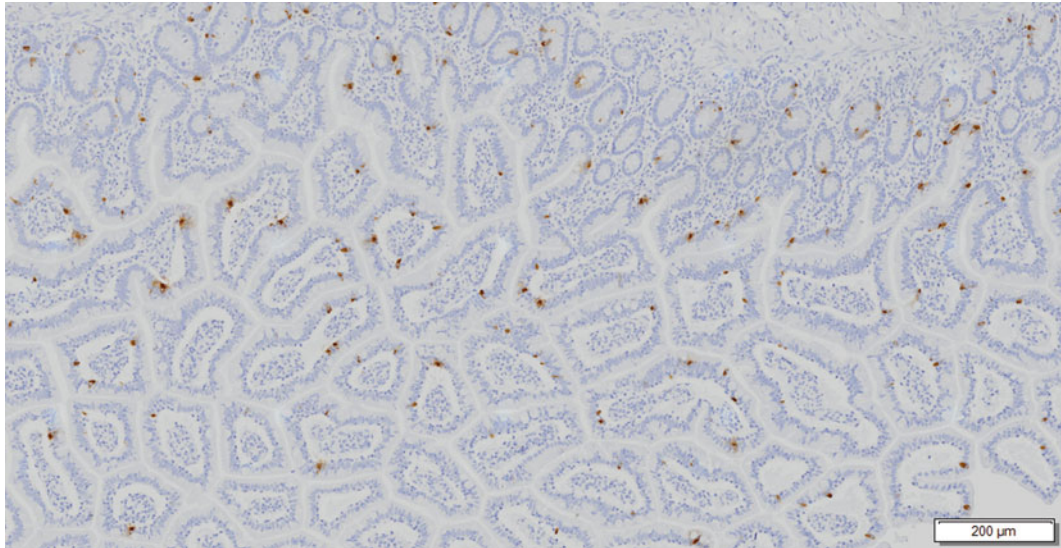
## 1 Anatomy and Physiology of the Enteroendocrine System

The gastrointestinal (GI) tract has been known to synthesize and release over twenty different hormones among several other bioactive molecules, which rendered it to be considered ‘the largest endocrine organ in the human body’ (Ahlman and Nilsson 2001). Although not exclusively, GI hormones are predominantly produced by a discrete endocrine-specialized cells population so called enteroendocrine cells (EEC). The EEC are found as scattered individual cells throughout the mucosa along the entire GI tract and comprise approximately 1% of the overall epithelial cell population (Fig. 1) (Rehfeld 2004; Buffa et al. 1978; Sternini et al. 2008).

EEC cell density is highest in the proximal small intestine and decreases throughout the gut until the distal colon. EEC cell density rises again in the rectum, a location where these cells can be found adjacent to each other in clusters, unlike what is observed in the rest of the gut (Cristina et al. 1978; Sjolund et al. 1983; Gunawardene et al. 2011).

The ECC can be categorized as “open-type” or “closed-type” according to the morphology and location within the GI mucosa. Open-type ECC exhibit prominent microvilli extending to the surface of the GI mucosa that enables the cells to react with the luminal contents by releasing secretory products, which by a variety of mechanisms activate local and distant target tissues and neuronal pathways. By contrast, the “closed-type” EEC are embedded in the GI mucosa with no part of the cell surface exposed to the luminal contents and are mainly regulated by neural and humoral mechanisms acting through the basolateral cell membrane (Sternini et al. 2008; Latorre et al. 2016; Hofer et al. 1999).

The distribution of EEC subpopulations responsible for secreting different hormones exhibits a characteristic pattern within the GI tract with ghrelin, somatostatin and gastrin being



**Fig. 1** Human small intestine staining for chromogranin A, used as a molecular marker specifically present in cells that store peptide hormones and monoamides, as occurs in enteroendocrine cells within the gastrointestinal tract (40x)

mainly expressed in the stomach; cholecystokinin (CCK) in duodenum and jejunum; glucose-dependent insulinotropic polypeptide (GIP) in the proximal small intestine; and glucagon-like peptide-1 (GLP1), oxyntomodulin (OXM) and peptide YY (PYY) in the distal small intestine and colon. Classically, EEC were classified according to the predominant hormone secreted. However, more recent evidence has demonstrated that each individual EEC usually expresses a variety of GI hormones. In turn, GI hormone secretion is not only determined by EEC distribution throughout the GI tract, but also modulated by the patterns of food intake, meal composition and nutrient absorption (Sjolund et al. 1983; Stengel and Tache 2009; Lamberts et al. 1991; Itoh 1997; Egerod et al. 2012; Svendsen et al. 2015; Posovszky and Wabitsch 2015; Monteiro and Batterham 2017; Grunddal et al. 2016) (Table 1). Besides that, the same EEC type may have different secretory profiles in different locations. For example, the EEC cells that produce GLP-1 and PYY (L-cells) although mainly present in the distal small intestine, are also present in the proximal gut. However, Svendsen *et al.*, found that in the proximal small intestine, there are more GLP-1-

positive cells than PYY- positive cells, suggesting that contrarily to the distal L-cells, not all the proximal L-cells produce PYY (Svendsen et al. 2015).

Besides that, the expression and the secretion of the GI hormones do not necessarily correlate. *In vivo* studies found that, although GLP-1-staining cells predominate in the distal small intestine, the same luminal and vascular stimuli of the proximal and distal small intestine induce similar GLP-1 secretion levels, suggesting that the secretory activity and responsiveness to the stimuli may be different in the proximal and distal gut (Svendsen et al. 2015).

GI hormones can act on peripheral and central organs that are reached through the blood stream or through modulation of the electrical activity of the vagal nerve afferent fibers (Browning and Travagli 2014; Ye and Liddle 2017). A considerable number of GI hormones are well known players in the regulation of energy and glucose homeostasis. In the past few decades, GI hormones have been extensively studied in what concerns the physiological roles in glucose homeostasis regulation and potential pharmacological use in the context of obesity and type 2 diabetes (T2D) treatments.

**Table 1** Summary of human enteroendocrine cells subsets, predominant GI tract location, hormones secreted, stimuli and physiological function

Cell type	Predominant location	Hormones	Main stimuli	Main functions
<b>P/DI-like cells</b>	Gastric fundus	Ghrelin Nesfatin-1	Fasting periods	Hunger drive, food intake stimulation, glucose homeostasis, growth hormone release
<b>G cells</b>	Pyloric antrum and duodenum	Gastrin	Gastrin releasing peptides; amino acids, stomach expansion	Stimulation of acid secretion, production of pepsinogen
<b>D cells</b>	Gastric body, pyloric antrum and small intestine	Somatostatin	Gastrin, CCK and H <sup>+</sup>	Inhibition of gastrin and acid secretion
<b>I cells</b>	Proximal small intestine	CCK	Long-chain fatty acid, peptides and amino acids	Gallbladder contraction stimulation, gastric emptying and food intake inhibition
<b>S cells</b>	Duodenum	Secretin	Secretin releasing peptide; low duodenal pH and digested proteins	Stimulation of pancreatic secretion and gastric emptying reduction
<b>K cells</b>	Proximal small intestine	GIP	Carbohydrates, long chain fatty acids and some amino acids	Insulin release, inhibition of gastric emptying and gastric acid secretion, food intake reduction
<b>L cells</b>	Along the entire small intestine with distal small intestine and large intestine predominance	GLP-1, GLP-2, PYY, OXM	Fatty acids, carbohydrates, amino acids	Nutrient sensing, gastric and intestinal motility inhibition, stimulation of insulin release, inhibition of glucagon release, appetite suppression and promotion of energy expenditure
<b>M cells</b>	Proximal small intestine	Motilin	Lipids, gastric distension, bile acids and low pH	Enhancement of gut motility
<b>N cells</b>	Distal small intestine	Neurotensin	Fatty acids	Inhibition of gastric secretion and gastric emptying, stimulation of pancreatic and intestinal secretion

*CCK* cholecystokinin, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *GLP-2* - glucagon-like peptide-2, *NT* neurotensin, *OXM* oxyntomodulin, *PYY* peptide YY

## 2 Experimental Data Supporting Enteroendocrine System Modulation through Interventional Therapies for Type 2 Diabetes

The unexpected observation that T2D could undergo clinical remission as a consequence of GI tract anatomical rearrangements induced by bariatric surgery interventions has led to the provocative hypothesis that T2D could be an intestinal disease (Rubino 2008).

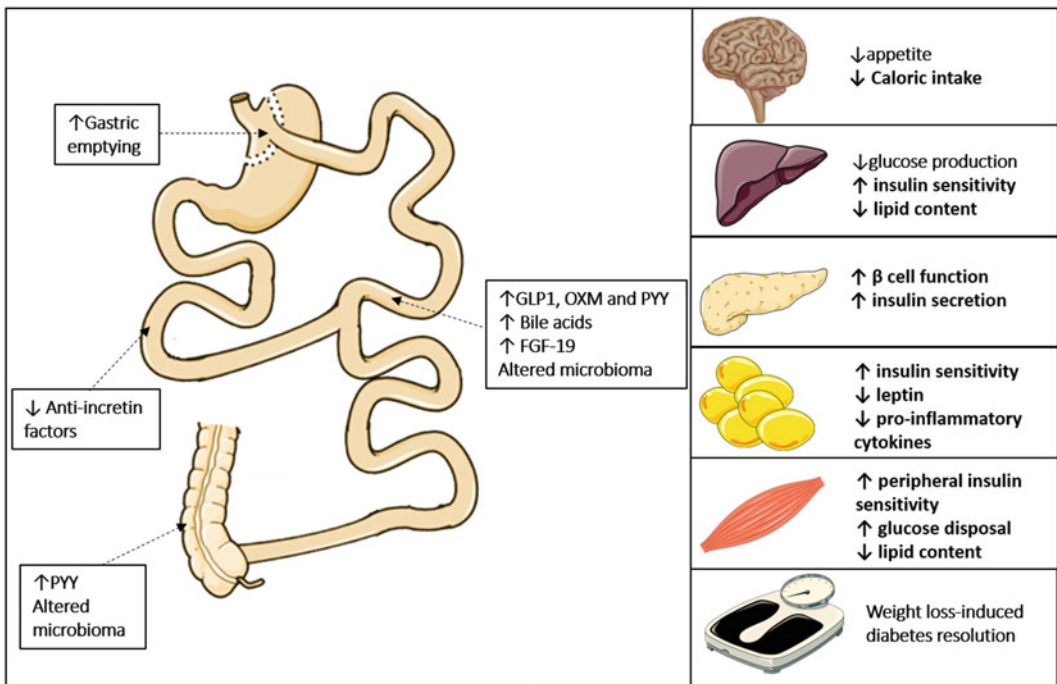
In fact, bariatric surgery interventions in individuals with obesity can be responsible not

only for rapid and sustained weight loss, but also for considerable improvements of several comorbidities and most particularly of T2D. Indeed, bariatric surgery is currently the most effective therapy for patients with obesity and concurrent T2D. However, the rates of T2D improvement and remission can be widely variable dependent not only on the patient clinical characteristics but also on the type of bariatric procedure performed, as described in further detail later in this chapter. Most importantly, these observations have changed the focus of interest of the scientific community working on addressing T2D disease mechanisms from the pancreas towards the gut.

Several lines of research enabled to dissect the mechanisms underlying the improved glycemic control induced by bariatric surgery, however despite deeply investigated these are still far from being completely disclosed. Nevertheless, the available data has made clear that the metabolic effects derived from bariatric surgery cannot be appointed nor justified by any single phenomenon but require the combination of multiple physiological mechanisms. Of notice is the relevance of caloric restriction for the anti-diabetic effects of bariatric surgery interventions, and most particularly in the early post-operative period. However, to estimate the relative contribution of caloric restriction, weight loss and GI hormone profiles for T2D improvement after bariatric surgery can be challenging. In addition, the relative contribution of each physiological mechanism can vary depending on the anatomical modification produced by different surgical procedures (Pérez-Pevida et al. 2019; Stefater et al. 2012).

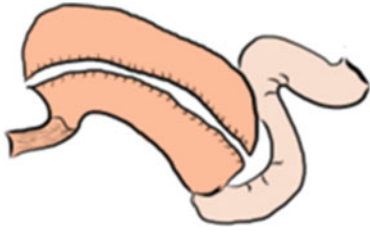
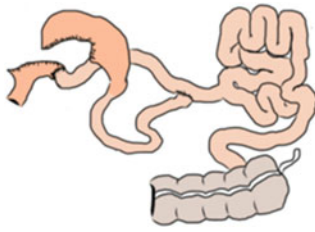
There is a large amount of evidence that support the hypothesis that the modification of GI hormones secretion profile by EEC induced by bariatric surgery, plays a significant role in the anti-diabetic effects observed in human subjects after these procedures (Madsbad et al. 2014). Although the authors acknowledge the importance of several weight loss dependent- and independent-mechanisms contributing for glucose homeostasis improvement after bariatric surgery, those are summarized in Fig. 2 but will not be addressed in further detail.

Since the first reports that GI tract anatomical rearrangements could modulate glycemic control (Barnes 1947), different levels of evidence have emerged supporting the effects of GI surgical interventions in improving or even inducing complete clinical disease remission in patients with T2D (Kodama et al. 2018; Khorgami et al. 2019; Vetter et al. 2012; Wang et al. 2015). Despite the fact bariatric surgery procedures were technically devised to induce weight loss through a negative energy balance by limiting the systemic available



**Fig. 2** Mechanisms of weight loss and T2D remission after gastric bypass

**Table 2** Summary of GI tract rearrangement and gut hormone profile modification induce by different bariatric surgery procedures

Surgical technique	Surgical description	Ghrelin	CCK	GIP	GLP-1	PYY	OXM
 <p>Vertical Sleeve Gastrectomy</p>	<p>Surgical removal of a large portion (~80%) of the stomach along the greater curvature</p>	<p>Fasting and post-prandial: ↓ (Langer et al. 2005; Karamanakos et al. 2008; Peterli et al. 2009; McCarty et al. 2019)</p>	<p>Post-prandial ↑ (Peterli et al. 2012; Mans et al. 2015; Lee et al. 2011)</p>	<p>Fasting and post-prandial = (McCarty et al. 2019; Valderas et al. 2011; Sista et al. 2017)</p>	<p>Fasting = Post-prandial: ↑ (Karamanakos et al. 2008; Peterli et al. 2009; McCarty et al. 2019; Valderas et al. 2010)</p>	-	
 <p>Roux-en-Y gastric bypass</p>	<p>Reduction of the stomach volumetric capacity by creation of a small gastric pouch (~30 mL) Direct anastomosis of the gastric pouch to the proximal small intestine with the exclusion of nutrients passage through the remaining stomach, duodenum, and proximal Jejunum (65–220 cm) Bile and pancreatic juices drainage into the proximal small intestine by a biliopancreatic limb, only mixed with food after the anastomosis of the alimentary (120–150 cm) and biliopancreatic limbs to create the common limb</p>	<p>Fasting: ↓ = ↑ Post-prandial: ↓ = (Peterli et al. 2009; Zhang et al. 2019; Pourmaras and le Roux 2010; Stoeckli et al. 2004; Holdstock et al. 2003; Geloneze et al. 2005; Morinigo et al. 2004; Pardina et al. 2009; Jacobsen et al. 2012)</p>	<p>Post-prandial ↑ = (Peterli et al. 2012; Jacobsen et al. 2012; Kellum et al. 1990)</p>	<p>Fasting = Post-prandial: ↑ = ↓ (Laferrere et al. 2007; Korner et al. 2007; Korner et al. 2009; Falken et al. 2011; Jorgensen et al. 2012)</p>	<p>Fasting = Post-prandial: ↑ (Laferrere et al. 2007; Korner et al. 2007; Korner et al. 2009; Falken et al. 2011; Jorgensen et al. 2012)</p>	<p>Fasting = Post-prandial: ↑ (Peterli et al. 2009; Valderas et al. 2010; Korner et al. 2009; Olivian et al. 2009)</p>	<p>Fasting = Post-prandial: ↑ (Falken et al. 2011; Laferrère et al. 2010)</p>

 <p>Biliopancreatic diversion</p>	<p>Reduction of the stomach volumetric capacity by creation of a gastric pouch (200–500 ml)                  Direct anastomosis of the distal part of the small intestine to the gastric pouch                  Intestinal rearrangement that results in an alimentary limb of ~200-cm, a common limb of ~75–100 cm, and a biliopancreatic limb of unknown length corresponding to the remainder of the small intestine</p>	<p>Fasting: ↓ = ↑                  Post-prandial: ↑                  (Adami et al. 2003; Valera Mora et al. 2007; Garcia de la Torre et al. 2008)</p>	<p>–</p>	<p>Fasting and post-prandial: ↓                  (Mingrone et al. 2009; Salinari et al. 2009; Gisse et al. 2017)</p>	<p>Fasting and post-prandial: ↑                  (Salinari et al. 2009; Gisse et al. 2017; Guidone et al. 2006; Valverde et al. 2005)</p>	<p>Fasting and post-prandial: ↑                  (Garcia-Fuentes et al. 2008; Tsoli et al. 2013)</p>
 <p>Biliopancreatic diversion with duodenal switch</p>	<p>Surgical removal of a large portion (~80%) of the stomach along the greater curvature                  The duodenum is divided 3 cm distal to the pylorus and anastomosed to the distal 300 cm of ileum                  Intestinal rearrangement that results in an alimentary limb of ~200-cm, a common limb of ~100 cm, and a biliopancreatic limb of unknown length corresponding to the remainder of the small intestine</p>	<p>Fasting: ↓ = ↑                  (Kotidis et al. 2006a, b; Plourde et al. 2014; Michaud et al. 2017)</p>	<p>–</p>	<p>Fasting =                  Post-prandial: ↓                  (Plourde et al. 2014; Michaud et al. 2017)</p>	<p>Fasting = ↑                  Post-prandial: ↑                  (Plourde et al. 2014; Michaud et al. 2017)</p>	<p>Fasting = ↑                  Post-prandial: ↑ =                  (Plourde et al. 2014; Michaud et al. 2017; Hedberg et al. 2011)</p>

= No significant changes in the majority of studies, ↑ Significantly increased in the majority of studies, ↓ Significantly decreased in the majority of studies, – No studies for this parameter, CCK Cholecystokinin, *GLP-1* Glucagon Like Peptide-1, *GIP* Glucose-dependent insulinotropic polypeptide, *OXM* Oxyntomodulin, *PYY* Peptide YY

of nutrients, these interventions are now well recognized to influence GI hormone dynamics in a manner that is highly dependent on the type of surgical procedure performed. In this context, GI hormones known to play a relevant role in the endocrine axis that regulate energy homeostasis, including ghrelin, CCK, incretins (GLP1 and GIP), OXM and PYY, have been more extensively studied. This information has been summarized in Table 2.

## 2.1 Ghrelin

Ghrelin is a GI hormone predominantly produced by gastric fundus that stimulates appetite, increases short-term food intake and reduces fat metabolism (Wren et al. 2001; Ariyasu et al. 2001; Pinkney 2014). Bariatric surgery is reported to influence ghrelin levels in an inconsistent manner that is highly dependent on the type of surgical procedure and timing after the intervention (Pournaras and le Roux 2010; Tymitz et al. 2011).

After laparoscopic sleeve gastrectomy (LSG) results are somehow consistent, with most studies reporting an anticipated reduction in fasting ghrelin levels, since this procedure removes a large portion of the stomach wall responsible for hormone secretion (Langer et al. 2005; Karamanakos et al. 2008; Peterli et al. 2009; McCarty et al. 2019). In contrast, after Roux-en-Y Gastric Bypass (RYGB), different studies have shown either a decrease, an increase or no change in fasting and postprandial ghrelin levels (Peterli et al. 2009; Zhang et al. 2019; Pournaras and le Roux 2010; Stoeckli et al. 2004; Holdstock et al. 2003; Geloneze et al. 2003; Morinigo et al. 2004; Pardina et al. 2009; Jacobsen et al. 2012). Technical differences in the procedure regarding the preservation of the vagus nerve and gastric pouch configuration (vertical vs horizontal pouch) have been appointed as possible explanations to justify the heterogeneity of ghrelin results (Fruhbeck et al. 2004). In a prospective randomized clinical trial, comparing RYGB and LSG, both procedures reduced fasting and post-prandial ghrelin levels, but the magnitude of this effect

was significantly higher after LSG. So, the authors suggested that the resection of the gastric fundus has a more powerful impact on ghrelin levels when compared to bypassing part of the stomach (Peterli et al. 2009; Pournaras and le Roux 2010). On the contrary, after other procedures that limit the stomach volumetric capacity, such as gastric banding and gastric plication, ghrelin levels were observed to increase (Stoeckli et al. 2004; Cummings et al. 2002).

To understand whether ghrelin plays a role in mediating LSG effects on body weight and glucose control, ghrelin-deficient mice and wild-type mice were submitted to vertical sleeve gastrectomy. This procedure led to similar results in both mice strains suggesting that ghrelin reduction is not imperative for the metabolic improvements observed after this type of bariatric surgery procedure (Chambers et al. 2013).

## 2.2 Cholecystokinin

CCK is a GI hormone that is mainly secreted in the duodenum in response to the presence of fatty acids and amino acids, which acts as an anorexigenic signal to the central nervous system (Liddle 1995). CCK levels were intuitively hypothesized to decrease after bariatric surgery procedures that exclude the duodenum from the alimentary tract, such as RYGB. However, through mechanisms not yet completely understood, CCK levels were reported to increase after RYGB (Peterli et al. 2012; Jacobsen et al. 2012). One of the mechanisms appointed as a possible explanation for the observed rise in CCK levels, was an increase of CCK producing cells density after RYGB. Indeed, increased proliferation of CCK producing cells was found in the Roux and common limbs of rats submitted to RYGB (Mumphrey et al. 2013). Besides that, after RYGB human intestinal biopsies presented higher numbers of CCK producing cells when compared to biopsies collected during surgery (Rhee et al. 2015). CCK levels were reported to be even higher after surgeries that maintain the duodenum in the alimentary transit, like LSG (Peterli et al. 2012; Mans et al. 2015; Lee et al. 2011).



*In vivo* studies found that CCK increases pancreatic  $\beta$ -cell proliferation (Kuntz et al. 2004; Chen et al. 2007; Lavine et al. 2010). However, RYGB was able to induce similar metabolic outcomes in rats lacking CCK-1 receptors and controls. So, the positive metabolic effects of RYGB appear to be independent of CCK (Hajnal et al. 2010).

### 2.3 Incretins

Incretins are hormones responsible for a phenomenon known as the incretin effect, which consists of a greater insulin secretion being elicited after oral glucose administration when compared to an isoglycemic intravenous glucose load. GIP and GLP-1 are the GI hormones so far identified to be implicated in mediating the incretin effect and are thus called incretin hormones.

GIP and GLP-1 secreting cells are differentially distributed throughout the small intestine (Jorsal et al. 2018; Guedes et al. 2015; Palha et al. 2018). GIP is secreted by K cells predominantly located in the proximal small intestine, duodenum and proximal jejunum, while GLP-1 is produced by the L cells mostly found in the distal small intestine (Jorsal et al. 2018; Guedes et al. 2015; Polak et al. 1973). The incretin effect was shown to be significantly reduced in patients with T2D (Nauck et al. 1986; Vilsboll and Holst 2004). Studies aimed to investigate GLP-1 secretion in individuals with and without T2D have shown that the insulinotropic effect of GLP-1 is substantially preserved in individuals in T2D (Nauck et al. 2011; Calanna et al. 2013). Besides that, GLP-1 secreting cell distribution seems to be similar in subjects with and without T2D (Jorsal et al. 2018; Palha et al. 2018). In contrast, a reduced GIP insulinotropic effect was found in patients with T2D, resulting in a possible compensatory increase in *GIP* expression in the gut (Jorsal et al. 2018; Xu et al. 2007; Vilsboll et al. 2003).

In individuals with T2D, an incretin effect recovery towards the magnitude observed in non-diabetic counterparts was demonstrated to occur as early as 1 month after the RYGB surgery

and maintained thereafter. This phenomenon seems to be independent of weight loss since the incretin effect was not reestablished in weight-matched individuals after similar weight loss achieved through caloric restriction (Laferrere et al. 2007; Laferrère et al. 2008).

The effect of bariatric surgery on GIP levels appears to be relatively modest and controversial, as different studies have found either an increase, decrease or no change after the interventions (Laferrere et al. 2007; Korner et al. 2007; Mingrone et al. 2009; Salinari et al. 2009; Kim et al. 2014). These findings were relatively unsurprising, since GIP is known to be predominantly secreted in the proximal small intestine portion that is bypassed after RYGB (Jorsal et al. 2018; Guedes et al. 2015). So, the number of GIP secreting cells available for stimulation and GIP release is lower. Nevertheless, GIP cell density seems to increase after RYGB in proportion to the compensatory villous hypertrophy (Rhee et al. 2015). Thus, contradictory results found in GIP levels across different studies could be attributed to technical variants of the RYGB surgery procedures using different limb lengths for intestinal reconstruction (Laferrère 2016). Moreover, the improved GIP insulinotropic effect after bariatric surgery is less likely to be due to modified GIP secretion but more likely secondary to decreased glucotoxicity (Hojberg et al. 2009; Aaboe et al. 2010).

In contrast to GIP, the effect of GI tract surgical manipulations on circulating GLP-1 levels are very consistent. The density of GLP-1 immunoreactive cells in the proximal intestinal limbs increase after surgical manipulation, while fasting and post-prandial GLP-1 levels are also higher after bariatric surgery (RYGB, LSG; biliopancreatic diversion and duodenal switch) (Lee et al. 2011; Laferrere et al. 2007; Guidone et al. 2006; Valverde et al. 2005; Plourde et al. 2014; Kim et al. 2014; Romero et al. 2012). Only a few days after RYGB surgery, GLP-1 levels were observed to increase over 10 times (Falken et al. 2011; Jorgensen et al. 2012).

The putative reasons for the enhanced GLP-1 secretion observed after bariatric surgery could be

related to an increased ileal exposure to undigested nutrients, where L cells prevail, thus contributing to the reversion of hyperglycemia, even in the absence of any gastric restriction. This so called “hindgut hypothesis” was proposed by Cummings et al., in 2004 (Cummings et al. 2004).

In a complex study, patients were submitted to a mixed meal tolerance test in two consecutive days before surgery, 1 week and 3 months after RYGB. In the first day patients were infused with a saline solution and in the other day a GLP-1 receptor antagonist (Exendin 9–39) was administered. The study showed that RYGB resulted in the predicted enhancement of GLP-1 responses: increased beta-cell sensitivity to glucose, increased insulin release and decreased fasting and postprandial glucose levels. However, these effects were completely lost after administration of a GLP-1 antagonist. Moreover, glucose and insulin levels were identical to those observed without the antagonists before the surgery (Jorgensen et al. 2013). In another study the effects of per oral versus gastroduodenal feeding on glucose metabolism were explored in a patient previously submitted to RYGB that presented a gastro-jejunosomy leak. In this study, a standard liquid meal was given through a gastric tube inserted into the bypassed gastric remnant on the first day and the same meal was given per orally on the second day. This study found that per oral compared to gastroduodenal feeding resulted in higher GLP-1 levels, improved glucose metabolism and  $\beta$ -cell function (Dirksen et al. 2010). These studies provided a powerful evidence that GLP-1 plays a major role in insulin response and T2D improvement after bariatric surgery, independently of weight loss and caloric restriction.

## 2.4 Peptide YY and Oxyntomodulin

PYY and OXM are both GI hormones secreted by the same L-cells responsible for GLP-1 secretion, which predominate in the distal small gut and colon (Jorsal et al. 2018). According to the “hindgut hypothesis”, a greater L-cell stimulation should enhance PYY and OXM secretion, which

would then contribute to control appetite and improve glycemic regulation. Indeed, postoperative OXM and PYY levels seem to match those observed for GLP-1 levels (Jacobsen et al. 2012; Falken et al. 2011). In fact, postprandial PYY levels seem to increase regardless the bariatric technique (Korner et al. 2009; Tsoli et al. 2013; Michaud et al. 2017). The role of PYY in mediating the effects of bariatric surgery have been mainly attributed to appetite and food intake regulation (le Roux et al. 2005). However a powerful effect on improving islet secretory function was also attributed to PYY, by a recent study that used isolated donor human pancreatic islets and blood samples from patients with T2D before and after bariatric surgery (Guida et al. 2019).

Contrarily to GLP-1 and PYY, the mechanisms of OXM action are not so well characterized. OXM and GLP-1 are both derived from the proglucagon gene (*Gcg*) and result from post-translational modifications during proglucagon processing (Pocai 2012; Drucker 1998). OXM is a full agonist of the GLP-1 receptor (GLP-1R) and the glucagon receptor (GcGR), but with lower affinity relative to native hormones (Baldissera et al. 1988; Kerr et al. 2010). GcGR activation by glucagon has beneficial metabolic effects that includes the modulation of lipid metabolism through activation of lipolysis and inhibition of lipid synthesis, energy intake regulation, brown fat thermogenesis stimulation and inhibition of gastric motility (Kuroshima and Yahata 1979; Billington et al. 1991; Amatuzio et al. 1962; Mochiki et al. 1998). Nevertheless, exogenous OXM administration was demonstrated to increase energy expenditure while reducing energy intake, body weight and increase insulin secretion (Wynne et al. 2005, 2006; Pocai et al. 2009). These observations triggered the development of GLP-1R/GCGR co-agonists (Brandt et al. 2018; Sánchez-Garrido et al. 2017). Pre-clinical and clinical studies demonstrated the efficacy of GLP-1R/GCGR agonists in the improvement of postprandial glucose control by reducing glucose absorption rate and increasing insulin sensitivity and  $\beta$ -cell function (Pocai et al. 2009; Brandt et al. 2018; Goebel et al. 2018; Zhou et al. 2017).

Furthermore, obese patients with prediabetes/T2D infused with a continuous subcutaneous combination of GLP-1, OXM, and PYY, replicating the postprandial gut hormone levels after RYGB, exhibited superior glucose tolerance and reduced glycemic variability, compared with RYGB and a very low-calorie diet (Behary et al. 2019). These satisfactory results lead to a growing interest in the development of molecules that combine the effects of multiple key metabolic hormones into a single entity of superior and sustained action relative to the native hormones. Indeed, the hormone receptors co-agonists are now emerging as a new pharmacological class for T2D treatment (Brandt et al. 2018).

## 2.5 Anti-incretin Factors

Based on the evidence that the most potent anti-diabetic effects are observed for bariatric surgery procedures that exclude the proximal small intestine from the passage of the nutrients [RYGB and Biliopancreatic Diversion (BPD)], Rubino et al., proposed the “foregut hypothesis” an attempt to provide an explanation for the phenomenon (Rubino and Gagner 2002). This hypothesis postulates that by excluding the proximal intestine from the alimentary transit, the secretion of unknown “anti-incretin” factors produced in the proximal small intestine, acting as a counterregulatory mechanism to the incretin-mediated insulin secretion to prevent postprandial hypoglycemia, would be reduced (Rubino and Gagner 2002; Rubino et al. 2006). These putative “anti-incretin” factors would contribute to reduce the incretin effect observed in patients with T2D.

Neuromedin U (NMU), an hormone expressed in the brain and GI has been appointed as an anti-incretin factor since it was able to reduce glucose-stimulated insulin secretion from isolated perfused rat pancreas and human pancreatic islets (Brighton et al. 2004; Alfa et al. 2015; Kaczmarek et al. 2006). However, other studies found contradictory results. Peripheral administration of NMU in mice led to the secretion of the incretin hormone GLP-1, which does not support the role of NMU as an anti-incretin (Peier et al. 2011).

Besides that, an *in vivo* study found that NMU was unable to affect the plasmatic levels of glucose, insulin or glucagon. The same study reported that rat and human pancreatic islets do not express NMU receptors (Kuhre et al. 2019).

Several experimental data come in support of the “foregut hypothesis” for the metabolic improvements observed after bariatric interventions that divert the alimentary transit from the proximal small intestine. In a study, conditioned medium of duodenum/jejunum obtained from small intestine explants prevent from insulin resistance mice (db/db mice) and insulin resistant and insulin sensitive human subjects’ was analyzed. Jejunal proteins either from insulin resistant mice and human subjects were demonstrated to be capable of impairing muscle insulin signaling, thus inducing insulin resistance (Salinari et al. 2013). In addition, an experimental procedure devised to examine the role of excluding the proximal small intestine in the absence of gastric restriction, named gastrojejunal bypass (GJB) was applied to Goto-Kakizaki nonobese T2D rats and was demonstrated to improve glycemic control without inducing weight loss (Rubino and Marescaux 2004). Moreover, the Duodenal-jejunal Bypass Liner (DJBL) consisting in the endoscopic placement of an impermeable sleeve into the proximal intestine, somehow able to mimic the surgical duodenal and jejunal exclusion induced by RYGB and BPD surgeries, lead to significant improvements in glycemic indexes of patients with obesity and T2D (Jirapinyo et al. 2018b). Besides that, DJBL induced superior weight loss and T2D improvement when compared with diet alone (Koehestanie et al. 2014).

Duodenal mucosal resurfacing (DMR), a novel minimally invasive upper endoscopic procedure, that involves circumferential hydrothermal ablation of the duodenal mucosa also brought solid evidences that support the “foregut hypothesis” (van Baar et al. 2018). Recent clinical trials showed that DMR induces a substantial clinical improvement in glycemic control and insulin resistance up to 12 months in patients with T2D. The length of the ablated segment was positively correlated with the improvement in glycemic

control (Rajagopalan et al. 2016). DMR efficacy is unlikely to be related with the malabsorption or the substantial weight loss often observed after the bariatric surgery and so, it supports a role of the duodenum as playing a major part in the development of insulin resistance and T2D (Rajagopalan et al. 2016; van Baar et al. 2019).

In sum, both the “foregut” and “hindgut” hypotheses provide reasonable explanations and have generated supporting evidence for the well-known anti-diabetic effects induced by widely used bariatric surgery procedures, such as RYGB, BPD and BPD with duodenal switch (BPD-DS). However, the relative contribution of each physiological mechanism modified by the different anatomical rearrangements still needs clarification.

## 2.6 Bile Acids and Gut Microbiota

Bile acids and gut microbiota were both demonstrated to play an active role in several metabolic pathways involved in glucose and energy homeostasis (Ahmad and Haeusler 2019; Shapiro et al. 2018; Gérard and Vidal 2019; Heiss and Olofsson 2018; Taoka et al. 2016). In addition, considerable changes on bile acid and gut microbiota with a potential positive metabolic impact were found to occur after bariatric surgery (Ulker and Yildiran 2019; Ejtahed et al. 2018). However, it is still unclear if whether these are a causal or consequence of diabetes improvement or remission after bariatric surgery.

Bariatric surgery was shown to interfere with bile acid enterohepatic circulation, leading to a consequent increase in circulating bile acid levels (Liu et al. 2018; Wang et al. 2019; Pérez-Pevida et al. 2019; Madsbad et al. 2014; Patti et al. 2009). In turn, bile acids are able to induce fibroblast growth factor 19 (FGF19) secretion, which acts through a G protein-coupled bile acid receptor (TGR5) to stimulate GLP-1 and PYY secretion (Liu et al. 2018; Sachdev et al. 2016). Thus, this bile acids mediated pathway has been appointed as an additional contributor mechanism for the metabolic benefits observed bariatric surgery.

There are several levels of evidence supporting a role of gut microbiota for the metabolic improvement observed after surgery. In fact, insulin sensitivity was significantly increased in subjects with metabolic syndrome that underwent fecal transplantation to receive gut microbiota from normal weight donors (Vrieze et al. 2012). Furthermore, gut microbiota transplantation from subjects’ previously submitted to RYGB operation to non-operated ones resulted in significant weight loss although the effects on glucose metabolism were not assessed (Tremaroli et al. 2015; Liou et al. 2013).

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## 3 Clinical Evidence on the Use of Gastro-Intestinal Interventions to Treat Type 2 Diabetes

### 3.1 Surgical Interventions

The links between T2D and GI surgery date back to the early 30’s, when the first cases of dramatic glycemic improvements after GI operations performed for peptic ulcers and cancer in patients with diabetes were reported (Friedman et al. 1955). However, at those times these anecdotal cases were unvalued and were not focus of further attention until the advent of bariatric surgery in the 1950s, when diabetes remission following GI surgery was increasingly reported (Pories et al. 1995). But it not until the 2000s that experimental evidence was raised to support of the influence of GI anatomy on glucose homeostasis regulation, which also provided a mechanistic rationale for the use of GI surgery for the primary goal of treating T2D (Rubino and Marescaux 2004).

Following bariatric surgery interventions most patients experience a rapid weight loss and continue to do so until 18–24 months after the procedure. Patients may lose 60% of excess body weight in the first six months, 77% of excess weight as early as 12 months after surgery and maintain a 50–60% excess weight loss up to 10–14 years after surgery (Wittgrove and Clark 2000). Notwithstanding the overall excess

weight-loss (EWL) in patients with T2D tending to be more modest than the observed for subjects without T2D (Carbonell et al. 2008). A systematic review and meta-analysis on the durability of weight loss at and beyond 10 years published in 2019 by O'Brien *et al.*, showed that the most impressive outcome was observed for the BPD techniques or its BPD-DS variant with a pooled effect size of 71% EWL followed by RYGB with 60% EWL (O'Brien et al. 2019).

In addition to the body weight reduction effects, RYGB and BPD, are also the most effective bariatric surgical treatments for T2D when compared to other procedures, which are followed by normalization of plasma glucose, insulin, and Hemoglobin A1c (HbA1c) in 80–100% of morbidly obese patients (Kodama et al. 2018; Schauer et al. 2003). In a considerable proportion of patients with T2D, the resumption of euglycemia and normal insulin levels occurs within days after surgery, long before any significant weight loss takes place (Rubino and Gagner 2002). In fact, the Greenville gastric bypass study reported that bariatric surgical interventions restored and maintained normal levels of glucose, insulin, and HbA1c in 91% of the patients for as long as 14 years (Pories et al. 1995).

Since then, several systematic reviews addressing the impact of bariatric surgery on T2D were performed, with disease remission rates varying according to the surgical procedure and duration of follow-up. Historically relevant are those performed by Buchwald et al., in 2004 and 2009, encompassing different surgical techniques that reported a T2D remission rate of 76.8% and 76.2% of insulin free patients, respectively (Buchwald and Williams 2004; Buchwald and Oien 2009). More recent analyses by Goh et al. (2017) and Kodama et al. (2018) report T2D remission rates ranging from 15% to 100% (Kodama et al. 2018; Goh et al. 2017). In 2018, Kodama et al. published a pooled analysis of the results of 25 eligible randomized controlled trials (RCTs) covering non-surgical treatments and surgical procedures performed in Western and Asian populations, with follow-up times ranging from

3 to 5 years. This study showed that patients with obesity and T2D submitted to bariatric surgery when compared to conventional medical interventions achieved higher disease remission rates (Kodama et al. 2018). In contrast, Koliaki et al. the applying a similar model in a meta-analysis that include only 12 RCTs conducted in Western populations only, concluded that bariatric surgery when compared to non-surgical treatments was associated with a greater weight loss, cardiovascular risk factors reduction, glycemic improvement and T2D remission rates from 24% to 95% within follow-up times ranging from 6 months to 3 years (Koliaki et al. 2017). The anti-diabetic effects of bariatric surgery were also found to be long-lasting, since at 5–18 years of postoperative follow-up time T2D remission rates ranging from 24% to 62% were still observed (Koliaki et al. 2017).

One should be aware that across different trials, depending on the criteria used to define T2D improvement and remission, the metabolic outcomes of bariatric surgery can be widely variable. In 2009, as an attempt to overcome this limitation, Sue Kirkman et al. proposed the use of universal criteria to define T2D remission after bariatric interventions (Buse et al. 2009).

The most frequent bariatric surgery procedures performed worldwide, namely LSG, RYGB and BPD or BPD-DS are associated with short- and medium-term T2D remission rates, widely variable across the different studies and type of procedures (Table 3) (Schauer et al. 2016; Koliaki et al. 2017).

In addition to the long lasting improvement in glycemic control observed after bariatric surgery, diabetes-related morbidity and mortality also experience a significant decline (Phillips and Shikora 2018). In post-bariatric patient populations, 30–40% reductions in myocardial infarction and stroke, 42% reduction of cancer in women, and 30–40% reduction in overall mortality were demonstrated (English and Williams 2018; Adams et al. 2007). Moreover, post-surgical weight loss improves overall quality of life along with obesity-related comorbidities and mortality rate (Faria et al. 2017).

**Table 3** Diabetes remission rates following bariatric surgery

Author and year	Surgical procedure	Number of patients with T2D	Mean T2D Duration (years)	Follow-up after surgery (years)	T2D remission rate (%)	T2D Remission criteria
Marceau et al. (2007)	BPD-DS	377	NA	7.3	92	T2D medications withdrawal
Hayes et al. (2011)	RYGB	127	4.5	1	84	FG <6.0 mmol/L and HbA1c < 6.0% with no diabetes medications
Blackstone et al. (2012)	RYGB	505	>3	1.2	43.2	FG <100 mg/dL and HbA1c ≤5.7% with no diabetes medications
Mingrone et al. (2012)	RYGB	20	6.0	2	75	HbA1c ≤6.5% with no diabetes medications
	BPD	20	6.0		95	
Schauer et al. (2012)	LSG	50	8.5	1	27	HbA1c ≤6% with no diabetes medications
	RYGB	50	8.2		42	
Ikramuddin et al. (2013)	RYGB	60	8.9	1	44	HbA1c ≤ 6.0%
Liang et al. (2013)	RYGB	31	7.39	1	90	NA
Schauer et al. (2014)	LSG	49	8.3	3	20	HbA1c ≤6% with no diabetes medications
	RYGB	48			35	
Golomb et al. (2015)	LSG	82	NA	1	50.7	FG <100 mg/dL and HbA1c ≤6% with no diabetes medications
				3	38.2	
				5	20	
Ikramuddin et al. (2015)	RYGB	60	8.9	5	20	HbA1c ≤ 6.0%
Mingrone et al. (2015)	RYGB	19	>5	5	42	HbA1c ≤6.5% with no diabetes medications
	BPD	19			68	
Park and Kim (2016)	RYGB	134	4.6	1	46.1	HbA1c level of <6.0% with no diabetes medications
Torres et al. (2017)	RYGB	97	4	3	55.2	FG <100 mg/dL and HbA1c ≤6% with no diabetes medications
	BPD-DS	77	6		70.4	
	SADI-S	97	8		75.8	
Baltasar et al. (2018)	BPD-DS	115	NA	22	98	HbA1c ≤ 6.0%

*BPD* Biliopancreatic diversion, *BPD-DS* Biliopancreatic diversion with duodenal switch, *FG* Fasting Glucose, *HbA1c* Hemoglobin A1c, *LSG* Laparoscopic sleeve gastrectomy, *NA* Not available, *RYGB* Roux-en-Y Gastric Bypass, *SADI-S* Single Anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy, *T2D* Type 2 Diabetes

In patients with obesity and T2D, comprehensive reduction of cardiovascular disease risk factors, including blood pressure and lipid profile are vital to prevent microvascular and macrovascular complications. Bariatric surgery also contributes for the resolution or improvement of cardiovascular risk factors other than hyperglycemia, once hypertension and hyperlipidemia is resolved or improved in 78.5 and 61.7% of the patients, respectively (Noria and Grantcharov 2013). In fact, patients with obesity and T2D undergoing bariatric surgical treatment,

sustained weight loss along with cardiovascular risk factors control, experience a remarkable 92% decrease in diabetes-related death (Adams et al. 2007).

In a recent meta-analysis, bariatric surgery was also demonstrated to be superior to conventional medical treatment in reducing overall incidence of microvascular complications in patients with T2D, namely the incidence of nephropathy and retinopathy were lower, while no significant difference was observed regarding peripheral neuropathy (Billeter et al. 2018).

Bariatric surgery, through weight loss-dependent and weight loss-independent mechanisms, also induces a significant improvement in NAFLD, including non-invasive parameters and liver histology (Yeo et al. 2019; von Schönfels et al. 2018).

Early intervention with tight glycemic control in patients diagnosed with T2D, is not only paramount for the overall prognosis of the disease, but also influences the propensity of disease remission after surgical interventions. A recent study examined the legacy effect of early glycemic control on diabetic complications and death. The study hypothesized that a glycemic legacy begins as early as the 1st year after diagnosis and depends on the level of glycemic exposure. In patients with newly diagnosed T2D and at least 10 years survival after diagnosis, first year glycemic control was strongly associated with future risk for diabetic complications and mortality, even after adjusting for glycemic control in the following years (Laiteerapong et al. 2019). This study suggested that failure to achieve an HbA1c < 6.5% (<48 mmol/mol) within the 1st year of diabetes diagnosis was enough to establish an irremediable long-term future risk of microvascular and macrovascular complications. In addition, failure to achieve an HbA1c < 7.0% (< 53 mmol/mol) within the 1st year after diabetes diagnosis may lead to an irreversible increased risk of mortality (Laiteerapong et al. 2019). Although most of the available evidence derives from patients with T2D and body mass index (BMI) > 35 kg/m<sup>2</sup>, there is a growing amount of data suggesting that individuals with T2D and a preoperative BMI of 30–35 kg/m<sup>2</sup> are likely experience similar benefits (Cummings and Rubino 2018).

Even though long-term T2D remission is observed after bariatric surgery interventions, disease recurrence is recognized to occur 5 years after surgery in 16–43% of patients. Still, relapsed T2D often presents as more “benign”, since longer periods of tight glycemic control significantly improve the prognosis of the disease with decreased risk of incident microvascular complications (Maleckas et al. 2015). This data provides further support for a legacy effect of

bariatric surgery, where even a transient period of surgically induced T2D remission is associated with lower long-term risks.

### 3.2 Endoscopic Interventions

More recently, several endoscopic devices and procedures were developed as potential alternatives or adjuvants to bariatric surgery.

Endoscopic Sleeve Gastroplasty (ESG), DMR, Transpyloric Shuttle, EndoBarrier and SatiSphere, Incision less magnetic anastomosis system are some of the multiple endoscopic techniques available, although most are considered experimental (Jirapinyo and Thompson 2017).

Amongst the endoscopic interventions so far described, DMR has gathered a great deal of enthusiasm and high expectations. DMR is a novel, minimally invasive upper endoscopic procedure devised for the primary treatment of patients with T2D. The hypothetical rationale that led to conceive this procedure is based on the “foregut hypothesis” that states that “anti-incretin” factors secreted in the proximal small gut are responsible for blunting the incretin effect observed in patients with T2D. Thus, the procedure aims to deplete the proximal small gut mucosa from enteroendocrine cells responsible for secreting putative “anti-incretin” factors, in order to promote the resurfacing of the mucosa with a new and potentially healthier cell population. The mucosal ablation is achieved by using a catheter alongside the endoscope, the duodenal mucosa is first lifted and then hydrothermally ablated. These cycles are repeated until at least 10 cm of the postpapillary duodenum is treated in a single endoscopic session. It has recently been shown that patients with T2D achieve significant improvements of glucose profiles after a single DMR procedure. It is thought that there is an effect of DMR on hepatic glucose production, possibly by an insulin-sensitizing mechanism, which is in line with observations in RYGB surgery. Still, the effect of DMR on HbA1c is less dramatic than observed after bariatric surgery interventions, which are currently the treatment intervention that has demonstrated to be highly

effective for long-term body weight reduction and glycemic control in patients with obesity and T2D. Nonetheless, it is interesting and fascinating that an endoscopic procedure involving solely the duodenum can elicit such glycemic improvement (Rajagopalan et al. 2016).

In sum, some endoscopic therapies hold promise to be used as complementary strategies to bariatric surgery or even to be considered as a primary intervention for patients who are unwilling to accept the potential complications associated with surgery or who may not be suitable for surgical intervention. Nevertheless, these interventions are still on an experimental phase and robust long-term data is needed to provide evidence on the log-term effectiveness for T2D treatment.

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#### 4 Current Clinical Recommendations and Guidelines

Given the evidence on the efficacy, safety and cost-effectiveness of bariatric surgery on T2D treatment, the second Diabetes Surgery Summit (DSS-II) endorsed by International Federation For the Surgery of Obesity (IFSO) consensus conference, placed bariatric surgery squarely within the overall diabetes treatment algorithm, recommending consideration of this approach for patients with inadequately controlled T2D and a BMI as low as 30 kg/m<sup>2</sup> or 27.5 kg/m<sup>2</sup> for Asian individuals (Rubino et al. 2016). These new guidelines have been formally ratified by 53 leading diabetes and surgery societies worldwide.

Recognizing the need to inform diabetes care providers about the benefits and limitations of bariatric surgery, the DSS-II was convened in collaboration with six leading international diabetes organizations: the American Diabetes Association (ADA), International Diabetes Federation, Chinese Diabetes Society, Diabetes India, European Association for the Study of Diabetes, and Diabetes UK. DSS-II guidelines were incorporated into the ADA Standards of Diabetes Care in 2017 (American Diabetes Association 2017).

The DSS-II concluded that a substantial body of evidence had been accumulated, including numerous, albeit mostly short- and mid-term RCTs, demonstrating that bariatric surgery can achieve excellent glycemic control and reduce cardiovascular risk factors. Although additional studies are needed to further demonstrate long-term benefits, there is now sufficient clinical and mechanistic evidence to support inclusion of bariatric surgery among anti-diabetes interventions for people with T2D and obesity (Cummings and Cohen 2016; Maggard-Gibbons et al. 2013; American Diabetes A 2019). Complementary criteria to the criterion used to select candidates for bariatric surgery, traditionally relying on BMI only, needs to be identified in order to achieve a better algorithm to select the most adequate treatment for patients with T2D. Bariatric surgery procedures when performed with the primary aim of targeting T2D and metabolic disorders are termed as metabolic surgery (Cummings and Cohen 2016).

Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team including surgeon, endocrinologist, nutritionist, behavioral health specialist, and nurse. People presenting for bariatric surgery should receive a comprehensive readiness and mental health assessment and should be evaluated on the need for ongoing mental health services to help them adjust to medical and psychosocial changes after surgery. Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after bariatric surgery, according to guidelines for postoperative management by national and international professional societies (Busetto et al. 2017).

According DSS-II, metabolic surgery indications are:

- Metabolic surgery should be a *recommended* option to treat T2D in appropriate surgical candidates with class III obesity (BMI  $\geq 40$  kg/m<sup>2</sup>), regardless of the level of glycemic control or complexity of glucose-lowering regimens, as well as in patients with



class II obesity (BMI 35.0–39.9 kg/m<sup>2</sup>) with inadequately controlled hyperglycemia despite lifestyle and optimal medical therapy.

- Metabolic surgery should also be *considered* to be an option to treat T2D in patients with class I obesity (BMI 30.0–34.9 kg/m<sup>2</sup>) and inadequate glycemic control despite optimal medical treatment by either oral or injectable medications (including insulin).
- All BMI thresholds should be reconsidered depending on the ancestry of the patient. For patients of Asian ancestry, the BMI values depicted above should be reduced by 2.5 kg/m<sup>2</sup>.

Contraindications include diagnosis of Type 1 Diabetes (unless surgery is indicated for other reasons, such as severe obesity); current drug or alcohol abuse; uncontrolled psychiatric illness; lack of understanding of the risks/benefits of the procedures, expected outcomes, or alternatives; and lack of commitment to nutritional supplementation and long-term follow-up required after surgery.

In addition to these guidance's, the American Society for Metabolic and Bariatric Surgery (ASMBS) practical guidelines, recommend as indications for bariatric surgery:

- Patients with a BMI  $\geq 40$  kg/m<sup>2</sup> without coexisting medical problems and for whom bariatric surgery would not be associated with excessive risk;
- Patients with a BMI  $\geq 35$  kg/m<sup>2</sup> and 1 or more severe obesity-related co-morbidity, including T2D, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (a combination of OSA and OHS), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), pseudotumor cerebri, gastroesophageal reflux disease (GERD), asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life, may also be offered a bariatric procedure. Patients with BMI of

30–34.9 kg/m<sup>2</sup> with diabetes or metabolic syndrome may also be offered a bariatric procedure although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit.

- There is insufficient evidence for recommending a bariatric surgical procedure specifically for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone, independent of BMI criteria.

Ultimately, physicians are responsible for providing updated evidence based information as a contribution to the process leading to patient-centered decision among the available treatments options for each given clinical condition. According to Purnell et al., if the number of gastric bypass operations performed in diabetic patients in USA was one million per year, the currently estimated 0.5% risk of perioperative death for all patients undergoing gastric bypass would mean that nearly 5000 patients would be expected to die of surgical related complications. On the other hand, using survey data from 2005 and estimating a per-year mortality rate of 3 per 1000 patients with diabetes, would suggest that approximately 15,600 deaths would occur over 5 years in a cohort of one million medically managed patients with diabetes. These types of competing timelines and risks should be part of risk-benefit discussions with patients (Purnell and Flum 2009).

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## 5 Concluding Remarks

In summary, major advances have been made since the identification of the first gastro-intestinal hormone and discovery of the enteroendocrine system. Amongst the different hundreds of bioactive molecules produced along the GI tract, some have been recognized to play a paramount role in glucose homeostasis regulation. This achievement has led the pharmaceutical industry to design gut hormone analogues that mimic the physiological actions known to be impaired in patients with T2D. These established or emerging

drug classes are now considered either a valuable or promising pharmacological tool in diabetes treatment. However, the major breakthrough has been the demonstration that enteroendocrine system modulation can be achieved through surgically induced anatomical rearrangements of the GI tract. These groundbreaking findings have now challenged the paradigms of disease mechanisms, treatment algorithms and beliefs about the natural history of T2D.

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