# The Duodenum harbors a Broad Untapped Therapeutic Potential

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The gastroenterologist, when performing an esophagogastroduodenoscopy, is the only medical care provider with easy access to the duodenum (Figure 1*A*). This simple fact is pivotal in this article that discusses why the duodenum has become such an important anatomic region of interest. Recent insights have revealed the critical physiologic and pathophysiologic role of the small bowel in metabolic homeostasis and its potential role as a driver of obesity, insulin resistance, and subsequent type 2 diabetes mellitus (T2DM). Although the other parts of the small bowel cannot be ignored when describing the potential mechanisms involved in the development of metabolic diseases and T2DM, the excellent endoscopic accessibility of the duodenum makes it a prime target for disease-modifying intervention.

## The Duodenum Has Emerged as a Key Player in Metabolic Diseases, Including Diabetes

With almost 1 in 10 people affected worldwide, T2DM and its complications are a huge burden for patients, the general community, and health care systems. Currently available treatment options are predominantly based on lifestyle modification and an array of oral and injectable glucose-lowering pharmacologic agents. Although combinations of medication, diet, and lifestyle changes are effective in many patients, a group of patients with T2DM still does not achieve optimal glycemic control. Importantly, none of these therapies can reverse the T2DM phenotype. In this regard, bariatric surgery (now often termed metabolic surgery) has emerged as a unique treatment modality that offers metabolic benefits far beyond anything that lifestyle or pharmacologic treatment can achieve in patients with T2DM. Bariatric surgery was initially performed to establish major weight reduction in severely obese patients. Interestingly, improvement of hyperglycemia occurs immediately and dramatically precedes any favorable changes in body weight in patients with T2DM after surgery. Although weight loss is largely driven by decreased food intake and less effective intestinal absorption of dietary calories, a large body of evidence suggests that other metabolic changes occur. Bariatric surgery is associated with more frequent T2DM remission than observed with lifestyle and pharmacologic approaches, and this metabolic improvement reduces the long-term microvascular and macrovascular complications.[1] The Roux-en-Y gastric bypass (RYGB) has historically been the mainstay of bariatric surgery and it involves several anatomic adjustments: reduction of gastric volume, movement of the distal small intestine closer to the gastric outlet, and bypass of the proximal small bowel (notably bypassing the whole duodenum) (Figure 1*B*). Gastric banding alone does not involve any form of small bowel bypass and does not achieve as good results as RYGB. Hence, bypass of the proximal small bowel has been proposed to be an important contributor to the metabolic benefits achieved after RYGB surgery.[2,3] Although vertical sleeve gastrectomy achieves similar effects on obesity and T2DM

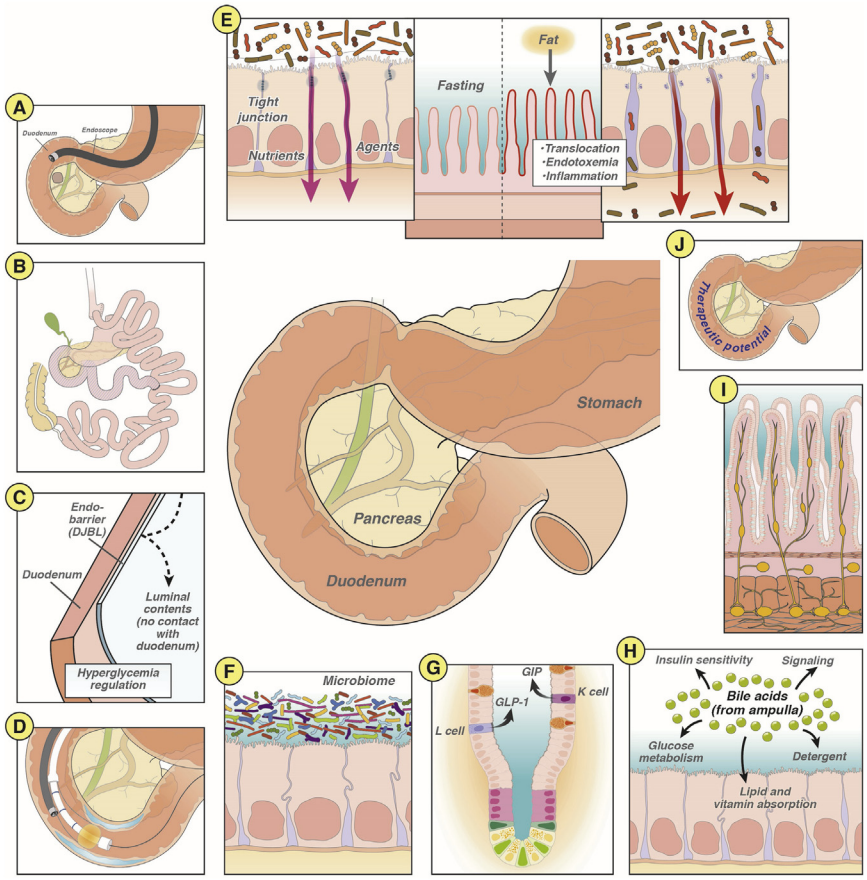


**Figure 1.** (*A*) Gastroduodenoscopy. (*B*) Roux-en-Y gastric bypass. (*C*) Duodenal-jejunal bypass liner (EndoBarrier). (*D*) Duodenal mucosal resurfacing (DMR). (*E*) Intestinal mucosal maladaptation in obesity and type 2 diabetes mellitus. (*F*) Duodenal microbiome. (*G*) Production of gut incretin hormones. (*H*) Bile acids affect glucose metabolism and improve insulin sensitivity. (*I*) Innervation by the enteric nervous system. (*J*) The duodenum harbors a broad therapeutic potential.

without bypassing the proximal small bowel, it seems that the chronically high gastric emptying rates and perturbations after both vertical sleeve gastrectomy and RYGB drive an equivalent process of intestinal adaptation. Both procedures have been shown to result in increased gastrointestinal hormone secretion and similar alterations in bile acid composition and the microbiome.[4] A new consensus statement authored by experts and endorsed by professional organizations advocates that bariatric surgery should be included in the T2DM treatment guidelines.[2,5] However, metabolic surgery is currently a treatment option only for a small subgroup of patients with T2DM because of the invasiveness of the surgical procedure. If a less invasive procedure without the surgery-related risks could effectuate similar metabolic effects, many more patients with T2DM could benefit from this new treatment modality and regain their well-being.

## Endoscopic Duodenal Bypass Regulates Hyperglycemia

The retrievable duodenal-jejunal bypass liner (DJBL), also called the EndoBarrier, is a commercially available device that leverages an important aspect of RYGB through a nonsurgical procedure. The DJBL is delivered endoscopically into the duodenal bulb, where the anchor is deployed and the 60-cm long impermeable liner is advanced into the small intestine to block the contact of luminal contents with the duodenum (Figure 1*C*). Modest body weight loss and improved glucose regulation were reported after implantation of the DJBL. This finding led initially to a randomized, controlled trial for patients with T2DM. However, a significant number of adverse events was associated with placement of the device.[6] The sham controlled ENDOtrial conducted in the United States (evaluating EndoBarrier therapy for the treatment of T2DM) terminated early after randomizing 325 patients, instead of the intended 500 patients, owing to 7 cases of hepatic abscess (incidence rate 3.5%). However, the efficacy of EndoBarrier therapy for glycemic control was replicated, albeit with these serious safety concerns (GI Dynamics press release, Boston, MA). The preclinical and clinical effects of the DJBL provide more evidence for a role of the duodenum in the interplay of obesity, the metabolic syndrome, and T2DM. However, based on the rather high adverse event rate, this will likely not be an appealing treatment option for patients.

## Endoscopic Duodenal Mucosal Resurfacing Elicits Improvement in Hyperglycemia

Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive upper endoscopic procedure to treat patients with T2DM. Using a catheter alongside the endoscope, the duodenal mucosa is first lifted and then ablated by a pressure-based hydrothermal balloon at the tip of the catheter (Figure 1*D*). 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 a single DMR procedure improves glycemia in patients with T2DM.[7] 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. The effect of DMR on hemoglobin A1c is less dramatic than observed after bariatric surgery, but it is nevertheless interesting that a minimally invasive endoscopic procedure involving solely the duodenum can elicit such glycemic improvement.[7] The precise mechanism of action of DMR remains to be elucidated, but its efficacy supports the hypothesis that alterations in the proximal small bowel, particularly the duodenum, play a major part in the development of insulin resistance and T2DM. Confirmatory randomized, controlled, double-blinded trials controlling for placebo effect are currently eagerly awaited.

## Diet, Nutrients, and Duodenal Mucosa

The intestinal mucosa is a highly malleable system in which epithelial cells turn over every 3 to 5 days. It has the ability to respond to a range of pathologic conditions, but also internal and external stimuli. The intestinal barrier is formed by epithelial columnar cells, tight junction proteins between the enterocytes, and mucus secreted from goblet cells that prevents unwanted agents and molecules in the lumen from crossing. Proper functioning of (epithelial) innate immunity is crucial for confining enteric bacteria to the lumen and for preventing bacterial translocation and subsequent (low-grade) endotoxemia. Interestingly, recent studies have demonstrated increased intestinal permeability, systemic endotoxemia, and inflammation in obese subjects and patients with T2DM. Intestinal mucosal maladaptation and bacterial translocation have been linked to the development of insulin resistance and T2DM in conditions of caloric overexposure (Figure 1*E*). For example, a high-sugar, high-fat, Western-style diet is associated with postprandial endotoxemia, most likely owing to alterations in the gastrointestinal barrier.[8] Chronic endotoxemia induces low-grade systemic inflammation, which is associated with increases in fasting plasma glucose, insulin, visceral adipose tissue, and bodyweight, all leading to the phenotypic features of the metabolic syndrome, obesity, and T2DM.[9] Reciprocally, chronic hyperglycemia itself is also correlated with longer intestinal villi, increased small enterocyte mass, and increased enterocyte turnover (Figure 1*E*). A high-fat diet also stimulates the proliferation of duodenal endocrine K cells, producing glucose-dependent insulinotropic polypeptide, which is thought to induce insulin hypersecretion.[10] These alterations may account for the apparently enhanced intestinal capacity to absorb glucose and the increased potential for intestinal gluconeogenesis in T2DM.[11] Upon

duodenal-jejunal bypass surgery, epithelial proliferation and tight junction expression are increased, which subsequently leads to decreased intestinal permeability.[11,12] In line with this observation, RYGB surgery is associated with decreased endotoxemia in patients with obesity and T2DM.[13] Thus, improved intestinal barrier function can help to explain the apparent improvement in the low-grade, proinflammatory state often seen in insulin resistance and T2DM after bariatric surgery. It would be attractive if other, possibly less invasive, procedures can also restore the small intestinal barrier in a similar manner.

## The Duodenum Has Its Own Microbiome

The duodenum, jejunum, and ileum are far from sterile. The human bowel contains trillions of bacteria with a steady increase of bacterial numbers from the duodenum (Figure 1*F*) to the colon. The small intestine in healthy subjects has a rich diversity and unique microbial signature compared with the rectum. Moreover, the small intestinal microbiota plays a major role in harvesting energy from ingested nutrients and the maintenance of body energy homeostasis.[14] In a general sense, it has been shown that the intestinal microbiome differs significantly between metabolically healthy versus unhealthy and between lean versus obese subjects. Obesity is associated with a reduction in the abundance of *Bacteroidetes* and a proportional increase in *Proteobacteria*, which could all be an epiphenomenon, but could also be the expression of a microbiota-related mechanism in the pathophysiology of obesity. Beneficial changes in small intestinal microbiome composition (eg, a decrease in Gram-negative endotoxin–bearing bacterial strains) have been reported upon lean donor fecal microbiota transplantation infused via duodenal tube.[15] The changes in the small intestinal microbiome composition were associated with increased peripheral insulin sensitivity in patients with the metabolic syndrome.[15] Likewise, RYGB surgery restores the gut microbiome toward a healthy composition, which includes an increased diversity in flora.[16] Altogether, an altered microbiome may directly influence metabolic homeostasis of the host and could be partially responsible for the development of T2DM in some individuals. Thus, this new research field might result in new interventions for T2DM based on small intestinal microbiome modulation.

## The Duodenal Mucosa Is Home to Incretin-Producing Cells

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide are incretin hormones that are intimately involved in the regulation of glucose homeostasis. Secretion of these gut hormones by endocrine L cells and K cells throughout the small intestine is stimulated by the presence of nutrients in the lumen (Figure 1*G*). Although both incretins are thought to play a key role in regulating glycemia under physiologic conditions, only GLP-1 has been shown to manifest profound antidiabetic effects when administered exogenously. It stimulates insulin secretion from pancreatic $\beta$-cells, inhibits glucagon secretion from pancreatic $\alpha$-cells, and decreases gastrointestinal motility, appetite, and food intake. The incretin effect is decreased in patients with T2DM, but the exact etiology is yet unknown.[17] The intestinal L cell density in the ileal mucosa does not differ in patients with T2DM.[18] It is still possible that the function of L cells in the duodenum or proximal jejunum is altered, causing the decreased incretin effect in patients with T2DM. Interestingly, treatment with a GLP-1 receptor agonist reduces bodyweight and hyperglycemia in patients with T2DM. So, if it were possible to increase endogenous GLP-1 secretion by resetting L cell function, one can assume that this would effectuate similar effects. Although a reset of the whole small intestine is currently impracticable, resetting the duodenal mucosa is within reach.

## Bile Acids, Secreted in the Duodenum, Are Not Solely Detergents But Are Also Important Signaling Molecules

Bile acids are released via the ampulla of Vater into the duodenum where they blend with the ingested nutrients. Beside facilitating absorption of lipids and vitamins, bile acids affect glucose metabolism and improve insulin sensitivity via specific bile acid signaling pathways (Figure 1*H*). For instance, the nuclear farnesoid X receptor in the liver and distal small intestine and Takeda G-protein-coupled receptor 5 in the terminal ileum are key target receptors for bile acids.[19] Through these signaling pathways, bile acids are capable of modulating energy expenditure, and glucose and lipid metabolism systemically. Takeda G-protein-coupled receptor 5, once activated by bile acids, induces direct secretion of GLP-1 from L cells of the small intestine.[20] Bile acids activate farnesoid X receptor in the terminal ileum postprandially, and induce expression and secretion of fibroblast growth factor 19 (FGF19). FGF19 in turn inhibits hepatic bile acid production.[19] Subjects with T2DM have lower levels of FGF19 and higher plasma bile acid levels before RYGB surgery. After surgery, both plasma FGF19 and bile acid levels increase when a subject experiences diabetes remission, suggesting a role for this pathway in the etiology and remission of T2DM after RYGB.[21] After RYGB and DJBL placement, the level of circulating bile acids is increased, independent of weight loss. Because this effect is not observed after gastric banding or intensive medical management,[22] it is tempting to speculate that there is a critical role for bile acids in the impact on metabolism of procedures in the duodenum. The duodenum is the anatomic location where bile acids accomplish their first intestinal effect after which they impact the entire intestinal tract. Intervening at this secretion site could, therefore, possibly lead to a long-acting downstream effect. Further studies into the effects of bile acids in

the duodenum and the identification of probable treatment targets in this complex system are urgently needed.

## The Duodenum Is Densely Innervated by the Nervous System

The duodenum is richly innervated by the enteric autonomous nervous system (ENS) (Figure 1*I*), just like the entire small bowel. Sensory neurons, a subclass of enteric neurons, are the primary sensors and regulators of the ENS that detect luminal contents. These neurons respond to mechanical and chemical stimuli by activating intestinal muscles and controlling secretion of enzymes, hormones (by endocrine cells) and neurotransmitters. The ENS transmits information to the central autonomic nervous system through afferent nerves of the small intestine which correspond with specific areas in the brain (the well-known gut–brain axis). These areas are involved in metabolic regulation through controlling the function of splanchnic organs, such as the liver and endocrine pancreas, and the regulation of appetite and satiation. Interestingly, insulin has a direct regulatory effect on this pathway, resulting in the inhibition of food intake and weight control.[23] In obesity and T2DM, this gut–brain axis is dysfunctioning.[24] Additionally, it has been observed that a high-fat diet and T2DM correlate with presence of neuropathy in the duodenal myenteric plexus, a decrease in the supporting enteric glial cells, and the loss of duodenal neurons.[25] Recovery of these neuronal pathways can be achieved; it has been suggested that both RYGB and vertical sleeve gastrectomy lead to improved energy homeostasis and metabolism by manipulation of vagal afferent fibers of the ENS.[24] Duodenal interventions and their effects could greatly help to unravel the gut–brain axis in humans and could lead to unexpected treatment modalities.

## Conclusion and Future Directions

Collectively, these arguments point to the broad therapeutic potential that the duodenum may harbor. It is an easily accessible part of the gastrointestinal tract where multiple external factors (eg, nutrients, microbiome) and internal factors (eg, bile acids, mucosal sensing, enteroendocrine function) contribute to metabolic (dys)regulation (Figure 1*J*). Because the regulation of hyperglycemia after specific interventions has suggested a relation with the duodenum and proximal jejunum, further translational research could help to unravel whether and to what extend the duodenum contributes to the pathophysiology of obesity and T2DM. The accessibility of the duodenum to gastroenterologists renders it an attractive target for new research lines aimed at finding novel diagnostic and therapeutic leads. Studies are currently being conducted to explore duodenal mucosa characteristics like enteroendocrine cells, tight junction proteins, and mucosal thickness in subjects with the metabolic syndrome and T2DM, including metabolomics and microbiome profiling. Additionally, an investigator-initiated study further explores the metabolic effects of the endoscopic DMR procedure and to elucidate mechanisms of action. These studies will hopefully unravel the interplay between duodenal features and metabolic deterioration or improvements in subjects with T2DM.

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**Conflicts of interest**

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