

REVIEW

Gut as an emerging organ for the treatment of diabetes: focus on mechanism of action of bariatric and endoscopic interventions

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Abstract

Increasing worldwide prevalence of type 2 diabetes mellitus and its accompanying pathologies such as obesity, arterial hypertension and dyslipidemia represents one of the most important challenges of current medicine. Despite intensive efforts, high percentage of patients with type 2 diabetes does not achieve treatment goals and struggle with increasing body weight and poor glucose control. While novel classes of antidiabetic medications such as incretin-based therapies and gliflozins have some favorable characteristics compared to older antidiabetics, the only therapeutic option shown to substantially modify the progression of diabetes or to achieve its remission is bariatric surgery. Its efficacy in the treatment of diabetes is well established, but the exact underlying modes of action are still only partially described. They include restriction of food amount, enhanced passage of chymus into distal part of small intestine with subsequent modification of gastrointestinal hormones and bile acids secretion, neural mechanisms, changes in gut microbiota and many other possible mechanisms underscoring the importance of the gut in the regulation of glucose metabolism. In addition to bariatric surgery, less-invasive endoscopic methods based on the principles of bariatric surgery were introduced and showed promising results. This review highlights the role of the intestine in the regulation of glucose homeostasis focusing on the mechanisms of action of bariatric and especially endoscopic methods of the treatment of diabetes. A better understanding of these mechanisms may lead to less invasive endoscopic treatments of diabetes and obesity that may complement and widen current therapeutic options.

Key Words

- ▶ type 2 diabetes
- ▶ bariatric surgery
- ▶ endoscopic treatment
- ▶ duodenum exclusion
- ▶ mechanism

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Introduction

Increasing prevalence of type 2 diabetes mellitus (T2DM) worldwide and its close interconnection with other pathologies such as obesity, arterial hypertension, dyslipidemia and many others commonly referred to as

metabolic or insulin resistance syndrome (Reaven 2002) makes T2DM one of the most significant therapeutic challenges of the 21st century (O'Rahilly 1997). This chronic disease currently affects more than 415 million

people around the globe (Guariguata 2012, Ogurtsova *et al.* 2017). Majority (more than 90%) of all diabetic patients suffer from type 2 diabetes whose increased incidence is associated with unhealthy lifestyle, lack of physical activity, overeating and obesity. Moreover, another 193 million people worldwide are supposed to suffer from undiagnosed diabetes (Beagley *et al.* 2013). It is estimated that by 2040, the number of subjects diagnosed with diabetes mellitus will reach 642 million (Whiting *et al.* 2011). However, the main socioeconomic problem of diabetes is neither its high prevalence nor its direct treatment costs, but the fact that its unsatisfactory control leads to the development of chronic macrovascular (accelerated atherosclerosis of large arteries) and microvascular (alteration of microcirculation in kidney, eye and peripheral nerves) complications that are responsible for the majority of diabetes-related treatment costs (Chatterjee *et al.* 2017). As a result, patients with T2DM have a 2- to 3-fold increased risk of development of cardiovascular complications including myocardial infarction, stroke and peripheral arterial disease (Haffner *et al.* 1998).

Numerous studies have shown that bariatric surgery, in particular, the operations based on exclusion of the proximal part of duodenum from the contact with food, not only effectively decrease body weight but also markedly improve glucose control beyond the positive metabolic effects of weight loss (Rubino & Marescaux 2004, Pournaras *et al.* 2012). In fact, high percentage of diabetics can achieve diabetes remission after bariatric surgery making this approach the only therapeutic intervention capable of modification of the course of diabetes (Porjes 2008, O'Brien 2010). Consequently, endoscopic methods mimicking some of the effects of bariatric surgery were introduced and have shown some promises as well (Sullivan *et al.* 2017). The aim of this review is to discuss the current bariatric and endoscopic methods for the treatment of diabetes with a special focus on the mechanisms behind their effects. In particular, we will outline the potential mechanisms behind novel endoscopic procedures.

The role of the gut in glucose control and development of diabetes

Although its importance has not been fully appreciated until recently, gut has the ability to affect glucose homeostasis on multiple levels. It is essential for nutrient absorption and its delivery to different organs

and tissues of human body (Kiela & Ghishan 2016). It utilizes a significant amount of energy to cope with its considerable size and constant turnover of epithelial cells, and it is responsible for the thermic effect of food, which contributes to total energy expenditure and energy homeostasis (van Baak 2008). Most importantly, the information regarding nutritional content, transluminal nutritional flux and other characteristics of ingested food is communicated to other organs and tissues, in particular, to the central nervous system. This information can markedly affect metabolic regulations including glucose metabolism and its modulation by bariatric surgery is the most likely explanation for the profound effects of bariatric surgery on type 2 diabetes control.

Nutrient sensing is a very important part of the regulatory loop whereby central nervous system is provided with accurate information regarding the amount and composition of ingested food (Tolhurst *et al.* 2012). Primary elements responsible for nutritional sensing within the gastrointestinal tract are specialized endothelial cells referred to as enteroendocrine cells or enteroendocrine system (Psichas *et al.* 2015). These cells have the ability to sense the nutritional content and the transluminal nutritional flux and consequently secrete gastrointestinal tract hormones that in turn provide the feedback loop to central nervous system and peripheral tissues. The original notion that there are distinct (single hormone-secreting) types of enteroendocrine cells producing distinct hormones has been challenged by recent data suggesting that multiple hormonal precursors are expressed within one cell (Egerod *et al.* 2012). However, the expression of different gastrointestinal hormones exhibits a characteristic pattern within the gastrointestinal tract with ghrelin, somatostatin and gastrin primarily produced in the stomach; GLP1 in jejunum, ileum and colon; GIP in duodenum; CCK in duodenum and jejunum and PYY in distal ileum and colon, respectively (Meek *et al.* 2016). With the exception of ghrelin-producing cells, which do not come into direct contact with gastric lumen (referred to as closed-type structures), other enteroendocrine cells are open-type structures with a narrow apical part facing the lumen (Steinert & Beglinger 2011). The gastrointestinal hormones are then typically released in the basolateral side where they either enter into the circulation (endocrine action), act on the neighboring epithelial cells (paracrine action) or activate vagal, enteric or spinal sensory neurons (neural action).

Gut chemosensing is a complex process involving a plethora of nutrient-specific receptors. Its detailed description is beyond the scope of the current paper

and numerous excellent reviews on this topic have been recently published (Tolhurst *et al.* 2012, Psichas *et al.* 2015). In brief, carbohydrates are primarily sensed as glucose via the sodium glucose cotransporter 1 receptor (SGLT1) with subsequent stimulation of GLP1 and GIP secretion (Nguyen *et al.* 2012). The principal importance of SGLT1 receptors in mediating glucose-stimulated GLP1 and GIP secretion has been demonstrated in SGLT1-knockout mice where secretion of both hormones in response to glucose was markedly impaired (Kellett 2012). Dietary proteins strongly stimulate CCK secretion and secretion of GLP1 and GIP with underlying mechanism being only partially understood. The candidate receptors include G-coupled calcium-sensing receptor, TIR1/TIR3 and GPRC6A receptors (Reimann *et al.* 2004, Greenfield *et al.* 2009). Lipid sensing is mediated through numerous G-coupled receptors including GPR120, GPR119 and FFAR1 activating GLP1 and GIP secretion (Akiba *et al.* 2015, Kleberg *et al.* 2015).

Non-nutrient stimuli of enteroendocrine cells include bile acids and inflammatory cytokines (Psichas *et al.* 2015). Bile acids are in addition to their role in lipid digestion important signaling molecules that act primarily through G-coupled receptor GPBAR1 (also known as TGR5) with high expression in L-cells of distal intestine, being thus a stimulus of GLP1 and PYY secretion (Thomas *et al.* 2009, Tan *et al.* 2017). Out of the inflammatory cytokines, interleukin-6 (IL6) has been shown to increase GLP1 secretion from GLUTag cells (Ellingsgaard *et al.* 2011). Interestingly, IL6 has been demonstrated to increase GLP1 secretion in cardiac surgery patients suggesting a direct link between inflammation and GLP1 secretion in humans (Kahles *et al.* 2014).

Various gut-derived nutritional signals are then transferred to central nervous system through neural (vagal, enteric or spinal sensory neurons) or endocrine pathways. Nutrient passage through the digestive tract is thoroughly sensed by enteroendocrine cells and converted into gut-derived neural and hormonal signals acting on both central nervous system and peripheral tissues (Latorre *et al.* 2016). This complex network is a much more likely candidate for the explanation of the effects of bariatric surgery on glucose metabolism as compared to simplified theories postulating changes in single hormonal factors or mechanistic explanations based on the surgery-induced changes of digestive tract anatomy.

Proximal part of the small intestine, in particular the duodenum, appears to be the key metabolic signaling center contributing to metabolic disturbances in T2DM (Cherrington *et al.* 2017). Experimental studies have

demonstrated morphological changes of duodenal mucosa in diabetic vs nondiabetic rats with a tendency toward increased expression of GIP-producing L cells possibly contributing to hyperinsulinemia typical for initial stages of T2DM (Bailey *et al.* 1986, Gniuli *et al.* 2010). Another study demonstrated impaired sensing and downstream neural signaling in the gut of diabetic rats (Lee *et al.* 2012). Interestingly, extracts from duodena of diabetic *db/db* mice impaired insulin signaling and caused insulin resistance in cultured muscle cells (Salinari *et al.* 2013b). Human studies show similar morphological changes of duodenal mucosa with mucosal hypertrophy and hyperplasia of enteroendocrine cells (Theodorakis *et al.* 2006). Functional studies using a balloon catheter for nutrient delivery to duodenum, proximal jejunum and mid-jejunum, respectively, have shown that bypassing the duodenum with a direct delivery of nutrients to jejunum markedly increased insulin sensitivity in both healthy and T2DM subjects (Salinari *et al.* 2013a). Breen and colleagues studied the role of bypassing duodenum and redirection of nutrients into jejunum (duodeno-jejunal bypass procedure) in the regulation of glucose metabolism (Breen *et al.* 2012). Intrajejunal nutrient administration decreased endogenous glucose production in normal rats through a gut-brain-liver network in the presence of unchanged plasma insulin concentrations. The glucose-lowering effect of intrajejunal nutrient administration was attenuated by the inhibition of jejunal glucose uptake or formation of long chain fatty acyl-coA in both normal rats and diabetic animals with streptozotocin-induced diabetes. These findings suggest a critical role of nutrient sensing in the jejunum for early improvements of glucose homeostasis after duodenal-jejunal bypass and possibly also after other bariatric or endoscopic procedures bypassing the duodenum.

Changes of intestinal gluconeogenesis were suggested to play a role in the glucose control after bariatric surgery (in particular gastric bypass) (Mithieux 2014). Troy and colleagues have demonstrated in mice with diet-induced obesity that under fasting conditions, intestinal gluconeogenesis is a major contributor to portal vein glucose levels and its detection via a GLUT2 and hepatoportal sensor pathway (Troy *et al.* 2008). Intestinal gluconeogenesis was significantly increased after gastric bypass procedure, and this increase in portal vein glucose could trigger the portal sensor to change insulin resistance thus contributing to quick improvements in glucose metabolism. Hayes and colleagues measured fasting glucose levels in portal and central venous blood in patients before and after gastric bypass (Hayes *et al.* 2011).

They found no significant difference in glucose levels in these two sites in diabetic patients before and after surgery thus not supporting the hypothesis that intestinal gluconeogenesis contributes to the resolution of T2DM seen after Roux-en-Y gastric bypass (RYGB).

Collectively, these data along with well-known effects of bariatric surgery involving duodenal exclusion on glucose homeostasis suggest an important and multifaceted role of the proximal gut in the regulation of glucose homeostasis.

Gut microbiota, nutritional sensing and metabolism

Gut microbiota has recently been suggested as an important player involved in metabolic regulations and modulation of local and systemic inflammatory reactions (Burcelin *et al.* 2013). Obesity and T2DM were associated with changes in the amount and composition of gut bacteria as well as their biological diversity (Koren *et al.* 2012, Bouter *et al.* 2017). The exact mechanisms by which intestinal microbiota influences metabolic traits are largely unknown but might include products of gut bacterial fermentation of ingested dietary fiber, especially short-chain fatty acids (SCFA – butyrate, propionate and acetate), which were shown to affect energy homeostasis (Kim *et al.* 2014). The recent discovery of receptors across a wide range of cell and tissue types, for which SCFA appear to be natural ligands, further highlights their potential central role in the gut microbiota–metabolism interactions (Zhang *et al.* 2016). Another potentially important mechanism of direct influence of gut microbiota on metabolic regulations may lie in its interconnection with the initiation and development of subclinical inflammation that in turn contributes to the development of insulin resistance/type 2 diabetes (Haffner 2003). It has been postulated that obesity and T2DM are associated with increased penetration of lipopolysaccharide from gut bacteria into circulation with subsequent activation of innate immune system in adipose tissue (Creely *et al.* 2007).

While modulation of gut microbiota effectively prevented obesity and improved metabolic status in rodent models of obesity and type 2 diabetes (Di Luccia *et al.* 2015), human data supporting such strong effects in obese diabetic patient are much less convincing. A recent study exploring the effect of lean donor fecal microbiota transplantation has shown modest improvements in insulin sensitivity in male recipients with the metabolic syndrome 6 but not 18 weeks after transplantation (Kootte *et al.* 2017).

As changes in the gut microbiota have been studied only in some types of bariatric surgeries and in none of the endoscopic methods of diabetes treatment, we do not cover this topic in detail in this paper (for extensive reviews please see (Wahlstrom *et al.* 2016, Magouliotis *et al.* 2017)).

From bariatric to metabolic surgery

Bariatric surgery is the only therapeutic strategy proven to sustainably reduce body weight along with accompanying complications in patients with higher degree of obesity (Sjostrom *et al.* 2007, Pories 2008). Furthermore, it not only markedly reduces body weight but also radically improves diabetes control or leads to its complete remission in a high percentage of patients. Although substantial metabolic improvements are present in all patients after bariatric surgery, different types of operations differ in the rate of diabetes remission as well as in the timing of metabolic improvements (Dixon *et al.* 2012). In this part of the paper, we describe the principles of various bariatric procedures with respect to changes of gastrointestinal anatomy. Mechanisms of action of these operations are discussed along with mechanisms of action of endoscopic procedures in the section ‘How do bariatric or endoscopic procedures improve glucose control’.

Traditional classification of bariatric operations into restrictive and malabsorptive is considered inadequate by some leaders in the field (Dixon *et al.* 2012) and may be misleading as far as the mechanism of action is concerned (Haluzik 2013). For example, recent data suggest that typical ‘restrictive’ operations such as sleeve gastrectomy in fact do not restrict the passage of the food into the duodenum but rather speed it up (Sista *et al.* 2017). Nevertheless, traditional classification into restrictive, malabsorptive and mixed operations can still provide a good base to understanding the degree of alteration of gastrointestinal tract anatomy and in some cases also the mechanism of weight loss achievement.

Restrictive procedures including gastric banding, gastric plication and sleeve gastrectomy are all based on the restriction of gastric volume as the primary anatomical alteration (Ashrafian *et al.* 2010) – see Fig. 1 for different types of surgeries. In case of gastric banding, it is achieved by an adjustable band that creates an artificially small upper portion of the stomach restricting the amount of food that can be consumed in one portion (Burton & Brown 2011). Gastric plication works on a similar premise restricting stomach size by 70% owing to

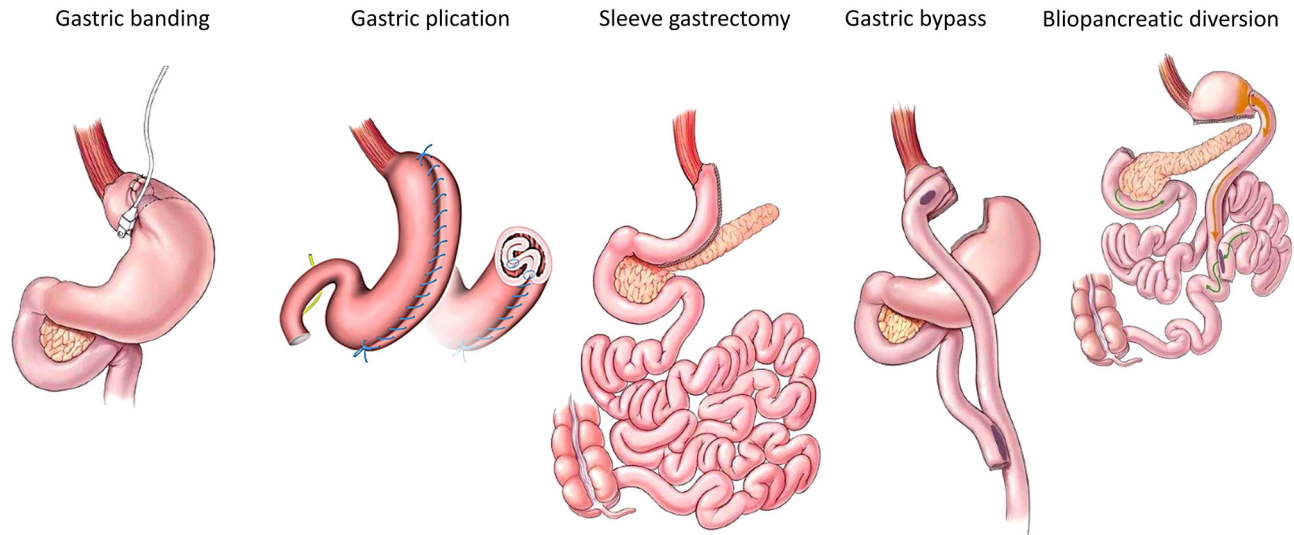


Figure 1
Different types of bariatric operations.

repeated folding (plicating) of the stomach wall inwards (Abdelbaki *et al.* 2012). Laparoscopic sleeve gastrectomy involves resection of two-thirds of the stomach including the gastric fundus – an important source of the orexigenic hormone ghrelin (Shi *et al.* 2010). In gastric banding and gastric plication, the decreased food intake and long-term weight loss are indeed achieved mainly by the restriction of the stomach size without any further weight loss-independent mechanisms in place. In contrast, sleeve gastrectomy appears to induce more complex responses resulting in better body weight-reducing and glucose control-improving efficacy than previous two procedures (Chambers *et al.* 2011).

In most of the malabsorptive procedures (e.g., biliopancreatic diversion (BPD), RYGB), stomach size is also partially restricted, and at the same time, a direct connection between the stomach and the lower part of the small intestine is created (Pournaras *et al.* 2010). Traditionally, bypass of a significant portion of the intestine was thought to decrease the absorption of nutrients, resulting in weight loss. Most recent data suggest that it may be only a partial explanation and that more complex mechanisms are in place (Kohli *et al.* 2013).

In any case, all bariatric procedures induce diabetes remission in a significant number of patients ranging from 30 to 95% of cases, with procedures involving the exclusion of a part of small intestine being generally more effective (Buchwald *et al.* 2004). The metabolic improvements after bariatric operations occur rather rapidly within the first days or weeks after the procedure when only negligible weight reduction is achieved.

This suggests that other mechanisms partially or completely independent of weight loss are playing a role (Ashrafian & le Roux 2009, Jackness *et al.* 2013).

The concept of metabolic surgery refers to clinical and scientific evidence that bariatric operations are able to cure or at least markedly improve type 2 diabetes by mechanisms only partially related to weight loss (Rubino & Cummings 2012). Bariatric surgery has traditionally been used for the treatment of 3rd degree (BMI >40 kg/m²) or 2nd degree obesity with complications (BMI 35–40 kg/m²) (Fried *et al.* 2014). Metabolic/bariatric surgery is according to the latest consensus advocated for the treatment of diabetes even in patients with BMI >30 kg/m² and poor glucose control (Rubino *et al.* 2016).

Endoscopic methods that mimic bariatric surgery

While bariatric surgery has proven high efficacy in improving glucose control and reducing body weight, it has still numerous disadvantages including the risks of general anesthesia, the operation itself and short-term and long-term postoperative complications (Bal *et al.* 2011). Furthermore, many patients are reluctant to have their diabetes treated by surgery when there are still possibilities of conservative therapy. To minimize the risks associated with the invasiveness of bariatric surgery while trying to maintain its favorable metabolic effects, endoscopic procedures mimicking some of the principles of bariatric surgery have been introduced (Kumar 2016,

Sullivan *et al.* 2017, Vairavamurthy *et al.* 2017). Here, we describe the principles and the efficacy of endoscopic procedures targeting pathophysiological mechanisms identified by bariatric operations. We intentionally leave out gastric balloons and aspiration therapy as short-term mechanistic procedures primarily intended for the treatment of obesity.

Duodenal-jejunal bypass liner (DJBL)

Duodenal-jejunal by-pass liner (DJBL) is an endoscopically implantable device that mimics some of the effects of gastric bypass operations (Patel *et al.* 2012). The principle of this device is based on the early animal (Rubino & Marescaux 2004) and human studies (Cohen *et al.* 2007) showing that surgical duodenal-jejunal bypass markedly improves glucose homeostasis without a marked effect on weight loss. In this operation, duodenum is transected and closed distally 1–2 cm below pylorus, creating pylorojejunostomy. Biliopancreatic limb is divided 30 cm from ligament of Treitz and anastomosed end-to-side 50 cm downstream in the jejunum (Cohen *et al.* 2007).

DJBL is a 60 cm long impermeable fluoropolymer sleeve that is inserted endoscopically into the small intestine for up to 12 months (Fig. 2) (Patel *et al.* 2012, Rohde *et al.* 2016). The ingested food is thus prevented from the contact with the proximal part of small intestine (duodenum, proximal jejunum) as it passes through the impenetrable liner. As a result, the food that reaches directly the medium part of jejunum is less digested. Both the exclusion of the proximal part of small intestine and the presence of less digested food in its distal parts are thought to be at least partially responsible for the weight loss and improvement of diabetes control seen in obese patients with T2DM after DJBL implantation (Cohen *et al.* 2013).

In general, the efficacy of DJBL varies among different studies (Kavalkova *et al.* 2016, Rohde *et al.* 2017, Vilarrasa *et al.* 2017). In a recently published meta-analysis of 5 randomized and 10 observational studies a DJBL implantation was accompanied by excess weight loss of 5.1 kg and a decrease of HbA1c of 0.9% and fasting plasma glucose by 3.7 mmol/L (Rohde *et al.* 2016). Adverse events consisted mainly of abdominal pain, nausea and less frequently vomiting. While most of the trials with DJBL demonstrated its good efficacy and safety, the pivotal US-based trial with this device has been terminated prematurely owing to higher rate of hepatic abscesses that was about 3.5%. Interestingly, this rate was almost 5 times

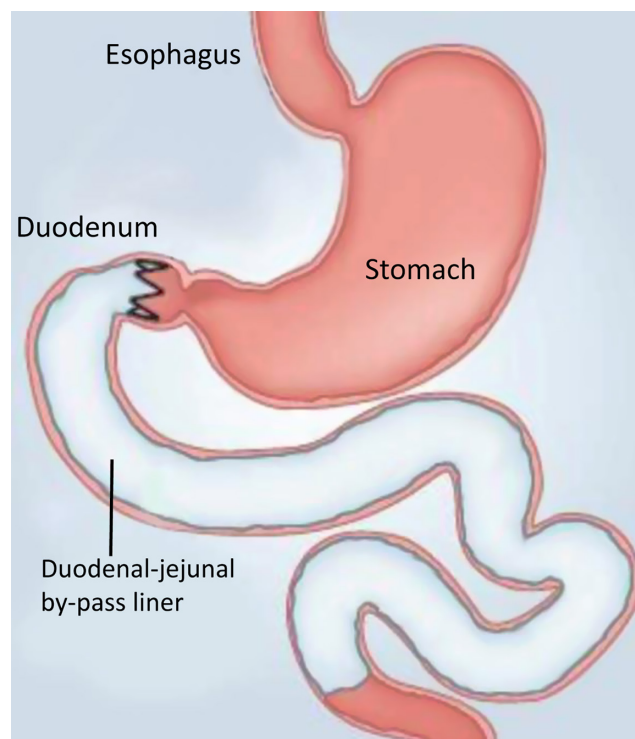
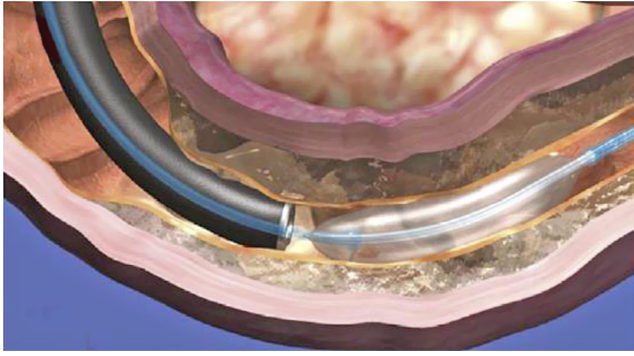


Figure 2
Duodenal-jejunal bypass liner.

higher than the rate of this complication in the centers outside the United States in other trials. Based on these safety data, DJBL has been withdrawn from the market in the USA and its safety is currently under close scrutiny by the European Medicines Agency as well.

Endoscopic duodenal mucosal resurfacing

Duodenal mucosal resurfacing is a minimally invasive endoscopic procedure based on the hydrothermal ablation of duodenal mucosa (Fig. 3 – reviewed in Cherrington *et al.* (2017)). Preclinical testing was performed on Goto-Kakizaki rats – a model of type 2 diabetes. In this study, hydrothermal ablation of duodenal mucosa significantly reduced postprandial glucose (unpublished data mentioned in Rajagopalan *et al.* (2016)). Phase I human study was performed as a single arm, non-randomized trial at a single center in Santiago de Chile. 44 patients with poorly controlled type 2 diabetes were included and underwent a single application of thermal energy ablation over 3–12 cm of duodenum (Rajagopalan *et al.* 2016). The procedure was well tolerated with no major acute side effects and good tolerance of oral diet by all patients after procedure. The most common side effect was abdominal

**Figure 3**

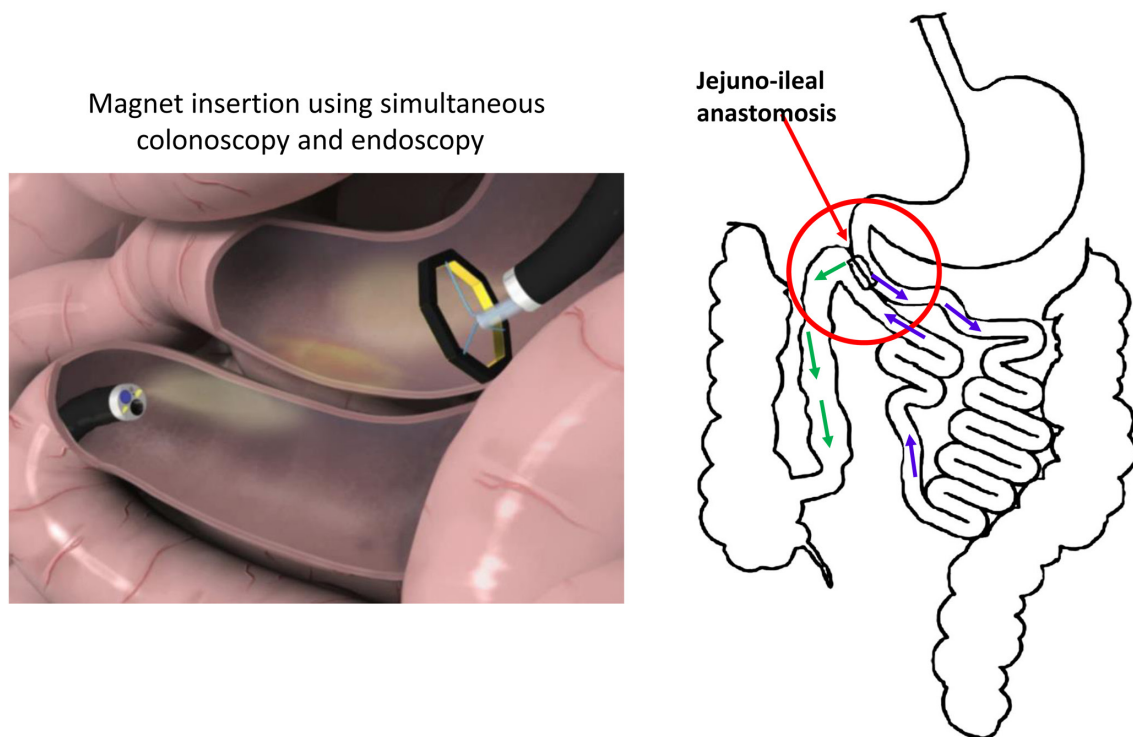
Hydrothermal ablation of the duodenal mucosa (reproduced, with permission, under the terms of the original Creative Commons licence from Cherrington *et al.* (2017)).

pain and three patients developed duodenal stenosis that was successfully treated by a single endoscopic dilation. After 6 months, HbA1c was reduced by 1.2% from the baseline value of 9.6%. Patients with ≥ 9 cm ablation had HbA1c reduced by 2.5% at three months and by 1.4% at six months as compared to 1.2% reduction in < 6 cm of duodenum ablation after three and 0.7% reduction of HbA1c after 6 months, respectively. Both fasting and postprandial blood glucose levels were significantly lowered in both subcohorts along with reduction or no

change in antidiabetic medication in the long segment cohort while in some patients from the short segment cohort treatment intensification was needed. In a combined group of all patients, body weight was reduced by 3.9 kg at three months and by 2.5 kg at 6 months, respectively.

Minimally invasive entero-ental dual-path bypassing using self-assembling magnets

This method uses an incisionless system based on the miniature self-assembling magnets, which create large-caliber anastomoses (Fig. 4). The incisionless magnet anastomosis system is preloaded into the biopsy channels of two endoscopes, and a simultaneous colonoscopy and enteroscopy are performed (Ryou *et al.* 2016a). After endoscopic deployment, the magnets self-assemble to form octagons in the jejunum and ileum. Subsequently, they couple to create a compression anastomosis allowing a portion of the ingested nutrients to bypass a part of the small bowel. Mated magnets then pass into the stool after the compression anastomosis is formed, typically in 1–2 weeks. The system has been successfully tested in two studies in 5 and 8 Yorkshire pigs, respectively

**Figure 4**

Minimally invasive entero-ental dual-path bypassing using self-assembling magnets.

(Ryou *et al.* 2016a,b). The procedure was safe with all animals surviving with anastomosis present three months after the procedure.

First human data with this approach have been presented recently. Simonson and colleagues studied 10 obese patients (4 with T2DM and 3 with prediabetes) who underwent dual-path enteral diversion using an incisionless magnet anastomosis system at baseline and 6, 12 and 18 months after the procedure, respectively (Machytka *et al.* 2017a). The mean weight loss after 18 months was 16.6kg. In patients with diabetes, HbA1c decreased from 7.8 to 6.0% despite reduction or cessation of antidiabetic medication. All 3 prediabetic patients returned to normal glucose tolerance. No major side effects were reported with diarrhea being the most frequent minor side effect. The interim 12-months results of this procedure have recently been published (Machytka *et al.* 2017b).

How do bariatric or endoscopic procedures improve glucose control?

Many possible explanations of metabolic improvements after bariatric surgery have been formulated with 'foregut' and 'hindgut hypotheses' being often mentioned (Dixon *et al.* 2012). The foregut hypothesis is based on the observation that bariatric procedures excluding the proximal part of the small intestine from the ingestion, such as gastric bypass or biliopancreatic diversion, are the most effective in the improvement or remission of type 2 diabetes. According to this hypothesis, exclusion of foregut from nutrient passage may inhibit the production of the postulated factor that impairs insulin secretion and possibly induces other metabolic disturbances. The hindgut hypothesis suggests that expedited delivery of nutrients to the distal parts of small intestine promotes metabolic improvements and weight loss by accentuation of ileal brake – a primary inhibitory feedback mechanism that regulates the transit of food through digestive tract to ensure optimal nutrient digestion and absorption (Maljaars *et al.* 2008).

It is now increasingly clear that simplified mechanistic explanations looking for a single hormonal factor or single mechanism are not capable of explaining the complex effects of bariatric surgery. The improvement of glucose homeostasis after surgery may include a plethora of mechanisms from pure restriction of food intake or malabsorption leading to weight loss to modulation of gastric emptying; the digestion of carbohydrates, lipids

and proteins; modification of absorption of glucose and its utilization by the intestine; changes in nutrient sensing and modulation of gastrointestinal hormone secretion, modulation of gut microbiota and many others (Fig. 5).

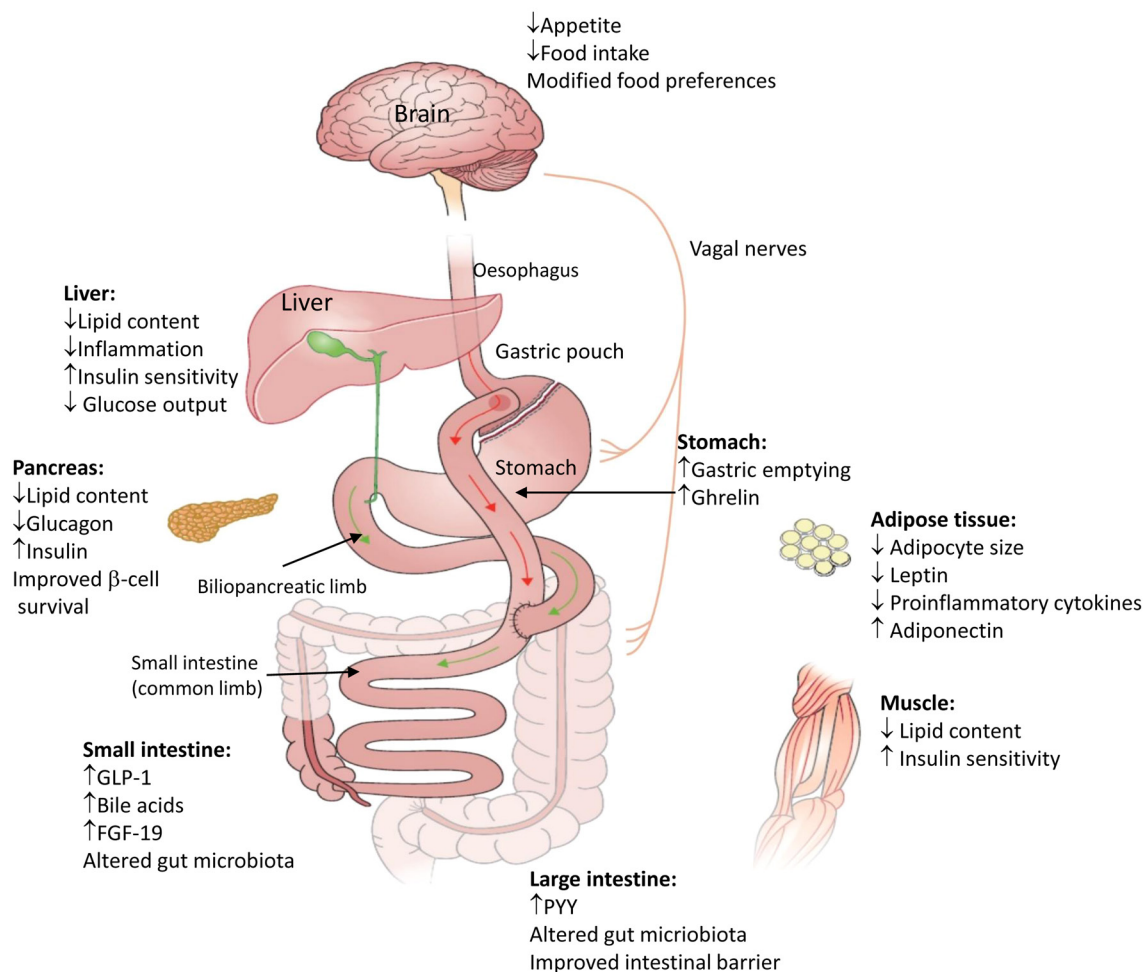
Weight loss and energy expenditure

Weight loss is an important part of the metabolic effects of bariatric surgery. For example, in the meta-analysis published by Buchwald and colleagues, the percentage of excess weight loss was 47% for gastric banding, 62% for RYGB and 79% after biliopancreatic diversion with duodenal switch (Buchwald *et al.* 2004). In the recently published 5-year results of the STAMPEDE trial comparing surgical vs medical therapy of T2DM, patients BMI decreased from 36.4 to 34 in the medical group, while it was lowered from 37 to 28.9 in gastric bypass and from 36 to 29.3 in sleeve gastrectomy group, respectively (Schauer *et al.* 2017). Similar results were reported in another study comparing surgical vs conservative treatment of type 2 diabetes (Mingrone *et al.* 2015).

By contrast in endoscopic procedures, relatively modest body weight decrease has been reported ranging mostly between 5 and 10kg or even less with duodenal mucosal resurfacing (Rohde *et al.* 2016). Changes in energy expenditure have not been systematically measured in most of the bariatric procedures. Available data suggest that energy expenditure decreases after bariatric surgery similar to changes seen in weight loss achieved by caloric restriction (Benedetti *et al.* 2000). There are no data available with respect to energy expenditure changes in patients after endoscopic procedures. Nevertheless, it is unlikely that major changes of energy expenditure after endoscopic procedures can be expected.

Gastric volume restriction

Gastric volume restriction and malabsorption have been extensively discussed in connection with the mechanism of metabolic effects of bariatric surgery. Laparoscopic gastric banding markedly restricts the size of the upper pouch of the stomach preventing the patients from eating large quantities of solid food. Smaller meal sizes are sufficient to create intraluminal pressure able to induce satiation probably through gastric sensory receptors and vagus nerve (Burton & Brown 2011). On the contrary, anorexigenic gastrointestinal hormones such as GLP1 and PYY are not affected by gastric banding, and ghrelin levels increase similarly to patients losing weight by dieting (Wang & Liu 2009). No data are available with respect to

**Figure 5**

Complex changes induced by bariatric surgery. Gastric bypass is pictured as an example of the operation combining weight-dependent and weight-independent effects. Exclusion of distal part of duodenum combined with accelerated entry of less digested food into jejunum increases GLP1 secretion that subsequently acts on the brain to decrease food intake and modify food preferences. Further input into the brain is mediated through nutrient sensing and other multiple mechanisms transferred by neural and endocrine pathways. Adapted, with permission, from [Madsbad *et al.* \(2014\)](#). Copyright 2014 Elsevier Ltd.

gastric plication and food passage or gastric emptying. Similar to gastric banding, gastric plication does not appear to consistently affect GLP1, GIP and PYY, and majority of the studies suggest increased ghrelin levels after this procedure similarly to changes after gastric banding or hypocaloric diet ([Buzga *et al.* 2015](#)).

Gastric volume is restricted in both RYGB and sleeve gastrectomy; nevertheless, this size restriction does not slow down the food passage into intestine but rather accelerates its entry ([Sista *et al.* 2017](#)). Consequently, nutrient sensing can be significantly altered and could thus explain some of the metabolic effects of surgery. Another possible consequence of accelerated food transit could be the modulation of hormonal secretion of enteroendocrine cells, which can attenuate food intake through neural mechanisms ([le Roux *et al.* 2007](#)).

Out of the endoscopic procedures, gastric emptying has only been studied in patients after DJBL implantation ([de Moura *et al.* 2015](#)). De Moura and colleagues found delayed gastric emptying after DJBL implantation that was reversible after its removal. Nevertheless, the changes in gastric emptying did not correlate with weight loss or T2DM control suggesting that other mechanisms were responsible for improved diabetes compensation ([de Moura *et al.* 2015](#)).

Malabsorption

Malabsorption of macronutrients is not seen with restrictive operations or RYGB while it is common in patients after BPD ([Madsbad *et al.* 2014](#)). In BPD, partial fat malabsorption is intended and considered

part of the weight-reducing mechanism (O'Brien 2010). On the contrary, micronutrient deficiencies are often seen especially after RYGB and BPD where parenteral supplementation of some vitamins (in particular vitamin D) may be needed (Pournaras & le Roux 2009). In our study with 10-month DJBL implantation in patients with poorly controlled T2DM, we noticed a decrease in serum concentrations of zinc, vitamin B12 and iron that were reversed three months after DJBL removal (Kavalkova *et al.* 2016). Overall, malabsorption of macronutrients only appears to play some role in the weight loss and metabolic improvements in patients after BPD while it is not present in other procedures. Micronutrient changes seen after some procedures are unlikely to have a significant role in alterations of glucose metabolism.

Changes in classical gastrointestinal hormones

Changes of circulating levels of gastrointestinal and pancreatic peptide hormones have been intensively discussed as important players potentially explaining the metabolic effects of bariatric surgery and some excellent reviews focused on this topic are available (Meek *et al.* 2016, Cavin *et al.* 2017). In general ghrelin, cholecystokinin and both incretins (GLP1 and GIP), and PYY have been studied most frequently with less information available with respect to other hormones.

Ghrelin is produced by the stomach and the pancreas and its elevated concentrations increase hunger and stimulate food intake (Tschop *et al.* 2000). Decreased ghrelin levels are present in patients with obesity, and they increase in response to diet-induced weight loss and restrictive bariatric surgeries that do not involve stomach resection (gastric banding, gastric plication) (Cummings *et al.* 2002, Dostalova & Haluzik 2009). Ghrelin levels were reported to increase after DJBL (de Jonge *et al.* 2015) while no information about its levels is available in patients after other endoscopic procedures.

Cholecystokinin is primarily secreted by I cells in duodenum and stimulates bile and pancreatic juice secretion into gut lumen, slows down gastric emptying and promotes satiety (Miyasaka & Funakoshi 2003). Cholecystokinin levels rise after RYGB or sleeve gastrectomy and decrease after DJBL (de Jonge *et al.* 2015) while no data are available for other bariatric or endoscopic procedures (Peterli *et al.* 2012, Dirksen *et al.* 2013b).

GLP1 is secreted from L cells mainly in the distal ileum and colon (Holst *et al.* 2008). Its well-known effects such as increased insulin and decreased glucagon

secretion, inhibition of food intake and slowing of gastric emptying are used therapeutically in patients with type 2 diabetes via DPP4 inhibitors and GLP1 receptor agonists commonly referred to as incretin-based therapies (Drucker *et al.* 2010).

Early experimental studies demonstrated an important role for increased GLP1 secretion as an important mediator of metabolic improvements after various types of bariatric surgery including not only gastric bypass (Shin *et al.* 2010), but also ileal transposition (Strader *et al.* 2005) and sleeve gastrectomy (Chambers *et al.* 2011). Interestingly though, the effects of RYGB on body weight and glucose homeostasis were preserved even in two mouse models of functional glucagon-like peptide-1 deficiency (Mokadem *et al.* 2014).

In human studies, RYGB markedly increases GLP1 levels that are undoubtedly responsible for some of the positive metabolic effects of this operation (Holst & Madsbad 2016) by multiple mechanisms including increased insulin and decreased glucagon secretion, slowed gastric emptying and central anorexigenic effects (Holst *et al.* 2008). Other bariatric procedures, even the restrictive ones, can also transiently increase GLP1 levels (Bradnova *et al.* 2014). Nevertheless, the concentrations are much lower as compared to the marked increase after RYGB. Postprandial GLP1 levels were reported to be either significantly increased (Rohde *et al.* 2017) or unchanged after DJBL implantation (Kavalkova *et al.* 2016, Vilarrasa *et al.* 2017) with no data available with respect to GLP1 changes after other endoscopic procedures. GIP is secreted from K cells in the proximal part of small intestine (Drucker 2006). It has an important insulinotropic and lipogenic effect and acts in concert with GLP1 to maintain normal insulin secretion. In contrast to GLP1, the effect of different bariatric operations on circulating GIP levels appears to be modest or none at all (Mingrone *et al.* 2009, Salinari *et al.* 2009). We noticed a small decrease in postprandial GIP peak after DJBL implantation while no data for other endoscopic procedures are available (Kavalkova *et al.* 2016).

PYY is produced by L-cells in the distal part of small intestine and in the colon (Batterham *et al.* 2003). It promotes satiety, delays gastric emptying, slows down colonic motility and reduces postprandial insulin production. In experimental studies, PYY appears to play an important role in mediating weight loss after bariatric surgery. Its importance was directly demonstrated in PYY-knockout mice that in contrast to control animals did not lose weight after gastric bypass (Chandarana *et al.* 2011). Restoration of normal glucose homeostasis in the diabetic

Goto-Kakizaki (GK) rat model was mediated by PYY and neutralization of PYY reversed these effects in diabetic rat islets *in vitro* (Ramracheya *et al.* 2016). In humans, some studies reported increased postprandial PYY levels after different types of bariatric operations (Dirksen *et al.* 2013a, Tsoli *et al.* 2013), which could theoretically contribute to increased satiety in patients after bariatric surgery. DJBL implantation and creation of a dual-path enteral diversion by incisionless magnetic anastomotic system, respectively, was also accompanied by increased PYY concentrations (Rohde 2016, Machytka *et al.* 2017a, Vilarrasa *et al.* 2017) while no data on PYY were reported for duodenal mucosal resurfacing.

Glucagon is produced by the alpha cells of pancreatic islets. It is a major counter regulatory hormone to insulin being released during fasting and promoting gluconeogenesis and glycogenolysis (Lund *et al.* 2014). Chronically increased glucagon concentrations contribute to hyperglycemia and excessive liver glucose production in patients with T2DM and its amelioration by incretin-based therapies is an important part of their mechanism of antidiabetic action (Martin *et al.* 2011). Weight loss is in general accompanied by decreased glucagon levels and a similar finding was reported in patients undergoing RYGB (Korner *et al.* 2006). In our study, DJBL decreased glucagon concentrations and this effect was abolished after DJBL removal (Kavalkova *et al.* 2016). No data are available with respect to glucagon changes after other endoscopic or bariatric procedures.

Changes in bile acids

Bile acids not only contribute to lipid digestion but also act as important signaling molecules in the liver through stimulation of farnesoid X receptor (FXR) (Prawitt *et al.* 2011) and TGR5 receptors (Thomas *et al.* 2009). These receptors have an important role in the regulation of numerous metabolic processes including glucose and lipid homeostasis. Therefore, modulation of circulating bile acids is a plausible mechanism to explain some of the metabolic effects of bariatric or endoscopic interventions. Bile acid-dependent changes after vertical sleeve gastrectomy (VSG) were studied in a mouse model with diet-induced obesity comparing mouse with intact vs targeted genetic disruption of FXR (Ryan *et al.* 2014). VSG increased circulating bile acids regardless of intact FXR signaling. However, in the absence of FXR, the ability of VSG to reduce body weight and improve glucose tolerance was substantially reduced. In another study, diversion of bile flow to the ileum induced metabolic changes similar

to RYGB including weight loss and improvements in glucose tolerance and hepatic steatosis underscoring the significance of bile acid signaling in the metabolic effects of bariatric surgery (Flynn *et al.* 2015).

Numerous studies have indicated that malabsorptive operations markedly affect the systemic concentrations of bile acids (Pournaras & le Roux 2013). Increased systemic levels of total bile acids have been described in patients after both gastric bypass and biliopancreatic diversion (Pournaras *et al.* 2012). In patients after sleeve gastrectomy, total bile acids were reported to be unchanged (Haluzikova *et al.* 2013) or increased (Escalona *et al.* 2016). Only transient elevation of the majority of circulating bile acids was found after gastric banding with only glycolithocholic acid being elevated chronically (Thoni *et al.* 2017). Out of the endoscopic interventions, bile acids were only measured after DJBL. In our study, we found a marked elevation in total circulating bile acid levels 10 months after DJBL implantation (Kavalkova *et al.* 2016).

Changes in fibroblast growth factor 19

Fibroblast growth factor-19 (FGF19) was originally discovered in human brain during embryonic and fetal development (Nishimura *et al.* 1999). Later studies have shown its important role in the regulation of bile acid synthesis and transportation and an important interplay between bile acids and FGF19 (Lundasen *et al.* 2006). Bile acids stimulate FGF19 expression and synthesis in enterocytes through stimulation of FXR (Wistuba *et al.* 2007). FGF19, on the other hand, inhibits the expression of Cyp7a1 – a rate-limiting enzyme in bile acids synthesis (Song *et al.* 2009). Numerous experimental studies have shown that administration of FGF19 or its transgenic expression prevented the development of obesity and insulin resistance in mice (Tomlinson *et al.* 2002). Furthermore, a recent study has demonstrated that administration of FGF15/19 and FGF19-based chimeric molecule protected from diet-induced hepatic steatosis and promoted liver regeneration after partial hepatectomy in a mouse model (Alvarez-Sola *et al.* 2017).

In humans, circulating FGF19 concentrations were decreased or unchanged in patients with type 2 diabetes and obesity relative to healthy subjects (Mraz *et al.* 2011, Gomez-Ambrosi *et al.* 2017). Similarly, FGF19 concentrations were reduced in obese adolescents with nonalcoholic fatty liver disease and were inversely related to the probability of development of nonalcoholic steatohepatitis and fibrosis (Gallego-Escuredo *et al.* 2015).

Bariatric surgery including RYGB, LSG and gastric banding consistently increased FGF19 (Haluzikova *et al.* 2013; Pournaras & le Roux 2013). FGF19 concentrations were also increased in our study after DJBL implantation in patients with T2DM (Kavalkova *et al.* 2016) while no data on FGF19 levels are available for other bariatric or endoscopic procedures. Taken together, available data suggest that increased FGF19 concentrations may play a role in metabolic improvements after bariatric surgery and DJBL implantation. This factor may also have an interesting potential in the treatment of obesity and related metabolic complications.

Conclusions and future directions

With steadily increasing prevalence of T2DM, novel therapeutic approaches are needed that are capable of not only achieving a temporary improvement of glucose control but also modifying the course of diabetes development, i.e. slowing down its progression or achieving its complete remission. Bariatric surgery is, at the moment, the only approach able to accomplish this goal. It is quite clear that the operations with highest metabolic efficacy act by multiple mechanisms with many of them being partially or completely independent of weight loss. Endoscopic methods mimicking some of the principles of bariatric surgery have been introduced and tested in patients with T2DM. Although promising, most of these methods are still in the early stages of clinical development. It can be expected that better understanding of the mechanisms of action of bariatric surgery will eventually lead to novel pharmacological therapies of T2DM possibly acting through modifications of nutritional sensing, manipulation of number or phenotype of enteroendocrine cells or alterations of signal transduction from enteroendocrine cells to central nervous system. Many hopes are also put into modification of gut microbiota as potential adjuvant therapy of T2DM although little data supporting the viability of this concept in humans is available to date. Refined endoscopic methods based on the principles of bariatric surgery could in the future complement and possibly even replace some of the methods of bariatric surgery. Collectively, treatment of diabetes by targeting the gastrointestinal tract appears to be one of the most promising approaches, we currently have to battle the emerging threat of type 2 diabetes mellitus and many interesting developments can be expected in this field in the near future.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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