EndoBarrier Gastrointestinal Liner

Delineation of underlying mechanisms and clinical effects

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The thesis is based on these four original papers

1. Rohde U, Hedbäck N, Gluud LL, Vilsbøll T, Knop FK: Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: protocol for systematic review and meta-analysis of clinical studies. *BMJ Open* 2013; 3: e003417. (***Study I***)
2. Rohde U, Hedbäck N, Gluud LL, Vilsbøll T, Knop FK. Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: a systematic review and meta-analysis. *Diabetes, Obesity and Metabolism* 2016; 18: 300-5. (***Study II***)
3. Rohde U, Federspiel CA, Vilmann P, Langholz E, Friis SU, Krakauer M, Rehfeld JF, Holst JJ, Vilsbøll T, Knop FK. The Impact of EndoBarrier Gastrointestinal Liner in Obese Patients with Normal Glucose Tolerance and Patients with Type 2 Diabetes. Manuscript accepted for publication September 2016 in *Diabetes, Obesity and Metabolism*. (***Study III***)
4. Rohde U, Sonne DP, Christensen M, Hansen M, Brønden A, Toräng S, Rehfeld JF, Holst JJ, Vilsbøll T, Knop FK. Cholecystokinin-Induced Gallbladder Emptying and Single-Dose Metformin Elicit Additive Glucagon-Like Peptide-1 Responses. *The Journal of Clinical Endocrinology and Metabolism* 2016; 101: 2076–2083. (***Study IV***)

INTRODUCTION

At a worrying pace, the prevalence of overweight and obesity has reached epidemic proportions. In their latest prognosis, The World Health Organization (WHO) has estimated that more than a quarter of the global population is overweight (body mass index (BMI) ≥25 kg/m^2), and 600 million are obese (BMI ≥30 kg/m^2) (1). Overweight and obesity entail an increased risk of a number of diseases including cardiovascular diseases, musculoskeletal diseases, certain cancers (e.g. colon, breast and endometrial cancers) and type 2 diabetes (T2D) that increase all-cause mortality and reduce life expectancy (2).

Given the high prevalence and serious consequences of obesity, therapeutic approaches to overcome obesity have become numerous. From a simplistic point-of-view, it is 'just' a matter of decreasing energy input or increasing energy expenditure (or both). Diet alone or combination therapy with the intestinal lipase inhibitor orlistat, or exercise combined with amfepramon (closely related to metamfetamin) represent regimens that reduce energy input and increase energy expenditure, respectively. However, placebo-controlled studies have shown that these regimens result in small-to-moderate and non-maintainable long-term weight losses often accompanied by frequent pharmacological side effects (3–5). These discouraging effects and the fact that it over time is nearly impossible to maintain a weight loss (6) leave us with the conclusion that effective medical or lifestyle intervention based treatment of obesity is virtually impossible.

Bariatric surgery comprises a range of different surgical procedures with the common aim of reducing body weight. The Roux-en-Y gastric bypass (RYGB) procedure probably represents one of the most frequently used type of bariatric surgery and has proven effective in inducing and maintaining substantial weight losses of up to 40% of the excess body weight (defined as percentage of excess body weight lost from a BMI in excess of 25 kg/m^2) (7). In parallel to the positive effects of weight loss on cardiovascular and musculoskeletal diseases (e.g. arthritis), insulin sensitivity is known to improve (8). Indeed, studies have shown that 40-80% of obese patients with T2D undergoing RYGB achieved remission of diabetes (9,10). Additionally, long-term studies have shown that dysregulated patients with T2D randomised to RYGB plus intensive medical therapy or intensive medical therapy maintained better glycaemic control (11), and that bariatric surgery significantly reduces all-cause mortality (12,13). Thus, without doubt bariatric surgery is truly effective.

One fundamental issue that remains to be fully elucidated is *how* the RYGB procedure mediates its effects. Interestingly, the improvement in glucose metabolism occurs shortly (days) after surgery and before any major weight loss is achieved (14,15). It has been speculated that the altered gastrointestinal tract anatomy following RYGB represents one of the main explanations of the improved glucose metabolism. Increasing evidence suggests that gut-derived hormones are important determinants of this improvement. Especially, RYGB-induced potentiation of the secretion of the appetite and glucose-lowering incretin hormone glucagon-like

peptide-1 (GLP-1) seems to be important (16,17). GLP-1 and the related incretin hormone glucose-dependent insulinotropic polypeptide (GIP) are secreted from enteroendocrine L cells and K cells, respectively, and play a pivotal role in maintaining normal fasting and postprandial glucose levels by increasing insulin secretion following ingestion of nutrients (18). This is referred to as the incretin effect, which accounts for up to 70% of insulin secretion following oral ingestion of glucose in healthy subjects. In patients with T2D however, the incretin effect is impaired, which is considered a significant and early part of the pathogenesis in T2D (19). Following RYGB, undigested nutrients bypass the proximal intestines and are expedited to distal and L cell-rich parts of the small bowel, giving rise to increased GLP-1 secretion and subsequent insulin secretion, which is a consistent finding in RYGB studies. On the other hand, the impact of RYGB on the secretion of GIP from enteroendocrine K cells which are found in highest numbers in the proximal small intestine, varies and postprandial GIP responses have been reported attenuated, unaltered or even increased after RYGB (15,17).

Another, and highly clinically relevant issue about bariatric surgery is the invasiveness of the procedures, and the risk of complications, both short-term (e.g. bleeding, anastomosis leak, ileus, internal herniation and thromboembolic episodes) and long-term (nutritional deficiencies due to micronutrient malassimilation, dumping syndrome or anastomotic strictures/bowel obstruction) complications. Indeed, in a systematic review *Chang et al*. (7) reported an overall postoperative complication rate of 21% following RYGB, a perioperative mortality rate within 30 days of 0.38% and a postoperative (>30 days) mortality rate of 0.72% with pulmonary embolism being the leading cause of death. Additionally, up to 20% of patients undergoing RYGB require reoperation due to long-term complications (20) and 51.3% and 22.7% develop iron deficiency or iron deficiency anaemia within one year after surgery, respectively (21). These side effects and complications remain a worrisome clinical problem and there is an unmet need for simpler and less invasive alternatives.

The EndoBarrier Gastrointestinal liner (or duodenal-jejunal bypass sleeve (DJBS)) could represent such an alternative. It is a reversible and endoscopic procedure for obesity and T2D treatment, which is thought to mimic the intestinal bypass component of a RYGB. The DJBS consists of a 60 cm long, hollow and highly flexible sleeve that is implanted into the upper proximal and postpyloric part of the small intestines. Following meal ingestion, gastric chyme flows down and inside the sleeve. The sleeve prevents the gastric chyme from stimulating the duodenal and proximal jejunal mucosa, thus shunting ingested nutrients to more distal parts of the intestines. The few (small-sized) studies that have appeared so far demonstrated that subjects treated with the DJBS lose weight, and that some subjects improve glucose metabolism (22,23). Despite intended as a RYGB mimetic, the exact mechanisms behind DJBS' effects still remain to be fully elucidated.

In addition to stimulation of gut hormone secretion, food intake elicits contraction of the gallbladder and relaxation of the sphincter of Oddi (in part mediated by nutrient-induced cholecystokinin (CCK) secretion from enteroendocrine I cells in the proximal gut) and flow of bile acids into the small intestinal lumen. The facilitation of lipid absorption has traditionally been considered the most important effect of meal-induced ejection of bile into the duodenum. However, over the last decade it has become clear that bile acids are not only fat-emulsifiers necessary for lipid assimilation, but also act as key metabolic integrators of glucose and energy metabolism. This mode of action is believed to involve activation of the nuclear farnesoid X receptor (FXR) and the membrane bound G-protein-coupled receptor 5 (TGR5) by bile acids in the gut. The exact pathways by which these receptors mediate their effects remain to be unravelled, but, interestingly, several *in vitro* and animal studies have reported bile acid-induced GLP-1 secretion via stimulation of TGR5 (24–26). Importantly, these findings have been confirmed in humans (27–31). However, the physiological impact of gallbladder emptying and subsequent ejection of bile acids into the intestines for human GLP-1 secretion remains to be clarified. As DJBS has been shown to increase bile acid concentrations in obese patients with T2D (32), one might speculate that the reported glycaemic improvements following DJBS treatment may involve bile acid-induced GLP-1 secretion. Moreover, the most widely used and first-in-line glucose-lowering drug in the management of T2D, metformin, has remarkably been shown to increase GLP-1 secretion (33–35), which may constitute an important part of metformin's glucose-lowering effect. The exact mechanisms underlying this phenomenon remain relatively unclear, but *in vitro* studies suggest that metformin inhibits bile acid reuptake through the apical sodium-dependent bile acid transporter (ASBT) in the ileum (36,37), which in turn can be thought to increase bile acid-induced activation of TGR5 on L cells and thereby elicit GLP-1 secretion. Also, metformin-induced inhibition of ASBT may reduce intracellular concentrations of bile acids in enteroendocrine L cells and, consequently, reduce activation of the nuclear FXR, which may increase GLP-1 production and secretion as suggested from recent studies by *Trabelsi et al*. (38). In line with these notions, increased faecal bile acid excretion in patients with T2D following metformin has been observed (34,39). Nevertheless, the effect of gallbladder emptying on human GLP-1 secretion and its potential role in metformin-induced GLP-1 secretion remain unknown. Hypothetically, metformin-induced GLP-1-secretion may be dependent on the presence of bile in the gut lumen and, thus, gallbladder emptying. Whether and how DJBS (covering the proximal small intestinal mucosa, which is rich in CCK-secreting I cells) may interfere with gallbladder emptying and bile acid and metformin-induced GLP-1 secretion remains unknown. Interestingly, however, results from the prematurely terminated ENDO trial, randomising obese patients with inadequately controlled T2D on oral antidiabetic medication to DJBS or sham-procedure (40), showed that DJBS lead to greater glycated haemoglobin A1c (HbA_{1c}) reductions than sham. Since the majority of participants were treated with metformin, one may speculate that metformin combined

with DJBS could contribute to any increase in GLP-1 secretion during DJBS treatment.

In the present thesis, the clinical efficacy and safety of DJBS treatment in subjects with obesity and patients with T2D was evaluated and the physiological impact of DJBS was investigated. Furthermore, the impact of gallbladder emptying and metformin on human GLP-1-secretion was assessed.

BARIATRIC SURGERY

ROUX-EN-Y GASTRIC BYPASS (RYGB) SURGERY

The history of bariatric surgery takes it beginning when *Kremen and Varco* in the early 1950s performed the jejunoileal bypass (41). Following this procedure, the proximal jejunum was connected to the terminal ileum by which the majority of the small intestines were bypassed. The jejunoileal bypass was indeed effective in terms of bodyweight loss, but had several important side effects and complications since many patients developed steatorrhea, diarrhoea, and electrolyte derangement, nephrolithiasis, vitamin deficiencies and liver failure postoperatively. The procedure was therefore abandoned. In 1967 the RYGB procedure was first introduced (42). First as an open surgical procedure, and later in 1993 as a laparoscopic procedure (43). RYGB alters the gastrointestinal tract anatomy (**Fig. 1**). Initially, the stomach is divided into two parts; a proximal small (30 ml) pouch connected to the oesophagus, and a larger distal part still connected to the duodenum and proximal jejunum. Approximately 30 cm distal to the *Ligament of Treitz* the small intestine is divided and the distal intestinal segment is brought up to the small gastric pouch to make a gastroenterostomy. Some 100 cm below the point of division, the bypassed segment (encompassing the remnant stomach, duodenum and proximal jejunum) is re-connected into a Y-configuration. This blind-ending part of the gastrointestinal tract constitutes the bilio-pancreatic limb. The distal part of the jejunum, anastomosed to the small gastric pouch, now represents the Roux or alimentary limb. The common limb refers to the small intestines from the Y-intersection to *valvula Bauhini* (44). The reconfigured gastrointestinal tract anatomy entails that orally ingested nutrients pass down the oesophagus into the small gastric pouch and directly into a relatively distal part of the small intestines; bypassing the stomach, duodenum and the proximal jejunum (45). The RYGB has traditionally been considered an irreversible restrictive and malabsorptive procedure. In terms of malabsorption, it is generally accepted that RYGB compromises intestinal uptake of micronutrients, i.e. cobalamin, vitamin D and iron (46–48). However, the absorption of macronutrients does not seem to be affected by the procedure (49,50) and the restrictive component of the procedure also seem unclear given the fact that the pouch empties almost instantaneously upon meal ingestion, even of solid foods (51). Therefore, classifying RYGB as a 'restrictive' and 'malabsorptive' procedure seems inappropriate. As aforementioned, RYGB implies rerouting of nutrients down to more distal parts of the small intestine, bypassing the duodenum and upper jejunum, whereby, in particular secretion of the gluco-homeostatic improving and satiety promoting incretin hormone GLP-1 is enhanced. The bypassed gastrointestinal tract anatomy with its increased nutrient-stimulated GLP-1 responses is thought to play an important role for the high rates of T2D remission and substantial weight loss.

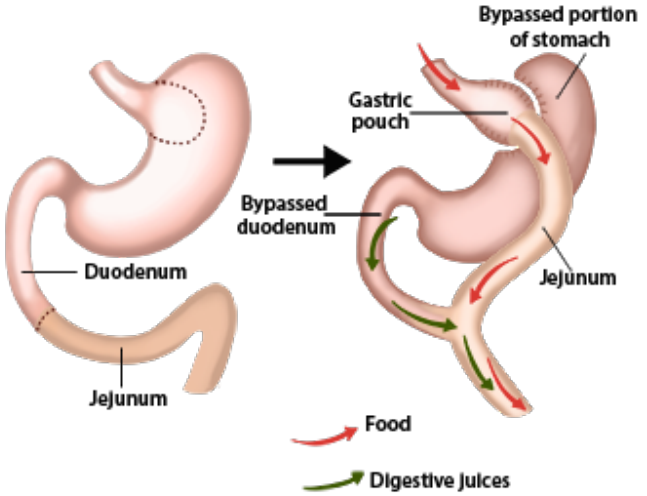

Figure 1. *Normal anatomy of the gastrointestinal tract (left panel), and the reconfigured gastrointestinal tract following RYGB (right panel). Food passes down the alimentary limb (red arrows). Digestive juices (containing bile and pancreatic juices) flow down the bilio-pancreatic limb (green arrows) and mix up with food in the common limb (red and green arrows). From www.codsindia.com.*

THE ENDOBARRIER GASTROINTESTINAL LINER

DJBS is a fully reversible procedure developed to treat obesity and T2D (52). It mimics the intestinal bypass component of RYGB by preventing contact between nutrients and the mucosa of the duodenum and proximal jejunum. Opposed to the invasiveness of the RYGB, the DJBS is implanted by the use of an endoscope. The device is approximately 60 cm in length and consists of two parts: a self-expanding stent-like proximal anchor made of nitinol (a nickel and titanium alloy) that expands within the duodenal bulb upon implantation, and a 60 cm long sleeve consisting of an impermeable, highly flexible material made of fluoropolymer (Teflon-like material). The entire device is pre-packed into a capsule, which is positioned at the end of a delivery system encompassing a specialised catheter and guide wire system. The DJBS implantation procedure is performed using an endoscope and fluoroscopy. Once the subject is sedated (using general anaesthesia or conscious sedation (53,54)), an upper endoscopy is performed to rule out pre-existing upper gastrointestinal tract pathology (e.g. ulcerations or tumours) that would contraindicate DJBS implantation (**Fig. 2**). Afterwards, the capsule is introduced via the mouth and placed in the pylorus aided by the endoscope. Upon correctly positioning in the pylorus, a small non-traumatic ball at the end of the capsule is pushed out into the duodenum and down to the proximal jejunum via an over-the-wire system inside the catheter. The non-traumatic ball is attached to the distal part of the sleeve, and by pushing the ball onwards the sleeve is pulled out of the

capsule and into the upper small bowel. Fluoroscopy is used to make sure the ball and sleeve progress unimpededly forward. When the sleeve is folded out in full length and the ball detached, the anchor is pushed out of the capsule into the duodenal bulb where it instantaneously expands. The expanding feature combined with small barbs engaging the intestinal mucosa, ensures that the device stays at its correct position. Contrast fluid and air are used to check patency of the device as well as correct positioning of the anchor. In order to minimise the risk of peptic ulcer formation or upper gastrointestinal tract bleeding, subjects are prescribed prophylactic proton pump inhibitor (PPI) (e.g. pantoprazole 40 mg twice-daily) when the device is *in situ*, and are instructed to continue for until three weeks after explantation. Dietary recommendations following device implantation include strictly liquid food the first week, and semisolid food during the second week. From the third week and henceforth subjects implanted with the DJBS are advised to chew food thoroughly, avoid doughy/sticky/thready foods and drink lots of fluids (water) during mealtimes to minimize the risk of food-induced device obstruction. Ingested food passes naturally down the oesophagus and into the ventricle and then - after having passed through the pylorus - enters the DJBS at the open proximal end. It then flows down the lumen of the sleeve in parallel with bile and digestive juices flowing down on the outside between the sleeve and intestinal wall. Due to the highly flexible sleeve material, peristaltic movements in the small intestines are capable of propelling nutrients inside the sleeve further down the gastrointestinal tract. At the distal end of the DJBS food and juices admix and digestion proceeds. Upon DJBS explantation (after a treatment duration of maximally 12 months), the endoscopist(s) uses the endoscope to grasp one of two drawstrings located on the anchor. Before introducing the endoscope to the stomach, a customised safety hood is placed at the tip of the endoscope. When pulling the string, the anchor collapses, and the anchor is retracted into the safety hood. The entire device is then pulled out of the duodenum, up through the ventricle and oesophagus and out the subject's mouth while retracting the endoscope; during the retraction manoeuver the endoscopist(s) uses fluoroscopy to make sure that the safety hood encloses every barb to avoid damage of the stomach and oesophagus.

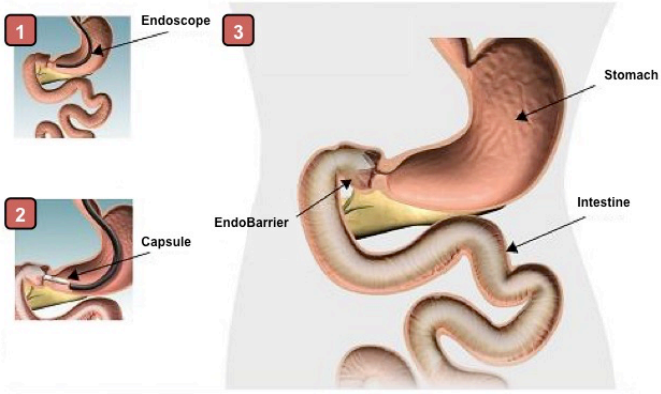

Figure 2. *Schematic presentation of the DJBS implantation procedure. The procedure begins with an upper endoscopy to rule out pre-existing upper gastrointestinal tract pathology (1) before the capsule containing the pre-packed DJBS device is positioned in the pylorus upon DJBS implantation (2). (3) The DJBS (EndoBarrier) correctly positioned in the upper small intestines. From GI Dynamics Inc.*

INCRETIN HORMONE PHYSIOLOGY

The incretin hormones, GIP and GLP-1, are responsible for the incretin effect, which contributes importantly to the regulation of postprandial glucose homeostasis (55–58). The incretin effect following oral glucose ingestion is defined as the beta cell secretory response evoked by gut derived factors other than glucose itself, and is the difference in insulin secretion following oral glucose ingestion compared to isoglycaemic intravenous glucose infusion (59,60). In healthy subjects, the incretin effect accounts for up to 70% of the total amount of insulin released in response to an oral glucose load (60).

The insulinotropic actions of GIP (a 42-amino acid polypeptide) and GLP-1 (a 30-amino acid polypeptide), released from enteroendocrine K and L cells, respectively, in the presence of intraluminal nutrients (61), result in an amplification of glucose-induced insulin secretion. GIP secreting K cells are mainly distributed in the epithelium of the proximal small intestine, whereas GLP-1 secreting L cells are found with increasing density distally in the gastrointestinal tract (61–63). However, the perception of 'one cell secretes one hormone' have been questioned recently as studies have found enteroendocrine cells co-expressing both GIP and GLP-1, as well as other gut hormones (i.e. peptide YY (PYY)) (62,64–66). The potentiating effects of GIP and GLP-1 on glucose-mediated insulin secretion in healthy subjects play an essential role in glucose homeostasis - in particular postprandial glucose levels (61). Additionally, GLP-1 enhances insulin biosynthesis as well as insulin gene transcription (67), up-regulates the genes for the cellular facilitation of insulin secretion, including the glucokinase and GLUT-2 genes (68), stimulates beta cell growth and proliferation, enhances differentiation of new beta cells from pancreatic progenitor cells, and inhibits beta cells apoptosis (69). Furthermore, GLP-1 strongly decreases pancreatic glucagon secretion from alpha cells (when glucose levels are above 4-5 mmol/L), and the combined effects on insulin and glucagon secretion result in inhibition of hepatic glucose production (70). Lastly, GLP-1 reduces appetite and slows gastrointestinal motility - restraining postprandial glucose excursions further (62). Once released from their endocrine cell into the circulation, GLP-1 and GIP are degraded by the enzyme dipeptidyl peptidase 4 (DPP-4). Due to rapid and extensive degradation (the half-lives of GLP-1 and GIP are ~2 and 5-7 minutes, respectively), only 10-15% of newly secreted GLP-1 reaches the peripheral targets as an active metabolite (62). The insulinotropic actions of GLP-1 and GIP are lost following DPP-4 mediated degradation (62).

As GIP and GLP-1 share several effects (i.e. stimulation of glucose-dependent insulin secretion and beta cell mass maintenance), and has been shown to contribute equally and additively to the incretin effect (18,71), it remains relatively unclear why the human organism is equipped with two incretin hormones. They do

differ with regard to some effects, however. Thus, in contrast to the glucagon-suppressive effect of GLP-1, GIP has in healthy subjects been shown to increase glucagon secretion during hypoglycaemia (72) which in turn would be thought to stimulate hepatic glucose output. Furthermore, during hyperglycaemia *Christensen et al.* (72) found no glucagonotropic effects in healthy participants but a strong insulinotropic effect. However, it has been demonstrated that the insulinotropic power of GIP is severely compromised in patients with T2D (73) and therefore leaves GIP as a primarily glucagonotropic hormone in these subjects. Also, there is growing evidence to suggest that GIP-mediated effects constitute a key link between consumption and deposition of fat and the development of obesity, insulin resistance and T2D (74). Lastly, recent observations by *Chia et al.* (75) suggest that GIP may actually worsen postprandial glucose excursions in people with T2D. Thus, there seems evidence to support the view that GIP perhaps constitutes a 'diabetogenic' hormone in patients with T2D.

TYPE 2 DIABETES

As a consequence of the global increase in the number of obese subjects, the prevalence of T2D increases correspondingly. Currently, worldwide more than 400 million people have diabetes (76). A genetic predisposition to the disease and, perhaps even more importantly, obesity due to imbalance between energy intake and energy expenditure constitute pathogenic factors of T2D (77). The central pathophysiological features characterising T2D are decreased sensitivity to insulin (and thus impaired insulin-mediated glucose uptake in liver and muscles), diminished beta cell function (and mass), increased glucagon secretion both during fasting and in response to a meal, and impaired incretin effect (19). The sum of these characteristics results in elevated fasting blood glucose and exaggerated postprandial glucose excursions. As elevated glucose concentrations increase, risk of microvascular (e.g. nephropathy, neuropathy, retinopathy) and macrovascular complications (e.g. cerebral and myocardial infarction) increases, and the keystone in T2D treatment, therefore, is good glycaemic control along with treatment of T2D-associated co-morbidities such as hypertension and dyslipidaemia. However, it is unclear to what extent pharmacological treatment of T2D is able to prevent or delay the continued decline in beta cell function and mass (78).

THE FOREGUT AND HINDGUT HYPOTHESES

Two hypotheses have been suggested to explain the rapid RYGB-induced resolution of T2D: the *hindgut hypothesis* (79), and the *foregut hypothesis* or more correctly, the lower gut and the upper gut hypothesis (80) (**Fig. 3**). The lower gut hypothesis suggests an expedited delivery of ingested nutrients to distal parts of the small intestine to augment secretion of factors improving glucose metabolism e.g. GLP-1 (GLP-1 responses have consistently been found to be enhanced after RYGB or other surgical procedures expediting the transit of ingested nutrients to the lower gut (9,15,81–85)), while the upper gut hypothesis postulates for an anti-diabetic effect of RYGB to depend on exclusion of nutrients from the duodenum and proximal jejunum (hindering release of assumed 'diabetogenic signals' in susceptible individuals - e.g. GIP or glucagon (86)). The role of GIP in the upper gut hypothesis seems supported by reports of blunted postprandial GIP in RYGB-operated patients as opposed to *laparoscopic adjustable gastric banding*-operated patients (the technique does not bypass parts of the intestines) and overweight control subjects, and that obese patients with T2D undergoing RYGB may experience postoperative declines in GIP levels paralleled by their resolution of diabetes (87). Similarly, postprandial GIP concentrations decrease in obese patients without T2D following surgery, which implies bypass of the proximal K cell-rich part of the small intestines (88–91). However, since other studies have shown postprandial GIP responses to remain unchanged (14,15) or even increase (81,92) the role of GIP in the upper gut hypothesis may not be that apparent.

It can be speculated, that RYGB-mediated circumvention of the upper gut can lead to non-release of a hitherto unknown diabetogenic signal (86). This, in combination with increased nutrient delivery to the lower gut and concomitant enhanced secretion of GLP-1 and perhaps other unidentified antidiabetic factors, might contribute to some of the endocrine changes leading to the striking proportion of patients being 'cured' for T2D after RYGB (**Fig. 3**). Simultaneous to enhanced GLP-1 levels, levels of the anorectic hormone PYY, which is also secreted from the L cells (93) also increase after surgery (15,82). Along with reports of diminished levels of the orexigenic hormone ghrelin (15,94), the three hormones may impair feelings of hunger sufficiently to facilitate the substantial weight losses that would furthermore improve glucose metabolism. Nevertheless, regardless of altered secretion of several gut hormones following RYGB, it seems that especially the increments in GLP-1 secretion are important for the positive effect of RYGB on T2D (95).

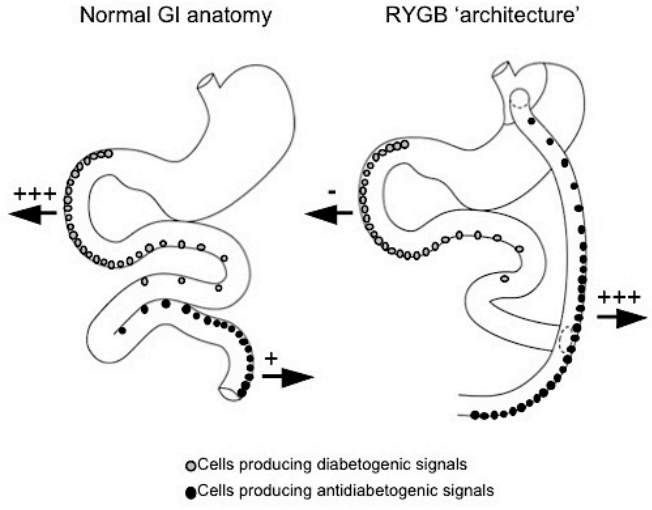

Figure 3. *Normal gastrointestinal anatomy (left) and gastrointestinal 'architecture' after RYGB (right). The lower gut (hindgut) hypothesis proposes that antidiabetic signalling (e.g. GLP-1 secretion) from the distal part of the small intestine is potentiated following RYGB, which expedites the transit of nutrients to the*

lower gut where GLP-1 secreting L cells are abundant. The upper gut (foregut) hypothesis postulates that upon over-stimulation of the proximal part of the small intestines with nutrients in susceptible individuals, it releases a diabetogenic signal (perhaps GIP from the K cells found in high numbers in the duodenum and proximal jejunum and/or currently unknown diabetogenic factors). The upper gut hypothesis emphasises that following RYGB, diabetogenic signalling is avoided.

BILE ACIDS AND GLP-1

Bile consists of water, electrolytes (primarily sodium, chloride and bicarbonate), bilirubin, phospholipids, fatty acids, cholesterol and bile acids. Stimulated by secretin, bile is actively secreted into the bile canaliculi by hepatocytes along with a watery bicarbonate-rich fluid from intra and extrahepatic bile ducts. Bile flows down the bile ducts and accumulates in the common hepatic duct before entering the duodenum via ductus choledocus. In between meals, half of the bile is diverted to the gallbladder where bile acids concentrate 10 to 20-fold due to reabsorption of sodium chloride and bicarbonate; the rest flows to the intestines (96). Nutrients, especially protein and lipids (97–99), elicit contraction of the gallbladder and release of bile after meal ingestion. This mechanism is partly mediated via CCK secreted from enteroendocrine I cells in the duodenum and jejunum (100). Aside from gallbladder contraction, which is known to be correlated to CCK concentration in plasma (101), CCK induces relaxation of the smooth muscles in the common bile duct. Furthermore, CCK relaxes the sphincter of Oddi. These actions combined eject bile from the gallbladder. Additionally, CCK stimulates exocrine pancreatic secretion important for digestion of carbohydrate, protein and lipids (102). The hepatic synthesis of bile acids represents a highly complex process comprising numerous enzymatic processes initiated by converting cholesterol into the primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA). The rate-limiting step in bile acid synthesis is hydroxylation of the carbon at position number seven in the cholesterol molecule by 7α-hydroxylase. Hepatocytes release bile acids as conjugated primary bile acids. In the intestine, primary bile acids are either actively absorbed in the terminal ileum via the apical sodium bile salt transporter (ASBT) on the enterocytes or passively throughout the entire small and large intestines (103,104). In total, 95% of bile acids are absorbed and returned to the liver through the portal circulation - known as the enterohepatic circulation. The remaining bile acids are excreted through faeces. Bile acids regulate their own synthesis by negative feedback mechanisms. Postprandially, the (re)uptake of bile acids via ASBT (105) stimulate the nuclear receptor farnesoid-X-receptor (FXR) within the enterocytes. Following FXR activation transcription of the hormone fibroblast growth factor 19 (FGF19) gene is enhanced (106). Released from the enterocytes, FGF 19 has two distinct effects. Firstly, it binds to the receptor complex FGFR4/β-klotho on the hepatocyte repressing transcription of the 7α-hydroxylase-gene (105–107). Secondarily, FGF19 induces refilling of the gallbladder with bile acids. Additionally, a diminished cholesterol formation by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity has been reported and further, bile acid-induced FGF19 secretion from enterocytes seem to suppress expression of ASBT, thus inhibiting active ileal and hepatic bile acid reuptake (108).

Bile facilitates lipid digestion mediated by the micelle forming bile acids. However, bile acids have recently been proposed to act as a link in the integration of food intake, glucose metabolism and energy expenditure. *Watanabe et al*. (109) showed that bile acid-induced TGR5 activation mediated deiodination of the inactive thyroid hormone thyroxine (T_4) to active triiodothyronine (T_3), which caused energy expenditure to increase in brown adipose tissue. In terms of glucose metabolism, a FXR-FGF19 pathway seems to be involved, as FXR knock-out mice are insulin resistant (110,111) and FGF19 activates glycogen synthase and inhibits gluconeogenesis (112). Additionally, bile acids are capable of inducing another gluco-regulatory mechanism. Cell and murine studies have shown that bile acids stimulate GLP-1 release from enteroendocrine L cells via activation of TGR5 (24–26). Human studies have confirmed these pre-clinical reports (27–29) and found increased GLP-1 concentrations following either rectal (28) or oral (31) administration of bile acids. In addition to TGR5-mediated GLP-1 release, a recent study in mice reported the existence an FXR-GLP-1 pathway as GLP-1 secretion was attenuated following bile acid-induced FXR activation in L cells (38). These results emphasise that bile acids are not solely fat emulsifiers, but constitute a link between bile and energy expenditure and may play an important role in glucose metabolism mediated by TGR5 and FXR activation in the intestinal L cells (113).

METFORMIN AND GLP-1

Metformin, a biguanide derivative, has been known and used as an antidiabetic drug for more than 50 years. In parallel with lifestyle modifications, metformin is the first-in-line drug for treatment of T2D (114). Metformin is effective with regard to glycaemic control, at least initially, it has a good safety profile and it is considered weight neutral. Additionally, the clinical experience is extensive; it does not increase the risk of hypoglycaemia and is inexpensive. Aside from metformin's antidiabetic actions, data have shown that it also exerts cardio-protective (115) and anti-inflammatory (116) actions, and even reduces the risk of some cancers (117–120). It is generally accepted that the liver is a main site of action for metformin. Via the organic cation transporter-1 (OCT-1) metformin enters the hepatocytes and directly inhibits the mitochondrial respiratory chain (complex 1). As a consequence, energy production (adenosine triphosphate (ATP) production via Kreb's cycle) declines leading to elevated intracellular adenosine monophosphate (AMP) concentrations in the hepatocyte. Increased AMP diminishes adenylate cyclase conversion of ATP to cyclic AMP (cAMP), which decreases protein kinase A (PKA) activity, which, in turn, diminishes expression of gluconeogenetic enzymes. Additionally, increased intracellular AMP inhibits fructose-1,6-biphosphatase, a key gluconeogenetic enzyme, and increases AMP kinase (AMPK) activity inhibiting lipid and cholesterol synthesis (121). The sum of these actions is a net

reduction in hepatic glucose production and a reduction of plasma glucose. OCT-1 seems crucial for the actions of metformin. *Shu et al*. (122) demonstrated that OCT-1 knock-out mice respond poorly to metformin. Complex 1 may not be the only site of action for metformin. Upon binding to its receptor on the hepatocyte, glucagon stimulates cAMP formation from ATP via adenylate cyclase, and increases hepatic glucose output (123). cAMP is, as described earlier, vital for further PKA activity and thus gluconeogenesis. In a gain and loss-of-function study, *Miller et al*. (124) reported how biguanides seem to antagonise glucagon-mediated cAMP formation, thus inhibiting hepatic glucose production, supporting another (yet still hepatic) molecular action of metformin. Even though, the liver is thought to be it's main site of action, increased glucose disposal has also been suggested to contribute to the glucose-lowering effect of metformin; thus, both *in vitro* and *in vivo* studies reported increased glucose uptake (125–127) and glucose utilisation in skeletal muscles (128) after metformin administration. *Duca et al*. (129) recently proposed that hepatic glucose output was not only dependent on metformin-induced hepatic AMPK activity. In a murine setting, the researchers reported increased duodenal AMPK activity in parallel with a decreased hepatic glucose production following intraduodenal bolus administration of metformin in insulin resistant rats. Furthermore, subsequent duodenal AMPK inhibition abated the diminished metformin-induced hepatic glucose output. GLP-1 seemed to be the link underlying this action via an intestinal AMPK-GLP-1-PKA pathway stimulating neural activity, which eventually caused the reduction in hepatic glucose output. However, the importance of duodenal AMPK activity and extrahepatic glucose uptake in addition to metformin's direct hepatic action remains unclear.

Metformin has also been shown to enhance endogenous GLP-1 secretion (34,130,131) and several human studies in patients with T2D (e.g. *Scarpello et al*. (39) and *Napolitano et al*. (34)) showed that orally administrated metformin increased faecal excretion of bile acids and decreased serum bile acid concentrations. Interestingly, in an *in vitro* study several years earlier, *Caspary and Creutzfeldt* observed that biguanides inhibited conjugated bile acid absorption (37). As aforementioned, bile acids are capable of inducing GLP-1 secretion through TGR5 and FXR interaction in L cells (25–29,31). Therefore, it may be that metformin's capacity to increase intestinal content of bile acids may induce GLP-1 secretion via the L cell and the two receptors TGR5 and FXR. However, other GLP-1 secreting mechanisms of metformin have been postulated. In an *in vitro* study using murine enteroendocrine cells, chronic metformin administration was found to protect L cells from lipid-induced apoptosis thereby increasing GLP-1 synthesis (132). Additionally, it is speculated that metformin increases GLP-1 secretion via parasympathetic nervous activity (133) and that metformin prolongs the half-life of GLP-1 by DPP-4-independent mechanisms (33,134). Furthermore, it has been hypothesised that metformin alters gut microbiota composition which in turn might foster formation of specific bile acids with GLP-1 secreting features (25,29).

Despite several hypotheses on metformin's GLP-1 enhancing property, the bile acid mediated pathway seems most attractive as metformin reduces ileal bile acid reabsorption, which has been found to increase GLP-1 via TGR5 activation and diminished FXR activity in the L cell. This may represent an important extrahepatic mode of action for metformin.

HYPOTHESIS AND OBJECTIVES

Since the current thoughts regarding the effects of the DJBS on weight loss and glycaemic regulation stem from a few rather small studies, we decided to retrieve and systematically review current evidence and perform meta-analysis in order to evaluate the clinical effects and safety of the DJBS for the treatment of obesity and T2D (***study I* and *study II***). We hypothesised that; collecting and analysing study results according to a pre-defined protocol would objectify DJBS' effects in an unbiased manner and thereby help guide clinical decision-making, which might result in better obesity and T2D treatment. Main objectives were changes in body weight, changes in HbA_{1c} and safety. The objective of ***study III*** was to map the endocrine impact of DJBS and evaluate the 'acute' (1 week) and 'long-term' (26 weeks) effects on glucose homeostasis in obese subjects with normal glucose tolerance (NGT) and obese patients with T2D. We investigated the influence of DJBS on fasting plasma/serum concentrations and postprandial plasma/serum responses of GIP, GLP-1, PYY, CCK, gastrin, insulin, C-peptide and glucagon. Furthermore, we aimed to assess sensations of appetite and satiety and registered food intake. We hypothesised, in line with the upper gut and lower gut hypotheses, that DJBS would cause changes in postprandial secretion of incretin hormones favouring secretion of insulin and inhibition of glucagon from the pancreatic islets, which, in turn, would give rise to an improvement in postprandial glucose metabolism. Moreover, we speculated that DJBS would increase the secretion of satiety hormones (e.g. GLP-1 and PYY) and, consequently, increase sensation of satiety and thus diminish food intake. Lastly, we monitored the effect on weight loss and the safety of DJBS. In ***study IV***, we aimed to elucidate the role of gallbladder emptying and metformin on human GLP-1-secretion. We hypothesised that CCK-induced gallbladder emptying would elicit a GLP-1 response. Furthermore, we speculated that metformin administration would inhibit bile acid reuptake from the small intestines, interact with TGR5/FXR in enteroendocrine L cells and, thus, potentiate the GLP-1 response mediated by CCK-induced gallbladder emptying.

SUMMARY OF STUDIES

Study I and II

In ***study II*** we collected data on the DJBS in order to investigate its clinical efficacy and safety in obesity and T2D treatment. Based on a previously prepared protocol (***study I***) we undertook a systematic review with meta-analyses of eligible trials according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (135) and the Cochrane Handbook for Systematic Reviews of Interventions (136). We searched for human

trials reporting weight loss and glycaemic improvements. Given the novelty of DJBS, we expected rather few publications, and therefore included all types of publications (e.g. full text articles and abstracts), irrespective of language, and included both randomised controlled trials (RCT) and observational studies in order to increase amount of data for our analyses. If necessary, corresponding authors were contacted for further information. Primary endpoints were weight loss, change in HbA_{1c} and safety. Secondary endpoints encompassed proportion of patients with T2D reducing or discontinuing antidiabetic medication, changes in fasting plasma glucose and changes in cholesterol levels. Random and fixed effects meta-analyses were performed and results displayed as mean differences (MD). Intertrial heterogeneity was assessed by I^2 statistics (a number between 0 to 100%). Heterogeneity in included studies was classified as: might not be important (I^2 0-40%), may represent moderate heterogeneity (I^2 30-60%), may represent substantial heterogeneity (I^2 50-90%) and considerable heterogeneity (I^2 75-100%).

Five RCTs (n=235 subjects) and ten observational studies (n=211) were included. All studies had high risk of bias in at least one domain (e.g. allocation concealment or blinding of participants and personnel). In the RCTs, subjects were allocated to the intervention group (DJBS + diet or lifestyle modifications, n=136) or the control group (sham + diet/lifestyle modifications *or* diet/lifestyle modifications alone, n=99). The observational studies reported the effect of the DJBS alone, or combined with diet or lifestyle modifications. In total, 20 subjects could not be implanted with the DJBS due to anatomical difficulties (i.e. short duodenal bulb). Median follow-up was 12 and 52 weeks for RCTs and observational studies, respectively. Overall, the subjects had a BMI ranging from 30.0 to 49.2 kg/m^2 and 10-100% had T2D. Meta-analyses showed that DJBS lead to an additional body weight loss and excess weight loss of -5.1 kg and 12.6%, respectively, compared to diet or lifestyle modifications. Furthermore, in patients with T2D, meta-analyses found no additional decline in HbA_{1c} or fasting plasma glucose. In general, patients with T2D treated with antidiabetic medication who were allocated to DJBS treatment were not reducing or discontinuing antidiabetic medication. Adverse events consisted mainly of dyspepsia, and 66 subjects had the DJBS removed earlier than planned due to the occurrence of a serious adverse event (e.g. gastrointestinal bleeding or device migration). No liver abscesses or deaths occurred. Cholesterol data were scarce and did not allow meta-analysis as only one RCT reported this outcome.

We concluded that DJBS treatment led to a moderate weight loss in obese subjects compared to diet and/or lifestyle modifications, and had no substantial impact on glycaemic control. The incidence of adverse events was high, but the symptoms were in general mild and transient and occurred within the first weeks after implantation. Nearly 20% discontinued DJBS treatment early. Given these results, we inferred that further research seemed necessary in order to evaluate the applicability of DJBS in clinical practice.

Study III

We aimed at describing DJBS' impact on postprandial physiology along with registration of its clinical effects. In a 26-week open observational prospective study, ten NGT obese subjects and nine age, body weight and BMI-matched patients with T2D implanted with the DJBS (**Table 1**) were studied prior to implantation (baseline), one week (1w) after implantation and following 26 weeks (26w) of DJBS treatment. According to study protocol and, given that the DJBS was well tolerated and the participants consented, the implantation period was extended by an additional 26 weeks. ***Study III*** reports the results of the first 26-week period. At the baseline, 1w and 26w study days, each subject underwent a standardised 525 kilocalories (kcal) liquid mixed meal test and a subsequent *ad libitum* meal test. We measured fasting and 4-hour postprandial plasma concentrations of glucose, as well as pancreatic and gut hormones. Additionally, appetite, food intake, gallbladder emptying and resting energy expenditure were evaluated. Gastric emptying rates were assessed using the paracetamol method (137). Furthermore, the participants consulted a study nurse once a month where anthropometric measurements (e.g. body weight) and type of adverse events were registered. At baseline and at 26w, total and visceral fat masses were measured by Dual Energy X-ray Absorptiometry.

During 26 weeks, obese NGT subjects and obese patients with T2D, respectively, lost a median (range) of 6.8 (2.5-16.1) kg and 6.2 (0.7-11.0) kg, which were accompanied by significant reductions in total and visceral fat masses. On all three study days, fasting plasma glucose was significantly higher in patients with T2D compared to NGT subjects. Otherwise, fasting NGT subjects and patients with T2D had similar concentrations of insulin, C-peptide, glucagon, GIP, GLP-1, PYY, CCK and gastrin. Noteworthy, fasting plasma gastrin concentrations in both groups of participants tended to increase throughout the 26-week study period, likely due to the prophylactic PPI treatment. Postprandial GIP responses were unaffected by DJBS in patients with T2D, but we saw attenuated 0-60 minutes postprandial plasma GIP responses in NGT subjects at 1w and 26w compared to baseline. Additionally, postprandial levels of GLP-1 and PYY increased one week after DJBS implantation in patients with T2D. GLP-1 increased further at 26w, but PYY concentrations remained stable (and equal to 1w) at 26w. In the NGT subjects, postprandial concentrations of GLP-1 and PYY were similar at baseline, 1w and 26w. Postprandial glucose, insulin, C-peptide, glucagon, CCK and gastrin responses were similar and unaffected by DJBS in both groups. Satiety and fullness sensations were significantly stronger and food intake reduced at 1w in NGT subjects, but returned to baseline levels at 26w; similar trends in appetite sensations or food intakes were observed in the T2D group. DJBS did not effect gallbladder emptying or gastric emptying. Adverse events consisted of mild-to-moderate dyspepsia. However, due to serious adverse events, five devices (21%) were removed earlier than planned due to intolerable recurrent abdominal pain (n=4) and one case of device obstruction caused by sleeve invagination (138).

In conclusion, 26 weeks of DJBS treatment resulted in modest weight losses in obese individuals with and without diabetes. The only marginal alterations in postprandial physiology (e.g. GIP and GLP-1 secretion) induced by DJBS, might explain the absent effect on postprandial glucose metabolism in our patients with T2D.

Table 1. Subject characteristics

	NGT	T2D
n (male)	10 (4)	9 (4)
Age (years)	49 (27-60)	50 (40-67)
Weight (kg)	101.1 (89.0-117.2)	103.7 (80.9-131.9)
BMI (kg/m^2)	34.3 (30.3-36.8)	38.6 (31.6-40.5)
HbA_{1c} (mmol/mol)	31 (25-43)	50 (32-77)*
Fasting plasma glucose (mmol/L)	5.4 (5.2-6.5)	8.7 (7.0-16.1)*
Duration of T2D (months)	NA	36 (16-81)

Median (ranges), * P<0.05

Study IV

In ***study IV*** we investigated the role of gallbladder emptying, single-dose metformin, and the combination, on human GLP-1 secretion. On four separate days, ten young healthy lean male NGT subjects with no family history of diabetes were studied. In a double-blinded fashion and in a randomised order, the participants were subjected to metformin or placebo at time point 0 (instilled in the stomach via a nasogastric tube), and a concomitant 60-minute intravenous infusion of saline or CCK (0.4 pmol/kg/min). Blood was subsequently sampled for four hours to evaluate postprandial responses of glucose, as well as pancreatic and gut hormone responses. Additionally, gallbladder volume was measured using bedside ultrasonography.

CCK-induced gallbladder emptying and metformin administration, respectively, elicited significant GLP-1 responses. In addition, an additive effect was seen when combining metformin with CCK-induced gallbladder emptying. Metformin alone or combined with gallbladder emptying augmented the PYY responses. Gallbladder emptying alone increased PYY responses too, however not significantly. A short-lasting (0-60 min) increase in GIP, independent of metformin, was seen following gallbladder emptying. The same trend was seen with regards to glucagon secretion. CCK infusions mediated an immediate gallbladder contraction and a rapid and major decrease in gallbladder volume. Gallbladder volume increased after CCK-infusions had terminated. Gallbladder volume remained unaffected by metformin. No effects were seen on glucose, insulin, C-peptide or gastrin concentrations, and gastric emptying rates, assessed by the paracetamol method (137), were not delayed.

We concluded that CCK-induced gallbladder emptying elicits significant GLP-1 secretion, which was potentiated by single-dose metformin. Further, we found increased PYY and GIP responses following gallbladder emptying. It made us speculate, that gallbladder emptying and subsequent TGR5 stimulation by bile acids elicited GLP-1, PYY and GIP secretion, and secondly, that metformin's mode of action seems to encompass both bile acid-dependent and independent stimulation of gastrointestinal hormone secretion.

DISCUSSION

The studies in this thesis provide evidence on the efficacy and safety of a novel endoscopic treatment modality, the DJBS, based on a protocol-based systematic review with meta-analyses of existing data, and a new observational clinical study. Additionally, we provide new data characterising the postprandial physiology (including gut hormone secretion) following DJBS treatment. Furthermore, we showed how gallbladder emptying and metformin, either alone or combined, enhances human GLP-1 secretion.

Since the first human studies reported on the effect of the DJBS, several reviews have been conducted (139–144). In line with the only other systematic review (by *Zechmeister-Koch et al.* (145)), our results from ***study II*** showed that DJBS treatment entails significant, yet moderate, weight losses in obese subjects accompanied by minor improvements in glycaemic control among obese patients with T2D. Given the novel nature of the DJBS, the amount of evidence is not as comprehensive as bariatric surgery (e.g. RYGB). Results and impact of meta-analyses rely on number and quality of studies. This fact inevitably influences our findings. Indeed, the low number of rather small sized RCTs (with high dropout rates) providing the basis of our analyses definitely limit the validity of our results. Furthermore, all studies had bias issues and moderate-to-considerable intertrial heterogeneity. In addition, we found funnel plot asymmetry in our primary endpoints of weight loss, as the number of eligible trials was low (or perhaps due to reporting bias). These limitations compromised the quality of our meta-analysis and could potentially overestimate results.

Conventional bariatric surgery (e.g. RYGB) have reported impressive weight losses (7) and remission rates of T2D (146). In contrast to bariatric surgery, and in line with our meta-analysis (***study II***) (147), we did not see any improvements in glycaemic control in our own observational study (***study III***), and weight losses were only moderate. However, in terms of weight loss, our participants showed great individual variances. Accordingly, some published studies reported excess weight losses comparable to the ones achieved by RYGB (148). RYGB is known to induce long-term weight losses, but so far only one study reported long-term weight loss data after termination of DJBS treatment. *Koehestanie et al*. (23) followed subjects treated with the DJBS for an additional six months after device explantation. Their data showed that DJBS (+diet) versus diet alone induced a 10.6 and 5.3 kg weight loss, respectively. Despite both groups regaining weight, the

weight loss was still lower in the DJBS group compared to the diet group. However, since these results were based on few observations they should be interpreted cautiously.

The moderate clinical effects mediated by DJBS treatment (***study III***) could be explained by the small changes in postprandial gut hormone secretion. Since DJBS is designed to mimic the bypass component of a RYGB, expediting undigested nutrients to the lower gut, enhanced release of antidiabetic and/or satiety promoting gut hormones (e.g. GLP-1 and PYY) would theoretically be expected. DJBS led to small increments of GLP-1 and PYY in patients with T2D. Despite being significant, peak GLP-1 plasma concentration was only modestly increased by two-fold as opposed to the ~10-to-20-fold increase seen shortly after RYGB (14,15,85). Since GLP-1 exerts powerful insulinotropic and glucagonostatic effects (62), we expected increased insulin secretion and diminished glucagon release. Additionally, as a consequence of duodenal exclusion by DJBS, GIP levels would be expected to fall in line with the upper gut hypothesis. In NGT subjects (not patients with T2D) GIP responses displayed a 0-60 minute decline after one week and 26 weeks of treatment. Opposed to its sister incretin hormone, GIP stimulates glucagon secretion from the alpha cells. Therefore, increased GLP-1 and diminished GIP could act in concert to lower postprandial plasma glucose values via increased insulin and diminished concentrations of glucagon. However, this was not the picture. *de Jonge et al.* (22) found greater impact of the DJBS in their 17 obese patients with T2D. In contrast to our results, they saw improved glycaemic control in parallel with attenuated GIP and glucagon responses, as well as enhanced GLP-1 secretion, but in consistency with our results, insulin levels were not affected. As glucagon promotes hepatic glucose output (149) *de Jonge* and co-authors speculated that improved fasting plasma glucose and postprandial glucose excursions were due to decreased endogenous (hepatic) glucose production.

GLP-1, PYY and CCK are considered anorectic hormones (15,101). We quantified food intake and qualified satiety sensation in subjects implanted with the DJBS. Obese NGT subjects felt significantly stronger satiety, greater fullness and reported smaller prospective food consumption. The sum of these sensations resulted in a reduced caloric intake shortly after DJBS implantation. However, the sensation abated at the 26th week, as did the reduction in food intake. The alterations in postprandial gut hormonal releases following DJBS treatment may represent the main explanation for the transient appetite and food intake reduction, and thus weight loss. Without doubt, nausea (a frequent and transient adverse event of DJBS) could affect food intake. However, sensation of nausea was unchanged, perhaps ruling this out.

Energy expenditure following RYGB remains controversial as studies have shown divergent results (150). However, if DJBS were to increase energy expenditure, as *Faria et al*. (151) reported following RYGB, this might contribute to our observed weight losses. Nevertheless, as resting energy expenditure was similar on the three study days, changes in resting energy expenditure do not seem to influence body weight in DJBS treated obese subjects.

Aside from inducing satiety, CCK elicits gallbladder contraction (101). As with GIP, complete duodenal exclusion would theoretically hinder nutrient stimulation of and release of CCK from I cells. We did not confirm this hypothesis. In line with the inconclusive changes in CCK secretion following RYGB (15,87,152,153), and compared to the opposing results by *de Jonge et al.* (154) who found decreased CCK concentrations, the effect of DJBS on CCK secretion remains unclear. Given that CCK was unaltered, one could question whether the DJBS is capable of fully preventing nutrients from contact with the mucosa of the duodenum and proximal jejunum. If the anchor were not fully expanded within the duodenal bulb, nutrients would unimpededly flow on the outside of the sleeve, mediating CCK release. If the DJBS is indeed tightly fitting within the intestines and thereby fully prevents 'nutrient leak' on the outside of the sleeve, the abundance of I cells in the distal part of the jejunum (155) could explain the unaltered CCK concentrations.

In ***study III***, we experienced the same rate of early DJBS explantation (approximately 20%) as reported in our systematic review (***study II)***. Additionally, we observed the same type of dyspeptic adverse events as well as their duration compared to previous DJBS studies. The most serious adverse event was device obstruction due to sleeve invagination (138). We did not see any liver abscesses, which have been reported recently (156) and lead the *Food and Drug Administration* to terminate the US multi-centre ENDO Trial prematurely (obese patients with T2D randomised to either DJBS or sham (157)) as the occurrence of liver abscesses (3.5%) exceeded a pre-defined safety threshold of 2% (158).

In ***study IV***, we observed increased and additive GLP-1 responses in healthy male subjects, mediated by CCK-induced gallbladder emptying and metformin. Previously, efforts have been made to investigate the impact of gallbladder emptying and subsequent release of bile acids into the intestines on GLP-1 secretion. *Ahrén et al.* (159) infused saline and CCK in two matched groups of postmenopausal women and found insignificant effects of CCK on postprandial GLP-1 secretion compared to saline. As they, in parallel to the infusions, administered a mixed meal containing enough fat to elicit complete gallbladder contraction in itself, the effect of gallbladder emptying *per se* on GLP-1 secretion cannot be derived from this study. A direct effect of CCK on GLP-1 secretion from enteroendocrine L cells should be considered. However, several studies have shown that infusion of CCK-8 in isolated perfused rat ileum and colon had no effect on GLP-1 secretion (160–163). *Hansen and Holst* (164) investigated the effect of CCK-8 on GLP-1 secretion in a setup using an isolated porcine ileum and found that only high concentrations of CCK-8 (100–500 times normal postprandial levels) was able to stimulate GLP-1 secretion slightly. Based on these studies, it seems improbable that the dose of CCK-8 used in our study (leading to slightly supraphysiological CCK concentrations) induced significant GLP-1 secretion. Utilising CCK receptor antagonism could shed light on the question of whether CCK has a direct effect on GLP-1 secretion. However, several considerations need to be taken into account when interpreting such studies. *In vivo* administration of the CCK recep-

tor antagonist loxiglumide would antagonise CCK-reduced gastric emptying. As the rate of gastric emptying is essential for postprandial GLP-1 secretion (62), the accelerated gastric emptying elicited by CCK receptor antagonism may explain why loxiglumide was shown to reduce oleate-induced GLP-1 response (165). Another explanation could be that a CCK receptor antagonist would inhibit pancreatic exocrine secretion, causing less intraduodenal lipase to enzymatically cleaving triglycerides (oleate) into 2-monoacylglycerol, which appears to be responsible for lipid-induced GLP-1-secretion. Furthermore, the intact GLP-1 responses observed by *Beglinger et al.* (165) were quite small (between 1 and 4 pmol/L) and actually below the detection limit of the assay raising doubt about the validity of the result. Given the above, it seems unlikely that CCK directly elicits GLP-1 secretion.

As metformin consistently has been shown to increase faecal content of bile acids (34,39), our metformin-induced GLP-1 responses may well be in line with the hypotheses that increased intraluminal concentrations of bile acids due to metformin, activates both TGR5 and FXR receptors.

The delayed responses of PYY, often considered to be co-secreted with GLP-1 from the L cells, could be explained by studies reporting the existence of proximal GLP-1-secreting cells and distal GLP-1/PYY-secreting enteroendocrine cells (64,65) and perhaps distal cells secreting PYY alone. Furthermore, as *Cho et al.* (64) pointed towards the existence of enteroendocrine cell sub-types secreting both GLP-1 and GIP this would, in line with the existence of other 'dual-secreting' enteroendocrine cell sub-types (e.g. distal GLP-1+PYY), represent a plausible explanation to our GIP findings.

STUDY LIMITATIONS

In ***study II***, we were limited by a low number of available RCTs, probably due to the novelty of DJBS as an obesity and/or T2D treatment. Therefore, we were not able to perform meta-regression analysis or evaluate other dichotomous outcomes. However, we still believe that it was important to conduct a systematic review (with meta-analyses) in order to objectify the advantages and disadvantages of the DJBS. Additionally, despite substantial efforts to contact corresponding authors, only a few responded. Of these only one gave us access to additional raw and unpublished data, the rest merely confirmed accuracy of reported results.

We conducted an observational prospective study. It would have been a stronger design if the study had been a double-blinded sham-controlled randomised study. Nevertheless, we had to take ethical considerations into account. For instance, as the DJBS previously has been shown to induce weight loss, it may be argued that a sham-arm involving anaesthesia and endoscopic procedures similar to DJBS implantation could be problematic from an ethical perspective. Circumventing this ethical issue could, to some extend, be done by including a diet/lifestyle modification arm or perhaps an arm treated with GLP-1 receptor analogues. Moreover, in terms of maximising weight loss, one might argue that a low-caloric diet should have been combined with DJBS. However, as diets are notoriously difficult to maintain and have not proven effective in long-term weight loss, we believe that the present study design allow for a better description of the effect of DJBS per se. Additionally, the patients with T2D were rather heterogeneous in terms of glycaemic control, and furthermore we would have liked the diabetic patients to be more dysregulated. However, the relatively extensive list of contraindications for DJBS implantation (e.g. ischaemic heart disease, anticoagulant therapy, history of coagulopathy, bleeding diathesis, inability to discontinue use of non-steroid anti-inflammatory drugs, known presence of gallstones, pancreatitis) hampered the planned rate of recruitment.

CONCLUSIONS

In our protocol-based systematic review with meta-analyses, we show that DJBS compared to diet or lifestyle modifications results in significant but moderate weight reductions in obese subjects. Unexpectedly, the data also showed that DJBS did not improve glycaemic control in patients with T2D. Despite the fact that most adverse events were transient and mild-to-moderate of nature, a relatively high rate of early DJBS removals was observed. In our own hands, a 26-week period of DJBS treatment resulted in similar modest weight losses along with small gastrointestinal tract hormone responses in obese NGT subjects and obese patients with T2D. However, in spite of the preconditions being present (i.e. weight loss and enhanced GLP-1 secretion), DJBS did not improve glucose metabolism and thus no patients with T2D achieved disease remission. In addition, adverse events and rate of early device removal due to serious adverse events were similar to our findings in the review. Based on our results, the feasibility of DJBS as a standard of care in the management of obese patients with T2D seems questionable.

Finally, our findings that CCK-induced gallbladder emptying mediated GLP-1 secretion in humans, a new observation, which has never been shown before, might contribute to a better understanding of the mechanisms underlying meal-induced GLP-1 secretion. Additionally, we have shed light on a potential new mode of action for metformin, as metformin stimulated GLP-1 secretion and potentiated GLP-1 responses induced by gallbladder emptying. These actions may be mediated via TGR5 and FXR activation and may identify this old drug as a GLP-1 secretagogue many are looking for. Furthermore, as DJBS does not interfere with gallbladder emptying and therefore does not hinder bile acids from eliciting their effects in the intestines, DJBS-induced GLP-1 secretion may also depend on the actions of bile acids.

FUTURE PERSPECTIVES AND RESEARCH

Data from 325 of 500 participants in the ENDO Trial, randomised to either a DJBS or sham-arm, shows that DJBS resulted in a 0.71% greater reduction in HbA_{1c} compared to sham. The remaining results (including weight loss data) from this trial are awaited with great interest. Even though the future for the DJBS seems uncertain, the DJBS concept remains intriguing. However, several aspects of the endocrine impact of the DJBS have not been investigated; for instance, given our findings of increased

postprandial GLP-1 concentrations in patients with T2D, would DJBS be capable of restoring the (lost) incretin effect in patients with T2D? Oral glucose tolerance tests and subsequent intravenous isoglycaemic glucose infusions (clamping technique) would be necessary to address this question. Additionally, by antagonising the GLP-1 receptor with the specific GLP-1 receptor antagonist exendin 9-39, it should be possible to tease out the impact of DJBS-induced increments in postprandial GLP-1 responses for the postoperative changes.

Furthermore, testing the DJBS against either conventional bariatric surgery or GLP-1-receptor analogues (GLP-1RA), assessing glycaemic control and weight loss, would provide information about the efficacy and safety of DJBS compared to these weight and glycaemia improving drugs including a comparison of cost-benefit relationships. In this regard, it will be interesting to see the results of the on-going REVISE-Diabesity Study (166) which randomises obese patients with T2D to either treatment with the GLP-1RA Liraglutide, DJBS alone or DJBS + Liraglutide.

In agreement with the fact that the subjects in ***study IV*** were metabolically healthy, we did not see any changes to postprandial glucose profiles. Therefore, it seems obvious to perform a similar study in patients with T2D. Within our research group, such study is currently under way.

SUMMARY

Bariatric surgery (e.g. *Roux-en-Y gastric bypass* (RYGB)) has proven the most effective way of achieving sustainable weight losses and remission of type 2 diabetes (T2D). Studies indicate that the effectiveness of RYGB is mediated by an altered gastrointestinal tract anatomy, which in particular favours release of the gut incretin hormone glucagon-like peptide-1 (GLP-1). The *EndoBarrier Gastrointestinal Liner* or *duodenal-jejunal bypass sleeve* (DJBS) is an endoscopic deployable minimally invasive and fully reversible technique designed to mimic the bypass component of the RYGB.

Not only GLP-1 is released when nutrients enter the gastrointestinal tract. Cholecystokinin (CCK), secreted from duodenal I cells, elicits gallbladder emptying. Traditionally, bile acids are thought of as essential elements for fat absorption. However, growing evidence suggests that bile acids have additional effects in metabolism. Thus, bile acids appear to increase GLP-1 secretion via activation of the TGR5 receptor on the intestinal L cell. Recently FXR receptors were postulated to contribute to GLP-1 secretion too. Furthermore, metformin has been shown to increase circulating GLP-1 levels but although the exact mechanism is not fully elucidated it may involve metformin-induced inhibition of bile acid reuptake from the small intestines.

Small-sized studies reported varying degrees of weight loss and, in some, improvement of glucose metabolism. Therefore, the objectives of this thesis were to collect existing information on the DJBS in order to evaluate clinical efficacy and safety (***study I and II***). Furthermore, since the endocrine impact of the DJBS is not fully elucidated, and DJBS is expected to mimic RYGB, we investigated postprandial metabolic changes following 26 weeks of DJBS treatment in ten obese subjects with normal glucose tolerance (NGT) and nine matched patients with T2D (***study III***). Finally, we studied the single and combined effects of CCK-induced gallbladder emptying and single-dose metformin on human GLP-1 secretion in ten healthy subjects (***study IV***). We hypothesized that metformin-induced GLP-1 secretion - at least partly - would be dependent on gallbladder emptying and the presence of bile acids in the gut.

DJBS appears to lead to moderate weight losses in obese subjects compared to diet or lifestyle modifications (***study II***). DJBS had insignificant and small effects (compared to diet) on glycaemic regulation. Adverse events consisted mainly of mild-to-moderate transient dyspepsia. Nearly 20% (n=66) of DJBS treated subjects experienced a serious adverse event (e.g. gastrointestinal bleeding or device migration), which resulted in early device removals. No deaths or liver abscesses were reported following DJBS treatment.

In our own ***study III*** we found similar, moderate weight losses as in ***study II***. GLP-1 and PYY concentrations increased in patients with T2D (not NGT subjects) after implantation. DJBS had no or minor effects on postprandial levels of glucose, insulin, C-peptide, glucagon, GIP, CCK or gastrin. Food intake decreased in parallel with an increased sensation of satiety in obese NGT subjects, but were transient. Dyspeptic episodes occurred in nearly all participants. Five devices (21%) were explanted early due to abdominal pain, and few changes of on-going antidiabetic medication were made.

Finally, ***study IV*** showed that both CCK-induced gallbladder emptying and metformin alone elicited significant GLP-1 responses that were additive upon combination. Moreover we saw significant PYY and short-lasting glucose-dependent insulinotropic polypeptide (GIP) responses following gallbladder emptying.

In conclusion, in spite of increased GLP-1 responses in patients with T2D and a modest weight loss, DJBS had no effect on postprandial glucose metabolism, and therefore no patient with T2D achieved disease remission. Based on our results, we cannot recommend DJBS to be implemented as a standard of medical care management of obese patients with T2D. Future larger trials may lead to different conclusions. In addition, the observed gut hormone responses following CCK-induced gallbladder emptying and metformin, make suggest that bile acid release into the small intestines with subsequent TGR5 and FXR involvement contributes to stimulation of GLP-1 secretion and, therefore, that metformin's mode of action encompasses both bile acid-dependent and independent stimulation of gut hormone secretion.

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