**ADAPTATIONS IN GASTROINTESTINAL PHYSIOLOGY AFTER SLEEVE GASTRECTOMY AND ROUX-EN-Y
GASTRIC BYPASS**

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62

63 **Abstract**

64 The growing obesity epidemic explains the increased demand for bariatric and metabolic surgery. To
65 date, Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) are the most common
66 performed procedures. Originally, bariatric procedures were described as purely restrictive,
67 malabsorptive or combined restrictive-malabsorptive procedures limiting food intake and/or nutrient
68 absorption. Nowadays, the anatomical alterations are known to affect the gastrointestinal
69 physiology. Consequently, these changes affect the digestion and absorption of nutrients and drugs.
70 Therefore, understanding the gastrointestinal physiology *per se* is crucial for the prevention of
71 postoperative nutritional deficiencies and the optimization of postoperative drug therapy. In this
72 review, we summarize the current knowledge on the impact of SG and RYGB on gastrointestinal
73 physiology and bring attention to the knowledge gaps in the field. Concisely, available (pre)clinical
74 research indicates that SG accelerates liquid and solid gastric emptying, accelerates small intestinal
75 transit and increases bile acid serum levels. The effect on gastrointestinal acidity, gastric and
76 pancreatic secretions, surface area and colonic transit remains largely unknown. Moreover, RYGB
77 diminishes gastric acid secretion, accelerates liquid gastric emptying and increases bile acid serum
78 levels. The effect on intestinal pH, solid gastric emptying, intestinal transit time, gastric enzyme
79 secretions and surface area remains largely unknown.

80

Introduction

According to the last report of the World Health Organization, the obesity prevalence has tripled worldwide with 650 million adults having a body mass index (BMI) ≥ 30 kg/m² (1). Overweight and obesity are linked with a significant increase in all-cause mortality (2,3). In parallel, the number of bariatric and metabolic surgery procedures has more than doubled worldwide (4). A lower rate of all-cause-mortality and lower risk of obesity-related comorbidities after surgery justifies the increased interest. A recent meta-analysis observed a significant overall BMI loss of 13.53 kg/m² (95% confidence interval (CI): 11.55-15.51) and 11.40 kg/m² (95% CI: 5.28-28.08) at one and five years after surgery, respectively. Regarding morbidity, significant improvements occur in obesity-related comorbidities including diabetes, cardiovascular diseases, obstructive sleep apnoea, fertility and some types of cancer (5–8). Nonetheless, bariatric surgery can result in unintended adverse events (complication rate: 17.0% (95% CI: 11.0%-23.0%)(5). Potential benefits and complications are discussed in Appendix 1.

These consequences have redirected bariatric research towards the mechanism behind the resolution of obesity-related comorbidities, the potential complications and how to avoid them (9,10). However, the original intention of surgery was to induce weight loss by restricting food intake and/or by introducing malabsorption through anatomical rearrangement (11–13). It is now understood that the anatomical alterations affect gastrointestinal physiology, whereby gut-brain-endocrine and adipose-brain-endocrine signalling pathways that regulate hunger, satiation, satiety and nutrient metabolism are altered (14). By targeting the gastrointestinal tract, the delivery and concentration of (undigested) nutrients to the nutrient sensing enteroendocrine cells is affected. Thereby, the secretion of gut-derived hormones involved in appetite, satiety and motility regulation changes (14–17). Our understanding of the changes in gut-brain signalling pathways is increasing. However, it is important to recognize as well that the effect of the anatomical alterations on the gastrointestinal physiology *per se* plays a crucial role in determining outcomes after surgery, but is largely unknown (18). Gastrointestinal conditions influence both digestion and absorption of nutrients as well as the disintegration, dissolution and absorption of orally administered drugs (19,20). An inherent risk of developing vitamin and mineral deficiencies is present after surgery (21–25). Next to nutritional deficiencies, new and/or persisting obesity-related comorbidities after surgery require adequate dosing for optimal pharmacotherapy. Significant changes in pharmacokinetics of different drug classes have been observed, potentially leading to unfavourable results (e.g. sub-therapeutic or toxic)(26,27).

Knowledge of the adaptations in gastrointestinal physiology may contribute to the prevention of postoperative nutritional deficiencies and optimize postoperative drug therapy. In this review, we summarize the current knowledge on the impact of the anatomical alterations of bariatric and metabolic surgery on the gastrointestinal physiology. We focus on gastrointestinal acidity, gastrointestinal motility including gastric emptying time and transit times, gastrointestinal surface area including the intestinal absorptive cells and the presence of transporters and receptors; and gastrointestinal enzyme secretions after Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB). The search strategy and selection criteria of the discussed articles is added in Appendix 2.

Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

Bariatric procedures have evolved throughout the years as discussed in Appendix 3. To date, SG and RYGB are the most commonly performed procedures constituting respectively 47.0% and 35.3% of performed procedures (4). The anatomical alterations of these procedures include the longitudinal resection of the greater curvature of the stomach for SG (restriction), and the formation of a small gastric pouch without a pylorus (restriction) and rerouting the small intestine for RYGB (malabsorption). For SG, the longitudinal resection of the stomach starts on the greater curvature between 3 to 6 cm proximal of the pylorus and the end of the Laterjet nerve up to the angle of His and leaves a long tubular gastric sleeve (28,29). Laparoscopic RYGB-procedures vary slightly depending on the technique of the surgeon with regard to the anastomotic technique and limb length. For RYGB, a small gastric pouch is formed by partitioning the stomach. The small intestine is then rearranged into a Y-configuration through the transection of the small intestine 30-50 cm below the ligament of Treitz, where the distal end is anastomosed to the gastric pouch with the formation

Figure 1: Laparoscopic Sleeve Gastrectomy (left) and Laparoscopic Roux-en-Y Gastric Bypass (right).

of the alimentary or Roux-limb. The continuity of the proximal end is restored by a side to side

jejunojejunal anastomosis and is called the biliopancreatic limb (28,29). Both procedures are visualised in Figure 1.

Gastrointestinal acid secretion after Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

The stomach acts as a storage organ where ingested components are collected and mixed with gastric fluid consisting of gastric acid, enzymes, electrolytes and mucus. The oxyntic glands located in the fundus and corpus of the stomach regulate gastric acidity through the secretion of hydrochloric acid (gastric acid) via parietal cells resulting in a median gastric pH between 1.5 and 1.9 (20). Gastrin

Figure 2: Anatomical regions of the sleeve (left) and the gastric pouch and remnant (right).

acts as a major stimulant of acid secretion, which is produced by the G cells of the antrum (30). Theoretically, the formation of a small gastric pouch from the cardia, fundus and/or corpus and the separation of the remaining stomach through the gastric remnant may lead to the assumption that gastric acid secretion is diminished or absent in the pouch after RYGB (Figure 2).

Two human studies demonstrated the virtual absence of gastric acid secretion in the gastric pouch in basal and pentagastrin stimulated conditions in patients with RYGB (31,32). Physiologically, the absence of gastric acid secretion resulted in a neutral environment ($\text{pH}=7.0 \pm 0.2$) in the proximal pouch of 37 RYGB patients, while the gastric remnant more or less conserved the expected acidity ($\text{pH}=3.3 \pm 2.2$)(33). Nonetheless, histological evaluation of gastric pouch mucosa in humans shows the presence of acid producing parietal cells (34). Furthermore, preclinical studies with RYGB-operated rats revealed an increased number of mucous neck cells and an increased number of larger parietal cells in the gastric pouch compared to sham-operated animals. Moreover, the parietal cells were characterized by a higher expression of the proton pump $\text{H}^+/\text{K}^+ \text{ATPase}$, while gastrin positive cells appeared to be absent in pouch mucosa (35). It is plausible that the reduced acidity of the gastric juice in the remnant stimulates antral gastrin release. Consequently, increased gastrin levels

157 may exert trophic effects on the parietal cells through the bloodstream. However, it is tempting to
 158 hypothesize that another mechanism might be involved. The number of mucous neck cells is

Figure 3: Potential gastric histological adaptations after Sleeve Gastrectomy (left) and Roux-en-Y Gastric Bypass (right).

159 elevated in the gastric pouch. Some of these cells might redifferentiate into parietal cells and thereby
 160 partially explain parietal cells hyperplasia (36,37). Altogether, these findings support the idea that the
 161 remaining pouch mucosa attempts (but partially fails) to fully recover the lost acid secretory
 162 capacities of the gastric remnant (Figure 3). However, direct interspecies extrapolation remains
 163 questionable.

164 In parallel, we assume that the formation of a gastric sleeve by resecting the greater curvature of the
 165 fundus, corpus and proximal antrum diminishes gastric acid secretion, but in a lesser amount as
 166 some acid-producing parietal and G cells are still present (Figure 2). Due to the absence of SG studies,
 167 clinical studies in patients with duodenal switch provide some first insights. Pre-pyloric pH
 168 monitoring during 24 hour indicated the preservation of the acidic gastric environment (pH: 2.66
 169 (Interquartile range of 1.74-5.81)) with an acidic pH < 4 measured during the majority of time
 170 (68.7%)(38). Whether these findings can be directly translated to patients with a SG remains unsure
 171 due to the difference in surgical procedure. A duodenal switch consists of a vertical gastrectomy
 172 followed by bypassing a large portion of the small intestine (39). Noteworthy, animal studies have
 173 found contradictory findings regarding gastric sleeve morphology (35,40). From a histological point of
 174 view, the gastric mucosa undergoes changes with increased numbers of mucous neck cells and
 175 increased numbers of enlarged parietal cells. While a significant reduction in number of antral G cells
 176 was observed compared to sham-operated rats (40% vs. sham, $P < 0.01$)(35). In line with the RYGB
 177 findings, it is plausible that the reduced acidity of the gastric juice elevates antral gastrin release and

178 exert trophic effects on the parietal cells. In addition, the number of mucous neck cells is elevated in
179 the gastric mucosa and some of these cells might redifferentiate into parietal cells (36,37). Direct
180 extrapolation to humans is not possible, but the loss of parietal cells could support the hypothesis
181 that resecting the greater curvature partially diminishes gastric acid secretion (Figure 3).

182 Hereafter, the content of the gastric pouch or sleeve is emptied in the Roux limb or duodenum,
183 respectively. In normal conditions, the gastric chyme is mixed in the duodenum with alkaline
184 digestive juices containing bile, pancreatic and enteric secretions resulting in median pH values
185 between 6.1 and 7.0 in fasted state (20). In the Roux limb, 24-hour pH measurement revealed a pH
186 below 4 in 10.5% (range: 0.3-37.7) of time at the level of the gastrojejunostomy (41). The discrepancy
187 with the above-mentioned neutral pH of the gastric pouch emphasizes the need for additional
188 studies to further elucidate pH levels. Furthermore, no information is available regarding pH values
189 at the lower Roux-limb, biliopancreatic limb, common limb or colon. For gastric sleeve, post-pyloric
190 pH monitoring during 24 hour in patients with a duodenal switch provides some first insights. Below
191 the duodenoileostomy, a more or less neutral environment (5.79 (4.75-7.58)) was observed with an
192 acidic pH < 4 measured during 13.0% (range: 0.0-34.6) of time. These findings suggest that the
193 Brunner's glands located in the duodenal bulb neutralize the acidic content of the gastric sleeve via
194 the secretion of alkaline mucus (38). Whether the buffering effect of the duodenal bulb neutralizes
195 the acidic content in case of a SG remains to be understood.

196 **Gastrointestinal motility after Sleeve Gastrectomy and Roux-en-Y Gastric Bypass**

197 Gastrointestinal motility covers the interplay of smooth muscle contraction and relaxation within the
198 gastrointestinal tract resulting in a predominant anterograde movement of the luminal content via
199 peristaltic and non-peristaltic flow. Therefore, it controls the ability of the gastrointestinal tract to
200 ingest, digest, transport and absorb nutrients from food and drugs.

201 ***Effect on gastric emptying***

202 During meal intake, the fundus and upper corpus accommodate the ingested food through the
203 relaxation of the proximal gastric wall without a significant increase in intragastric pressure.
204 Relaxation of the gastric reservoir is mediated through vagovagal reflexes. After relaxation, tonic
205 contractions shift the gastric content distally. In the midcorpus, peristaltic contraction waves arise
206 from the gastric pacemaker activity, known as interstitial cells of Cajal, located along the greater
207 curvature and proceed towards the pyloric sphincter. Forceful contractions result in the partial
208 occlusion of the antrum. Pyloric contractions generate retropulsion of the gastric content towards
209 the proximal stomach, thereby facilitating digestion through mixing with gastric secretions and
210 mechanically breaking up solid particles to < 1 to 2 mm. Consequently, the pylorus relaxes and the

211 digested content enters the duodenum during pyloric relaxation, referred to as gastric emptying.
212 Both tonic and peristaltic muscular contractions are regulated by vagovagal reflexes and
213 enteroendocrine hormones that accelerate (e.g. gastrin) or slow down gastric emptying (e.g.
214 glucagon-like peptide 1 (GLP-1) and peptide YY (PYY)) (42,43). Theoretically, the resection of the
215 fundus may increase intragastric pressure after SG due to the loss of relaxation and accommodation
216 capacities. Furthermore, gastric contractile frequency may change as a result of the resection of the
217 pacemaker area of the corpus. The distal nerve endings of the *nervus vagus* are transected, which
218 might affect vagal signalling. In addition, the reduced gastric acidity might increase gastrin levels and
219 affect the rate of emptying (44). Moreover, anatomical gastric remodelling may result in an
220 accelerated emptying and rapid transit into the duodenum after SG (Figure 2). Different studies
221 investigated pre- and postoperative gastric emptying of (semi-)solids using – the gold standard –
222 scintigraphy (Table 1) (45–54)(55). The majority of studies indicate that the time required for half of
223 the (semi)-solid meal to leave the sleeve ($GET_{1/2}$) is significantly shorter up to two years after surgery
224 (46–48,50–54). More specifically, pooled analysis revealed the tendency for SG to accelerate $GET_{1/2}$
225 of solids with 29.2 minutes (95% CI, -40.9 to -17.5 min) at three months despite high heterogeneity
226 (I^2 - 91.4%)(56). In parallel, $GET_{1/2}$ of liquids is accelerated as well after SG (Table 1)(46,50). In order
227 to elucidate the mechanism underlying accelerated GE, a magnetic resonance imaging study
228 investigated and revealed the preservation of antrum motility with an increasing antral fold speed.
229 However, the proximal part of the sleeve lost peristalsis (57). Regarding vagovagal reflexes, a rodent
230 study revealed sprouting of the *nervus vagus* afferents in the hindbrain after surgery (58). These
231 findings might indicate a compensatory mechanism that overcomes the disruption of the distal nerve
232 endings of the *nervus vagus*. Therefore, it is tempting to suggest that the elevated gastrin levels
233 stimulate antral motility, resulting in accelerated emptying. Consequently, the rapid emptying of
234 undigested nutrients leads to elevated levels of the satiety hormones GLP-1 and PYY. These
235 hormones contribute to the efficacy of SG to improve and resolve obesity-associated comorbidities
236 (reviewed elsewhere)(17).

237 For RYGB, the formation of a small gastric pouch without relaxation and accommodation capacities, a
238 pacemaker area and a pylorus may lead to an accelerated emptying and rapid transit of nutrients
239 into the jejunum (Figure 2). Moreover, the dorsal and ventral gastric branches of the *nervus vagus*
240 are transected during pouch formation. These alterations will affect vagal signalling and may also
241 contribute to the accelerated emptying. Gold standard scintigraphy studies reporting both pre-and
242 postoperative $GET_{1/2}$ of solids and liquids are absent. However, few studies investigated pre- and
243 postoperative emptying using indirect methods. Paracetamol (acetaminophen) and d-xylose
244 absorption tests indicate faster liquid emptying after surgery (59–63). Noteworthy, a more or less

immediate maximal paracetamol plasma concentration is observed after surgery (60,61). Furthermore, multiple studies investigated postoperative pouch emptying or retention with/without the comparison to stomach emptying of healthy controls using the gold standard scintigraphy (64–69) (Table 2). For solids, Dirksen *et al.* observed accelerated pouch emptying in patients compared to controls (64). Other studies differed in outcome measurements, making comparison impossible (65,68,69). For liquids, Dirksen *et al.* and Nguyen *et al.* confirmed the accelerated liquid emptying of the absorption tests observed using scintigraphy (64,67). To elucidate the mechanism underlying accelerated emptying, a study using high-resolution manometry revealed a moderately increased intraluminal pressure without a difference between the pouch and the Roux-limb. These findings suggest that the pouch and proximal Roux-limb may act as a common cavity (70). In addition, a rodent study observed differences in the anatomical integrity of the *nervus vagus*, which is suggestive for alterations in gut-brain communication. However, the precise role of the altered *nervus vagus* function in regulating gastric emptying after surgery remains unknown (14). Nonetheless, it is known that rapid emptying of undigested nutrients in the Roux-limb releases the satiety hormones GLP-1 and PYY and contributes to the efficacy of RYGB to improve and resolve obesity-associated comorbidities (reviewed elsewhere)(17).

Effect on gastrointestinal transit time

The small intestine acts as the major area for absorption, where peristalsis pushes luminal content in an aboral direction and segmentation causes mixing of the luminal content. These characteristics facilitate the contact of the luminal content with the mucosal absorptive cells, named enterocytes. Therefore, gastrointestinal residence time defines interaction time with both digestive enzymes, receptors and transporters (42,71). Theoretically, the shorter gastric emptying time and therefore, the premature arrival of gastric content into the small intestine may accelerate intestinal transit for SG. Melissas *et al.* investigated the time between completion of a semisolid meal and the initiation of terminal ileum emptying into the caecum using scintigraphy (referred to as oro-caecal transit time) pre- and postoperatively. The initiation of caecal filling was significantly delayed from 182 minutes (range: 120–275) to 210 minutes (range: 142–310) after surgery. In the same study, the small bowel transit time was significantly decreased from 71.8 minutes (range: 38–141) to 62.6 minutes (25–118) postoperatively (53). These findings are in line with Shah *et al.*, who compared small bowel transit time of a solid meal in SG-patients (199.0 ± 65.7 minutes) with small bowel transit time of healthy (298.1 ± 9.2 minutes) and obese (281.5 ± 46.2 minutes) controls using scintigraphy (72). All together, these (limited) findings might suggest that the gastrointestinal content reaches the terminal ileum faster, while arriving later at the caecum. The delay in caecal filling might result from changes in

terminal ileal pressure, intracaecal pressure or changes in the ileocaecal valve tone, but the origin is currently unknown. Regarding colonic transit, no information is available for SG.

For RYGB, the bypass of the pylorus and the proximal small intestine may as well accelerate transit along the Roux-limb and the common limb. Morinigo *et al.* investigated pre- and postoperative oro-caecal transit time in six subjects using a lactulose breath test (Preoperative: 115.0 ± 22.4 min; six weeks postoperative: 75.0 ± 24.7 min; $P < 0.05$)(61). In addition, Nguyen *et al.* observed a significant faster caecal arrival time in ten RYGB patients compared to ten healthy controls using scintigraphy ($P < 0.001$)(67). While, Carswell *et al.* did not observe a significant difference in oro-caecal transit time between seven RYGB patients and ten obese controls using a sulphasalazine absorption test (RYGB: 180 min (173–210); controls: 180 min (150–240); $P = 0.935$)(73). The data related to oro-caecal transit time is more or less inconsistent, which could reflect the variation of techniques. The validity of the different absorption tests used in an altered gastrointestinal tract is questionable. In addition, Dirksen *et al.* observed a significant slower small bowel transit time of solids in patients compared to controls, while colonic transit did not differ between patients and controls (64). Altogether, available research on the effect of RYGB on gastrointestinal transit times is rather limited and inconsistent.

Gastrointestinal secretions after Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

The gastrointestinal system secretes enzymes that initiate the enzymatic breakdown of meal components into smaller pieces for absorption(19,74).

Effect on gastric enzyme secretions

The effects of bariatric procedures on gastric acid secretion were already addressed in the third section of this review. Theoretically, stomach alterations could impair the secretion of gastric enzymes including pepsinogen and gastric lipase after bariatric surgery. Furthermore, the reduced gastric acid secretion may affect the conversion of inactive pepsinogen into active pepsin (maximal activity between pH 1.5 to 2.5)(75). Without active pepsin, protein molecules may remain intact and circumvent absorption. To date, human data is lacking regarding gastric secretion of lipase and pepsinogen after bariatric surgery. However, a decrease in serum pepsinogen 1 has been observed after RYGB and SG. Serum pepsinogen may reflect peptic secretion as a small amount of pepsinogen leaks into the bloodstream (76,77). Despite a potential decrease in pepsinogen secretion that could affect protein digestion, Tessier *et al.* revealed an improved protein digestibility in RYGB-operated rats in comparison to SG-operated and sham-operated rats (78). Contrary to these findings, Gandarillas *et al.* observed a lower protein digestibility in RYGB-operated pigs in comparison to SG-operated pigs with ileal transposition and to sham-operated pigs. Furthermore, they observed as well

a significant decrease in fat digestibility in RYGB-operated pigs in comparison to SG-operated pigs with ileal transposition and to sham-operated pigs (79). Although there is no comparable preclinical and no clinical data available whatsoever, these studies emphasize the lack of understanding regarding gastric enzyme secretion related to the digestibility of dietary protein and fat after bariatric surgery.

Effect on pancreatic and gallbladder secretions

After RYGB, the interaction of pancreatic enzymes and biliary secretions with the food bolus is delayed due to intestinal rearrangement. Bypassing the duodenum circumvents the initial contact between nutrients and the neuroendocrine cells that stimulate pancreatic and gallbladder secretion (80). Moreover, the presence of undigested food in the distal small intestine may trigger a higher secretion of ileal brake hormones (i.e. PYY, CCK and GLP-1) that inhibit secretion and motility to maximize absorption (14,81). Recently, a lower secretion rate of trypsin, amylase and lipase was observed in common channel aspirates after infusion of a liquid meal in patients after RYGB compared to controls (82). These findings are in line with the reduced pancreatic secretion after a gastric bypass observed by Ito and Mason in 1971 (83). A reduced pancreatic secretion may affect the digestion of all macronutrients, culminating in the loss of nutrients for absorption. Besides affecting pancreatic secretion, different studies reported higher plasma bile acids ($\pm$ twofold increase) in fasted and fed state after RYGB (84–93). The increase was observed in both primary and secondary bile acids, yet the mechanism remains unknown. Higher serum levels may result from the accelerated contact of more undiluted bile acids with the ileum, leading to a more profound intestinal uptake and therefore, delivery to the liver. However, fasting plasma bile acids are also increased after SG, but to a lesser extent compared to RYGB (85,93,94). Increases in circulating bile acid levels are known to activate the hepatic fibroblast growth factor 19 (FGF19) – fibroblast growth factor receptor 4 (FGFR4) signalling pathway. This pathway inhibits bile acid synthesis by suppressing the gene encoding hepatic cholesterol 7 α -hydroxylase (CYP7A1), the rate-limiting enzyme of bile acid synthesis. Contrary to expectations, Flynn *et al.* observed that hepatic CYP7A1 expression was dramatically increased in a gastric bypass mouse model (95). Interspecies extrapolation remains unclear, but these findings support the idea that other factors may contribute to elevated circulating bile acids in bariatric patients including altered biliary secretion, altered gut microbiota and dietary changes.

Gastrointestinal surface area after Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

Key to the intestinal absorption of nutrients, electrolytes and solutes is a monolayer of intestinal epithelial cells including absorptive enterocytes that line the inner surface of the intestine. The small

intestine maximizes absorption through the organization of epithelial cells into crypts and villi, resulting in an absorption area of approximately 32 m² (96). Along the base of the crypts, multipotent stem cell continuously give rise to a range of absorptive cells (e.g. enterocytes) and secretory cells (e.g. goblet, enteroendocrine and paneth cells) that are characterized with a high cellular turnover (3.48 ± 1.55 days)(20,97,98). In response to a variety of internal and external stimuli, the intestinal epithelium can undergo morphological and/or functional adaptations known as intestinal adaptation or enteroplasticity(99,100). For instance, anatomical alterations and an altered nutrient supply may lead to remarkable morphological (i.e. hypertrophy/hyperplasia) or functional changes (i.e. altered proliferation or altered expression of receptors and/or transporters)(101).

Effect on the intestinal absorptive cells

For RYGB, the rapid delivery of (undigested) nutrients into the Roux-limb could induce enteroplasticity to maintain maximal nutrient absorption. Likewise, the rapid delivery of (undigested) nutrients to the duodenum and the potential affected gastrointestinal acidity may affect intestinal absorptive cells to undergo morphological and functional changes after SG. To date, different preclinical and clinical studies have demonstrated some degree of enteroplasticity after different bariatric procedures (102–121). For RYGB, most rodent studies reported hypertrophy of the nutrient-exposed limbs. Morphologically, the absorptive area expanded generally through an increase in the limbs' diameter, mucosal thickness, villus height and crypt depth. Epithelial proliferation increased at the level of the crypt (102,103,105,106,109,116,119,121). Intestinal adaptation occurred maximally in the Roux-limb followed by the common limb and the colon (119). The disparity in morphological changes within the nutrient-exposed limbs highlights the potential of intestinal undigested nutrient exposure as a trigger for intestinal adaptation. This hypothesis is supported by the presence of hypertrophy in the nutrient exposed limbs and the presence of mucosal atrophy in the nutrient excluded area of rats with jejunoileal bypass (115). Nutrient exposure may therefore exert local effects on the mucosa as a compensatory mechanism to restore absorptive capacity of the compromised biliopancreatic limb. However, human studies reported contradictory findings of intestinal adaptation in the Roux-limb ranging from mild hypotrophy to no adaptations to hypertrophy (106,110–113). Intestinal mechanisms of adaptations may vary between rodents and humans, which highlights the need for additional clinical data for definitive conclusions. After SG, there are no signs of cellular hyperplasia at the level of the duodenum, jejunum, corresponding to the Roux-limb, or at the level of the ileum of rodents (105,106). However, some studies reported signs of jejunal and ileal villus adaptations including increased villus height and width in combination with higher levels of crypt cell proliferation (104,106–108). By comparing RYGB and SG, these

findings suggest that intestinal rearrangement is essential to obtain maximal intestinal adaptation. Nonetheless, the lack of human studies makes it difficult to be conclusive.

Effect on transporters and intestinal enzymes

The majority of nutrients are absorbed along the small intestine, while the colon is predominantly responsible for water and electrolyte transport (42). Beyond nutrient transport, different enzymes and transporters are distributed along the small intestine for the metabolism and transport of drug compounds across the cell membrane (20). The complexity of functional adaptation with the invasive nature of the processes to assess adaptation underline the limited availability of human evidence. Functional adaptations have been shown to occur after bowel resection (122,123). The extent of adaptation depends on the site of anatomical alteration, the presence of luminal nutrients and a variety of hormones and growth factors (i.e. human growth hormone and glucagon-like peptide 2) (124,125). Given the intestinal rearrangement of bariatric surgery, we might assume that some degree of functional adaptation occurs especially after RYGB. For instance, a modified transporter expression could increase the absorptive capacity of the remaining nutrient exposed intestine to substantiate the bypassed biliopancreatic limb with its nutrient transporters or receptors

Figure 4: Macro- and micronutrient absorption sites along the gastrointestinal tract after Roux-en-Y Gastric Bypass.

(Figure 4).

Given the importance of type 2 diabetes research, a substantiate amount of research regarding functional adaption covers the field of glucose absorption after RYGB (106,116,121,126–128). Preclinical research in a porcine model detected a reduced intestinal glucose uptake in the Roux-limb. A lower luminal sodium content in the Roux-limb, derived from the exclusion of sodium-rich bile, diminished glucose uptake via the apical SGLT1, but not its expression. Unexpectedly, the non-intestinal glucose transporter-1 (GLUT1) appeared at the basolateral side to potentially compensate the lack of luminal glucose (127). Interestingly, various non-clinical and clinical studies reported

however an elevated intestinal glucose uptake in the Roux-limb (106,126–128). Basolateral expression of GLUT1 in rodents and humans increased to the extent that expression levels were the second highest next to the brain. Glucose remained within the Roux-limb as a way to maintain their own cells energy requirements. Remarkably, the transporter-related adaptations are confined to the Roux-limb that is exposed to luminal nutrients, but not to pancreatic secretions. These findings might suggest that functional remodelling is triggered via undigested nutrient exposure. Expression of other glucose transporters including SGLT1, GLUT2, GLUT3 and GLUT5 remains controversial (106,116,121,126–128). Contrary to the Roux-limb, no functional adaptation of any glucose transporter occurred in the jejunum after SG (105,106). For micronutrients, the expression of the divalent metal transporter 1 (DMT1) for iron absorption has been observed to differ in the jejunal mucosa of the Roux-limb in patients after RYGB. Despite a decreased number of DMT1 along the jejunal mucosa, the expression increased in the cytoplasm of the enterocytes located in the apex of the villi of the jejunal mucosa. The authors hypothesize that morphological alterations induce the relocation of the enterocytes, leading to a higher number of DMT along the apex of the villi (111). No information is available regarding other transporters involved in the iron metabolism (e.g. ferroportin). Up to now, limited information is available regarding other transporters for micronutrient absorption after RYGB and SG.

Drug absorption may depend on the apical presence of the efflux transporter P-glycoprotein (P-gp), which facilitates the transport of substrates back into the intestinal lumen, and the presence of cytochrome P450 (CYP) enzymes, which facilitate the first-pass metabolism of drug compounds (e.g. CYP3A4 – the most abundant intestinal drug metabolising enzyme). Their expression varies along the different parts of the small intestine with an increasing expression of P-gp from the proximal to the distal small intestine, whereas the expression of CYP3A4 decreases towards the ileum (129–132). According to their distribution, the bioavailability of CYP3A4 substrates could increase due to the bypass of some CYP3A4 activity. On the other hand, the bioavailability of P-gp substrates could remain more or less unaltered as absorption may have occurred before they reach the distal part of the intestine where P-gp expression is higher (133). However, a large variability is observed in postoperative bioavailability of drugs that undergo first-pass metabolism by CYP3A4 and/or are P-gp substrates (133–137). In some cases, a higher dose of a drug is reported to be necessary to provide similar exposure as in non-bypass patients (134,137). Others report that dose alterations cannot be generalized for all bariatric patients and every patient should be drug-specific monitored to prevent unfavourable sub-therapeutic or toxic results (133,135). These opposing results underline the complexity of predicting CYP3A4 and/or P-gp substrates' bioavailability by solely relying on expression levels. The period of postoperative care remains essential as intestinal adaptation of P-gp

expression may occur likewise other conditions (e.g. bowel resection) (136,138,139). Other determining factors for expression include the low-grade inflammation related to obesity as well as CYP3A4 and/or P-gp genotype (140,141).

Implications for nutrient and drug bioavailability after Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

Lifelong nutritional monitoring is necessary after any bariatric procedure as gastrointestinal adaptations are not limited to the stomach. Dietary evaluation and laboratory screening for nutritional deficiencies should be an extensive, postoperative routine for all patients, particularly since patients have a higher risk to develop nutritional disorders than matched obese controls after bariatric surgery (142). The smaller pouch and sleeve reduces food and thus nutrient intake after surgery. Furthermore, dietary intolerance might contribute to a lower nutrient intake (143). The stomach requires an acidic environment for the initiation of protein digestion, releasing protein-bound vitamin B12, lipid digestion, optimising calcium solubility, optimising iron solubility and reducing iron into the absorbable ferrous form (144). By resecting or bypassing the oxyntic glands, it is thus plausible that digestion and/or absorption of these nutrients is affected. Moreover, the resection of the oxyntic glands results in an inadequate secretion of intrinsic factor from parietal cells, which is needed for vitamin B12 absorption further on in the ileum (145). In addition, accelerated pouch or sleeve emptying delivers nutrients rapidly into the small intestine that are partially undigested due to a reduction in gastric mixing. After RYGB, protein, carbohydrate and lipid digestion is further postponed until the ingested food reaches the pancreatic enzymes and biliary secretions in the common limb. Consequently, delaying lipid digestion may result in malabsorption of fat-soluble vitamins A, D, E and K that in turn affect the absorption of other nutrients (e.g. vitamin D – calcium interaction). Moreover, a major area for nutrient absorption with region-specific transporters is bypassed (Figure 4). More rapid absorption of ethanol has been observed after bariatric surgery, leading to higher and earlier maximum blood-ethanol concentration versus obese controls. Moreover, blood alcohol concentrations remain higher post-dosing. Altered ethanol kinetics might increase the risk for relapsing or developing new-onset alcohol use disorder and consequently, the risk of developing thiamine deficiency after surgery (146–149). In terms of laboratory screening for nutritional deficiencies, attention should be drawn to the definition of deficiencies with regard to the (combination of) diagnostic tests and associated cut-off values used. For accurate diagnosis, a list of preferred laboratory assays with their cut-off values should be proposed per nutrient. In case of nutritional deficiency, additional supplementation needs to be added to the standard postoperative supplementation regimen. The current regimen includes daily multivitamin and -mineral supplementation containing vitamin B1, vitamin B12, folate, vitamin A, vitamin D, vitamin E, vitamin

467 K, calcium, iron, zinc and copper. However, the available evidence supporting the current nutritional
468 recommendations is graded as intermediate evidence (150).

469 Gastrointestinal physiology also affects drug bioavailability. For instance, gastric motility enhances
470 disintegration of solid immediate release dosage forms. Gastric pH determines drug dissolution and
471 solubility in case of pH-dependency, while gastric emptying is often the rate-limiting step of
472 absorption. Intestinal motility results in the mixing of the intestinal content with pancreatic and
473 biliary secretions, which enhances the interaction between the drug and the gastrointestinal surface
474 area. Moreover, the intestinal transit time usually controls the absorption rate of low-solubility and
475 low-permeability drugs as well as the release from modified release formulations. While the
476 gastrointestinal surface area facilitates absorption, the presence of transporters may modulate
477 absorption (20). Thus bariatric surgery can affect drug bioavailability at different levels depending on
478 the drug's physiochemical properties, the drug product, and the type of surgery. For instance, an
479 increase in serum thyroid-stimulating-hormone (TSH) concentrations has been observed after RYGB
480 in patients receiving levothyroxine as a tablet formulation. After switching to a liquid formulation, a
481 substantial decrease in serum TSH levels was observed. These findings may indicate a higher
482 absorption from a liquid formulation as it circumvents the need for tablet disintegration and drug
483 disintegration (151). Regarding elevated gastric pH after surgery, decreased solubility is expected for
484 basic drugs, while an increased solubility is expected for acidic drugs. This may affect the rate and
485 extent of absorption further down the intestinal tract. These assumptions are confirmed by the
486 decrease in exposure of posaconazole (weak base) and the higher serum concentrations of
487 furosemide (weak acid) observed after RYGB (152,153). Additionally, the T_{max} of furosemide was
488 significantly shorter, which may result from accelerated pouch emptying (153). After administration
489 of an immediate- and controlled-release metoprolol formulation, a tendency towards a higher
490 exposure was observed and suggest that there is no impact of an accelerated transit on modified-
491 release formulations. However, other mechanisms might overcome a reduced drug release.
492 Metoprolol is metabolized by CYP2D9 that is expressed in the bypassed area. The first-pass
493 metabolism may thus be bypassed and could contribute to a higher exposure due to a lower
494 presystemic biotransformation (154). The bypass of the proximal small intestine delays the inlet of
495 pancreatic enzymes and biliary secretions until the common limb. These changes might reduce the
496 dissolution or solubility of lipophilic drugs. However, the exposure of the lipophilic drug fenofibrate
497 was not altered after RYGB. These observations may result from a higher secretion of bile acids or
498 from a comparable time between oral ingestion and bile acid contact due to accelerated pouch
499 emptying (152). Clinical findings indicate that the rate or extent of drug absorption can increase,
500 decrease or remain unaltered after surgery. Nonetheless, changes in drug absorption appear to be

drug-specific, and the oral bioavailability of various drugs has been summarised in systematic reviews (26,27,155). The biggest impact is observed for drugs that are intrinsically poorly absorbed, highly lipophilic or undergo enterohepatic recirculation. Therefore, clinicians and caregivers should be familiar with gastrointestinal alterations and their possible impact on oral drug bioavailability. Although the number of clinical studies is limited and SG may have a different effect to RYGB, a few theoretical considerations can be made based upon the gastrointestinal adaptations (155–159). First, a liquid formulation or crushing a solid formulation could circumvent lower absorption if impaired drug disintegration is expected. Second, lipophilic drugs are likely to be affected after RYGB as they depend on the solubilizing capacity created by bile salts. However, it is possible that other mechanisms compensate the expected reduction in absorption. Close monitoring of the patient for therapeutic effects and/or drug plasma levels is warranted. Third, there is little data available concerning the effect of bariatric surgery on modified-release formulations. From a hypothetical point of view, one might assume that the accelerated gastrointestinal transit may affect drug release from these formulations. Fourth, drugs that depend on cytochrome P450 enzymes may have a reduced first pass metabolism and a higher exposure. Finally, drugs with a narrow therapeutic window should be handled with caution, and therapeutic drug monitoring may be considered. Further studies are required to ensure the validity of the proposed measures.

Future directions

This review summarizes current knowledge regarding the effect of bariatric surgery on gastrointestinal physiology. Available data indicate an accelerated gastric emptying of solids and liquids, a faster small intestinal transit and an increase in bile acid serum levels after SG. Moreover, available data suggest that RYGB reduces gastric acid secretion, accelerates gastric emptying of liquids and increases bile acid serum levels $\pm$ twofold. Despite the growing popularity of both procedures, important questions remain regarding gastrointestinal acidity, gastric and pancreatic secretions, surface area and colonic transit after SG and regarding intestinal pH, solid gastric emptying, intestinal transit time, gastric enzyme secretions and surface area after RYGB. Especially, the field of SG requires more attention where the ‘simplicity’ of the anatomical procedure in comparison to RYGB has sometimes led to the belief of being less extreme in complication type and incidence. Equal or greater importance is whether these gastrointestinal differences affect the patient’s underlying condition or the susceptibility to adverse reactions. To respond, clinicians, caregivers and their patients need to be aware that the anatomical induced gastrointestinal alterations affect nutrient and drug bioavailability. However, novel and standardised approaches are necessary to further investigate the influence on nutritional and drug therapy to develop evidence-

534 based guidelines with the sole goal of avoiding postoperative nutritional deficiencies or inefficient
535 drug dosing.

Proposed display items

Figures

- Figure 1: Laparoscopic Sleeve Gastrectomy (left) and Laparoscopic Roux-en-Y Gastric Bypass (right).
- Figure 2: Anatomical regions of the sleeve (left) and the gastric pouch and remnant (right).
- Figure 3: Potential gastric histological adaptations after Sleeve Gastrectomy (left) and Roux-en-Y Gastric Bypass (right).
- Figure 4: Macro- and micronutrient absorption sites along the gastrointestinal tract after Roux-en-Y Gastric Bypass.

Tables

- Table 1: Overview of Sleeve Gastrectomy studies investigating pre- and postoperative (semi-) solid and liquid gastric emptying using scintigraphy.
- Table 2: Overview of Roux-en-Y Gastric Bypass studies investigating (semi-) solid and liquid gastric emptying in patients and controls using scintigraphy.

Contributors

NS and CM conceptualised the review. NS performed the literature search, drafted the manuscript and adapted the figures. All authors contributed in their field of expertise and reviewed the article and approved the final version.

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NS, TV, PA, JT, AM, ML, BVDS and CM declare no competing interest.

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1007

1008 **Appendix 1: Benefits and complications of bariatric and metabolic surgery**

1009 The percentage of postoperative remission for diabetes, hypertension and dyslipidaemia is 92.0%
1010 (CI: 84.7-97.2%), 75.2% (CI: 61.5-86.4%) and 75.8% (CI: 55.6%-91.5%), respectively. Moreover, a
1011 postoperative remission rate of 96.2% (CI: 86.7-99.8%) is observed for obstructive sleep apnoea (5).

Regarding cancer incidence, bariatric surgery is associated with a significant reduction in overall (pooled odds ratio: 0.72; 95% CI: 0.59-0.87) and obesity-related cancer incidence (pooled odds ratio: 0.55; 95% CI: 0.31-0.96). For women, a significant reduction in breast cancer incidence (pooled odds ratio: 0.50; 95% CI: 0.25-0.99) is observed (6). Moreover, maternal and neonatal complications are less likely to occur for women who become pregnant after bariatric surgery in comparison to obese women who become pregnant (160). These findings support the fact that bariatric surgery is associated with a lower all-cause mortality (hazard ratio: 0.59; 95% CI: 0.52-0.67)(8).

Nonetheless, bariatric surgery can result in unintended adverse events (complication rate: 17.0% (95% CI: 11.0%-23.0%)(5). A higher risk of hospital admission is observed in patients after surgery compared to matched controls due to gastrointestinal and nutritional disorders. Among nutritional disorders, iron deficiency and malnutrition are the most common (142). Other prevalent nutritional disorders include different nutritional deficiencies (e.g. calcium, vitamin D, vitamin B12, thiamine and folic acid), osteomalacia and dumping syndrome (161).

Appendix 2. Search strategy and selection criteria

References for this review were identified between Sept 1, 2019 and May 15, 2020 through searches of PubMed with the search terms “Gastric pH”, “Gastric Acid Secretion”, “Gastric Emptying”, “Gastric Motility”, “Intestinal Transit”, “Transit Time”, “Mucosa” “Epithelia”, “Pepsin”, “Pepsinogen”, “Pancreatic secretion”, “Bile”, “Enterocyte”, “Enteroendocrine cells”, “Enteroplasticity”, “Cytochrome”, “P-Glycoprotein”, “Absorption”, “Deficiency”, “Pharmacokinetics” and “Bariatric Surgery” and were published between 1963 and 2020. Articles were also identified through searches of the authors’ own files and snowball sampling (e.g. investigating the references of the search results). Papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Appendix 3. History of bariatric and metabolic surgery

Originally, bariatric procedures were intended to induce weight loss with the first clinical research description in 1963. A jejunoileal bypass was performed in ten patients with ‘uncontrolled’ obesity, defined as at least 125 pounds (or 56.7 kg) of overweight. The malabsorptive procedure included dividing the jejunum at 35 to 50 cm distal from the ligament of Treitz and establishing an end-to-side anastomosis to the proximal transverse colon. The procedure resulted in an average weight loss of 123 pounds (or 55.8 kg). Nonetheless, a combination of electrolyte (e.g. Ca^{+} and K^{+}) imbalance and diarrhoea necessitated partial or complete restoral of gastrointestinal continuity (162). From then onwards, different bariatric procedures and techniques (e.g. surgical/laparoscopy) have been developed and technically refined to induce and sustain weight loss, while minimizing post-operative

1045 morbidity and mortality (28,163). Although the origin of these procedures focussed on the
1046 management of morbid obesity, benefits extend beyond weight loss (5–8) . The recognition of these
1047 benefits provided rationale for the emergence of the term metabolic next to bariatric surgery (164).
1048 Based on the definition of Henry Buchwald and Richard Varco, metabolic surgery refers to “*the*
1049 *operative manipulation of a normal organ or organ system to achieve a biological result for a*
1050 *potential health gain*”(165).