Best Practice & Research Clinical Gastroenterology 40-41 (2019) 101638

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

The pros and cons of gastric bypass surgery – The role of the Roux-limb

Per Björklund, Lars Fändriks*

Institute of Clinical Sciences, Department of Gastrosurgical Research and Education, The Sahlgrenska Academy at the University of Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 15 February 2019
Accepted 18 July 2019

Keywords:
Intestinal motility
Bariatric
Manometry
Abdominal pain
Opioid analgesics

ABSTRACT

The prevalence of overweight and obesity has exploded in the post-industrial era. Life style interventions like dieting and exercise can induce a marked weight loss, but the main problem for most patients is to maintain the reduced body weight over time. Gastric bypass surgery is a commonly performed and very effective method for achieving a pronounced and sustained weight loss including metabolic improvements in obese patients. Despite the therapeutic successfulness there are known side-effects like chronic postprandial nausea and pain that in some patients become intractable. The pathophysiology is complex and partly unexplored. The physician or surgeon handling a patient with "post-bariatric symptoms" must be aware of the risk for symptom aggravations due to iatrogenic opioid-associated intestinal dysmotility. The present paper gives a brief overview of obesity surgery and its associated postsurgical conditions with a focus on the unexplored role of the Roux-limb following gastric bypass surgery.

Introduction

Bariatric surgery is regarded as the only anti-obesity method that in most patients results in a maintained weight loss. Bariatric surgery has, therefore, become to be among the most common benignant procedures currently performed. The IFSO Worldwide Survey reported that 579,517 bariatric/metabolic surgical procedures were performed worldwide the year 2014. Currently around 50% of the procedures are vertical sleeve gastrectomy (VSG) and approximately 40% are Roux-en-Y Gastric Bypass (RYGBP) [1]. VSG has gained popularity only during recent years, whereas RYGBP has been performed over decades. Consequently the number of patients in the general population living with RYGBP can be expected to be in the order of millions in the world. RYGBP is a very effective weight reducing operation that also is associated with improved metabolic health and prolongs life for the obese patients. However, despite the successful effects there are also side-effects and complications that may occur without direct association to the surgical procedure. A common complaint is chronic meal-induced nausea and abdominal pain. Mild, diet-dependent postprandial discomfort probably helps the patient to change eating habits, but if this effect becomes intractable the patient will seek care. The knowledge about the clinical pictures following bariatric surgery is generally low among physicians and can thus be a source for mistakes. The present paper gives a brief overview of obesity surgery and its associated postsurgical conditions with a focus on the unexplored role of the Roux-limb following gastric bypass surgery.

The obesity epidemic

The prevalence of overweight and obesity has exploded in the post-industrial era. Actually, most of the world's population live in countries where overweight and obesity associated diseases kill more people than underweight [2,3]. The WHO has reported that, in 2014, 39% of adults aged 18 years and over were overweight and 13% were obese. Obesity thus implies a substantial burden not only on the individual, but also on the health care systems both in developed and developing countries [3]. Commonly the term "Body Mass Index (BMI) is used for classifying obesity and is calculated as body weight (kg) per the square of height (m^2). In adults a "normal" BMI is 18.5–25 kg m^{-2}; overweight is BMI 25 to 30, while obesity is defined as BMI over 30 kg m^{-2}. WHO have classified obesity into 3 classes where class I relates to a BMI 30.00 to 34.99; class II is between 35.00 and 39.99 and BMI >40.00 kg m^{-2} is regarded as class III obesity [4]. In addition, BMI >50 kg m^{-2} is sometimes termed superobesity.

The biological background to overweight and obesity is

* Corresponding author.
E-mail addresses: per.bjorklund@vgregion.se (P. Björklund), lars.fandriks@gastro.gu.se (L. Fändriks).

https://doi.org/10.1016/j.bpg.2019.101638
1521-6918/

complex. During the development of mankind it has been an evolutionary asset to be able to store energy. The individuals that survived periods of starvation were the ones who reproduced. This led to a natural selection of bodily control mechanisms for preserving energy and to promote eating. From the perspective of modern living with unlimited access to high-energy foods and low demand on physical activity for survival, it is not surprising that weight gain becomes prevalent in the population. Apart from being a social stigma in many cultures obesity is associated with an increased risk of several medical conditions and also with a shortened lifespan. Typically obesity is associated with type 2 diabetes, hypertension, dyslipidaemia and cardiovascular disease, but also brings an increased risk for sleep apnea, musculoskeletal disorders such as osteoarthritis, certain forms of cancer and impaired fertility. Obesity is also associated with an increased prevalence of mood disturbances, anxiety, and other psychiatric disorders [4–6].

Obesity therapy

The prime goal for public health care systems is to prevent obesity by lifestyle changes aiming to reduce calorie intake and to increase calorie expenditure i.e. by increased physical activity. Unfortunately, once a manifest obesity is established these measures only have moderate or no effect. Over the years serious attempts have been made to find an effective pharmaceutical support to life style changes, but so far unsuccessful. Marked weight loss can indeed be achieved by life style interventions like dieting and exercising but the main problem is to keep the reduced body weight over time. Within 1–2 years most people regain the lost weight and usually exceed the pre-treatment level. Today surgery is regarded as the only effective treatment for achieving a pronounced and sustained weight loss [4]. Obesity surgery is also called bariatric surgery and can be defined as a surgical intervention in the gastrointestinal tract with a weight reducing purpose.

Bariatric surgery techniques

In the 1950s the first surgical procedures to induce weight loss was introduced in the form of intestinal resection or shunting operations aiming to induce malabsorption. Today true malabsorptive constructions are uncommon but are sometimes used (e.g. biliary-pancreatic diversion) in superobese patients (BMI>50 kg m^{-2}). Another bariatric surgery principle is to restrict the ability of the individual to ingest food. One dramatic historic example was to clamp the patient's teeth together, thereby disabling them from eating. A more sophisticated modern way to restrict food intake is to place a rigid band around the stomach to induce early satiety when the upper part is filled (Fig. 1). Following this operation, the patient remains hungry but cannot eat large meals. However, many 'food intake-restricted' patients adapt by increasing the number of (smaller) meals with easy ingestible high-energy dishes resulting weight regain [7,8]. In addition, the maintained hunger and negative reward of food intake that cause pain and nausea are experienced as a severely lowered quality of life. Gastric banding-procedures are therefore performed less often and many previously banded patients have been converted to other surgical constructions, most often RYGBP [8,9].

Based on the observation of weight loss among patients that underwent partial stomach removal for peptic ulcer or malignant diseases, the gastric bypass procedure was developed by Dr E Mason during the 1960 ies [10]. The gastric bypass has since then been developed further into its current form, the laparscopic Roux-en-Y gastric bypass (RYGBP) (Fig. 2). After a gastric bypass, the swallowed food arrives directly in the jejunum, whereas the

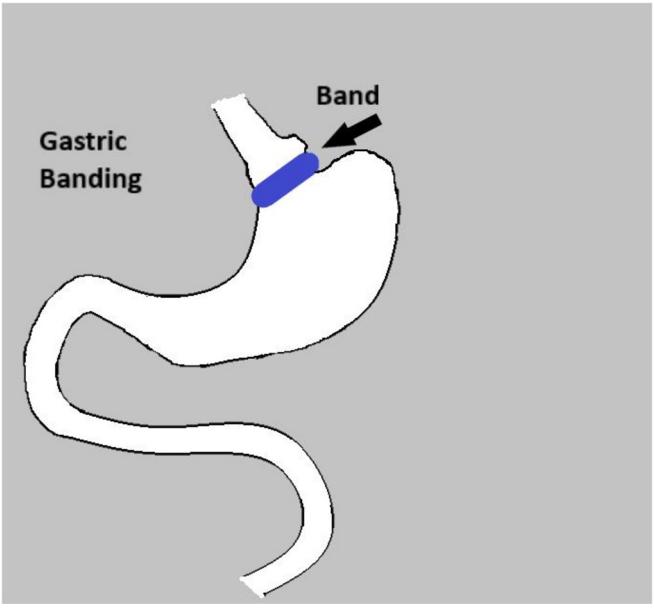

Fig. 1. Principal illustration of the Gastric Banding. Note that the anatomical proportions are erroneous.

secretions of the bypassed stomach and duodenum (including bile and pancreatic secretions) enter more distally in the small intestine. This change of routing the ingested nutrients in relation to the entrance of digestive factors like pancreatic enzymes and bile, results (in most cases) in a powerful weight loss also sustained over a long period [11].

Vertical sleeve gastrectomy (VSG) is an operation that recently has become very popular. The VSG was initially a part of the more extensive biliopancreatic diversion with duodenal switch, but was introduced as a single procedure in 2005 [12]. The anatomical route for food is preserved after VSG but the gastric volume capacity is markedly reduced (Fig. 3). Short term effects on body weight and obesity-related metabolic diseases are similar to gastric bypass, but the long-term results and mechanisms of action following sleeve

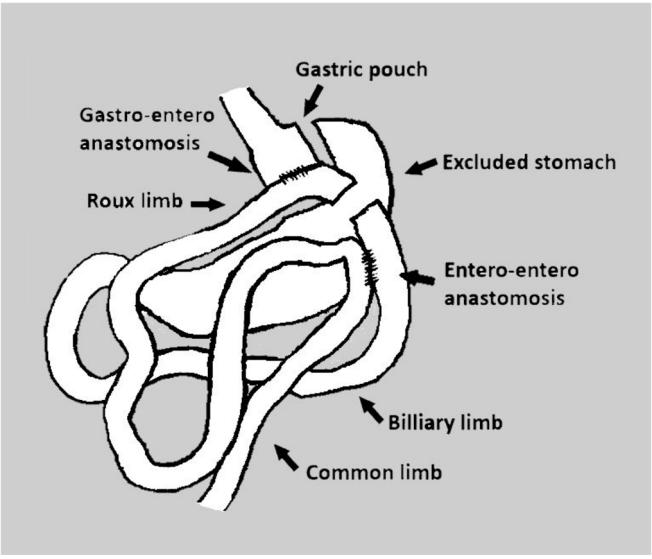

Fig. 2. Anatomical features of the Roux-en-Y Gastric Bypass. Note that the anatomical proportions are erroneous.

gastrectomy are less well studied. As with gastric bypass, after sleeve gastrectomy, ingested food is rapidly delivered to the distal small intestine activating the hindgut mechanisms (see below). However, there are significant differences between VSG and RYGBP related to gastroduodenal functions [13].

Metabolic surgery

The advantage of bariatric surgery is that the induced weight loss is maintained over long time. The Swedish Obese Subject (SOS) trial reports a weight loss following RYGBP of 27 ± 12% after 15 years, whereas the comparator (non-surgical interventions, i.e. life style changes and pharmacological treatments), was principally without effect over this time. The SOS-study also reports that gastric banding procedures are effective, but not as pronounced as following RYGBP. Controlled long term studies (>5–8 years) on the effects of VSG are still few, but weight loss up to 5 years are similar as following RYGBP [14–17].

May studies and reviews have reported weight-loss associated improvements in obesity related comorbidities like type 2 diabetes mellitus (T2DM), hypertension, metabolic syndrome, sleep apnea and to the end, overall mortality [4,6,11,18,19]. Interestingly, some of the metabolic improvements occur before body weight is reduced indicating direct actions on metabolic control by the altered gastrointestinal anatomy and functions. Because the attention is moving away from weight loss the term *metabolic surgery* has been coined and is defined as the use of gastrointestinal operations with the primary intent being the treatment of for example T2DM.

The indication for surgery as treatment for obesity has followed, in most countries, the NIH consensus statement in 1991 that recommended bariatric surgery for patients with severe obesity that had a BMI of ≥35 kg/m2 with at least one comorbid condition such as T2DM, hypertension and/or obstructive sleep apnea, or a BMI of ≥40 kg/m2 [20]. A joint statement by several international diabetes organizations stated in 2016 that metabolic surgery should be recommended in patients with class II & III obesity, and considered in patients with class I obesity with poor glycemic control [21].

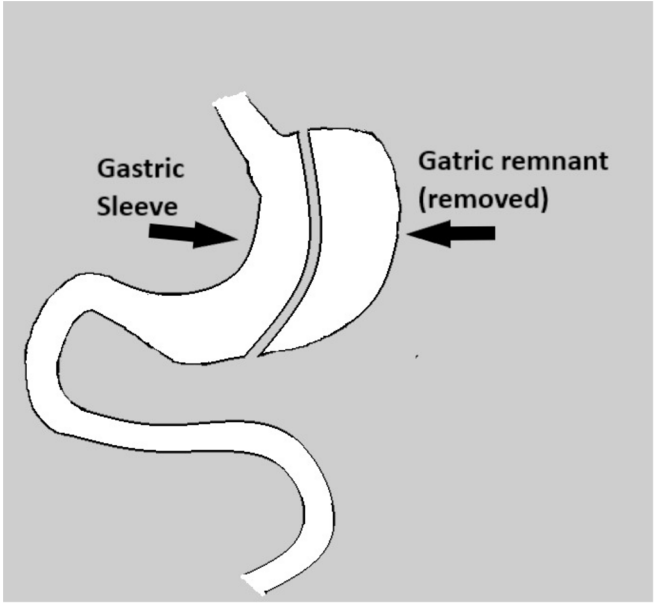

Fig. 3. Anatomical features of the Vertical Sleeve Gastrectomy. Note that the anatomical proportions are erroneous.

The mechanisms of gastric bypass

As already mentioned, RYGBP has been a dominating bariatric procedure during many years and it follows that most mechanistic research relate to this operation why these are discussed below. Perhaps a bit surprising the weight loss and improved comorbidities of gastric bypass is achieved neither by malabsorption, nor by a mechanical restriction of food intake. The main driver for weight loss is rather an altered eating behaviour that reduces energy intake [22,23]. Two connected principles have emerged as potential working mechanisms of gastric bypass; the foregut theory and the hindgut theory. The foregut theory teaches that by bypassing the stomach and the duodenum these organs are deprived of the exposure to food and nutrients thereby altering the secretion of gut-derived hormones originating from this area, e.g. the liberation of glucose-dependent insulinotropic peptide (GIP) from the duodenal mucosa. The hindgut theory, on the other hand, is based on the fact that the parts of the intestine that originally are situated more distally, i.e. in the distal the jejunum and ileum, are now exposed to nutrients and digestion earlier during food intake resulting in a faster humoral responses. Changes in the concentrations of gut-derived hormones, including peptide YY (PYY), glucagon-like peptide 1 (GLP-1), ghrelin, GIP, oxyntomodulin and cholecystokinin (CCK) have been reported to occur after RYGBP [22–26]. PYY and GLP-1 are secreted from L-cells in the ileum and colon and acts as satiety promoting hormones, while hunger is stimulated by ghrelin secreted from P/D1 cells in the gastric fundus. GLP-1 is also active in the glycemic control. It has been shown that the meal induced release of PYY and GLP-1 increases after RYGBP, from subnormal levels in obese subjects, to more normal levels that also reduce food intake [27]. It has been proposed that modulating these humoral systems with pharmacological agents may be a future way to treat obesity without surgery [28].

In addition to regulating food (energy) intake, data have emerged demonstrating increased energy expenditure in RYGBP patients. Interestingly, it appears not to be the basal metabolic rate (BMR) that becomes upregulated, rather the thermogenesis associated to meal intake [29,30]. The mechanism is not completely known, but according to experimental animal data it can be explained as a reprogrammed mucosal metabolism in the Roux limb [31]. Two other recently investigated aspects on the working mechanism of RYGBP are alterations of circulating bile acids and the intestinal microbiota. It is hypothesized that bile acids regulate glucose metabolism through the TGR5 receptor expressed on L-cells, causing release of GLP-1, and also induce synthesis and secretion of fibroblast growth factor 19 (FGF19) which might improve insulin sensitivity, thus improving glycaemic control [32]. Studies have shown that transplanting faeces from RYGB-treated to germ-free mice resulted in significantly greater weight loss compared with mice receiving faeces from sham-surgery treated mice [23]. Also, germ-free mice transplanted with faecal microbiota from obesity operated human patients accumulated less fat than mice transplanted with microbiota from obese patients [33]. The development of knowledge in these research areas is evolving precipitously, but few results have yet shown clinical relevance.

The “forgotten” Roux-limb

The science is well established around the bypassed stomach and duodenum, as well as the rapid delivery of nutrients to the distal intestine, but until today very little interest has been put in the novel prime food recipient, the Roux-limb. By repositioning the small intestine to a position principally following on the oesophagus its internal environmental will be radically altered. Prior to RYGBP the role of the stomach was to store ingested food, grind it to

smaller parts, disinfect it from bacteria with gastric acid, initiate degradation, and then to deliver it into the duodenum and small intestine in a regulated manner. After gastric bypass surgery those tasks have to be taken over by the Roux-limb implying that several morphological and functional features become challenged. The features of the Roux-limb are far from fully characterised and below are given some examples from recent research.

Is there a role for the gastric pouch?

The clinical experience was that the patients ate less after surgery, and this was confirmed by showing a radical decrease in preferred portion size during the first postoperative year [34,35]. The reason for reduced meal size was long explained as a function of the size of the gastric pouch. However, the role for the gastric pouch as a reservoir can principally be ruled out by the fact that the current surgical technique prescribes a minimal gastric pouch ($\approx$20–30 mL) and a large-calibre gastro-entero anastomosis (GEA), thus theoretically without outflow "restriction" [36,37]. Even though it for surgical technical reasons seems improbable, the question remained if there exists a restriction in the GEA with a flow resistance that creates a distension of the gastric pouch during meal intake. Since mechano-receptors for distension are present also in the gastric pouch, it could still be the site for a pressure induced satiation response. A relevant measure is the pressure-profile that is built up in the pouch-to-Roux segment during food intake. By use of high-resolution manometry it could be shown that there was no intraluminal pressure-gradient between the pouch and the Roux-limb during eating [38]. Thus, the small pouch and Roux-limb should be regarded as a common cavity and a role of the GEA as the site for restriction can, at least with regard to the modern surgical procedure, be excluded.

Mucosal inflammation

A more plausible explanation is that the Roux-limb is the determining meal intake. Hypothetically, it could be expected that the jejunal mucosa in the Roux limb gets inflamed by the new intraluminal milieu and, in turn, starts an anti-ingestive signalling. However, a careful examination of the postoperative mucosa did not give any support for this hypothesis [39]. Although some pro-inflammatory signs were present, the Roux-limb mucosa did not show any manifest inflammation, thus consistent with a study by Csendes et al. [40]. In the study from our laboratory the villi were flattened that combined with an increased epithelial replication rate, speak in favour of a mucosal adaptation to food reception/transportation/protection rather than appetite signalling [39].

Mechano-sensitivity and luminal clearance

It is reasonable to assume that the food-receiving capacity of the Roux-limb is restricted due to its mechanical properties. Thus, food intake would be followed by an increased intraluminal pressure, immediately propagated to volume- or stretch-sensitive neural elements in the intestinal wall that in turn report to the CNS. To mimic the response to a food bolus the Roux-limb was stimulated by inflating a luminal balloon. The balloon distension allowed a standardized local stimulus without outflow in distal direction, and also without the simultaneous activation of mucosal chemo-sensitivity that would have been the case if food was instead installed. When using this technique, subjects with a low perception threshold to distension of the Roux limb preferred large meal sizes and *vice versa* [34]. This finding appears a bit counter-intuitive. At first it seems more reasonable that an abdominal sensation to intraluminal distension is interpreted as a satiety signal thereby reducing food intake. However as the opposite was the case, one can instead speculate that in parallel to the perceived sensation there is a triggering of peristalsis in distal direction that clears the lumen and makes it ready to receive more food (i.e. a larger meal). This indeed appears to be the case as shown in a follow-up study where food ingestion clearly induces Roux limb propulsive motility [38]. So, the Roux-limb appears to have a "receptive clearance" that disposes its content in the distal direction more or less immediately. So far the actual rate of Roux-limb clearance has not been assessed. The above proposed idea that that "big-mealers" have a low-threshold for inducing Roux limb clearance motility thus awaits confirmation. Another perhaps more expected finding was that the subjects that responded with high intra-balloon pressure to a given volume distension were the ones that chose to eat small meals [34]. These results suggest that individuals with low mechanical compliance in the Roux-limb (i.e. a large net pressure increase following a given volume) have the most optimal effect regarding reduction of food intake. This finding supports that RYGBP has a restrictive component and that the restriction is located to the Roux limb [34]. Because of the small size of the investigated population, it was not possible to conclude to what extent this "Roux-limb restriction" influenced BMI.

Taken together it appears that food intake and intestinal sensing can be determined by the bio-mechanic properties of the Roux limb wall. The functional state of the intestinal wall musculature can vary considerably for example in response to luminal nutrient degradation (e.g. fat digestion), or to neuroendocrine factors (e.g. vagal activity, prokinetic hormones), as well as to pharmaceuticals (e.g. NSAIDs and opioids) [41–43]. It follows that the Roux-limb should be ascribed a sort of "dynamic restrictive property". To what extent such a dynamic flow restriction of the Roux limb really has a food-intake regulating relevance remains to be investigated. If verified, it opens for exciting possibilities. One is that the Roux-limb mechanical compliance should be possible to regulate by pharmaceutical agents. This may be useful to, for example, counteract or treat weight regain that sometimes occur also after RYGBP.

Complications and procedure dependent side effects of bariatric surgery

The perioperative mortality rate of bariatric surgery is very low and with an average value of 0.3% it is comparable to a routine cholecystectomy [44]. There is a spectrum of typical postoperative complications some of them being severe like anastomotic leakages and infections, as well as internal herniations [45]. The incidence of internal herniation has become dramatically lowered after mesenteric defects are routinely closed during the operation [46]. Greenstein and O'Rourke list a number of causes for abdominal pain in the gastric bypass operated patient spanning from more general disorders and cholelithiasis to the procedure-dependent internal herniations and gastro-gastric fistulas. These authors state that in the absence of a clear diagnosis, the threshold for surgical exploration should be low [47]. In addition to typical surgical complications there are also procedure-dependent side effects like excess skin with need for additional esthetic surgery [48], dumping symptoms and postprandial hypoglycaemias [49], as well as deficiency of micronutrients (vitamins and minerals) [50].

Chronic pain and nausea after gastric bypass

Also after excluding obvious surgical reasons, including procedure-dependent symptoms, there are still a substantial number of RYGBP-patients with chronic pain of unknown origin. In a cohort study from 2016 Gribsholt et al. reports that 54% of RYGBP operated patients had symptoms of abdominal pain and that 34%

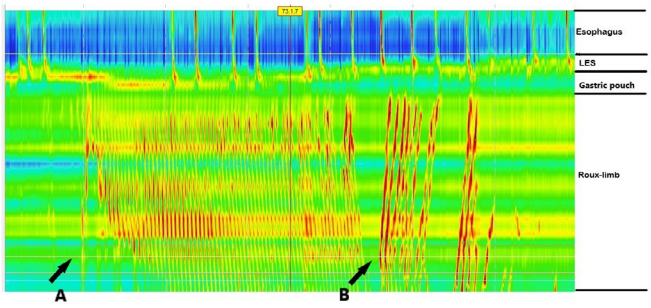

Fig. 4. High resolution manometry in a 43 yrs old woman with opioid demanding abdominal pain after Laparoscopic Gastric Bypass and two reoperations. Standing medication; fentanyl patch 50 mkg/h. Note the contractions in the distal Roux-limb at onset of phase–III–like high activity complex (A) and retrograde direction of the contractions at the end of the activity complex (B).

had been in contact with the healthcare system because of such symptoms [51]. In a 5-year follow up study by Høgestøl et al., chronic abdominal pain was reported in 34% of patients operated with RYGBP [52]. Underlying mechanisms of chronic abdominal pain after gastric bypass are still enigmatic and of paramount importance to elucidate. Furthermore, also the prevalence of functional bowel disorders in the patients before surgery needs investigation. Today it is not known of such conditions become aggravated by the procedure, or if surgery induces a novel clinical picture. The Roux-en-Y construction was originally developed to ameliorate the problem of bile-reflux after partial gastrostomies for gastric cancer or ulcer disease. A disadvantage of this method is that it sometimes results in a series of symptoms called the Roux stasis syndrome (RSS) which presents with pain, nausea and vomiting that is worsened by eating [53], and the motility of the Roux-limb has, this far, essentially been studied in this context. RSS carries much resemblance to symptoms that is encountered by patients with problems after gastric bypass surgery. There have been several suggestions on causative mechanisms behind the RSS with the current focus being on a delayed gastric emptying [54,55]. In an attempt to elucidate RSS as underlying cause to severe post-prandial abdominal pain in RYGBP-patients in our clinic, we used high resolution manometry of the upper gut. Generally we found no signs of congestion in the gastric pouch or Roux-limb after food intake (unpublished) confirming our previous data in uncomplicated RYGBP-patients [38], except in one case with a suspected narrowness in the gastro-entero anastomosis. Thus, these preliminary findings speak generally against a condition with a stasis in the Roux-limb. In the same cohort of RYGBP-patients with chronic pain/nausea we noted different kinds of disturbed fasting migrating motility complexes (MMC) in 12 out of the 17 examined patients. Several of the manometry recordings contained examples of retrograde propulsion and distal pacemaker activity (Fig. 4). A finding of particular interest was cases with distal contractions at the proximal onset of phase III high complexes (publication in preparation). Such dys-coordinated motor activity suggests increased risk for symptom generation.

The risk for opioid misuse

Interestingly, at the time of manometry a majority of the above mentioned patients were on prescribed opioid-type analgesics, and 8 of these patients had opioids in slow-release form on regular basis. Long-term intake of morphine-derivatives for analgesic purposes may lead to Opioid Induced Bowel Dysfunction with constipation, nausea and vomiting, as well as the Narcotic Bowel Syndrome (NBS). Grunkemeier et al. characterize NBS as chronic or intermittent colicky abdominal pain that worsens when the narcotic effect wears down and where tachyphylaxis leads to need for increasing doses [56]. A chronic need for opioid analgesics after surgical interventions has during recent years been highlighted as a growing problem [57,58]. This is true also for patients with post-operative abdominal pain after bariatric surgery. In a retrospective cohort study from 2014 Raebel et al. reports that 4% of patients that was not chronic opioid user became chronic opioid users after bariatric surgery [59]. These findings are supported by King et al. who reported that opioid analgesics are increasingly prescribed 7 years after surgery [60].

Postoperative prescription of pain-killing opioids can be dubious for susceptible individuals who may end up with the narcotic bowel syndrome (NBS), *i.e.* a vicious circle of chronic abdominal pain induced by and demanding opioid–based analgesics [61]. Opioids are well known for causing symptom-generating gastrointestinal dysmotility that, in turn, can cause a demand for continued prescription of pain killing opioids, but now with focus on the abdominal discomfort. The vicious circle is reinforced by development of opioid tolerance and need for higher doses to achieve analgesia [62]. Thus, great attention must be paid to the risk for iatrogenic drug dependency and NBS in these patients.

Summary

Gastric bypass is a very effective method for sustained weight loss and metabolic improvements in obese patients. Despite its therapeutic successfulness there are known side-effects that in some patients become intractable. The pathophysiology is complex and partly unexplored. The physician or surgeon handling a RYGBP patient with chronic postprandial nausea and pain must be aware of the risk for iatrogenic opioid-associated symptom aggravations.

Practice points

- The prevalence of obesity is increasing world-wide and bariatric surgery is the only effective treatment for achieving pronounced and sustained weight-loss.
- Chronic abdominal pain is common in patients that have undergone Gastric Bypass Surgery.
- Chronic need for opioid-based analgesics is a growing problem after surgical interventions.
- There is a risk of iatrogenic drug dependency with which also may bring aggravated abdominal symptoms from opioid induced dysmotility and Narcotic Bowel Syndrome.

Research agenda

- Abnormal gastrointestinal motor behaviour in patients after Gastric Bypass Surgery has to be further explored and correlated to symptomatology.
- There is a need for developing methods without catheter manometry to be able to study GI motor behaviour during realistic food-intake in a larger patient population.

Conflicts of interest

None.

Funding

Financial support was obtained from the Sahlgrenska University Hospital ALF grants and from the Gothenburg Medical Association,

Gothenburg, Sweden.

References

[1] Angrisani L, Santonicola A, Iovino P, et al. Bariatric surgery and endoluminal procedures: IFSO worldwide Survey 2014. Obes Surg 2017;13(10):017–2666.
[2] WHO. World Health Organisation. Obesity and overweight fact sheet [updated June 2016]; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/; 2016.
[3] Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: a systematic literature review. Int J Environ Res Public Health 2017;14(4).
[4] Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. Cochrane Database Syst Rev 2014;8:CD003641.
[5] Bray GA, Fruhbeck G, Ryan DH, Wilding JP. Management of obesity. Lancet 2016;387(10031):1947–56.
[6] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376(15):1492.
[7] Olbers T, Bjorkman S, Lindroos A, et al. Body composition, dietary intake, and energy expenditure after laparoscopic Roux-en-Y gastric bypass and laparoscopic vertical banded gastroplasty: a randomized clinical trial. Ann Surg 2006;244(5):715–22.
[8] Werling M, Fandriks L, Bjorklund P, et al. Long-term results of a randomized clinical trial comparing Roux-en-Y gastric bypass with vertical banded gastroplasty. Br J Surg 2013;100(2):222–30.
[9] Overs SE, Freeman RA, Zarshenas N, et al. Food tolerance and gastrointestinal quality of life following three bariatric procedures: adjustable gastric banding, Roux-en-Y gastric bypass, and sleeve gastrectomy. Obes Surg 2012;22(4):536–43.
[10] Mason EE, Ito C. Gastric bypass in obesity. Surg Clin N Am 1967;47(6):1345–51.
[11] Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273(3):219–34.
[12] Buchwald H. The evolution of metabolic/bariatric surgery. Obes Surg 2014;24(8):1126–35.
[13] Cavin JB, Couvelard A, Lebtahi R, et al. Differences in Alimentary Glucose Absorption and Intestinal Disposal of Blood Glucose After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy. Gastroenterology 2016;150(2):454–464 e9.
[14] Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376(7):641–51.
[15] Peterli R, Wolnerhanssen BK, Peters T, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: the SM-BOSS Randomized Clinical Trial. Jama 2018;319(3):255–65.
[16] Ikramuddin S, Korner J, Lee WJ, et al. Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A1c, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study. Jama 2018;319(3):266–78.
[17] Salminen P, Helmio M, Ovaska J, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss at 5 Years Among Patients With Morbid Obesity: the SLEEVEPASS Randomized Clinical Trial. Jama 2018;319(3):241–54.
[18] Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol 2017;14(3):160–9.
[19] Corcelles R, Daigle CR, Schauer PR. MANAGEMENT OF ENDOCRINE DISEASE: metabolic effects of bariatric surgery. Eur J Endocrinol 2016;174(1):R19–28.
[20] NIH conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. Ann Intern Med 1991;115(12):956–61.
[21] Rubino F, Nathan DM, Eckel RH, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39(6):861–77.
[22] Manning S, Pucci A, Batterham RL. Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms. J Clin Investig 2015;125(3):939–48.
[23] Makaronidis JM, Batterham RL. Potential Mechanisms Mediating Sustained Weight Loss Following Roux-en-Y Gastric Bypass and Sleeve Gastrectomy. Endocrinol Metab Clin N Am 2016;45(3):539–52.
[24] Fandriks L. Roles of the gut in the metabolic syndrome: an overview. J Intern Med 2017;281(4):319–36.
[25] le Roux CW, Bueter M. The physiology of altered eating behaviour after Roux-en-Y gastric bypass. Exp Physiol 2014;99(9):1128–32.
[26] Mulla CM, Middelbeek RJW, Patti ME. Mechanisms of weight loss and improved metabolism following bariatric surgery. Annals of the New York Academy of Sciences; 2017.
[27] le Roux CW, Welbourn R, Werling M, et al. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. Ann Surg 2007;246(5):780–5.
[28] Webb DL, Abrahamsson N, Sundbom M, Hellstrom PM. Bariatric surgery - time to replace with GLP-1? Scand J Gastroenterol 2017;52(6–7):635–40.
[29] Werling M, Olbers T, Fandriks L, et al. Increased postprandial energy expenditure may explain superior long term weight loss after Roux-en-Y gastric bypass compared to vertical banded gastroplasty. PLoS One 2013;8(4):e60280.
[30] Werling M, Fandriks L, Olbers T, et al. Roux-en-Y Gastric Bypass Surgery Increases Respiratory Quotient and Energy Expenditure during Food Intake. PLoS One 2015;10(6):e0129784.
[31] Saeidi N, Meoli L, Nestoridi E, et al. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. Science 2013;341(6144):406–10.
[32] Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol 2014;2(2):152–64.
[33] Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y Gastric Bypass and Vertical Banded Gastroplasty Induce Long-Term Changes on the Human Gut Microbiome Contributing to Fat Mass Regulation. Cell Metabol 2015;22(2):228–38.
[34] Bjorklund P, Laurenius A, Een E, et al. Is the Roux limb a determinant for meal size after gastric bypass surgery? Obes Surg 2010;20(10):1408–14.
[35] Laurenius A, Larsson I, Bueter M, et al. Changes in eating behaviour and meal pattern following Roux-en-Y gastric bypass. Int J Obes 2012;36(3):348–55.
[36] Lonroth H, Dalenback J, Haglind E, Lundell L. Laparoscopic gastric bypass. Another option in bariatric surgery. Surg Endosc 1996;10(6):636–8.
[37] Olbers T, Lonroth H, Fagevik-Olsen M, et al. Laparoscopic gastric bypass: development of technique, respiratory function, and long-term outcome. Obes Surg 2003;13(3):364–70.
[38] Bjorklund P, Lonroth H, Fandriks L. Manometry of the Upper Gut Following Roux-en-Y Gastric Bypass Indicates That the Gastric Pouch and Roux Limb Act as a Common Cavity. Obes Surg 2015;25(10):1833–41.
[39] Spak E, Bjorklund P, Helander HF, et al. Changes in the mucosa of the Roux-limb after gastric bypass surgery. Histopathology 2010;57(5):680–8.
[40] Csendes A, Smok G, Burgos AM. Endoscopic and histologic findings in the gastric pouch and the Roux limb after gastric bypass. Obes Surg 2006;16(3):279–83.
[41] Deloose E, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. Nat Rev Gastroenterol Hepatol 2012;9(5):271–85.
[42] Shin HS, Ingram JR, McGill AT, Poppitt SD. Lipids, CHOs, proteins: can all macronutrients put a 'brake' on eating? Physiol Behav 2013;120:114–23.
[43] Lichtenberger LM, Bhattarai D, Phan TM, et al. Suppression of contractile activity in the small intestine by indomethacin and omeprazole. Am J Physiol Gastrointest Liver Physiol 2015;308(9):G785–93.
[44] Flum DR, Belle SH, King WC, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 2009;361(5):445–54.
[45] Schulman AR, Thompson CC. Complications of bariatric surgery: what you can expect to see in your GI practice. Am J Gastroenterol 2017;112(11):1640–55.
[46] Stenberg E, Szabo E, Agren G, et al. Closure of mesenteric defects in laparoscopic gastric bypass: a multicentre, randomised, parallel, open-label trial. Lancet 2016;387(10026):1397–404.
[47] Greenstein AJ, O'Rourke RW. Abdominal pain after gastric bypass: suspects and solutions. Am J Surg 2011;201(6):819–27.
[48] Biorserud C, Olbers T, Staalesen T, et al. Understanding excess skin in post-bariatric patients: objective measurements and subjective experiences. Surg Obes Relat Dis : Ofc J Am Soc Bariatr Surg 2016;12(7):1410–7.
[49] van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. Obes Rev : Ofc J Int Assoc Study Obes 2017;18(1):68–85.
[50] Parrott J, Frank L, Rabena R, et al. American society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. Surg Obes Relat Dis : Ofc J Am Soc Bariatr Surg 2017;13(5):727–41.
[51] Gribsholt SB, Pedersen AM, Svensson E, et al. Prevalence of self-reported symptoms after gastric bypass surgery for obesity. JAMA Surg 2016;151(6):504–11.
[52] Hogestol IK, Chahal-Kummen M, Eribe I, et al. Chronic abdominal pain and symptoms 5 Years after gastric bypass for morbid obesity. Obes Surg 2017;27(6):1438–45.
[53] Mathias JR, Fernandez A, Sninsky CA, et al. Nausea, vomiting, and abdominal pain after Roux-en-Y anastomosis: motility of the jejunal limb. Gastroenterology 1985;88(1 Pt 1):101–7.
[54] Otsuka R, Natsume T, Maruyama T, et al. Antecolic reconstruction is a predictor of the occurrence of roux stasis syndrome after distal gastrectomy. J Gastrointest Surg : Ofc J Soc Surg Am Aliment Tract 2015;19(5):821–4.
[55] Herbella FA, Silva LC, Vicentine FP, Patti MG. Roux-en-Y limb motility after total gastrectomy. J Gastrointest Surg : Ofc J Soc Surg Am Aliment Tract 2014;18(5):906–10.
[56] Grunkemeier DM, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol : Ofc Clin Pract J Am Gastroenterol Assoc 2007;5(10):1126–39. quiz 1-2.
[57] Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med 2016;176(9):1286–93.
[58] Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg 2017;152(6).

e170504.
[59] Raebel MA, Newcomer SR, Bayliss EA, et al. Chronic opioid use emerging after bariatric surgery. Pharmacoepidemiol Drug Saf 2014;23(12):1247–57.
[60] King WC, Chen JY, Belle SH, et al. Use of prescribed opioids before and after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. Surg Obes Relat Dis : Ofc J Am Soc Bariatr Surg 2017;7(17):30172–7.
[61] Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology 2016;150(6):1408–19. https://doi.org/10.1053/j.gastro.2016.02.034. pii: S0016-5085(16)00225-0.
[62] Allouche S, Noble F, Marie N. Opioid receptor desensitization: mechanisms and its link to tolerance. Front Pharmacol 2014;5:280.