Gastrointestinal consequences of bariatric surgery
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CHAPTER 9

Summary & General Discussion
In this final chapter we will summarize the results of the studies we have performed, and discuss the consequences and our thoughts on future developments in bariatric surgery.

Bariatric surgery has been performed since the 1950’s. The very first bariatric operation was a jejunoileal bypass, a procedure that was later abandoned because of the high number of severe complications. (1) Roux-en-Y gastric bypass (RYGB) was first described in 1967, and first performed laparoscopically in 1994. (2, 3) The laparoscopic sleeve gastrectomy (LSG) was not performed as a stand-alone procedure until this century. Earlier it was only performed as a first-stage procedure for superobese patients before a RYGB or duodenal switch could be done. (4)

By now, the health effects and short-term surgical complications of the RYGB have been thoroughly studied. However, there are still large gaps in our knowledge when it comes to the physiological mechanisms behind the changes that occur after RYGB, as well as the long-term effects of these alterations. We are only starting to comprehend the influence the RYGB has on all the known and unknown intestinal and metabolic processes.

A closer look on gastrointestinal symptoms

In Chapter 2, we studied the gastrointestinal complaints that patients experience two years after RYGB. It was already known that RYGB might aggravate certain gastrointestinal symptoms, and that it may cause intolerance for specific foods in many patients. (5-12) However, the long-term prevalence of these symptoms had never been well studied. We asked 313 patients who underwent RYGB two years before, to complete questionnaires on general health, gastrointestinal symptoms (GSRS) and food intolerance. The response rate was very high with 94%. The results were compared to a control group of 335 morbidly obese patients who completed the same questionnaires when they came for preoperative screening. We found that the patients two years after RYGB experienced more gastrointestinal symptoms than the obese controls (median score on the GSRS 2.19 vs. 1.75, p<0.001). The scores were highest on the symptoms flatulence and borborygmus. Furthermore, food intolerance was very common, as 71% of RYGB patients noted intolerance for one or more foods compared to 17% of obese controls. The foods reported most often were all non-essential types of food, such as fried products, soda and pastries. Food intolerance and gastrointestinal complaints were positively correlated, but neither was related to weight loss. There was only a mild correlation between abdominal pain and weight...
loss (rho = 0.156, p = 0.014). It is often assumed that the weight loss after RYGB is a result of the abdominal complaints patients experience when they eat. However, the limited correlation between gastrointestinal symptoms and weight loss indicates that the presence of these symptoms is not the main causative factor in weight loss in our cohort of patients. Possibly, the feeling of satiety patients experience is something different than the fact that in case of overeating, they might experience abdominal pain or symptoms of dumping. These findings suggest that other factors, such as increased satiety and metabolic changes, are more important contributors to the weight loss after RYGB than the gastrointestinal symptoms. Furthermore, the results of this study contribute to a better context in which to view the gastrointestinal symptoms patients present with after surgery. This is important in postoperative care, but also facilitates preoperative counselling.

The findings of the previous study were confirmed in Chapter 3, where we studied the course of gastrointestinal symptoms of 168 patients from the previous control group, who eventually underwent RYGB. Patients were found to suffer from more gastrointestinal complaints after RYGB than before (total mean GSRS score 2.31 versus 1.69). The only baseline characteristic associated with the intensity of symptoms after surgery was the intensity of gastrointestinal symptoms prior to surgery. No correlation was found for other baseline characteristics. The subgroup of patients who had already undergone a different type of bariatric surgery prior to RYGB, mostly gastric banding, was studied separately. It was found that these patients had more complaints prior to revisional RYGB than the patients coming for primary RYGB. However, after two years the revisional RYGB patients were indistinguishable from the primary RYGB patients when it comes to gastrointestinal symptoms (total mean GSRS score 2.38 versus 2.31). Furthermore, we evaluated the use of a proton pump inhibitor (PPI) in this chapter. In the absence of a specific indication such as a marginal ulcer, patients are advised to discontinue the use of a PPI after the first year. However, many patients were found to continue the use of a PPI, possibly because of poorly understood abdominal complaints. The use of a PPI was indeed related to the severity of gastrointestinal symptoms patients experienced. The fact that these patients experienced more complaints despite continued PPI use can mean that these patients would have experienced even more complaints without a PPI, or more likely that the use of the PPI has little effect on the complaints and the cause and solution should be found elsewhere.

In light of the high number of patients using a PPI, we decided to evaluate the prevalence of PPI-induced hypomagnesaemia in Chapter 4. The files of 931 patients
were studied, in whom the serum magnesium level was measured before and after surgery. None of these patients was found to have developed hypomagnesaemia likely related to PPI use. Therefore, we concluded that the risk is very low or even absent and standardized screening is not necessary in this population. It is likely that the absence of PPI-induced hypomagnesaemia in our study is due to the low prevalence of additional risk factors. Hypomagnesaemia is more prevalent in older patients, with insulin resistance, and using thiazide diuretics. (13, 14) Despite the absence of PPI-induced hypomagnesaemia in this cohort, the high number of patients using a PPI two years after RYGB might still be problematic. There is emerging evidence regarding the negative effects of long-term PPI use, such as a higher prevalence of chronic kidney disease and increased chance of fractures and osteoporosis. (15, 16) Furthermore, PPIs alter the intestinal microbiome, which is in turn implicated to have a role in weight loss after RYGB. (17, 18)

Looking back at the results in Chapter 2 and 3, an important question arising from these results is what the origin of the postoperative increase in abdominal complaints is. Borborygmus and flatulence were the most prevalent symptoms, but almost no studies have been performed regarding these symptoms. Diet, especially fibre intake, has a significant influence on intestinal gas production and thereby on flatulence. (19, 20) It is therefore likely that the altered diet after RYGB explains part of the increase in borborygmus and flatulence. Furthermore, it is well known that most of the air ingested with the meal is stored in the stomach and removed via belching. (21)

However, since the meal no longer reaches the remnant stomach after RYGB, but passes quickly from the gastric pouch into the jejunum, one might hypothesize that the ingested air also ends up in the jejunum, causing bloating and borborygmus. (22) Bloating might in turn cause abdominal pain, which was also among the symptoms that are scored higher after RYGB than before surgery. (23) The high prevalence of abdominal pain was also found in other studies, with one longitudinal study specifically reporting on the increase after RYGB. (24) Another study found that five years after RYGB, 33.8% of patients report abdominal pain. (25) In approximately one-third of cases, the cause of the abdominal pain remains unclear. (26)

The correlation between pre- and postoperative symptoms indicates that other factors than purely the surgery performed in RYGB, are also involved in abdominal pain. Especially psychological factors have been thoroughly studied to explain part of the perceived symptoms, as well as the amount of weight loss, after RYGB. (27) Eating behaviour also plays an important role in the presence of abdominal symptoms, especially in the case of dumping syndrome. (28) We hypothesize that other factors,
for example, changes in intestinal microbiome, small intestinal bacterial overgrowth, gastritis of the stomach remnant, or intestinal inflammation due to other causes, contribute to the abdominal pain patients experience after RYGB. This is discussed in the next chapter.

**Faecal tests and intestinal inflammation**

In Chapter 5, we studied the levels of faecal calprotectin, elastase-1 and alpha-1-antitrypsin in patients who had undergone RYGB at least one year before. Faecal calprotectin is a protein present in many cell types, but mainly in the neutrophil granulocyte, where it makes up 60% of the proteins in the cytoplasm. It is secreted in the intestinal lumen in case of inflammation and the faecal calprotectin level is therefore a marker of intestinal inflammation.(29) It is used in clinical practice as a diagnostic test for inflammatory bowel disease.(30) We hypothesized that due to the altered anatomy, the secretion and intestinal metabolism of these proteins might change after RYGB, possibly impairing the usefulness of these tests. We found in the study that the majority of patients (104 out of 122; 87%) had a faecal calprotectin level above the reference value of <50 μg/g, with a median level in this cohort of 163.5 μg/g. It seems highly unlikely that all 104 patients will develop inflammatory bowel disease in the nearby future, although a recent case series suggested an increased prevalence of inflammatory bowel disease after RYGB.(31) It is theoretically possible that most of these patients already had an increased faecal calprotectin prior to surgery. Previous studies did find a slight increase in faecal calprotectin in patients with morbid obesity, little physical activity, higher age, high fibre intake, or use of certain medication such as an NSAID or proton pump inhibitor.(32-35) Yet, the faecal calprotectin was never higher than the internationally maintained reference value of 50 μg/g in these patients. Only a longitudinal study, starting preoperatively and continuing for several years postoperatively, can give a definitive answer to most questions. With the current results, we deem it very likely that faecal calprotectin is not an appropriate test to rule out inflammatory bowel disease in the RYGB population. It is likely that use of this test with the current cut-off value will lead to a high number of unnecessary endoscopies performed.

A question that remains after reading chapter 5 is: what is the origin of the elevated level of calprotectin we found in the faeces? The collection and testing of the samples were done according to current standards, as is described in detail in the discussion of the chapter, so a sampling error seems unlikely. A previous study also found elevated faecal calprotectin levels in RYGB patients, although only seven patients
were included.(36)

Our hypothesis is that the elevated faecal calprotectin is a consequence of persistent low-grade intestinal inflammation after RYGB. The correlation with faecal alpha-1-antitrypsin we found, supports this hypothesis as the faecal level of alpha-1-antitrypsin is also known to increase with intestinal inflammation.(29, 37) Where exactly in the gastrointestinal tract this inflammation is located remains unclear. One study found persistent pro-inflammatory changes in the rectum after RYGB. (38) However, a recent study could not confirm these findings.(39) Unfortunately, it is unknown whether surgical alterations of the gastrointestinal anatomy other than RYGB also influence the faecal calprotectin level.(40) It is hypothesised that faecal calprotectin levels are more likely to be elevated when there is inflammation of the colon than in small bowel inflammation. However, the evidence is conflicting.(41) Furthermore, the colon’s anatomy is not altered in RYGB and it does therefore not seem the most likely source of increased calprotectin excretion.

It is more likely that the cause of the increase in faecal calprotectin originates in the parts of the intestinal tract that are altered by RYGB. Endoscopy of the gastric pouch and proximal intestine is easy and frequently performed after RYGB. Although the jejunal mucosa of the Roux-limb adapts to the increased bacterial load, this was not found to induce macroscopic or histologic evidence of inflammation in the majority of patients.(42, 43) The parts of the intestine that are excluded from the alimentary tract, i.e. the stomach remnant and the biliopancreatic limb, are more difficult to investigate. A majority of patients has evidence of chronic gastritis in the stomach remnant.(44-47) However, in non-RYGB patients gastritis was not found to increase the faecal calprotectin.(48, 49) No studies have been performed that investigate inflammation in the blind loop. Inflammation in this part of the intestine could be due to the toxic effect of gastric acid, bile acids and pancreatic enzymes on the intestinal epithelium. These are not buffered by ingested food, as would happen in the normal anatomy, and are known to cause damage to the enterocytes.(50)

The bacterial flora of the intestinal tract might also lead to inflammation and thereby influence markers of intestinal inflammation. After RYGB, there is a rapid and significant change in gut microbiota.(18) Bacterial overgrowth in the stomach remnant or the biliopancreatic limb has been described.(51-53) In non-RYGB patients with small intestinal bacterial overgrowth the faecal calprotectin did not increase, but other studies showed that the faecal calprotectin level can respond to changes in gut microbiota.(54, 55) It is problematic that the standard test for small intestinal bacterial
overgrowth, the hydrogen breath test, has not been validated in RYGB patients. This complicates future studies and should be taken into account when interpreting the results of this test.\(^{(56)}\)

**Future perspectives from Chapter 2 - 5**

One could say that the studies described in chapter 2 to 5 have raised as many questions as they have tried to answer, especially concerning the cause of and the connection between the increase in abdominal symptoms and the increased faecal calprotectin. The correlation between these two matters, symptoms and faecal calprotectin, was not investigated in chapter 5. Future longitudinal studies should assess this correlation, using validated questionnaires for abdominal pain. It should also determine the course of the faecal calprotectin level over time, starting prior to bariatric surgery and continuing up to several years postoperatively. In such a study, patients undergoing LSG should also be included. This will not only provide insight in the effects of the LSG, but might also elucidate the role of the biliopancreatic limb in both abdominal pain and the increase in faecal calprotectin. Recent studies suggested that bile reflux into the stomach remnant might be a cause of unexplained chronic abdominal pain after RYGB.\(^{(57, 58)}\) Evidence of bile reflux gastropathy in the stomach remnant was found in many of these patients.\(^{(58, 59)}\) Treatment with ursodeoxycholic acid decreased symptoms in most patients, but this was only studied in an uncontrolled way in a small number of patients.\(^{(59)}\) Some insight into the role of bile acid reflux in the stomach remnant could also be provided by the UPGRADE trial, which will be discussed later, by comparing the prevalence of unexplained abdominal pain in the ursodeoxycholic acid group and the placebo group.

Bacterial overgrowth, alterations in the composition of the intestinal microbiome, or chronic bowel ischemia, have never been studied in bariatric patients and may also attribute to abdominal pain and intestinal inflammation after RYGB. Future studies into these topics might unveil some more effects of the RYGB that we are not yet aware of.

**Diagnostic and therapeutic endoscopy**

The following chapters continue on the diagnostic evaluation of gastrointestinal complaints and the treatment of specific abdominal complications. In Chapter 6 we studied the diagnostic yield of upper endoscopy after RYGB. In the first two years after RYGB, around 13% of all patients undergo an upper endoscopy.\(^{(60)}\) It was previously described that in the majority of these upper endoscopies no abnormalities
are found.\textsuperscript{(61)} We studied all patients who underwent a diagnostic upper endoscopy after RYGB, and examined the results of these upper endoscopies and the predictive value of patient characteristics for the outcome of upper endoscopy. The study population consisted of 250 patients, of which 98 (39\%) had a relevant finding at upper endoscopy. Marginal ulcer (\(N = 46\), 18\% of all upper endoscopies) and stomal stenosis (\(N = 26\), 10\%) were the most prevalent relevant findings. Several factors were associated with a relevant finding at upper endoscopy: sex (OR for female 0.29 (0.09-0.90)), alcohol consumption (OR 7.27 (1.58-33.36)), dysphagia or suspicion of bleeding as reason for upper endoscopy (OR 3.62 (1.54-8.52) and 39.93 (4.96-321.47) respectively, when compared to abdominal pain as referral reason), an abnormal upper gastrointestinal series (OR 6.81 (2.06-22.48)), and not performing an abdominal ultrasound prior to endoscopy (OR 7.41 (1.48-37.08) compared to a normal ultrasound). This last finding was surprising. Possibly, patients who underwent an ultrasound prior to upper endoscopy presented with complaints that were less specific and therefore more difficult to interpret for the physician. The predictive value of the symptoms patients present with was already suggested in previous studies.\textsuperscript{(61-63)} It was confirmed in our study that the chance of a relevant finding at upper endoscopy is lower in patients who present with abdominal pain or nausea when compared to patients presenting with dysphagia or suspected bleeding. With these results, we created a final model with which the chance of a relevant finding at upper endoscopy can be calculated. When the findings from our study and the resulting prediction model are validated in an external cohort, this can be used to significantly reduce the number of upper endoscopies that are performed after RYGB.

In Chapter 7 we investigated the use of endoscopic stent placement in postoperative leakage after bariatric surgery. We studied a new type of stent, the Niti-S Beta stent, and demonstrated that it was effective as a treatment for anastomotic leaks in 25 out of 38 patients (66\%). This stent was specifically designed for staple line leaks after bariatric surgery. It was hypothesized that because of the double-bump structure, migration would be less prevalent than with other types of stents. Although comparison with other studies is hampered by the retrospective nature of all studies, our results did not support this hypothesis. Migration occurred in 12 patients (32\%), a prevalence comparable to other stents.\textsuperscript{(64-70)} The success rate was also similar to other studies.\textsuperscript{(64-66, 68-77)}

\textbf{Future perspectives from Chapter 6 & 7}
It is important to realize that the study in chapter 6 was not designed to assess the total prevalence of gastrojejunal complications in our bariatric population, nor to find risk factors for the development of a complication. Rather, we determined the chance of finding an abnormality at upper endoscopy in a patient presenting with gastrointestinal complaints postoperatively. However, it is noticeable that the number of marginal ulcers (n= 46) and stomal stenoses (n = 26) we diagnosed was low, given that 3533 bariatric operations were performed in the study period, of which 3400 RYGB. This can be partially explained by the fact that in approximately one-quarter of the patients who underwent an upper endoscopy in the first two years after RYGB, this was performed in another hospital. Furthermore, in a meta-analysis on the prevalence of marginal ulcers the mean prevalence in the included studies was 4.6%, but varied from 0.6% to 25%.(78) It is likely that the prevalence found in older studies is not representative of the present-day results in most bariatric centres. Over the years, the prevalence of marginal ulcer and stomal stenosis has likely decreased due to improvements in surgical technique and perioperative care. In many older series patients underwent open RYGB, which has a significant difference in postoperative complications.(63, 79, 80) Furthermore, in some series all patients were subjected to upper endoscopy regardless of the presence of symptoms. This increases the number of marginal ulcers found since smaller asymptomatic ulcers are counted.(81) The last important factor influencing the development of marginal ulcer or stomal stenosis is postoperative PPI prophylaxis. Most centres nowadays prescribe patients standard PPI prophylaxis. This is often met with scepticism when it is assumed that, as the gastric pouch is created from the proximal part of the stomach, there will be hardly any parietal cells present in the pouch to produce acid. However, this assumption was proven to be incorrect when studies found that there is still significant production of acid in the gastric pouch.(82, 83) A further indication of the importance of acid in the development of marginal ulcer was the finding that a longer pouch leads to more marginal ulcers.(84) PPI prophylaxis was proven to decrease the prevalence of marginal ulcer in a cohort study with historical comparison.(85) In this study, PPI prophylaxis was prescribed during the first 6 months after surgery. In 2015, the duration of PPI prophylaxis was shortened from one year to 3 months in our centre. A future comparison of the prevalence of marginal ulcer in these two time periods will give a further indication of the optimal duration of therapy. Naturally, a randomized controlled trial would be superior. However, given the low prevalence of marginal ulcer, several thousands of patients would have to be included to have sufficient power, which is hardly feasible.

In chapter 7, patients who underwent stent placement as initial treatment had a much
higher chance of leak remission than those undergoing stent placement after other treatments had failed. Of course, it seems logical that patients with larger or persistent leaks have less chance of successful treatment than those with minor leaks that are initially treated with stent placement. Nevertheless, it is remarkable that almost no studies have investigated early versus delayed treatment of anastomotic leakage.(73) As with all questions regarding stents, including the comparison of different types of stents, uncertainty remains because almost all studies are retrospective. Although probably hampered by the heterogeneity of patients presenting with anastomotic leakage, we suggest a prospective trial. In this trial, patients who are not in need of emergent revisional surgery should be included. Routine stent placement directly after leakage is diagnosed can then be compared to conservative treatment with salvage stent placement only when the leak persists.

Recently, alternative therapies have been proposed for the treatment of anastomotic leakage, such as over-the-scope clipping and endoluminal vacuum therapy. Over-the-scope clips are sometimes used to fixate the stent to the intestinal wall to prevent migration.(86, 87) Other studies have investigated the success of the over-the-scope clip as stand-alone treatment for anastomotic leaks, with varying success.(88-90) Endoluminal vacuum therapy was introduced as treatment of anastomotic leak after rectal surgery but has recently been studied in upper gastrointestinal leaks as well.(91, 92) It appears to be very effective even when stent placement or revisional surgery has failed, but it requires frequent procedures over a longer time period, which for the moment impedes introduction as first-line treatment.

**Gallstone disease: Chapter 8**

Finally, in Chapter 8 we present the protocol for a randomized controlled trial that is currently being performed, addressing one of the most frequent complications of bariatric surgery: symptomatic gallstone disease. Approximately 11% of patients undergoing bariatric surgery who still have a gallbladder develop symptomatic gallstone disease in the first two years after surgery.(60) The UPGRADE trial (ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery) will answer the long-standing question whether ursodeoxycholic acid (UDCA) is effective in the prevention of symptomatic gallstone disease after bariatric surgery. Several studies have concluded that UDCA prevents gallstone formation after bariatric surgery.(93-98) However, none of these studies had symptomatic gallstone disease as an endpoint. This is essential, because the majority (60-80%) of patients with gallstones will never develop symptoms.(99, 100)
The most frequently posed question when it comes to gallstone disease after bariatric surgery, is why the gallbladder is not removed concurrently with the initial bariatric operation. However, concomitant cholecystectomy has been thoroughly studied and the benefits - prevention of postoperative gallstone disease - do not outweigh the risks of the cholecystectomy.(101, 102) The only exception is when patients already suffer from symptomatic gallstone disease before they undergo bariatric surgery, in which case a cholecystectomy should be performed first.(103) Other studies have tried to identify patients with an increased risk of symptomatic gallstone disease after bariatric surgery. It was found that by far the strongest predictor for the development of symptomatic gallstone disease was the amount of weight lost.(104-106) However, predicting the weight loss beforehand is what can be called the 'holy grail' in bariatric surgery, and many studies have failed in trying to develop a prediction model with enough precision. The weight loss after bariatric surgery is multifactorial and is influenced by psychological characteristics, socio-economic status, lifestyle, age, and medical comorbidities. Therefore, predicting the risk of gallstone disease prior to bariatric surgery with sufficient certainty is at this time not possible.

The fact that weight loss is such a strong promoter for gallstone development after bariatric surgery has several determinants. Two important variables are involved in gallstone development: the composition of bile and the emptying of the gallbladder. (107) The composition of the bile changes after RYGB, especially in patients developing gallstones. The cholesterol concentration rises and so does the cholesterol / bile acid ratio, which in turn increases the lithogenicity of the bile.(100) The increased concentration of mucin and calcium in the bile is also thought to play an important role in gallstone formation.(108) The second determinant, gallbladder emptying, is also strongly impaired after RYGB. At first it was thought that this is due to less secretion of hormones that stimulate gallbladder motility from the duodenum, caused by the exclusion of the duodenum after RYGB. However, recent findings suggest that gallbladder emptying is far more complex than previously thought. One study showed that gallbladder emptying is independent of the duodenal exclusion, by infusing a meal through a tube in the stomach remnant.(109) Furthermore, the level of hormones promoting gallbladder emptying, such as cholecystokinin, are increased instead of decreased after RYGB.(110-112) The levels of cholecystokinin are even higher after sleeve gastrectomy then after RYGB, but nevertheless the risk of gallstone formation is similarly high after these two surgeries.(98, 113) It is unclear whatever factors do influence the impaired gallbladder emptying after RYGB, as most studies investigating the cholecystokinin level after RYGB emphasized on the
metabolic effects of this hormone and did not link this to gallbladder emptying. Possibly, impaired or delayed secretion of pancreatic enzymes also influences the rate of gallbladder emptying. (109, 114) Another explanation can be that other gastrointestinal hormones, such as gastrin or secretin, play a more important role in gallbladder emptying than we think. (115) It was shown that gastrin levels decrease after RYGB. (116) No studies have determined the relation between these hormones and gallbladder emptying after RYGB though.

**Future perspectives from Chapter 8**

Whether UDCA prevents symptomatic gallstone disease after bariatric surgery will become clear when the UPGRADE trial has finished. Possibly, the data coming from this study can also shed light on other beneficial effects of UDCA. Previously we mentioned the effect UDCA had on abdominal pain in a small number of RYGB patients with gastritis of the stomach remnant due to bile reflux. It will be very interesting to see whether there is a difference in abdominal complaints and the number of diagnostic studies performed between the patients in the intervention group and those in the control group, extending beyond symptoms and diagnostics related to gallstone disease. Furthermore, it has long been hypothesized that bile acids have positive effects on the metabolism of obese patients, influencing amongst others fatty liver disease and insulin resistance. (117) After bariatric surgery, there is an increase in circulating plasma bile acids. (118) Maybe the UPGRADE will have an unexpected result, and we will find that patients taking UDCA experience additional metabolic improvement, or weight loss, on top of the effects of the bariatric surgery itself.

**Conclusion**

In conclusion, many of the effects of bariatric surgery in general and RYGB in particular are yet incompletely understood. This thesis aims to provide more insight especially in the prevalence, pathophysiology and treatment of the long-term gastrointestinal complications of RYGB. At the end of this chapter, we would like to make a case for more high-quality research in the field of bariatric surgery, with emphasis on longer duration of follow-up and minimization of loss to follow-up. There are still many questions that need to be answered, for example about the effects of the RYGB on pharmacokinetics. New types of surgery such as the sleeve gastrectomy and the mini gastric bypass are rapidly implemented in clinical practice without a good understanding of the long-term effects. The number of bariatric interventions
performed, the centralization in high-volume centres, and the important questions still unanswered, are fertile ground for multicentre studies with long-term follow-up.
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