

# Implications of surgical and endoscopic interventions in the upper GI tract (with focus on management of GERD and Weight Control)

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## Summary, discussion and future perspectives

### Part 1: Surgical treatment of gastroesophageal reflux disease

#### Complications of antireflux surgery (ARS)

ARS has proven to be a good treatment modality for GERD, both on the short and long term.<sup>1-9</sup> It should be taken into account that symptoms of the majority of GERD patients are well controlled by medical therapy.<sup>10</sup> Therefore, only a strictly selected group of GERD patients should be referred for ARS. Indications for referral include: patients with persisting symptoms not sufficiently responding to medical therapy and unwillingness for maintenance medical therapy. One should realize that ARS, as other surgical procedures, may be associated with or followed by complications.<sup>11</sup>

Vagus nerve injury (VNI) is one of the most feared complications. In **Chapter 2** an overview of the current literature has been presented with respect to the effect of intended and accidental VNI on the outcome of antireflux surgery. Intended VNI added to an antireflux procedure showed a higher prevalence of diarrhea, dumping syndrome and nausea after ARS. It is not known whether vagus nerve injury always leads to symptoms or whether vagus nerve injury may go clinically unnoticed in the majority of cases. Therefore we need an objective measurement or method to quantify vagus nerve injury.

In **Chapter 2** we reported that up to now only two prospective studies have objectively investigated the effect of accidental VNI on the outcome of antireflux surgery. The prevalence of VNI seen after ARS was more than 10%. On short term no effect of VNI on control of reflux symptoms, gastric emptying and 24-hour pH monitoring were seen after ARS. It should be taken into account that follow-up in these two studies was short and the patient cohorts were small with respect to number of patients that were studied.<sup>12,13</sup> Therefore in **Chapter 3**, we investigated the short and long term effects of VNI, objectively measured by the response of plasma pancreatic polypeptide to insulin-induced hypoglycemia (PP-test), on the outcome of antireflux surgery in a large cohort of GERD patients both before and after ARS. VNI was present in up to 20% of patients and was associated with more dissatisfaction, worse symptomatic outcome and a higher re-operation rate during long term follow up. Furthermore, gastric emptying measured by scintigraphy was significantly impaired after VNI compared to the group without vagus nerve injury. This was observed for both the rate of gastric emptying and for emptying half time. Failure of antireflux surgery is scored by persistence of reflux symptoms and by recurrence or new onset of reflux symptoms. Standard follow-up of patients undergoing ARS consist of outpatient clinic visits where evaluation of symptoms is the first step in assessing the success of the ARS procedure. In patients with recurrent

symptoms, the subsequent diagnostic evaluation consists of manometry, pH-monitoring and gastric scintigraphy for emptying. As shown in **Chapter 2 and 3**, vagus nerve injury may present itself with recurrent reflux symptoms, nausea, vomiting, gastric stasis or dumping syndrome and diarrhea. As mentioned earlier, we were able to demonstrate that gastric emptying was more delayed in postoperative patients with VNI compared to the vagus nerve intact group. One should take into account that in patients that have undergone ARS, usually gastric emptying is more rapid or even accelerated postoperatively when compared to preoperatively.<sup>12,14</sup>

During ARS the fundus of the stomach is mobilized and wrapped around the gastro esophageal junction thereby reducing the gastric storage capacity of the fundus. This reduces the proximal gastric accommodation response and thereby enhances the propulsion of food from the proximal stomach to the antrum. This may be one of the more prominent factors leading to an accelerated gastric emptying.<sup>14-16</sup>

Postoperative recurrence of reflux symptoms combined with impaired gastric emptying may be one of the first signs indicative for the presence of VNI. As shown in **Chapter 3**, patients with VNI are re-operated more often. In patients with VNI who present with recurrent or new onset of reflux symptoms treatment should *not* consist of re-operation since this does not treat the underlying pathophysiological mechanism. Instead, treatment should consist of symptom control using a step up approach in which dietary measurements, motility reducing (for diarrhea, dumping syndrome) or motility enhancing (nausea, vomiting, stasis) drugs, gastric rest with enteral feeding, pyloric botulin toxin injections or surgical or endoscopic pyloromyotomy should be considered as treatment options depending on symptom presentation and persistence.

### Conclusion and future perspectives

We have clearly shown that the prevalence of VNI is much higher than previously assumed and is associated with a worse outcome of ARS on the longer term. We emphasize that careful evaluation of patients who present with recurrent or new symptoms after ARS is of utmost importance. Here, evaluation of vagus nerve function is indicated. However, the vagus nerve integrity test is time consuming and demanding for patients. Therefore vagus nerve testing by PP response to insulin-induced hypoglycemia will not become a standard procedure in routine evaluation of patients for (redo) ARS. However in patients with unsuccessful primary ARS the presence or absence of vagus nerve injury helps to determine which steps should be taken.

## Part 2: Safety and efficacy of new minimal invasive endoscopic and surgical techniques in the treatment of obesity

The Roux-and-Y Gastric Bypass and Sleeve Gastrectomy are the most commonly used techniques in the surgical management of morbid obesity. These techniques have shown to be very effective in reducing weight and to prevent or minimize comorbidities associated with obesity on short and long term.<sup>17-19</sup> However, these procedures remain associated with morbidity and mortality and are only available for a selected group of patients.<sup>20-24</sup>

During the last decade several new techniques to treat obesity have emerged trying to provide a less invasive and safer solution for the overweight and (morbidly) obese populations.

### Innovative structural surgical and endoscopic techniques

In **Chapter 4** we reviewed the efficacy and safety of endoluminal techniques that structurally change the upper gastrointestinal anatomy in the treatment of obesity. In this review we divide the different types of restrictive endoluminal procedures into two groups. One group consists of procedures that exclude the greater curvature of the stomach by using a suturing or stapling system. The second group consists of endoluminal procedures that base their restrictive effect on volume reduction by applying sutured or stapled plications. After short-to medium term follow-up we found an overall EWL ranging from 24% to 58%. In addition, of the 277 patients included in this review only 7 patients had post procedure complications for which only one patient required additional surgical intervention. However, only half of the studies reported on the effects of the procedures on comorbidities accompanied with obesity. Most prominent was a regression in type 2 diabetes mellitus associated factors. Although these interventions show promising results with regards to efficacy in weight loss and safety, it must be mentioned that some of these techniques suffer from procedure-related failure. In three of these techniques (TGVR, EVG and TOGA) over 50% of patients had disruptions of the applied sutures or staple lines.<sup>25-31</sup> These disruptions might be explained by the placement of superficial sutures during these techniques thereby not reaching a full thickness bite and thus mainly approximating the mucosal lining of the stomach. The relatively rapid turnover of the mucosal lining of the stomach might cause early disruption seen after these techniques. Furthermore, these procedures owe their restrictive component to their endoscopically created gastric sleeve. High intragastric pressure build up during food ingestion with low compliance of the gastric sleeve combined with superficial staple/suture placement might also explain the reduced durability of these techniques. Further technical improvement of these techniques is warranted before they can be implemented as standard care in the treatment of morbid obesity.

Another potentially promising laparoscopic surgical treatment preserving the anatomy and trying to treat obesity by influencing gastric function is Gastric Electrical Stimulation. The proposed mechanism of action of this new technique is to impair gastric motor function thereby inducing a delay in gastric emptying leading to an increase in satiety followed by a reduction in food intake thus resulting in weight loss. Over the past decade several GES systems have been developed. Early studies conducted on GES showed significant weight loss at 12 months follow-up.<sup>32,33</sup> However, a double-blinded randomized trial failed to show a clear effect of GES on body weight.<sup>34</sup> In **Chapter 5**, we investigated the first human experience with a new GES system. We evaluated its effect on gastric emptying rate, food intake, glucose metabolism and weight loss. Optimal pacing settings for this new GES system were extensively investigated with promising results in animal studies.<sup>35</sup> We have shown in this first in human study that this new GES system is safe. However, we were unable to demonstrate any beneficial effect of GES on the forementioned parameters such as gastric emptying, intake, satiety or weight loss. Our data do not completely exclude a role for gastric stimulation in weight management. We strongly recommend to start more basic research with focus on electrophysiology of the stomach, an area that is practically unexplored. Future studies should focus on unraveling the pathophysiological mechanisms by which GES might affect the gastric motor and/or sensory function of the stomach and on finding optimal pacing protocols/algorithms.

### A temporary endoluminal device (the duodenal bypass liner) to treat obesity

In **Chapter 6** we investigated the safety and efficacy of 6 and 12 months DJBL treatment for obesity and its related comorbidities after a controlled 6 month diet period. We found that an additional DJBL treatment resulted in a further decrease in weight, and an improvement of cardiovascular and type 2 diabetes mellitus parameters. During the first 6 months of treatment the most pronounced changes were observed. These data are in line with extensive research over the past decade on 6 and 12 months of DJBL treatment.<sup>36-38</sup>

Not only the effect of this temporary in situ endoluminal technique on obesity and on its associated comorbidities is important, also safety is a relevant issue. In this thesis a low complication rate was seen after placement of the DJBL device. However a recent large study by Betzel et al., on safety of the DJBL showed a complication rate of 10%. Serious adverse events consisted of GI bleeding, hepatic abscess, pancreatitis and anchor perforation.<sup>39</sup> In case these adverse events occur, the DJBL can easily be removed. Thereafter most complaints and complications usually resolve. Patients undergoing this procedure should be under tight surveillance in centers specialized in and experienced with these type of endoluminal procedures.

Up till now no studies assessing the long term outcome of DJBL treatment on obesity are available. Therefore in **Chapter 7** we evaluated and described the effect of DJBL

treatment on obesity 4 years after explantation of the device. Four years after explantation one-third of the patients had been re-operated. In the patient group that was not re-operated no significant difference in weight, type 2 diabetes mellitus or cardiovascular parameters was seen.

When overlooking the current available data we can conclude that DJBL treatment seems to be effective in the treatment of obesity and type 2 diabetes mellitus on the short term. However, after removal of the liner its effect appears to diminish over time. Therefore its role in the treatment of obesity is under debate. This raises the question whether a place should be reserved for the DJBL in the treatment of obesity in the near future.

### Conclusion and future perspectives

Innovative bariatric techniques have shown beneficial effects on obesity and its comorbidities on the short term. Techniques that structurally alter gastro-intestinal anatomy and function show the most promising results. Conventional bariatric surgery still is superior compared with novel and innovative techniques both for short and long-term treatment of obesity. However one should take into account that most of these innovative procedures are less invasive than conventional bariatric surgery. The innovative procedures mostly have lower complication rates and mortality has not been reported so far. Therefore in the future, these novel techniques may come to play a more prominent role in the treatment of the overweight and mild obese population ( $BMI \leq 35 \text{ kg/m}^2$  without comorbidities) that does not directly qualify for bariatric surgical treatment. Finally, future research is warranted assessing the effect of these techniques on obesity and their comorbidities in randomized clinical trials on the short term and especially on the longer term. Such studies will provide more detailed insight which role these techniques could play in the treatment of obesity.

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