Obesity: Barrett's Esophagus and Esophageal Cancer Risk

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5.1 Introduction

The gastro-esophageal reflux disease (GERD) is the passage of gastric content into the esophagus. It can lead to non-erosive or erosive esophagitis due to acid and/or bile.

The frequency of upper gastrointestinal symptoms like abdominal pain, vomiting, diarrhea, and actually GERD is highly increased in obese patients (BMI > 30 kg/m^2).

The association between obesity and GERD reflux has been demonstrated in the United States where obesity rates are the highest and have also been seen in Europe and Eastern Asia [1].

A study on 10,545 American nurses showed that the relative risk of frequent GERD (more than once a week) is linearly correlated with the BMI to reach 2.9 for obese patients [2]. A similar link was seen in the results from 80,110 insurance members from the Kaiser Permanente Multiphasic Health Check-up cohort [3]. The association between BMI and GERD was stronger among whites compared with black members, with ORs of 1.58 and 1.33, respectively.

The high prevalence of GERD was confirmed by a study on 24 h-pH testings performed on 100 obese patients waiting for bariatric surgery [4]. An increase of

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time exposure of the lower esophagus to acid was observed in 46% of the cases. The pH testing was altered according to the BMI.

The effect of weight change on GERD symptoms has been studied. Jacobson [2] studied select individuals from the Nurses' Health Study and found that an increase of BMI by more than 3.5 kg/m^2 when compared with no weight change was associated with an increased risk of frequent symptoms of reflux.

Based on a systematic review, the prevalence rate of GERD in Europe was estimated to be 15% for the period 2005–2009 [5]. The epidemiologic relation between obesity and GERD has been observed in Europe as well. The German National Health Interview and Examination Survey found the OR for GERD to be 1.8 for overweight and 2.6 for obese individuals [6]. In England, the Bristol Helicobacter Project found that obese individuals had an OR of 2.91 for heartburn and an OR of 2.23 for regurgitation [7]. In a cohort of 1001 Swedish patients representing the whole population and having had an endoscopy, the patients who had a BMI > 30 kg/m^2 had an esophagitis in 26.5% of the cases compared with 9.3% in nonobese patients [8].

5.2 Factors Leading to GERD

The factors leading to GERD are mechanical or related to changes in esophageal motility.

The existence of a hiatal hernia, especially if it is a huge one, is associated with an increase in the seriousness of the GERD symptoms. The reason is that the hiatal hernia alters the function of the lower esophageal sphincter (LES) and increases the time during which the esophageal mucosa remains in contact with gastric acid. Stene-Larsen showed in a prospective study in 2019 patients that the overweight patients had a higher prevalence of hiatal hernia than the patients with normal weight [8]. This was even more correlated with patients having associated esophagitis. An other case-control study [9] showed that overweight (BMI between 25 and 30 kg/m^2) is associated with 2.5 times more risk of hiatal hernia (IC 95%: 1.5–4.3) compared with slim patients and the risk is 4.2 times more (IC 95%: 2.4–7.6) in obese patients.

The association between hiatal hernia and esophagitis was almost ten times more frequent in obese patients compared with control patients (OR: 9.9; IC 95%: 8.8–11.1).

In a series of patients with a BMI equal to or above 35 kg/m^2, a hiatal hernia was found in 39.4% and an esophagitis in 6.4%. Suter and colleagues [10] studied morbidly obese patients with history of reflux symptoms with upper endoscopy, 24-h pH monitoring, and manometry. They observed that of 345 subjects approximately half had a hiatal hernia.

These studies suggest that the increase of BMI is associated with a higher risk of hiatal hernia.

The impairment of the esophageal motility or the lower esophageal sphincter (LES) could lead to GERD in overweight or obese patients. Deficiency of the LES is frequently associated with GERD as demonstrated by this systematic manometric study on motility disorders in 100 patients waiting for bariatric surgery [11].

Decrease of the LES pressure is noted in 69% of the patients. Two similar studies have reported multiple motility disorders in morbidly obese patients waiting for bariatric surgery. In one [12] 54% of the patients had abnormal manometric findings: in 33 patients out of 61, ten had a defective LES whereas eleven had a hypertensive LES, two had diffuse esophageal spasm, three had nutcracker esophagitis, one presented ineffective esophageal disorder, and fourteen had nonspecific esophageal motility disorder. Some patients had more than one disorder.

In the other study, Jaffin [13] showed in 111 patients with mean BMI of 50.7 ± 9.4 kg/m^2 that there is no correlation between BMI and LES pressure. But 61% of the patients had esophageal motility disorders (25% defective, 14% nutcraker, 14% nonspecific, 7% diffuse spasm, and 1% achalasia). These authors noted that 59% of these patients having esophageal motility disorders did not suffer from any symptom (heartburn, dysphagia, or chest pain), suggesting that obesity might be accompanied by an alteration of the sensation of the visceral pain.

Central obesity seems also to be related with GERD. Central obesity has an effect on esophago-gastric junction even without creating a hiatal hernia. Pandolfino [14] performed high-resolution manometries in three groups of patients (normal weight, overweight, obese). Compared to both other groups, the obese group showed an increase of intragastric and intraesophageal pressure and an increase of the gastro-esophageal gradient. Abdominal obesity increases intra-abdominal pressure. Lambert and colleagues studied morbidly obese patients with a urinary catheter as a surrogate for intra-abdominal pressure and found that obese patients compared with nonobese patients had higher intra-abdominal pressures [15].

The increase of the intra-abdominal pressure deteriorates also the LES. A Chinese team [16] combined a 2 h-long postprandial manometry to a 24 h pH testing after a standard meal in three groups of patients (normal weight, overweight, and obese). The LES basal pressure was similar in the three groups, but transient LES relaxation was particularly frequent in the last two groups, with association between LES relaxation and GERD. The postprandial increase of transient LES relaxation in overweight and obese patients was considered as related to the increase of the intragastric pressure.

In conclusion, the potential pathogenic mechanisms in the obese leading to GERD are:

- Increase of intra-abdominal and intragastric pressures.
- Increase of transient relaxation of lower esophageal sphincter.
- Hiatal hernia.
- Decrease of lower esophageal sphincter pressure.
- Esophageal dysmotility.

5.3 Obesity, Barrett's Ulcer, and Risk of Cancer

The main complication of GERD is the occurrence of a Barrett's esophagus (BE). It is a typical endoscopic pattern presenting glandular mucosa above the esophago-gastric junction and histologically a specialized mucosa with

intestinal metaplasia. The odds-ration of BE increases with the BMI: 2.43 (Confidence Interval 95%: 0.68–4.2, $p = 0.261$) for overweight patients to 4.0 (CI 95%: 1.4–11.1, $p = 0.008$) for obese patients, independently from sex and ethnicity [17].

The link between obesity and esophageal neoplasia may be via altered secretion of adipokines such as adiponectin and leptin. Adiponectin is a protein that has anti-inflammatory and immunomodulatory functions and stimulates apoptosis. Secretion of adiponectin decreases with obesity. In a case-control study, Rubenstein [18] found an inverse association between plasma adiponectin levels and the presence of BE. Leptin is secreted by adipocytes and gastric chief cells. Leptin levels correlate directly with obesity [19]. Leptin has been shown to have mitogenic properties and induce proliferation in human cell lines including esophageal cancer cells [20].

Abdominal diameter index is a stronger predictor of prevalent Barrett's esophagus than BMI or waist-to-hip ratio [21]. In a recent study, 31 BE patients have been compared to 27 control patients. The BE cohort were older and had a higher rate of hiatal hernia. The mean abdominal diameter index for patients with BE was 0.65 ± 0.07 and without BE was 0.60 ± 0.07 ($p = 0.01$). The abdominal diameter index appeared to be the only significant predictor of BE in multivariate analysis.

A meta-analysis including seven studies [22] found an increased risk of lower esophageal adenocarcinoma in overweight patients (OR: 1.52: CI 95%: 1.15–2.01) and in obese patients (OR: 2.78; CI 95%:1.85–4.16).

The recent increase of the incidence of the adenocarcinoma of the cardia has been related to the increase of obesity.

The acid attack on the esophagus is the main trigger for BE but bile reflux has its own role. In BE reflux is mostly mixt, presenting both acid and bile. A long history of GERD and a deficient LES can lead to an extended BE (more than 3 cm long) and there is a relation between the length of the BE and the exposure of the esophagus to acid and/or bile.

The main complication of BE is its conversion into adenocarcinoma. Incidence reported in older series is between 0.2 and 2.1% patient/year of follow-up, which represents an increased risk of cancer by 30 or 50 times more than the general population [23]. Most of the studies have been done for long BE, the risk of cancer after short BE seems to be lower but not well known.

The prevalence of the dysplasia depends on the length of the BE [24]: around 8.5% for short BE (<3 cm), between 15 and 25% in long BE. The evolution of a non-dysplastic mucosa to a cancer can take at least 4 years. The probability for a low dysplasia to progress to a high dysplasia is between 6 months and 4 years. When the BE contains high dysplasia, the risk to evolve to a cancer is great. In a series of 76 patients endoscopically surveyed for high dysplasia, the cumulative incidence of cancer was between 60 and 80%, respectively, 4 and 6 years after the diagnosis of the dysplasia compared with patients without dysplasia or with low dysplasia where the incidence of cancer was only 10% after 10 years.

5.4 Bariatric Surgery and the Risk of GERD

The typical manifestations of gastro-esophageal reflux disease (GERD) are heartburn and/or regurgitation. GERD can be further classified into erosive and non-erosive GERD based on endoscopic appearance of esophageal mucosa. The recognized sequelae of GERD include Barrett's esophagus and esophageal adenocarcinoma. Obesity, defined as a Body Mass Index (BMI) ≥ 30, is common in the Western world and is increasing in other parts of the world, particularly Asia. Epidemiologic data demonstrate that overall obesity is a risk factor for both GERD [25] and esophageal adenocarcinoma [26]. There is evidence that central abdominal obesity, including increased abdominal pressure, is the most important factor associated with Barrett's esophagus [1].

Cross-sectional epidemiological studies have demonstrated a higher prevalence of GERD in obese individuals compared to the nonobese. Jacobsen et al. used a supplemental GERD questionnaire to show that subjects that reported at least weekly symptoms had a near linear increase in the adjusted odds-ratio for reflux symptoms for each BMI strata [2].

Approximately one-half of morbidly obese patients have objectively documented GERD (by either endoscopy or esophageal pH monitoring), even though some patients with these abnormalities do not report reflux symptoms. While fundoplication is the mainstay for the treatment of severe GERD, the outcomes and durability in the setting of obesity are poor [27]. Bariatric surgery is an effective approach to weight loss, and the data has generally shown that this weight loss can have positive effects on GERD [28].

5.5 GERD Following Restrictive Procedures

5.5.1 Laparoscopic Adjustable Gastric Banding

Laparoscopic adjustable gastric banding (LAGB) has gained increasing acceptance throughout the world because of its relative simplicity, safety, efficacy, and its low complication rate [29, 30]. Although it has proven effective in weight reduction, the effect on esophageal function and gastro-esophageal reflux is still unclear and published data on the effects of gastric banding on GERD reveal conflicting results [31, 32].

A review of the current literature on gastric banding shows a pattern of short-term improvement of GERD after band positioning, which can reverse course to an eventual worsening of this pathology. Although there is some symptom data supporting improvement of pre-existing GERD after 3 years [33], different studies suggest a relapse after several years: Himpens et al. [34] recorded 20.5% of de novo GERD 3 years after LAGB and Gutschow et al. [35] found pathologic reflux rates both on endoscopy and with pH-metry 3–4 years after LAGB. Moreover, a case of Barrett's esophagus has been communicated as late complication of this procedure by Varela [36].

The anti-reflux effect of the band is thought to be related to augmentation of the lower esophageal sphincter (LES) by creating a longer intra-abdominal pressure zone. On the other side, the incidence of esophageal dilation after gastric banding is significant and can worsen GERD postoperatively: this is probably due to the inflated band which reduces trans-stomal flow by narrowing the esophageal outlet, leading to reduced esophageal clearance, stasis of ingested food and refluxed material, and exerting physical expansion of the distal esophagus [37, 38]. Due to these and other long-term complications (slippage, intragastric migration, band and weight loss failure), the numbers of performed LAGB are decreasing worldwide [39].

Considering the adverse outcomes in relation to GERD in the long term, obese patients with GERD or esophageal dysmotility should be cautioned on receiving LAGB.

5.5.2 Laparoscopic Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy (LSG) is nowadays the most performed bariatric procedure worldwide, which underlines the importance of the increasing discussion about the incidence of de novo GERD after LSG. Tai et al. [40] found a significant increase in the prevalence of GERD symptoms (47%) and erosive esophagitis (66.7%) 1 year after LSG. Of the population analyzed by Howard and colleagues [41], 18% were noted to have new-onset GERD on their postoperative upper gastrointestinal swallow test after their LSG procedure. Furthermore, in a recent long-term evaluation of the impact of LSG on Indian population, Garg et al. [42] found new-onset GERD in 2.8% and a worsened pre-existing GERD in 11.4% of patients at 7 years follow-up. Indeed, Nocca et al. reported GERD as the most common late complication after LSG in 39.1% of the patients [43] and Himpens et al. described de novo GERD in a follow-up of 6+ years in 21% of patients [44].

A worsening of the disease was also seen by Weiner et al. [45] who reported that 16% patients having postoperative GERD were healed by conversion to laparoscopic Roux-en-Y gastric bypass (RYGB). Lacy [46] in his paper of post sleeve revisional surgery, mentioned persistent reflux as cause of reoperation between 5 and 36%, and 15% had to be converted to bypass due to intractable reflux.

There are multiple factors that may explain the worsening of GERD after sleeve gastrectomy: first is the alteration of the angle of His which normally acts as a valve to prevent reflux of stomach contents into the esophagus; moreover, the transection near the angle of His during gastrectomy may hesitate in a decrease of LES pressure as reported by Burgerhart et al. [47]. LSG induces a significant elevation in intragastric pressures and gastro-esophageal pressure gradient [48]. Finally, in an effort to avoid fistulas, surgeons can also leave excess fundus at the time of operation, which then results in a sleeve-tube with a conical shape and the creation of a neo-fundus; the neo-fundus may serve as a reservoir for food and it may determine gastric stasis and increased acid production [49].

Another important aspect related to development of GERD is the appraisal of Barrett's esophagus. One year after LSG, Braghetto and Csendes found [50], among

their 231 patients operated, reflux symptoms in 57 (23.2%), erosive esophagitis in 38 patients (15.5%), and histological examination confirmed Barrett's esophagus (BE) in 3/231 cases (1.2%) with presence of intestinal metaplasia. A higher percentage of BE was found by Felsenreich et al. [51] from a total of 43 patients over a period of 130 months, six of them (14.0%) were converted to RYGB due to intractable reflux. De novo hiatal hernia was found in 45% of the patients and Barrett's metaplasia in 15%.

Finally, Genco et al. in a total of 110 patients with a mean follow-up of 58 months, found an increased incidence of GERD symptoms compared with preoperative values (68.1% versus 33.6%), at upper endoscopy. The group demonstrated an upward migration of the "Z" line and a biliary-like esophageal reflux in 73.6 and 74.5% of cases. At same time, authors found a significant increase in non-dysplastic Barrett's esophagus, which was newly diagnosed in 19 patients (17.2%) [52].

The fifth international consensus conference indicates pH and manometry study pre-laparoscopic sleeve gastrectomy [53]. Although sleeve gastrectomy is now considered an effective weight loss surgery, considering the consistent data regarding development and worsening of GERD, it generally is not recommended in patients with pre-existing reflux.

5.6 GERD Following Gastric Bypass Procedures

5.6.1 Laparoscopic Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is still the gold standard in bariatric surgery despite its complex surgical technique and potential complications, due to its excellent outcomes in weight loss and its metabolic impact.

In his study on 55 patients with preoperative GERD, Schauer et al. [54] demonstrated that no patient had aggravation of the disease and 96% showed improvement or resolution of symptoms.

In a large multicenter study on 130,796 patients with 1-year follow-up, Sudan and colleagues compared outcomes from LAGB, LSG, RYGB, and biliopancreatic diversion with duodenal switch (BPD/DS). They found RYGB being the best procedure for resolution of GERD, and odds of resolution were 1.5 higher compared with other surgical techniques; this is probably due to the dimensions of the stomach pouch which after RYGB is smaller than in the other procedures, and acid and bile are directed downstream to help improve GERD symptoms [55].

Also, Pallati et al. [56] analyzed GERD score after various bariatric procedures in a cohort of 116,136 patients, 36,938 of which had evidence of GERD preoperatively; the review underlines an improvement of GERD symptoms significantly highest in RYGB patients (56.5%), followed by LAGB (46%) and LSG patients (41%). Worsening of GERD was seen in a small number of patients, mostly in LSG (4.6%), followed by RYGB (2%) and LAGB (1.2%).

There are small case-series examining the effect of RYGB on Barrett's esophagus. Houghton et al. found complete or partial regression in four of five Barrett's

esophagus patients following RYGB at an average of 34 months postoperatively [57]. Moreover, Csendes et al. studied 15 patients with long- and short-segment Barrett's esophagus; they found a 100% resolution of reflux and erosive esophagitis with a variable complete regression rate [58].

The superior efficacy of RYGB in morbidly obese patients with GERD is likely due to the anatomic configuration of a low-acid producing pouch, a low-pressure system and diversion of bile reflux by a Roux-en-Y re-construction, and the intra-abdominal pressure changes related to postoperative weight loss. By this point of view, RYGB is currently recommended for morbidly obese patients with GERD or Barrett's esophagus given the superior reflux control of both acid and non-acid events compared to other bariatric surgeries [59].

5.6.2 Mini/One Anastomosis Gastric Bypass

Since its introduction by Rutledge in 1997 [60], the Mini Gastric Bypass, named as One Anastomosis Gastric Bypass in the Spanish variant [61], (MGB/OAGB), has encountered the favor of a large number of surgeons, becoming the fourth most performed surgery in Europe and in the Asia/Pacific area [39].

Despite first skepticism in this technique, different authors have reported interesting results in terms of weight loss, low rate of mid- and long-term postoperative complications, and resolution of obesity-related comorbidities [62]. Moreover, compared with other bariatric procedures, MGB/OAGB has the advantage of being technically simple and easy to learn with less morbidity and mortality rate, especially in super obese patients with high operative risk [63].

In a recent Italian multicenter study on 2678 patients [64], a retrospective analysis was conducted to define the complication rate following the MGB in the short- and mid-term period. The risk of postoperative GERD, or better duodenal-gastro-esophageal reflux (DGER), was analyzed too. Despite a preoperative diagnosis of GERD present in 122/2678 patients (4.5%), Musella and colleagues found a GERD/DGER at 5-year follow-up in 28/683 patients (4.0%). Among them, on 18 patients presenting preoperative GERD, 4 (22.2%) worsened following MGB/OAGB, 10/18 (55.5%) reported a decrease in proton pump inhibitors (PPI) usage, while 4/18 (22.2%) experienced a documented improvement. Conversely, a total de novo GERD/DGER globally occurred in 14/683 patients in the follow-up (2.0%).

Tolone et al. [65] in a recent article have demonstrated, with usage of high-resolution impedance manometry (HRiM), that MGB/OAGB, in contrast with LSG, did not compromise the esophago-gastric junction function and that MGB/OAGB statistically diminishes intragastric pressures and gastro-esophageal pressure gradient.

Revising literature on this bariatric procedure, the incidence of bile reflux in MGB has been deeply discussed. Interesting results have been reported in the experimental setting by Chevallier [66], while retrospective studies with large numbers of patients have stated a rate of reflux much lower than 1%. Lee et al. [67] have described three cases out of more than 1300 MGBs (0.2%) with severe bile reflux

that had to be converted to RYGB whereas in another study from Italy, Musella et al. [68] have found a rate of 0.9% during upper endoscopy in almost 1000 MGB patients. Finally, Plamper et al. have found a comparable rate of 0.6% in his MGB patients [69]. The statistical correlation of postoperative duodenal-gastro-esophageal reflux (DGER) with a gastric pouch shorter than 9 cm [64] underlines the importance of performing the right anatomical technique to minimize bile reflux.

The advantages of MGB/OAGB include the low-pressure system and the intra-abdominal pressure changes related to postoperative weight loss. Further studies remain however necessary to define the positive effects of MGB/OAGB on GERD/DGER control.

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