Review Article

Biliary reflux after bariatric surgery and after gastroesophageal surgery for gastroesophageal reflux disease

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Abstract: Biliary reflux refers to the ascent of duodenal fluid, biliary and pancreatic secretions into the stomach and esophagus. It is a primitive phenomenon or it can be secondary to gastric or biliary surgery. In particular, biliary reflux seems common after bariatric surgeries with, however, unknown incidence. Current data show that the prevalence of biliary reflux was higher after minigastric bypass as compared to the other bariatric surgeries. Nevertheless, biliary reflux resulted to be a relevant risk factor for the development of reflux-related complications, such as erosive esophagitis and Barrett esophagus, and its persistence over time seems to be an independent risk factor for gastric cancer. Its evaluation is challenging, and several methods have been proposed to date. Hepatobiliary iminodiacetic acid (HIDA) assessment is a non-invasive technique which showed a good correlation with gastric bile acids in several clinical investigations. Impedance-pH monitoring has been shown to correctly identify non-acidic reflux, but it is not considered a valid tool to diagnose the occurrence of bile reflux episodes in the esophagus since its inability to distinguish bile from other non-acidic components of the refluxate like food. Fibreoptic spectrophotometric probe (Bilitec) was proposed to quantify bile reflux in an ambulatory setting and over a prolonged period, using bilirubin as a marker for the presence of duodenal contents. Only few studies have addressed the impact of anti-reflux surgeries on treating biliary reflux, although these procedures appear to be effective to improve clinical and objective outcomes of this complication.

Keywords: Impedance-pH; Bilitec; reflux; gastroesophageal reflux disease (GERD); duodenal reflux

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Introduction

Gastroesophageal reflux disease (GERD) develops when the backflow of gastric contents into the esophagus causes troublesome symptoms and/or complications. GERD is characterized by several symptoms classified into typical and atypical (i.e., asthma, chronic cough, laryngitis, hoarseness,

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chronic sore throat, dental erosions, and non-cardiac chest pain). GERD is a highly prevalent disease in Western countries, ranging from 10% to 30% basing on different population-based studies. The clinical impact of GERD is emphasized by the risk of developing erosive esophagitis, Barret's esophagus, and esophageal cancer in which a correct endoscopic follow-up is mandatory (1).

The pathophysiology is a complex orchestra of patient's specific characteristics, such as hiatal hernia and habitus (i.e., obesity), transient lower esophageal sphincter relaxations, esophageal hypersensitivity, esophageal motor disorders and, impaired esophageal clearance. In this context, anatomical changes induced by foregut surgery may increase the risk of gastroesophageal reflux. Endoscopic assessment is negative in about 70% of patients with GERD symptoms, and for this reason reflux testing with a pH-impedance monitoring or wireless pH-metry capsule is useful to discriminate between non-erosive reflux disease (NERD) and patients with functional heartburn or reflux hypersensitivity (2).

Nowadays, proton pump inhibitor (PPI) represents the gold standard treatment of GERD to reduce gastric acid secretion and allow mucosal healing, while alginate-based compounds or mucosal protectants may be helpful in controlling residual symptoms. Furthermore, the long-term administration of PPI reached adequate consensus and is considered safe in patients with persistence or recurrence GERD-related symptoms (3). Unfortunately, GERD therapy is still challenging because PPIs provide symptom relief in only 60–70% of patients, while the others are classified as non-responders. One of the main reasons of this partial efficacy of PPIs is represented by the occurrence of non-acid reflux, and in particular biliary reflux. This underlies the existence of an unmet need that still claim scientific investigation.

What is biliary reflux?

The gastric refluxate primarily contains acid, pepsin, conjugated bile salts, pancreatic enzymes, water, and a mixture of these substances combined with food in the post-prandial periods. The main role of acid and pepsin in causing symptoms and esophageal damage is irrefutable and derives from many human and animal studies (4).

Biliary reflux or duodeno-gastro-esophageal reflux (DGER) refers to the ascent of duodenal fluid, biliary and pancreatic secretions into the stomach and eventually into the esophagus. This can be a primitive phenomenon or it can be secondary to gastric or biliary surgery. Biliary reflux has been associated with typical reflux symptoms, including heartburn and regurgitation. Indeed, esophageal infusion of bile acids can generate heartburn, although with lower rapidity and intensity than acid infusion. In real life, clinical symptoms associated with DGER are often nuanced and nonspecific, like dyspepsia, epigastric pain, heartburn, bitter taste, poor appetite/weight loss and nausea with bilious vomiting (5).

If a subject with DGER has never undergone gastric or biliary surgery, we refer to the term of "primary biliary reflux" (PBR). The pathophysiology of PBR is complex and not fully clear; mainly it is due to gallbladder dysfunction, gastroduodenal dysmotility and/or disorder of gastroduodenal hormones [in particular gastrin, cholecystokinin, gastric inhibitory peptide (GIP) and secretin] (5). Opioids and type II diabetes mellitus are also arising causes of biliary reflux due to their ability on modulating gut contractility (5). Conversely, the relationship between DGER and *Helicobacter pylori* (*Hp*) infection remains controversial. Ladas *et al.* hypothesized that *Hp* infection may induce biliary reflux, being both triggers to chronic gastritis and its consequences (6). Moreover, according to Sobala and co-workers intestinal metaplasia is more common in patients affected by *Hp* infection and DGER diagnosis (7). Assessing the prevalence of this condition appears to be unclear, due to the great heterogeneity of studies, different sample sizes and lack of uniformity in diagnostic criteria. A recent systematic review by Basnayake *et al.* tried to assess the prevalence of DGER, but they reported a very wide range, between 10–97% (8).

"Secondary biliary reflux" (SBR) represents the eventual consequence of biliary and/or gastro-duodenal surgery, which leads to a change in anatomy and physiology of this area. Also the prevalence of SBR is poorly known, due to the lack of prospective studies aimed to further understand this phenomenon with the state-of-art methods able to measure DGER.

The likely mechanism of bile acids inducing esophageal symptoms is the release of intercellular mediators via damage to lipid membranes. The reflux of duodenal contents via the stomach into the esophagus is also able to induce mucosal injury and this has been shown both in animals and in humans (9). Conjugated bile acids enter the mucosal cells in unionized form (predominant form at low pH) through the lipophilic lipid membrane and then accumulate as intracellular ionization results in entrapment (10). This high concentration of bile acids causes intracellular damage by the dissolution of cell membranes and tight junctions.

The pathogenetic role in the esophagus of duodenal contents consisting of bilirubin, bile acids and pancreatic enzymes have been confirmed by the development of erosive esophagitis in patients undergoing total gastrectomy or in those with achlorhydria (11). Moreover, esophageal exposure to both acid and DGER was shown to be present in 100% of patients with complicated Barrett's esophagus, 89% of uncomplicated Barrett's esophagus, 75% of erosive esophagitis and 50% of NERD by using combined 24-hour pH and Bilitec monitoring (12). These latter findings by Vaezi *et al.* confirm that there is a synergy between acid and DGER, which contributes to induce not only the presence but also the severity of esophageal mucosal lesions (12). Recent *in vitro* studies support the synergistic action of acid and bile in the pathogenesis of Barrett's esophagus, as the upregulation of the protein product of the c-myc oncogene and the induction of cyclo-oxygenase 2 were determined by acidified bile in biopsies from Barrett's patients (13). In another study on 392 patients with GERD the presence of hiatal hernia, increasing body mass index and DGER resulted to be relevant risk factors for the development of esophagitis, whose severity was, however, mainly induced by the presence of acid (14).

Biliary reflux could be easily misdiagnosed or misinterpreted, but considering the certified involvement in the pathogenesis of precancerous lesions, its evaluation is pivotal. Moreover, other studies have documented that bile reflux is an independent risk factor for gastric cancer, thus highlighting the importance of its assessment (15).

How to measure biliary reflux [Bilitec, multichannel intraluminal impedance-pH (MII-pH)] in clinical practice

Several methods have been proposed over the years to measure DGER and all of them have strengths and limitations.

Scintigraphic studies

They have the advantage to be non-invasive and use the hepatobiliary iminodiacetic acid (HIDA), which has been shown to present a good correlation with gastric bile acids in several clinical investigations. When biliary reflux is present, HIDA shows a tracer movement from small intestinal loops into the stomach, then in the esophagus. However, the reliability and accuracy of this technique has been questioned because it is, at best, semi-quantitative and several technical problems can interfere with the measurement (16). For instance, in about one third of the examinations the overlap of small bowel and stomach does not permit the technique to be greatly informative. Still, HIDA has other limitations and drawbacks, including lack of a validated universal protocol for biliary reflux detection, high costs, limited availability in some countries and the need for prolonged duration protocols to increase the diagnostic yield of the test (17).

Impedance-pH monitoring

This technique has become the most important diagnostic tool for the diagnosis of gastroesophageal reflux episodes and has replaced the traditional 24-hour esophageal pH-metry because it allows us to detect not only acid, but also weakly acidic and alkaline reflux events over the circadian cycle. Accordingly, it has been proposed as a valid method to identify bile reflux on the basis of the assumption that an alkaline shift of pH equates with the presence of DGER. However, the number of alkaline reflux events registered by this technique is very scant compared with the acid and weakly acidic ones and, moreover, investigations combining aspiration and pH monitoring have shown that the reading of pH measurements above 7 pH units does not mean the certain presence of duodenal contents in the esophagus (18). It has been suggested that alkaline pH values might reflect the presence of esophageal bicarbonate secretion or episodes of increased salivation. The same problem exists in the stomach, where alkaline pH values do not equate with the presence of duodenal material in this organ and, on the other hand, the occurrence of DGER episodes does not determine the immediate shift of gastric pH toward alkaline values (19).

For the above reasons, impedance-pH monitoring is not considered as a valid tool to diagnose the occurrence of bile reflux episodes in the esophagus and indeed, all the reviews on the diagnostic yield of this innovative technique do not mention its reliability in this setting (20).

Fibreoptic bilirubin monitoring

Bechi *et al.* (21) were the first to propose this new fibreoptic spectrophotometric probe (Bilitec) to quantify bile reflux in an ambulatory setting and over a prolonged period, using bilirubin as a marker for the presence of duodenal contents. Indeed, bilirubin has a characteristic absorbance spectrum (its absorption band is of 450 mm) and the continuous monitoring at two wave-lengths by

the esophageal refluxate permits to detect the presence of bilirubin. Several studies have shown a good correlation between Bilitec measurements and bile acid concentrations. Indeed, ambulatory aspiration studies found a significant correlation between the total bilirubin concentration of aspirated samples and the fibreoptic reading of bilirubin concentration. Moreover, a good correlation was found between total bilirubin content and the concentrations of pancreatic enzymes in the refluxate, suggesting that bilirubin is a good tracer for DGER (22).

However, it must be emphasized that some dietary restrictions need to be followed in order to prevent relevant artifacts in the use of this technique. Solid food impaction is possible and several common foods, such as soups, tea and coffee give high Bilitec readings and may interfere with adequate bile reflux measurement (23). So, this examination requires the use of liquid-only meals and a strict compliance from the patients.

Biliary reflux after bariatric surgery

Nowadays, biliary reflux is commonly encountered in clinical practice in parallel with the increasing prevalence of bariatric surgeries, particularly gastric banding and sleeve gastrectomy, whereas after the mini gastric bypass (MGB) procedure the data are more conflicting (24). For instance, Johnson *et al.* performed a multicenter study that aimed to review the complications and the redo prevalence after MGB (single anastomosis) and found that bile reflux esophagitis is a major concern and leads to mucosal damage, symptoms provocation and healthcare burden (25). Indeed, biliary reflux after sleeve gastrectomy and minigastric bypass currently represents an important cause of conversion to Roux-en-Y surgery. On the other hand, Tolone and colleagues evaluating the esophageal function and reflux occurrence by high-resolution manometry and impedance-pH monitoring in one hundred and twelve obese subjects undergoing various bariatric procedures (i.e., endoscopic balloon placement, gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, mini-gastric bypass, biliointestinal bypass, and biliopancreatic diversion) observed that only gastric banding and sleeve gastrectomy negatively impacted on esophageal function and reflux exposure, whereas patients who underwent MGB had a marked decrease in number of all types of refluxes at control impedance-pH testing (26). Likewise, in another study comparing reflux exposure after MGB and Billroth II, Tolone and co-workers found by using impedance-pH monitoring that in contrast to Billroth II, MGB did not increase any kind of reflux after surgery (27). These authors hypothesized that the difference between the two surgical techniques was due to the fact that high-resolution impedance manometry features did not vary significantly after MGB, whereas intragastric pressure and gastroesophageal pressure gradient statistically diminished as compared after Billroth II. Finally, Tolone *et al.* studying 15 patients undergoing MGB with endoscopy plus high-resolution impedance manometry and 24-hour pH-impedance monitoring, showed that MGB did not compromise the gastroesophageal junction function and did not increase gastroesophageal reflux as compared to patients undergoing SG, and again this was explained by the lack of increased intragastric pressures and gastroesophageal pressure gradient as assessed by high-resolution impedance manometry (28). Nevertheless, although MGB seems to have a lower detrimental effect on gastroesophageal junction and reflux occurrence as compared to the other bariatric procedures, further evaluation and confirmation in larger prospective studies is need.

The prevalence of biliary reflux after bariatric surgeries has been heterogeneously reported in a number of studies. Lasheen *et al.* assessed the prevalence of bile reflux gastritis and esophagitis in over 40 patients after MGB and found that 20% of them had bile reflux as diagnosed by gastric pouch biopsy and gastric aspirate examination (29). Two studies that used gastric pouch biopsy to diagnose biliary reflux, over a total of 142 patients after MGB, reported a prevalence of 7.8% and 30%, respectively (30,31). More recent studies that used HIDA scan for the diagnosis of bile reflux among groups of patients undergoing bariatric surgeries (i.e., sleeve gastrectomy, gastric bypass and MGB) reported higher rates of bile reflux after all type of surgical procedures (31.6–75%) (32,33). On the other hand, Carbajo *et al.* reported a very low incidence of bile reflux (per endoscopy) after surgery (2%) over 1,200 patients post-MGB, although this small rate might be due to the lack of proper diagnostic tools such as HIDA and impedance-pH monitoring (34). Possible elucidations for this varying reported prevalence include utilization of dissimilar HIDA protocols, inclusion of different patient groups, different type of surgeries, lack of follow-up documentation and different expectations as well as preferences from both surgeons and patients. Notably, the reported prevalence of biliary reflux was higher after MGB as compared to the other bariatric surgeries and when HIDA was used to measure biliary reflux as compared to endoscopy and gastric pouch biopsies.

Biliary reflux after gastroesophageal surgery for GERD

Few studies have addressed the impact of antireflux surgery, particularly the Nissen Fundoplication, on the neutralization of biliary reflux. Elhak *et al.* performed a comparative study that included 96 GERD patients who underwent at baseline esophageal manometry, endoscopy and 24-hour pH monitoring combined with Bilitec 2000. A total of 28 patients underwent Nissen Fundoplication, while the others received medical therapy. Some parameters were compared between the two groups and authors found that, at 6 months follow-up, the operated patients had less symptoms, greater lower esophageal sphincter pressure and less acidic and bile reflux (35). An interesting study by Brillantino *et al.* (36) assessed the impact of Nissen Fundoplication on acidic and bile reflux on 28 patients with GERD. The main finding of the study was that Nissen Fundoplication improved acid and bile reflux. Stein *et al.* found that anti-reflux surgery was able to correct bile reflux sufficiently and Nissen fundoplication was the most frequently adopted anti-reflux procedure (37). More recently, laparoscopic fundoplication of the excluded stomach as a novel treatment procedure for biliary reflux after MGB is being performed and gaining more popularity. An Australian study over 12 patients who underwent minigastric bypass and fundoplication of the excluded stomach found that the procedure was effective in controlling biliary reflux (38).

Conclusions

In conclusion, biliary reflux seems to be a prevalent complication after bariatric surgeries, particularly the most restrictive procedures like gastric banding and sleeve gastrectomy. However, its exact prevalence is unknown, probably due to the utilization of various modalities for detecting biliary reflux as well as the inclusion of small samples of heterogeneous patients. Furthermore, anti-reflux procedures appear to be efficient to control biliary reflux, mainly Nissen Fundoplication. To further clarify the prevalence and link between bariatric surgeries and biliary reflux as well as to better understand the role of anti-reflux surgeries in the control of biliary reflux, more prospective international studies with more homogeneous patient groups and the utilization of validated and uniform diagnostic modalities to detect biliary reflux are eagerly warranted.

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Footnote

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