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REVIEW ARTICLE

Development of Ulcer Disease After Roux-en-Y Gastric Bypass, Incidence, Risk Factors, and Patient Presentation: A Systematic Review

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Abstract Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the gold standard in bariatric surgery. A long-term complication can be marginal ulceration (MU) at the gastrojejunostomy. The mechanism of development is unclear and symptoms vary. Management and prevention is a continuous subject of debate. The aim was to assess the incidence, mechanism, symptoms, and management of MU after LRYGB by means of a systematic review. Forty-one studies with a total of 16,987 patients were included, 787 (4.6 %) developed MU. The incidence of MU varied between 0.6 and 25 %. The position and size of the pouch, smoking, and nonsteroidal inflammatory drugs usage are associated with the formation of MU. In most cases, MU is adequately treated with proton pump inhibitors, sometimes reoperation is required. Laparoscopic approach is safe and effective.

Keywords Anastomotic ulcer · Bariatric surgery · Bleeding ulcer · Gastric bypass · Ischemic ulcer · Marginal ulcer · Morbid obesity · Perforation · Roux-en-Y gastric bypass · RYGB · Ulcer

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Introduction

In the USA, the prevalence of obesity (a body mass index (BMI) of >30) is around 30 % in the adult population [1]. The incidence is increasing, and the World Health Organization predicts that in 2025 there will be 300 million obese people worldwide [2].

Obesity is associated with a range of comorbidities such as metabolic syndrome, early osteoarthrosis, obstructive sleep apnea, and a high risk of cardiovascular disease [3]. At present, bariatric surgery is the only long-term effective treatment for morbid obesity (BMI of >40). It aims at inducing weight loss by reducing the gastric volume and/or absorptive capacity of the intestines. A wide variety of bariatric procedures have been developed such as (laparoscopic) adjustable gastric banding, (laparoscopic) gastric sleeve resections and laparoscopic Roux-en-Y gastric bypass (LRYGB). LRYGB is considered the gold standard because of the superior results. Compared to gastric banding, LRYGB produces sustained weight loss and higher resolution of obesity-associated morbidities. The laparoscopic approach is associated with faster recovery, shorter length of stay, higher success rate, and lower morbidity and mortality compared to the open procedure (RYGB) [4–7].

At present, bariatric surgery is mainly performed in high-volume centers. The LRYGB is a major operation with potentially severe early and late complications. The majority of the complications occur during the procedure or in the early phase afterwards. Due to a more sufficient follow up and increasing performance of the procedures, a higher number of late complications are identified [8].

One of these late complications is marginal ulceration. A marginal ulcer is defined as an ulcer at or near the gastrojejunostomy (GJS). In medical literature, at least three synonyms are used: marginal, ischemic, and anastomotic ulcer. In this text, we will use the term marginal ulcer (MU). As

the number of LRYGB performed worldwide rises, the number of patients with MU will subsequently increase [4, 9, 10].

The incidence of MU is unclear, and reports vary from 0.6 to 25 %. MU is associated with, sometimes severe, morbidity and can be potentially lethal [11–13]. Patients may present with perforation or massive bleeding after an asymptomatic onset. Other, less acute symptoms are epigastric burn and/or vomiting [14–17].

This systematic review analyses literature published about MU. The main focus will be the incidence and risk factors for development of MU. The evidence for preoperative testing and treatment of *Helicobacter pylori*, standard prescription of proton pump inhibitors (PPIs) prophylaxis and symptoms at presentation were also assessed. To the best of our knowledge, no review of the available literature has been published yet.

Materials and Methods

Literature Search

The Cochrane Database of systematic reviews, the Cochrane central register of controlled trials and the PubMed database were independently searched by two separate investigators (UKC, ABG) using the keywords *((Peptic ulcer disease OR marginal ulceration OR anastomotic ulcer OR ischemic ulcer OR ulcers OR ulcera*)) AND (((((“Bariatric Surgery”[Mesh:noexp]) OR “Gastric Bypass”[Mesh])) OR (gastric bypass*[tiab])) OR (bariatric[tiab])* in order to identify studies published until the first of October 2012. MeSH terms and free text words were combined to avoid exclusion of recent articles that had not been given a MeSH label yet. Only full texts published in English were included. Electronic links to related articles and references were cross-checked.

Study Selection and Data Extraction

The PRISMA statement for systematic reviews and meta-analysis was used for study selection and data extraction [18]. From the potentially eligible publications, only studies that reported on ulcer disease around the GJS were included. A clear definition of study objectives, description of data collection, and a minimum of four patients were required for inclusion.

Exclusion criteria were less than four cases, full text in a language other than English, words used in a different context, pathology in the remnant gastrointestinal tract, gastrogastric fistulae, or radiologic diagnosis of MU. Studies about the reoperative management but not about incidence or pathophysiology of MU were left out of the analysis but included in the text for additional information. Data was retrieved from the articles only. No attempt was made to obtain missing/additional data from the authors or institutions.

Data Synthesis

Each of the selected studies was thoroughly analyzed by two investigators (UKC and ABG). The data was extracted from the original articles by using a preformatted sheet as proposed by the Cochrane Collaboration. Study period; study design (randomization, prospective, or retrospective consecutive data collection); comparability of study groups; adequate follow up; and presence of performance, selection, attrition, or detection bias were assessed. In cases of retrospective analysis of data collected from a prospective consecutive database, the study was qualified as being prospective. Any differences of opinion between the two investigators were discussed and resolved during a consensus meeting.

Results

Included Studies

Search process and study selection are displayed in a flowchart (Fig. 1). With the above search terms, 394 publications were retrieved. Three hundred eighteen contained the search

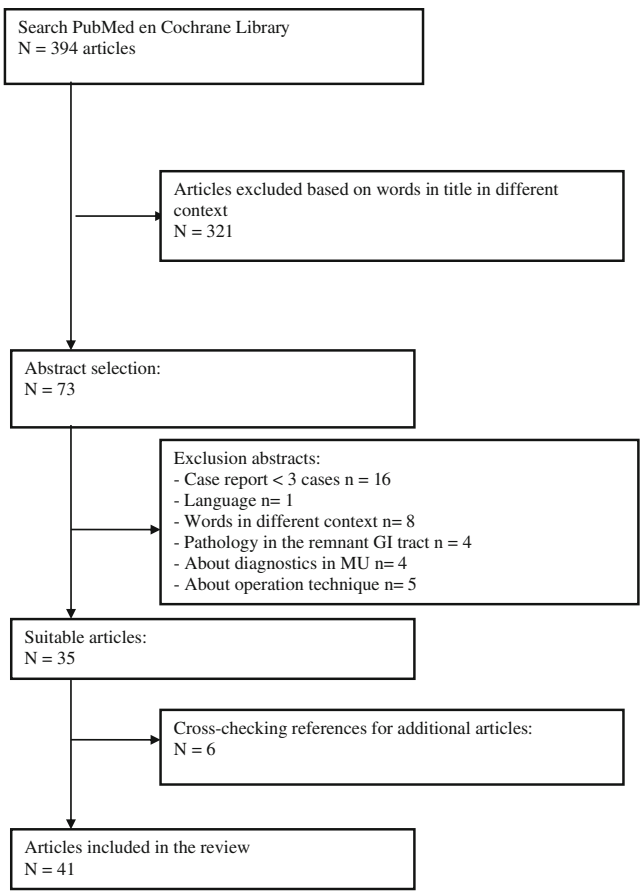

Fig. 1 Flowchart of a systematic review about the incidence and symptoms of marginal ulceration after Roux-en-Y gastric bypass

items in a different context and were therefore deemed irrelevant. A total of 76 articles were selected for closer reading. Forty-one were excluded based on the abstracts. Of the 36 remaining articles, one was not written in English and therefore discarded. References were cross-checked and six additional articles were found. A total of 41 articles were scrutinized and examined for data. Other articles were kept for additional information [9, 11, 12, 14, 15, 17, 19–41]. The additional Table 1 contains the included studies and rates their quality.

Patients

All patients met the criteria for morbid obesity and a total of 16,987 patients (mainly female patients; with age ranging from 16 to 72) underwent a LRYGB and were included in the present review. During follow-up, 787 (4.6 %) patients developed MU. The time between surgery and presentation with MU varied between 1 month and 6 years [22, 31, 32, 42].

In three studies, standard screening was performed, both asymptomatic and symptomatic patients with MU were traced [22, 23, 25]. In the other studies, only symptomatic patients were analyzed.

Age and weight were normally distributed in most research groups and did not predispose for the development of MU. Male sex seemed to increase the risk for MU but not significantly [15, 32, 43].

Risk Factors

The incidence of marginal ulceration (ranging from 0.6 to 25 %) is listed in Table 2 together with the use of prophylactic PPIs, the technique by which the anastomosis is created and the symptoms.

Type of Procedure and Suture Material

Thirty-two articles mentioned surgical technique; 78.3 % RYGB was performed laparoscopically. No difference in ulcerogenic potential was found between open and laparoscopic procedure [12, 21] (Table 2). Capella et al. showed that the use of staples results in a higher incidence of MU compared to absorbable suture materials. In the study by Rasmussen et al., 32 % of the ulcer beds showed remnants of suture material at esophagogastroduodenoscopy [19–21, 32, 34, 44]. Local ischemia seems to enlarge the risk for MU [45].

Position of the Pouch and the Role of Gastric Acid

Historically, the first focus of interest was the position and size of the pouch. The concentration of the parietal cell mass in the stomach is divided into areas [46]. Most parietal cells are situated in the antrum, whereas proximal in the stomach almost no cells are present [20]. Patients with a large, less proximal pouch have a higher risk for MU because a part of the antrum is included. In biliopancreatic diversion, the pouch is more obliquely orientated, containing more parietal cells and there is a higher incidence of ulcers. A small proximal pouch, limited to the cardia, reduced the occurrence of MU from 5.2 to 0.01 % in 1 year [43]. In LRYGB with a micropouch, the incidence of MU is also lower [46, 47]. The technique for pouch creation in RYGB is now standardized [48].

H. pylori

The incidence of infection with *H. pylori* in patients who are screened for bariatric surgery differs between 22 and 67 % [26, 41, 49–51]. In this review, 12 articles tested the presence of *H. pylori* at the MU site. In 10.5 %, the test was positive for infection [12, 23, 26, 28, 32, 33, 37, 41, 52–54].

Two studies found an association between preoperative infection and eradication of *H. pylori* in relation to MU and other gastrointestinal complications [26, 32, 55]. The recent published study of Rawlins et al. did not show a significant difference in the rate of complications between patients who were infected preoperatively with *H. pylori* or not [56].

Suggs et al. published a study of 23 patients with MU after surgery who all tested negative for *H. pylori* with the *Campylobacter*-like organism test [28, 31, 37, 41, 52]. Marano et al. and D'Hondt et al. were also unable to demonstrate a relationship between infection with *H. pylori* and MU [30, 52].

NSAIDs, Smoking, Diabetes Mellitus, Cardiovascular Disease, and Other Patient Demographic Risk Factors

The use of nonsteroidal inflammatory drugs (NSAIDs) increase the incidence of peptic ulcer disease (PUD) significantly [57, 58]. Another risk factor for PUD is the abuse of tobacco [59]. Wilson et al. performed a uni- and multivariate analysis on the use of NSAIDs and tobacco after LRYGB. Both factors independently predicted formation of MU. Protection against MU was achieved when PPIs were simultaneously used with NSAIDS [60]. In this review, 19 of the included articles scored the use of NSAIDs in the patients with MU. Of the 365 patients, 98 used NSAIDs at the time of presentation [61–64]. The use of NSAIDS is not only related to the formation of MU, they also inhibit healing of ulcer disease [65].

Ten articles mentioned smoking. A mean of 35.8 % of the patients smoked while developing MU. Smoking is a risk factor, particular for perforated MU. After healing, Patel et al. present three patients who developed recurrent ulceration—all heavy smokers. Another study showed a significant

Table 1 Quality of included studies (additional)

Publication	Follow up (months)	Prospective or retrospective consecutive data	Statistical method described	Comparability	Low risk of performance bias	Low risk of selection bias	Low risk of attrition bias	Low risk of detection bias	Total
Azagury [15]	34.8	Prospective	+	+	−	−	+	−	4
Bendewald [19]	14.4	Prospective	+	+	+	−	+	−	5
Capella and Capella [20]	44–63	Retrospective	−	−	−	−	−	−	0
Csendes et al. [23]	84	Prospective	−	−	+	+	+	+	5
Csendes [22]	22	Prospective	+	−	+	+	+	+	6
Dallal and Bailey [24]	19.8	Prospective	+	−	+	−	+	+	5
D'Hondt et al. [52]	6	Prospective	+	+	+	−	−	+	5
El-Hayek et al. [67]	–	Retrospective	+	−	−	−	−	+	2
Felix et al. [14][a]	48	Prospective	+	−	−	+	+	+	5
Garrido et al. [25]	2	Prospective	+	−	+	+	+	+	6
Gumbs et al. [68]	12	Prospective	+	+	+	−	−	−	4
Hartin et al. [26]	11	Retrospective	+	−	−	−	+	+	3
Higa et al. [17]	–	Prospective	−	−	−	−	−	+	2
Howard et al. [13]	12–78	Retrospective	+	+	−	−	−	+	3
Jordan et al. [27]	39	Prospective	−	−	−	−	+	−	2
Kligman et al. [66]	–	Retrospective	+	+	−	−	+	+	4
Kalaiselvan et al. [28][a]	24	Prospective	−	−	−	+	+	+	3
Lublin et al. [29][a]	13	Prospective	+	+	+	+	+	+	7
Luján et al. [53]	25.5	Prospective	−	−	−	−	+	+	3
Marano [30]	24	Prospective	−	−	+	−	−	+	3
MacLean et al. [11]	12–96	Prospective	+	−	−	−	+	+	3
Papasavas et al. [86]	18	Prospective	+	−	−	−	+	+	4
Patel et al. [31]	–	Prospective	+	−	−	−	−	+	3
Pope et al. [70]	>24	Retrospective	+	+	−	−	−	+	3
Printen et al. [43]	75	Retrospective	−	−	−	−	−	−	0
Ramirezet al. [54]		Retrospective	+	+	+	−	+	+	5
Rasmussen et al. [32]	10.2	Retrospective	+	+	−	−	+	+	4
Rawlins et al. [56]	21	Retrospective	+	+	−	+	−	+	4
Ruiz-de-Adana et al. [33]	–	Retrospective	−	−	−	−	+	+	2
Sacks et al. [34]	12	Retrospective	+	+	−	−	+	+	4
Sanyal et al. [9]	>12	Prospective	−	−	+	−	+	+	4
Sapala et al. [12]	36	Prospective	−	−	−	−	−	+	2
Sasse et al. [35][a]	–	Retrospective	−	−	−	+	+	+	3
Spaulding [36]		Retrospective	+	−	−	−	−	+	2
Suggs et al. [37]	13.8	Retrospective	+	−	−	−	+	+	3
Suter et al. [38]	–	Prospective	+	+	+	−	−	+	5
Vasquezet al. [39]	3	Prospective	+	−	−	−	−	+	3
Wheeler et al. [40][a]	–	Retrospective	−	−	−	−	+	+	2
Wilson et al. [60]		Retrospective	+	−	−	−	−	+	2
Yang et al. [41]	–	Prospective	+	+	−	−	+	+	5

Prospective=1 point, retrospective=0 points, +=1, −=0, maximum points is 7

[a] Perforated marginal ulcer

difference in the formation of MU as well as in healing capacities between smokers and nonsmokers [14, 31, 35, 67].

Seven studies mentioned patient's comorbidities. Two studies focused on the influence of diabetes mellitus (DM) and

Table 2 Baseline characteristics, incidence of MU, operative characteristics, evaluation of patients, and proton pump inhibitor prophylaxis

Author	*N*	N ulcer (%)	Sex F/M	BMI	Age	Laparoscopic or open approach (L/O)	Hand-sewn Anastomosis	Staple line anastomosis	Time to MU (months)	PPI Y/N (months)	Follow up (months)	Symptomatic (S) or all patients (A) assessed
Azagury	–	103	83	–	45±11	–	–	–	22 (0.5–240)	–	–	
Bendewald	181 654	60 (7.2)	157/24 566/88	48.6 50.2	45.7 44.7	L L	181 0	0 654	–	Y (1)	14.4	S
Capella and Capella [20]	623	78 (12.5)	–	–	–	O	–	–				S
Csendes et al. [23]	550	6 (1.0)	5/1	–	49 (32–70)	O N=392 L N=158	–	–	–	N	18–96	A
Csendes [22]	441	25 (5.7)	358/97	43	41	O N=360 L N=81	81	360	1	N	17	A
Dallal	201	7 (3.5)	–	–	–	ON=3 L N=198	Front	Backside	7.4 (3–14)	Y (3)	19.8	S
D'Hondt	449		314/135	43 (35–63)	39 (16–68)	L	449 (over sewn)	449				
El-Hayek	–	112	95/17	–	49.3±10.6	–	–	112	–	Not mentioned	Not mentioned	S
Felix[a]	3430	35 (1.0)	3051/379	46		L	3430	0	18 (3–70)	N	48	S
Garrido	118	9 (7.6)	100/18	44.1 (5.9)	42 (11)	O N=74 L N=44	74	44	2	Y (2)	2	A
Gumbs	347	16 (4.0)	278/69	51.1	41.5	L	118 oversewn	118	6.3 (1–13)	N	Not mentioned	S
Hartin	183	23 (12.7)	153/30	49	42	O N=10 L N=173	–	–	8 (2–16)	N	12 (9–14)	S
Higa	1,040	30 (3,1)	859/181	47.8 (35–78)		L	0	1040	–	N	Not mentioned	S
Howard	20	5 (25)	15/5	–	38.1±1.9	O	–	–	–	N	12–78	S
Jordan	412	34 (8.3)	–	–	–	O	0	412	–	N		S
Kalaiselvan[a]	1213	10 (0.8)	–	51.9 (39.1–78.4)	–	L	1213	0	13.5 (6–19)	Y (24)	24	S
Kligman	160	1 (0.6)	147/13	47.3±6.4	41.1±8.6	L	0	160	–	N	–	S
Lublin[a]	902	8 (0.9)	777/125	47.7	44	L	902	902	5.2 (1.7–12.4)	Y (1)	13	S
Luján	350	11 (2.8)	–	–	–	L	–	350	1.5–36	N	25.5	S
MacLean	123	20 (16.0)	–	–	–	O	–	–	–	N	12–96	S
Marano	12	12 (6.0)	20/3	–	–	L	–	–	–	N	15	S
Papasavas	116	4 (3.4)	101/15	49.3 (35–77)	42.4	L	–	116	–	N	18	S
Patel	2282	122 (5.3)	–	–	–	O N=1621 L N=661	0	2282	–	N	Different	S
Pope	158		114/44	53	42	O	0	158				
Printen	653	20 (3.1)	–	–	–	O	–	–	–	N	Not mentioned	S
Ramirez	287	14 (4.9)	255/32	47.3	40.7	L	0	NRCS: *N*=182 RCS: *N*=105	–	N	12	S
Rasmussen	260	19 (7.0)	234/26	44	42	L	260 outer layer	260 inner layer	4.3 (1–12)	N	10.2	S
Rawlins	228	5 (2.2)	–	–	–	L	228 (ovesewn)	228	–	Y (>3)	21	S
Ruiz-de-Adana	232	2 (1.0)	195/37	46±4	–	L	232	0	–	Y (?)	Not mentioned	S
Sacks	1,095	28	–	49.6	45.2	L	1,095 (non absorbable)	0	–	N	22.8	S

Table 2 (continued)

Author	*N*	N ulcer (%)	Sex F/M	BMI	Age	Laparoscopic or open approach (L/O)	Hand-sewn Anastomosis	Staple line anastomosis	Time to MU (months)	PPI Y/N (months)	Follow up (months)	Symptomatic (S) or all patients (A) assessed
Sacks	2,190	29	–	50.7	44.1	L	2,190 (absorbable suture)	0				
Sanyal	191	24 (12.5)	–	–	–	O	–	–	–	N	12	S
Sapala[b]	173	1 (0.6)	–	50.5	46.6	O	173	0	14	N	36	S
Sasse	1,690	7 (0.4)	1,453/237	47	44	–	–	–	–	N	36	S
Spaulding[a]	150	14 (9.3)	105/45	55.7	41	O	–	–	–	N	Not mentioned	S
Suggs	438	25 mm stapler: 19 (5,4) 21 mm stapler: 4 (6,3)	–	–	–	L	0	438	–	N	13.8 (1–42)	S
Suter	1,128	9	865/263	45.1	40.3	L	0	1,128	–	Y (1)	Not mentioned	S
Vasquez	231	Permanent 31/231 (13.4)	–	–	–	L	231 permanent	0	–	N	3	S
	84	Absorbable 2/84 (2.3)	–	–	–	L	84 absorbable					
Wheeler[a]	–	6	–	–	–	–	–	–	0.9–48	Y, *n*=2 N, *n*=4	Not mentioned	S
Wilson	1,001	81 (8.1)	–	–	–	O/L	–	–	20 (1.0–103)	Y/N	Not mentioned	S
Yang [c]	20	22 (3,5)										
(10 LRYGB)	–	42.6	34.6	L	–	–	–	N	Not mentioned	S		
Total	16.987[d]	787[e]								–	–	–

NRCS not reinforced circular staples, *RCS* reinforced circular staples, *BMI* body mass index, *PPI* proton pump inhibitor, *MU* marginal ulcer, *PPI* proton pump inhibitor post operative

[a] Describes only patients with perforated ulcer (not calculated in total to avoid bias)

[b] Series consisted of "micropouch" patients only

[c] Symptomatic patients who underwent LRYGB

[d] Csendes [22]: 441 patients are not calculated because already 550 patients from Csendes (2011) was included. Azagury et al. and El-Hady et al. were excluded because only patients GI with symptoms were included

[e] Csendes et al. [23]: six of the six patients with MU from the 550 patients were included because they had a different kind of ulcer than other patients with MU in the 441 patients from Csendes [22]. Azagury et al. and El-Hady et al. were excluded because only patients with GI symptoms were included

cardiovascular disease on MU. One found an increased risk for MU in patients who suffered from DM. The other study did not [12, 15, 32–35, 52]. None of the studies found a correlation between the use of alcohol and the presence of MU [67].

Symptoms

Csendes and Garrido found that of all patients with MU, 28–100 % does not have "typical" symptoms as epigastric or abdominal pain, nausea, and/or vomiting. Some patients have no symptoms at all (Table 3) [22, 25].

A total of 30 articles (777 patients) described symptoms at presentation. Of the 777 patients, 441 (56.8 %) experienced epigastric burn. In 117 (15.1 %) patients, bleeding was the main symptom. Patients with perforated MU will present with signs of acute abdomen at the emergency room [14, 15, 17, 24, 26–29, 31, 34, 35, 37, 40, 43, 68].

Suggs et al. described 23 patients who developed MU, only seven had the classical, non-acute symptoms such as abdominal pain. Ten presented with melena (four also had hematemesis) and eight required blood transfusion. Of the patients, 17 out of 23 were readmitted.

Perforation

The incidence of perforated MU after LRYGB is around 1–2 % in the total population, which means that around 20 % of the patients with MU present with perforation [14, 24, 26, 28, 29, 35, 40]. Felix et al. described that 69 % of the patients with a perforated MU had identifiable risk factors including smoking, use of NSAIDs or steroids. Although 31 % had no identifiable risk factor, roughly a third of this group had a history of treatment for MU. Twenty percent of the patients had no warning signs prior to perforation [14].

Ulcer Treatment: Pharmaceutical Treatment, Reoperation, and Upper Endoscopy

Medical treatment of MU consists of PPIs, H2 antagonists, Sulcrafate®, or a combination of these medications. Thirty-one articles mentioned a form of treatment. Of the 801 (including patients with perforation) patients, 67.9 % could be sufficiently treated with medication alone [9, 11, 13, 22–25, 27, 30, 33–35, 37, 43, 52–54, 56, 67–70]. Endoscopy confirmed the healing properties of PPIs in late MU. Other patients were treated by radiologic or endoscopic interventions. Around 23 % of all patients needed one or more reoperations for complete healing [13, 15, 27, 31, 43, 52–54, 67].

Most of the patients in need of surgery are those with perforation, dilated pouch, retractable marginal ulcer, or gastrogastric fistulae. The majority of data about revisional surgery for marginal ulceration reflects the open operation technique which is known for its greater complication rate including leakage, wound infection, blood loss, and higher mortality rate. At present, laparoscopic revisions are effective and safe also after open primary procedure [31, 35, 45, 71–75]. All patients who presented with perforation needed reoperation or at least radiology-assisted drainage [14, 26, 28, 35, 40].

Patel et al. presented a case series of reoperation for marginal ulceration with a success rate of 87 % [31]. In some studies, an attempt was made to enhance the healing process by removal of the foreign material with upper endoscopy [15, 32, 34, 67, 70].

Proton Pump Inhibitors as Prophylaxis

In the last few years, the prophylactic prescription of PPIs after RYGB has become standard procedure. However, no consensus exists about the duration of usage (Table 2). In the literature, the time of postoperative PPI administration differs between 30 days to 2 years, some authors argue for lifelong usage [19, 24, 25, 28, 29, 33, 40, 52].

D'Hondt et al. found that there was no statistical significance in the incidence of MU between patients who did or did not receive PPIs postoperatively. The incidence of MU in this study was 10.7 % with a minimal follow up of 6 months [52].

As previous described, NSAIDS increase the risk on ulcer formation. However PPIs provide significant protection used simultaneously with NSAIDS [60].

Discussion

The performance of Roux-en-Y gastric bypass (both primary and as revisional procedure) is globally increasing to enormous numbers with a subsequent rise in its associated complications such as marginal ulcer. Most articles in this systematic review on MU are retrospective.

The majority of studies examined symptomatic patients. The two studies examining a consecutive group of patients show that the incidence of MU is underestimated. One of the studies had a follow-up period of 2 months after surgery. It is likely that the ulcers were still superficial due to the early detection and therefore less prone to cause symptoms.

As soon as the importance of the position of the pouch became known, the operation was internationally standardized. Introduction of the laparoscopic technique further contributed to a standard pouch formation procedure [12, 48]. A dilated pouch may predispose to late ulceration because of the increasing number of parietal cells after dilatation [12, 76]. Some authors advocate a vagotomy in an attempt to reduce the secretion of gastric acid [12, 15, 43, 76, 77]. Acid secretion is also partially regulated by gastrin levels. Because of the

Table 3 Characteristics of symptomatology of MU

Author	N with MU	Epigastric pain/vomiting	Bleeding	Perforation	Asymptomatic
Azagury	103	82	24	0	–
Csendes et al. [23]	6	5	1	0	0
Csendes [22]	25	21	1	0	7
Dallal	7	3	3	1	0
D'Hondt	48	–	–	1	–
El-Hayek	112	49/12	3	–	–
Felix	35	0	0	35	–
Garrido	9	0	0	0	9
Gumbs	16	10	16	0	0
Hartin	23	–	9	6	8
Higa	30	–	6	2	–
Howard	5	–	–	–	–
Jordan	34	29	9	2	1
Kalaiselvan	10	–	0	10	–
Lublin	8	2	0	8	6
Luján	11	10	0	1	0
Marano	12	5/7	1	0	0
Papasavas	4	1	2	1	–
Patel[a]	39	26	8	1	–
Pope	26	26	–	–	–
Printen	20	10	10	–	–
Ramirez	14	–	–	1	–
Rasmussen	19	17	4	–	–
Ruiz-de-Adana	2	–	2	–	–
Sacks	28	22	2	3	–
Sacks	29	21	5	0	–
Sanyal	24	24	–	–	–
Sapala	1	–	–	–	–
Sasse	7	–	0	7	–
Spaulding[b]	14	+	+	+	–
Suggs	23	7	10	–	–
Suter	9	–	1	–	–
Wheeler[c]	6	–	1	6	–
Wilson	81	81	–	–	–
Yang	10	–	–	–	–
Total	850[d]	443	118	134	

MU marginal ulcer

[a] Only 39 of the 122 patients who underwent operative revision presented with MU are discussed in the paper

[b] The volume of patients presenting with symptoms is not described

[c] Only six (with perforation) are discussed in detail

[d] All the patients, also those with perforation are included

negative feedback mechanism, acid secretion rises when pouch pH is high [78–80]. A decrease in pH increases the development of MU. In most patients, treatment with PPIs alone is adequate to treat and prevent MU. This supports the role of gastric acid in the formation of MU [27, 68, 70, 76].

The protective mechanism of stomach evacuation is probably due to the subsequent absence of acid production by the remnant stomach, caused by the hormonal feedback mechanism. The formation of fistulae between the remnant stomach and the pouch and gastrogastric fistulae enhance the development of MU because they increase the amount of gastric acid. The vulnerable jejunal mucosa is exposed to the harmful acid [11, 21, 32, 76, 81].

Various ways to create the gastrojejunostomy are described [82]. Evidence supports the use of absorbable suture material, as foreign materials are found in a third of the MUs [21].

The incidence of *H. pylori* infection found at the preoperative screening in patients undergoing bariatric surgery ranges from 22.4 to 61.3 % depending on the patients region of origin [50, 51, 83, 84]. Some authors suggest that *H. pylori* increases

a variety of gastrointestinal symptoms after gastric bypass and therefore advise standard eradication therapy even without testing in patients prior to surgery. In perforated ulcer disease, Hartin et al. hypothesize that preoperative detection and eradication of *H. pylori* infection may decrease the incidence and/or severity of peptic ulcer-related problems but this is not scientifically supported [26, 50].

Some studies advocate the opposite and in the literature only some of the patients presenting with MU tested positive for *H. pylori*. In this review, the mean incidence of *H. pylori* infection in MU is 12 % (range, 0–33). The percentage of *H. pylori* infection in normal gastric and/or duodenal ulcers is between 70 and 97 % [64, 85–89]. Although patients with perforated MU were not included in the total group of patients to prevent bias, analysis of these patients is important because early identification of MU can prevent this serious complication [14]. All patients described needed reoperation or drain placement. After Sasse et al. adopted a two-step approach to ulcer prevention, no new cases of perforation occurred. This protocol included a 12-week empirical treatment with PPI direct postoperative and a zero-tolerance policy towards the use of NSAIDs [35].

The ulcerogenic potential of NSAIDs has been extensively studied in the general population. NSAIDs achieve the anti-inflammatory effect by inhibiting the cyclo-oxygenase (COX)-2 pathway. COX 2 is responsible for the tissue prostaglandin production. They also interfere with the COX-1 and thereby the production of the PGE_2 prostaglandin responsible for the gastric mucous barrier [61–63]. The exact significance of NSAIDs as a factor in MU is unknown because quantification of usage is difficult to assess. Most patients describe over-the-counter usage of NSAIDs on an as needed basis [34]. The same principal applies to smoking. Although the percentage of smokers is given in the affected population, the percentage in control groups is unknown. Only one study mentioned the use of alcohol, it was not significantly related to the development of MU.

Prophylactic PPI administration was introduced in some research groups after evaluation. However, the variety of duration in administration, the small number of patients, and the lack of follow up made it impossible to provide solid evidence concerning the benefits of this protocol; a positive effect does seem to exist [19, 24, 28, 29, 52].

This review did not focus on the treatment of MU. Most patients respond well on PPIs and lifestyle adjustments alone [32–34]. In order to achieve healing, NSAIDs should be stopped; patients who are smokers must be motivated to quit smoking and anticoagulation therapy should be antagonized in case of hemorrhagic presentation. Revisional bariatric surgery is technically challenging and has been associated with high morbidity rates and can be potentially lethal. However, the laparoscopic approach has shown to be safe with good results [31, 35, 45, 71–73].

Conclusion

This systematic review represents the best available evidence to date. The incidence of MU ranges from 0.6 to 25 % and no methodological high-quality studies are available for identification of the risk factors.

The pathophysiology of MU remains unclear. The only evidence-based consensus is that the risk of MU can be diminished with proximal pouch orientation and the use of absorbable suture material. Risk factors seem to be NSAID usage without PPIs, smoking [14, 17, 28, 31], and use of non-absorbable suture material [19, 21].

It can be concluded that the pathogenesis of MU formation after RYGB is different compared to PUD. Various factors contribute to this complication [28, 31, 32, 37].

Symptoms at presentation such as epigastric burn, vomiting, hematemesis, or melena merit diagnostics for MU. An acute abdomen, weeks to months and even years after RYGB, may indicate perforation. MU can be treated with PPIs, sometimes with Ulcogant®. When perforated, reoperation or (percutaneous) drainage is often required.

A trend is noticed in favor of postoperative prophylactic PPI administration to prevent MU. With the increasing number of LRYGB and the consequent rise in MU, many of which are asymptomatic, more knowledge about the pathophysiology, prevention, and treatment is required.

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References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA. 2006;295(13):1549–55.
2. WHO Director-General. Life in the 21st century: a vision for all. Geneva: World Health Organization; 1998.
3. Khaodhiar L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions. Clin Cornerstone. 1999;2(3):17–31.
4. Colquitt JL, Picot J, Loveman E, et al. Surgery for obesity. Cochrane Database Syst Rev. 2009;2, CD003641.
5. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
6. Mingrone G, Panunzi S, De GA, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85.
7. Siddiqui A, Livingston E, Huerta S. A comparison of open and laparoscopic Roux-en-Y gastric bypass surgery for morbid and super obesity: a decision-analysis model. Am J Surg. 2006;192(5):e1–7.
8. Schneider BE, Villegas L, Blackburn GL, et al. Laparoscopic gastric bypass surgery: outcomes. J Laparoendosc Adv Surg Tech A. 2003;13(4):247–55.

9. Sanyal AJ, Sugerman HJ, Kellum JM, et al. Stomal complications of gastric bypass: incidence and outcome of therapy. Am J Gastroenterol. 1992;87(9):1165–9.
10. POLS gezondheid en Welzijn, RIVM, Obesitas. http://www.nationaalkompas.nl/gezondheidsdeterminanten/persoonsgebonden/lichaamsgewicht/hoeveel-mensen-hebben-overgewicht-of-ondergewicht/. 27 March 2012.
11. MacLean LD, Rhode BM, Nohr C, et al. Stomal ulcer after gastric bypass. J Am Coll Surg. 1997;185(1):1–7.
12. Sapala JA, Wood MH, Sapala MA, et al. Marginal ulcer after gastric bypass: a prospective 3-year study of 173 patients. Obes Surg. 1998;8(5):505–16.
13. Howard L, Malone M, Michalek A, et al. Gastric bypass and vertical banded gastroplasty—a prospective randomized comparison and 5-year follow-up. Obes Surg. 1995;5(1):55–60.
14. Felix EL, Kettelle J, Mobley E, et al. Perforated marginal ulcers after laparoscopic gastric bypass. Surg Endosc. 2008;22(10):2128–32.
15. Azagury DE, Abu Dayyeh BK, Greenwalt IT, et al. Marginal ulceration after Roux-en-Y gastric bypass surgery: characteristics, risk factors, treatment, and outcomes. Endoscopy. 2011;43(11):950–4.
16. Caruana JA, McCabe MN, Smith AD, et al. Risk of massive upper gastrointestinal bleeding in gastric bypass patients taking clopidogrel. Surg Obes Relat Dis. 2007;3(4):443–5.
17. Higa KD, Boone KB, Ho T. Complications of the laparoscopic Roux-en-Y gastric bypass: 1,040 patients—what have we learned? Obes Surg. 2000;10(6):509–13.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
19. Bendewald FP, Choi JN, Blythe LS, et al. Comparison of hand-sewn, linear-stapled, and circular-stapled gastrojejunostomy in laparoscopic Roux-en-Y gastric bypass. Obes Surg. 2011;21(11):1671–5.
20. Capella JF, Capella RF. Staple disruption and marginal ulceration in gastric bypass procedures for weight reduction. Obes Surg. 1996;6(1):44–9.
21. Capella JF, Capella RF. Gastro-gastric fistulas and marginal ulcers in gastric bypass procedures for weight reduction. Obes Surg. 1999;9(1):22–7.
22. Csendes A, Burgos AM, Altuve J, et al. Incidence of marginal ulcer 1 month and 1 to 2 years after gastric bypass: a prospective consecutive endoscopic evaluation of 442 patients with morbid obesity. Obes Surg. 2009;19(2):135–8.
23. Csendes A, Torres J, Burgos AM. Late marginal ulcers after gastric bypass for morbid obesity. Clinical and endoscopic findings and response to treatment. Obes Surg. 2011;21(9):1319–22.
24. Dallal RM, Bailey LA. Ulcer disease after gastric bypass surgery. Surg Obes Relat Dis. 2006;2(4):455–9.
25. Garrido Jr AB, Rossi M, Lima Jr SE, et al. Early marginal ulcer following Roux-en-Y gastric bypass under proton pump inhibitor treatment: prospective multicentric study. Arq Gastroenterol. 2010;47(2):130–4.
26. Hartin Jr CW, ReMine DS, Lucktong TA. Preoperative bariatric screening and treatment of *Helicobacter pylori*. Surg Endosc. 2009;23(11):2531–4.
27. Jordan JH, Hocking MP, Rout WR, et al. Marginal ulcer following gastric bypass for morbid obesity. Am Surg. 1991;57(5):286–8.
28. Kalaiselvan R, Exarchos G, Hamza N, Ammori BJ. Incidence of perforated gastrojejunal anastomotic ulcers after laparoscopic gastric bypass for morbid obesity and role of laparoscopy in their management. Surg Obes Relat Dis. 2011;8(4):423–8.
29. Lublin M, McCoy M, Waldrep DJ. Perforating marginal ulcers after laparoscopic gastric bypass. Surg Endosc. 2006;20(1):51–4.
30. Marano Jr BJ. Endoscopy after Roux-en-Y gastric bypass: a community hospital experience. Obes Surg. 2005;15(3):342–5.
31. Patel RA, Brolin RE, Gandhi A. Revisional operations for marginal ulcer after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2009;5(3):317–22.
32. Rasmussen JJ, Fuller W, Ali MR. Marginal ulceration after laparoscopic gastric bypass: an analysis of predisposing factors in 260 patients. Surg Endosc. 2007;21(7):1090–4.
33. Ruiz-de-Adana JC, Lopez-Herrero J, Hernandez-Matias A, et al. Laparoscopic hand-sewn gastrojejunal anastomoses. Obes Surg. 2008;18(9):1074–6.
34. Sacks BC, Mattar SG, Qureshi FG, et al. Incidence of marginal ulcers and the use of absorbable anastomotic sutures in laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2006;2(1):11–6.
35. Sasse KC, Ganser J, Kozar M, et al. Seven cases of gastric perforation in Roux-en-Y gastric bypass patients: what lessons can we learn? Obes Surg. 2008;18(5):530–4.
36. Spaulding L. The impact of small bowel resection on the incidence of stomal stenosis and marginal ulcer after gastric bypass. Obes Surg. 1997;7(6):485–7.
37. Suggs WJ, Kouli W, Lupovici M, et al. Complications at gastrojejunostomy after laparoscopic Roux-en-Y gastric bypass: comparison between 21- and 25-mm circular staplers. Surg Obes Relat Dis. 2007;3(5):508–14.
38. Suter M, Donadini A, Calmes JM, et al. Improved surgical technique for laparoscopic Roux-en-Y gastric bypass reduces complications at the gastrojejunostomy. Obes Surg. 2010;20(7):841–5.
39. Vasquez JC, Wayne OD, Farrell TM. Fewer gastrojejunostomy strictures and marginal ulcers with absorbable suture. Surg Endosc. 2009;23(9):2011–5.
40. Wheeler AA, de la Torre RA, Fearing NM. Laparoscopic repair of perforated marginal ulcer following Roux-en-Y gastric bypass: a case series. J Laparoendosc Adv Surg Tech A. 2011;21(1):57–60.
41. Yang CS, Lee WJ, Wang HH, et al. The influence of *Helicobacter pylori* infection on the development of gastric ulcer in symptomatic patients after bariatric surgery. Obes Surg. 2006;16(6):735–9.
42. Snyder JM. Peptic ulcer following gastric bypass. Obes Surg. 2007;17(10):1419.
43. Printen KJ, Scott D, Mason EE. Stomal ulcers after gastric bypass. Arch Surg. 1980;115(4):525–7.
44. Frezza EE, Herbert H, Ford R, et al. Endoscopic suture removal at gastrojejunal anastomosis after Roux-en-Y gastric bypass to prevent marginal ulceration. Surg Obes Relat Dis. 2007;3(6):619–22.
45. Madan AK, DeArmond G, Ternovits CA, et al. Laparoscopic revision of the gastrojejunostomy for recurrent bleeding ulcers after past open revision gastric bypass. Obes Surg. 2006;16(12):1662–8.
46. Siilin H, Wanders A, Gustavsson S, et al. The proximal gastric pouch invariably contains acid-producing parietal cells in Roux-en-Y gastric bypass. Obes Surg. 2005;15(6):771–7.
47. Sapala JA, Wood MH, Sapala MA, et al. The micropouch gastric bypass: technical considerations in primary and revisionary operations. Obes Surg. 2001;11(1):3–17.
48. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, Roux-en-Y: preliminary report of five cases. Obes Surg. 1994;4(4):353–7.
49. Csendes A, Burgos AM, Smok G, et al. Endoscopic and histologic findings of the foregut in 426 patients with morbid obesity. Obes Surg. 2007;17(1):28–34.
50. Ramaswamy A, Lin E, Ramshaw BJ, et al. Early effects of *Helicobacter pylori* infection in patients undergoing bariatric surgery. Arch Surg. 2004;139(10):1094–6.
51. Erim T, Cruz-Correa MR, Szomstein S, et al. Prevalence of *Helicobacter pylori* seropositivity among patients undergoing bariatric surgery: a preliminary study. World J Surg. 2008;32(9):2021–5.
52. D'Hondt MA, Pottel H, Devriendt D, et al. Can a short course of prophylactic low-dose proton pump inhibitor therapy prevent stomal ulceration after laparoscopic Roux-en-Y gastric bypass? Obes Surg. 2010;20(5):595–9.

53. Luján JA, Frutos MD, Hernandez Q, et al. Experience with the circular stapler for the gastrojejunostomy in laparoscopic gastric bypass (350 cases). Obes Surg. 2005;15(8):1096–102.
54. Ramirez MC, Rodriguez J, Varghese F, et al. Reinforced circular stapler in bariatric surgery. JSLS. 2010;14(3):358–63.
55. Schirmer B, Erenoglu C, Miller A. Flexible endoscopy in the management of patients undergoing Roux-en-Y gastric bypass. Obes Surg. 2002;12(5):634–8.
56. Rawlins L, Rawlins MP, Brown CC, Schumacher DL. Effect of *Helicobacter pylori* on marginal ulcer and stomal stenosis after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2012;9(5):760–4.
57. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet. 2002;359(9300):14–22.
58. Tytgat GN. Etiopathogenetic principles and peptic ulcer disease classification. Dig Dis. 2011;29(5):454–8.
59. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, *Helicobacter pylori*, and smoking. J Clin Gastroenterol. 1997;24(1):2–17.
60. Wilson JA, Romagnuolo J, Byrne TK, et al. Predictors of endoscopic findings after Roux-en-Y gastric bypass. Am J Gastroenterol. 2006;101(10):2194–9.
61. Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs. 1996;52 Suppl 5:13–23.
62. Hayllar J, Bjarnason I. NSAIDs, Cox-2 inhibitors, and the gut. Lancet. 1995;346(8990):1629.
63. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclooxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006;55(12):1731–8.
64. Arroyo MT, Forne M, de Argila CM, et al. The prevalence of peptic ulcer not related to *Helicobacter pylori* or non-steroidal anti-inflammatory drug use is negligible in southern Europe. Helicobacter. 2004;9(3):249–54.
65. Konturek SJ, Konturek PC, Brzozowski T. Prostaglandins and ulcer healing. J Physiol Pharmacol. 2005;56 Suppl 5:5–31.
66. Kligman MD, Thomas C, Saxe J. Effect of the learning curve on the early outcomes of Laparoscopic Roux en Y gastric bypass. Am Surg. 2003;69(4):304–9.
67. El-Hayek K, Timratana P, Shimizu H, Chand B. Marginal ulcer after Roux-en-Y gastric bypass: what have we really learned? Surg Endosc. 2012;26(10):2789–96.
68. Gumbs AA, Duffy AJ, Bell RL. Incidence and management of marginal ulceration after laparoscopic Roux-Y gastric bypass. Surg Obes Relat Dis. 2006;2(4):460–3.
69. Azagury D, Dumonceau JM, Morel P, et al. Preoperative work-up in asymptomatic patients undergoing Roux-en-Y gastric bypass: is endoscopy mandatory? Obes Surg. 2006;16(10):1304–11.
70. Pope GD, Goodney PP, Burchard KW, et al. Peptic ulcer/stricture after gastric bypass: a comparison of technique and acid suppression variables. Obes Surg. 2002;12(1):30–3.
71. Racu C, Dutson EP, Mehran A. Laparoscopic gastrojejunostomy revision: a novel approach to intractable marginal ulcer management. Surg Obes Relat Dis. 2010;6(5):557–8.
72. Brolin RE, Cody RP. Impact of technological advances on complications of revisional bariatric operations. J Am Coll Surg. 2008;206(3):1137–44.
73. Kolkman JJ, Meuwissen SG. A review on treatment of bleeding peptic ulcer: a collaborative task of gastroenterologist and surgeon. Scand J Gastroenterol Suppl. 1996;218:16–25.
74. Nguyen NT, Hinojosa MW, Gray J, et al. Reoperation for marginal ulceration. Surg Endosc. 2007;21(11):1919–21.
75. St Jean MR, Dunkle-Blatter SE, Petrick AT. Laparoscopic management of perforated marginal ulcer after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2006;2(6):668.
76. Hedberg J, Hedenstrom H, Nilsson S, et al. Role of gastric acid in stomal ulcer after gastric bypass. Obes Surg. 2005;15(10):1375–8.
77. Hedberg J, Hedenstrom H, Sundbom M. Wireless pH-metry at the gastrojejunostomy after Roux-en-Y gastric bypass: a novel use of the BRAVO system. Surg Endosc. 2011;25(7):2302–7.
78. Yao X, Forte JG. Cell biology of acid secretion by the parietal cell. Annu Rev Physiol. 2003;65:103–31.
79. Sandvik AK, Waldum HL. Aspects of the regulation of gastric histamine release. Scand J Gastroenterol Suppl. 1991;180:108–12.
80. Kidd M, Modlin IM, Tang LH. Gastrin and the enterochromaffin-like cell: an acid update. Dig Surg. 1998;15(3):209–17.
81. Mason EE, Munns JR, Kealey GP, et al. Effect of gastric bypass on gastric secretion. Am J Surg. 1976;131(2):162–8.
82. Giordano S, Salminen P, Biancari F, et al. Linear stapler technique may be safer than circular in gastrojejunal anastomosis for laparoscopic Roux-en-Y gastric bypass: a meta-analysis of comparative studies. Obes Surg. 2011;21(12):1958–64.
83. Papasavas PK, Gagne DJ, Donnelly PE, et al. Prevalence of *Helicobacter pylori* infection and value of preoperative testing and treatment in patients undergoing laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2008;4(3):383–8.
84. Renshaw AA, Rabaza JR, Gonzalez AM, et al. *Helicobacter pylori* infection in patients undergoing gastric bypass surgery for morbid obesity. Obes Surg. 2001;11(3):281–3.
85. Nishikawa K, Sugiyama T, Kato M, et al. Non-*Helicobacter pylori* and non-NSAID peptic ulcer disease in the Japanese population. Eur J Gastroenterol Hepatol. 2000;12(6):635–40.
86. Jyotheeswaran S, Shah AN, Jin HO, et al. Prevalence of *Helicobacter pylori* in peptic ulcer patients in greater Rochester, NY: is empirical triple therapy justified? Am J Gastroenterol. 1998;93(4):574–8.
87. Marshall BJ. One hundred years of discovery and rediscovery of *Helicobacter pylori* and its association with peptic ulcer disease. In: Mobey HLT, Mendz GL, Hazell SL, editors. *Helicobacter pylori*: physiology and genetics. Washington (DC): ASM Press; 2001.
88. Ciociola AA, McSorley DJ, Turner K, et al. *Helicobacter pylori* infection rates in duodenal ulcer patients in the United States may be lower than previously estimated. Am J Gastroenterol. 1999;94(7):1834–40.
89. Rollason TP. Campylobacter-like organisms in the human stomach. A review. Acta Gastroenterol Belg. 1986;49(1):63–9.