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Risk Factors for Marginal Ulcer After Gastric Bypass Surgery for Obesity

A Population-based Cohort Study

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Objective: This study aimed to assess risk factors for developing marginal ulcer (MU) after gastric bypass (GBP) surgery for obesity.

Background: MU is a common and potentially serious complication of GBP surgery, little is known about its etiology.

Methods: This population-based cohort study of GBP in 2006–2011 evaluated MU in relation to diabetes, hyperlipidemia, hypertension, chronic obstructive pulmonary disease (COPD), ulcer history, use of proton pump inhibitors (PPIs), aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs). Multivariable Cox proportional hazard regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for confounding.

Results: Among 20,294 GBP patients, diabetes and peptic ulcer history entailed statistically significantly increased risk of MU (HR = 1.26, 95% CI 1.03–1.55 and HR = 2.70, 95% CI 1.81–4.03), although hyperlipidemia, hypertension, and COPD did not. PPI users had an increased HR of MU (HR = 1.37, 95% CI 1.17–1.60). Aspirin and NSAID consumption less than or equal to median entailed decreased HRs of MU (HR = 0.56, 95% CI 0.37–0.86 and HR = 0.30, 95% CI 0.24–0.38), although aspirin and NSAID users more than median had an increased risk and no association with MU, respectively (HR = 1.90, 95% CI 1.41–2.58 and HR = 0.90, 95% CI 0.76–1.87). The use of SSRI less than or equal to median had a decreased risk of MU (HR = 0.50, 95% CI 0.37–0.67), although use more than median entailed increased HR (HR = 1.26, 95% CI 1.01–1.56).

Conclusions: Diabetes and peptic ulcer history seem to be risk factors for MU, but not hyperlipidemia, hypertension, or COPD. Limited doses of aspirin, NSAIDs, and SSRIs might not increase the risk, although higher doses of aspirin do. The association with PPI could be due to confounding by indication.

Keywords: anastomotic ulcer, bariatric surgery, ischemic ulcer, Roux-en-Y gastric bypass, RYGB

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Marginal ulcer (MU) is one of the most common complications after gastric bypass (GBP) surgery for obesity, and it is probably underreported. A single-center study in 2009 carried out routine endoscopy of 442 patients and found that 28% of MUs after GBP for obesity were asymptomatic.[1] Because MUs are often difficult to treat and might cause heavy bleeding or perforation, they can result in severe morbidity and even mortality. Recent studies indicate that MU occurs in 1%-9% of cases,[2] and a recent systematic review of 41 studies reported a mean frequency of 4.6% occurring between 1 month and 6 years after GBP.[3] The pathogenesis of MU seems to differ from that of peptic ulcers, and might involve gastric acid and impaired microcirculation.[4,5] The etiology of MU is largely unknown, which is due to a low number of studies and small sample sizes and contradictory findings in the available literature.[3] If patients with an increased risk of MU can be identified, it would enhance preoperative risk assessments and facilitate tailored prophylaxis regimens, patient instructions, and clinical follow-up. Surgical technique is probably involved in the mechanism behind MU. Earlier studies have suggested that a smaller gastric pouch is to prefer from this point of view,[6] and that choice of suture technique could play a role.[7] This can be due to amount of acid production, level of ischemia and inflammatory reaction in the tissue. Diabetes, hyperlipidemia, hypertension and tobacco smoking have been suggested as risk factors for MU, because they might interfere with the microcirculation and local perfusion.[8–10] The metabolic syndrome is characterized by insulin resistance, which in turn causes tissue damage through several pathways, including an overabundance of proinflammatory cytokines, vasoconstriction by circulating fatty acids, and activation of prothrombotic factors (eg, fibrinogen and plasminogen activator inhibitor 1). Both impaired microcirculation and inflammatory mechanisms have been suggested as contributors to MU after GBP. The role of peptic ulcer history is not well-studied in a larger, population-based setting. Earlier studies have established that there are overlapping risk factors between peptic ulcer disease (PUD) and MU.[9,11] A US study addressed this issue in 2007, but that study only included 7 patients with a history of peptic ulcer.[11] The potential benefit of prophylactic proton pump inhibitors (PPIs) is uncertain, because the incidence of MU is still significant after PPI-prophylaxis,[12] although a prophylactic effect has been suggested.[13] MUs often heal slowly, which results in prolonged PPI treatment,[10] and any effects of *Helicobacter pylori* (*H. pylori*) eradication seem limited.[10,14] Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been proposed to enhance the risk of MU, but this is under debate.[8] Use of serotonin re-uptake inhibitors (SSRIs) increase the risk of peptic ulcer bleeding, which might be due to anticoagulant properties, and also ulcerogenic effects on the intestinal mucosa.[15,16] We aimed to assess exposure to diabetes, hyperlipidemia, hypertension, chronic obstructive pulmonary disease (COPD, as a proxy for tobacco smoking), ulcer history, and use of PPI, aspirin, NSAIDs, and SSRIs, in relation to the risk of developing MU after GBP for obesity in a large cohort study.

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METHODS

Study Design

This population-based cohort study included all patients in Sweden who underwent GBP for obesity between January 1, 2006, and December 31, 2011, according to the Swedish Patient Registry. This register provides data on all hospitalizations with diagnoses and surgical procedures in Sweden since 1987. The exposure diagnoses diabetes, hyperlipidemia, hypertension, COPD, and ulcer history and the outcome diagnosis MU, were defined by the codes given in the International Classification of Diseases (ICD) versions 7–10. Surgical procedures were classified according to the Nordic Medico-Statistical Committee (NOMESCO, Swedish version, 1997), and the codes that defined laparoscopic and open GBP were JDF11 and JDF10, respectively. The Swedish Patient Registry has a 85%–95% validity of diagnoses in general,[17] and codes representing upper gastrointestinal surgery have been shown to have up to 99.6% positive predictive value.[18] Data on drug use were retrieved from the Swedish Prescribed Drug Registry, which was initiated in July 1, 2005. This register records all prescribed and dispensed drugs in the entire Swedish population (approximately 9.5 million inhabitants).[19] The register contains information on names of prescribed drug substances according to the anatomical therapeutic chemical (ATC) classification, and it also contains individual data on what amounts of the drug-specific Defined Daily Dose (DDD) that has been dispensed. Data on mortality and migration were collected from the National Registry of the Total Population, which provides complete information on updated dates of birth, death and migration in Sweden with a maximum of 14 days delay. This information enabled censoring of person-time no longer at risk of MU in the cohort due to death or emigration. All registers used in this study contain personal identity numbers, a 10-digit identifier assigned to all Swedish residents, which enabled all linkages of individuals in the study cohort to register data. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Definition of the Study Exposures

Among the 9 study exposures, 5 were the diagnoses diabetes, hyperlipidemia, hypertension, COPD (used as a proxy for tobacco smoking), and history of peptic ulcer, which were recorded in the Patient Registry before or at the time of GBP surgery. The remaining 4 exposures were use of the medications PPI, aspirin, NSAID, and SSRI, as recorded in the Prescribed Drug Registry. The following codes were used to identify the study exposures:

1. **Diabetes** was defined by ICD7 codes 260, ICD8 code 250, ICD9 codes 249–250 and ICD10 codes E10.0–E14.9.
2. **Hyperlipidemia** was defined by the ICD8 code 272, the ICD9 code 272, the ICD10 code E78, and also identified by use of lipid lowering agents defined as dispensed prescriptions of drugs with ATC-code C10.
3. **Hypertension** was defined by the ICD7 codes 444–447, ICD8 codes 400–404, ICD9 code 401, and ICD10 codes I10-I15.
4. **COPD** was defined by the ICD7 code 502, the ICD8 codes 491–492, the ICD9 codes 491—492, and the ICD10 codes J44.0-J44.9.
5. **History of peptic ulcer** was defined by the ICD7 codes 540–541, the ICD8 codes 531–533, the ICD9 codes 531–533, and the ICD10 codes K25-K27.
6. **Use of PPI was** defined by dispensed prescriptions of drugs with ATC-codes A02BC and A02BD.
7. **Use of aspirin** was defined by dispensed prescriptions of drugs with ATC-code B01AC.
8. **Use of other NSAIDS** was defined by dispensed prescriptions of drugs with ATC-codes M01AB, M01AC, M01AE, and M01AH.
9. **Use of SSRI** was defined by dispensed prescriptions of drugs with ATC-code N06AB.

To achieve statistical power, NSAIDs other than aspirin were analyzed as one group, because they have similar effects and indications. In Sweden, aspirin is mainly prescribed as primary or secondary prophylaxis for circulatory diseases.

Definition of Marginal Ulcer

The study outcome was a diagnosis of MU, as recorded in the Patient Registry. We used 2 definitions for MU, which were analyzed separately. First, we used a broad definition, including the code for ulcer at the gastro-entero anastomosis (for gastro-jejunal ulcer) and the codes for peptic ulcer in general (IDC10 codes K25-K28). Secondly, we used a narrow definition of MU, only including the specific code for gastro-jejunal ulcer (ICD10 code K28).

Statistical Analysis

Cox proportional hazard regression models were used to estimate the relative risk between the study exposures and MU, presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Absence of the studied exposure was used as reference category. Multivariable models were created to adjust for age (below or equal to median or above median), sex (male or female), and exposure status of all other 9 study variables (yes or no). Sensitivity analysis was carried out combining the GBP with obesity diagnosis (ICD10 code E66) with the purpose of excluding any patients undergoing GBP for other reasons than obesity, eg incurable gastric cancer or peritoneal metastases. Follow-up continued until a diagnosis of MU, death, emigration, or end of study period (December 31, 2011), whichever occurred first. Two analysis approaches were utilized to assess drug use: (1) At least 1 prescribed and dispensed prescription of the drug from 100 days before GBP surgery until end of follow-up (categorized into yes or no), and (2) amount of exposure based on defined daily dose (DDD), expressed as sum of DDD divided by follow-up time. Among study subjects with prescriptions of the study drugs, the median amount was calculated based on the total amount of the drug the patients collected during the study period. Study subjects with no collected prescription of the drug were assigned to a separate group of nonusers, and thus not included in calculation of the median use.

We confirmed that the proportional hazards assumption was not violated in our model. All statistical analyses were conducted using the statistical software SAS 9.4 (the Statistical Analysis System, SAS Institute, Cary, NC).

RESULTS

Study Participants

In total, 20,924 patients who underwent GBP were included in the study cohort and the mean follow-up time was 2 years. Basic characteristics of all GBP patients, the 694 GBP patients (3.3%) who developed MU are shown in Table 1. There were no major differences in the sex or age distribution between all patients and those who developed MU, but open surgery was over-represented compared with laparoscopic surgery among patients with MU (26%) versus those in the total cohort (14%). The frequencies of the 9 study exposures differed between the total cohort and the MU patients as presented in Table 1.

Medical Conditions and Risk of Marginal Ulcer

Among patients with diabetes, the adjusted HR of MU was 26% increased (HR 1.26, 95% CI 1.03–1.55) (Table 2). Patients with hyperlipidemia, hypertension, or COPD (proxy for smoking) did not have any statistically significantly increased risk of MU (HR 1.20,

TABLE 1. Demographic and Clinical Characteristics of the Study Cohort, Patients Undergoing Gastric Bypass Surgery for Obesity in Sweden Between 2006 and 2011

	Total	Patients Developing Marginal Ulcer
Total cohort	20,924	694
Sex		
Male	5057 (24%)	201 (29%)
Female	15,867 (76%)	493 (71%)
Age (median = 41)		
≤41 years	10,563 (50%)	321 (46%)
>41 years	10,361 (50%)	373 (54%)
Open surgery	2994 (14%)	179 (26%)
Laparoscopic surgery	17,930 (86%)	515 (74%)
Diabetes	3387 (16%)	155 (22%)
Hyperlipidemia	1732 (8%)	84 (12%)
Hypertension	5069 (24%)	210 (30%)
COPD*	309 (11%)	7 (1%)
Ulcer history	266 (1%)	25(4%)
PPI† use	11,251 (54%)	424 (61%)
Aspirin use¶	1626 (8%)	82 (12%)
NSAID‡ use	10,088 (48%)	282 (41%)
SSRI§ use	4453 (21%)	148 (21%)

*Chronic obstructive lung disease.
†Proton pump inhibitors.
‡Nonsteroidal anti-inflammatory drugs.
§Selective serotonin reuptake inhibitors.
¶Use is defined as at least one dispensed prescription from 100 days before surgery until end of follow-up.

95% CI 0.95–1.59, HR 1.17, 95% CI 0.97–1.43, and HR 0.56, 95% CI 0.26–1.17, respectively). Patients with a history of peptic ulcer disease experienced a strongly increased HR of MU (HR 2.70, 95% CI 1.81–4.03) (Table 2).

Use of Medication and Risk of Marginal Ulcer

Users of PPI had an increased HR of MU (HR 1.37, 95% CI 1.17–1.60). When doses were considered, PPI consumption below or equal to median was associated with a decreased HR of MU (HR 0.64, 95% CI 0.52–0.80), although a higher consumption was instead associated with an increased HR of MU (HR 2.49, 95% CI 2.11–2.95). The HR of developing MU among aspirin users was not significantly increased (HR 1.11, 95% CI 0.86–1.44) (Table 3), and the point HR remained unchanged after adjusting for use of PPI (data not shown). Aspirin consumption below or equal to median was rather associated with a decreased HR of MU compared with no consumption (HR 0.56, 95% CI 0.37–0.86), although aspirin use above the median was associated with an increased HR of MU compared with nonusers (HR 1.90, 95% CI 1.41–2.58). Users of NSAIDs had a decreased HR of MU (HR 0.56, 95% CI 0.48–0.66), which did not change after adjusting for PPI use (data not shown). The HR of MU was strongly decreased with consumption below or equal to median compared with no consumption (HR 0.30, 95% CI 0.24–0.38), although no association remained among study participants using NSAIDs above the median (HR 0.90, 95% CI 0.76–1.87). The HR of developing MU among all SSRI users was not statistically significantly increased. Regarding doses, study participants using SSRI below or equal to median experienced a decreased HR of MU compared with nonusers (HR 0.50, 95% CI 0.37–0.67), although SSRI consumption above the median was associated with a slightly increased risk of MU (HR 1.26, 95% CI 1.01–1.56).

DISCUSSION

This study indicates that diabetes and a history of ulcer are risk factors for MU after GBP surgery for obesity, although hyperlipidemia, hypertension and COPD are not. PPI use might not strongly decrease the risk of MU. Limited doses of aspirin, NSAIDs, or SSRIs do not seem to increase the risk of MU, although higher doses of aspirin seem to increase this risk.

Among strengths of this study are the population-based design, the large sample size, the completeness of follow-up, and the availability of several potential risk exposures that enabled adjustments for potential confounding. Moreover, the register data used are valid and complete, which guarantee robust identification of exposures and outcomes with minimal missing data or loss to follow-up. There are also several limitations. There might be some level of

TABLE 2. Risk of Developing Marginal Ulcer Among Patients Undergoing Gastric Bypass Surgery for Obesity in Sweden Between 2006 and 2011

	Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI
Diabetes	1.52	1.27–1.81	1.26	1.03–1.55
Hyperlipidemia	1.58	1.26–1.99	1.23	0.95–1.59
Hypertension	1.43	1.22–1.68	1.17	0.97–1.43
COPD	0.69	0.33–1.45	0.55	0.26–1.17
Ulcer history	2.95	1.98–4.40	2.70	1.81–4.03
PPI use†	1.39	1.19–1.62	1.37	1.17–1.60
Aspirin use	1.50	1.19–1.89	1.11	0.86–1.44
NSAID use	0.56	0.48–0.65	0.56	0.48–0.66
SSRI use	0.83	0.69–1.00	0.83	0.69–1.00

*Adjusted for sex, age, diabetes, hyperlipidemia, hypertension, COPD, and ulcer history when applicable.
†Use is defined as at least one dispensed prescription from 100 days before surgery until end of follow-up.
CI indicates confidence intervals; COPD, chronic obstructive pulmonary disease; HR, hazard ratios; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitor.

TABLE 3. Risk of Developing Marginal Ulcer Among Patients Undergoing Gastric Bypass Surgery for Obesity in Sweden Between 2006 and 2011

	Number of Cases	HR*	95% CI
No PPI use	271	1.00	Reference
PPI use ≤ median†	114	0.64	0.52–0.80
PPI use > median	309	2.49	2.11–2.95
No aspirin use	612	1.00	Reference
Aspirin use ≤ median	23	0.56	0.37–0.86
Aspririn use > median	59	1.90	1.41–2.58
No NSAID use	412	1.00	Reference
NSAID use ≤ median	83	0.30	0.24–0.38
NSAID use > median	199	0.90	0.76–1.07
No SSRI use	546	1.00	Reference
SSRI use ≤ median	50	0.50	0.37–0.67
SSRI > median	98	1.26	1.01–1.56

*Adjusted for sex, age, diabetes, hyperlipidaemia, hypertension, chronic obstructive lung disease, and ulcer history.
†Based on defined daily dose divided by follow-up time.
CI indicates confidence intervals; HR, hazard ratios; PPI, proton pump inhibitors; NSAID, nonsteroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibotor.

misclassification in the coding of MU. To assess any influence of such misclassification, we analyzed both standard peptic ulcer codes and the specific code for ulcer after gastro-jejuno-anastomosis, and the similar results argue against major influence of misclassification of the outcome. As in any observational study, influence of residual confounding by factors not adjusted for cannot be dismissed. Direct data on smoking and *H. pylori* status were not available in the registers, nor were data on body mass index (BMI). However, we did adjust the results for COPD, as proxy for tobacco smoking. The vast majority of patients suffering from COPD are tobacco smokers, typically with a long period of smoking history. The misclassification of the exposure to smoking among COPD patients should therefore be limited. We also adjusted for history of peptic ulcer, which might be regarded as a proxy for *H. pylori*. Another concern in nonrandomized studies of drug use is confounding by indication (protopathic bias),[20] and it is possible that use of the 4 drug exposures was influenced by the reasons for its use. Furthermore, some drugs obtained over the counter cannot be taken into account, particularly regarding NSAIDs, but long-term use is typically based on prescriptions, which counteracts influence of over the counter use. This source of error should be limited and random, and might therefore only slightly dilute risk estimates. However, aspirin for circulatory diseases is not sold over the counter in Sweden, and results for these drugs were similar.

Regarding the association between diabetes and MU, the results from previous studies diverge. A US study of 103 GBP surgery patients found an increased risk of MU among patients with diabetes, whereas another US study of 763 operated patients and an earlier Danish study of 260 patients found no such association.[8,9,11] The present study, based on many more GBP surgery patients, does suggest a role of diabetes in the etiology of MU, which should not be dismissed.

Peptic ulcer history has, to the best of our knowledge, not previously in a large population-based setting been investigated in relation to risk of MU. The strongly increased risk for MU in the present study is therefore particularly interesting. The mechanism underlying this association is not clear, but it may reflect an impact of *H. pylori* infection. A Danish study found that 32% of MU patients were infected with *H. pylori*, compared with 12% of controls,[11] and a Belgian study showed better treatment effect of PPI use among *H. pylori* positive MU patients compared with noninfected MU patients.[13] However, other studies have found no support for *H. pylori* being a risk factor for MU.[10,14] It is possible that a subgroup of patients with MU have *H. pylori* infection with ulcers that behave more like regular peptic ulcers, and thus are easier to treat with standard regimens.[13]

Hypertension was indicated as a risk factor for MU in a retrospective single-center study comprising 763 GBP operated patients.[9] However, another single-center study comprising 328 patients did not find any consistent association,[10] and a retrospective study of 260 GBP patients found no increased risk of MU among patients with hypertension.[11] Adding to these studies, the negative results of the present much larger study seem to indicate that hypertension is not a strong risk factor for MU.

The hypothesis that hyperlipidemia is a risk factor for MU has been addressed in only 2 previous studies, both showing no association with MU.[9,11] This is consistent with the findings of the present study.

Two US studies have indicated that tobacco use might be a risk factor for MU.[8,10] In our study using COPD as proxy for smoking, no increased risk of MU was found. However, there were few patients with COPD in our study and the exposure was only an indirect measure of smoking, why this finding must be interpreted cautiously.

Regarding PPI, a single-center study comprising 2535 GBP patients found an incidence of 2.3% MU after administrating routine prophylactic treatment with PPI to all patients 90 days after surgery, and 44% of the patients with MU needed surgical intervention, which suggests that PPI treatment is not effective in preventing MU or its complications. Another single-center study found that prophylactic treatment with PPI did not influence the risk of MU among patients who tested negatively for *H. pylori* before surgery, but reduced the risk of MU among preoperatively *H. pylori* positive patients.[13] There was no clear association between PPI use and MU in the present study. The increased risk among users of high doses of PPI might be due to confounding by indication with reverse cause and effect, particularly because there are no reasons to believe that such PPI use would increase the risk of MU. Because patients with symptoms of MU are likely to use PPI for their epigastric discomfort before the MU diagnosis is confirmed, the outcome probably precedes the exposure in this study. Yet, taken together with previous research, it seems likely that PPI is less effective in the treatment of MU compared with peptic ulcer disease.

This study revealed no clearly increased risk of MU after treatment with low doses of aspirin or NSAID, although higher doses of aspirin seem to increase this risk. As opposed to other NSAIDS, aspirin causes an irreversible and unselective inhibition of the cyclooxygenase (cox) enzyme and after suppression of prostaglandin synthesis. This prolonged damaging effect on the mucosa might partly explain the difference between the 2 groups. In the NSAIDs group, a lesser amount of more selective cox-2 inhibitors were also included, which could also account for some differences. As mentioned, OTC NSAIDs is not accounted for in this study. Although this is not, as explained, so much of an issue for aspirin, we cannot exclude that OTC consumption in the group we defined as nonusers could slightly dilute the results for NSAIDs. The seemingly protective effects of low doses of these drugs might speculatively be due to their anti-inflammatory and anticoagulant properties. Another potential explanation is confounding by indication, because pain caused by MU might lead to an increased use of analgetics like NSAIDs. Use of aspirin and other NSAIDs is a well-established risk factor for peptic ulcer disease, but has not been proven to increase the risk of MU,[8,10] although some studies contradict this.[21] The results of the present study seem to support the notion that low doses of aspirin and NSAIDs are not strong risk factors for MU.

Use of SSRIs has not previously been investigated in relation to risk of developing MU. As in the case of aspirin and NSAIDs, it is possible that the anticoagulant properties of low doses of SSRI might have a limited protective effect, but more research is needed to make any conclusions about this potential association.

In conclusion, this large and population-based cohort study suggests that diabetes and peptic ulcer history might be risk factors for developing MU after GBP surgery, although hyperlipidemia, hypertension, and COPD might not. PPI use might not be an effective prophylaxis of MU, and limited intake of aspirin, NSAIDs, and SSRIs does not seem to increase the risk of MU, although higher doses of aspirin seem to be associated with an increased risk of this condition.

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