Original Article

Evaluation of the Incidence of the Esophagogastric Pre-Cancerous Mucosal Lesions after Bariatric Surgery

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Abstract

Background: Bariatric surgery is associated with significant risk reduction for obesity-related and hormone-mediated cancers; however, few studies report gastric or esophageal cancer development after bariatric surgery. This study evaluates the incidence of pre-cancerous mucosal lesions one year after bariatric surgery.

Materials and Methods: Eligible patients for omega-loop gastric bypass and classic Roux-en-Y gastric bypass (RYGB) underwent upper endoscopy before bariatric surgery and one year after the procedure. Several biopsies were obtained from esophagogastric mucosa, all of which were evaluated by pathologists regarding the development of any pre-cancerous lesion.

Results: A total of 108 patients were included in the study. Seventy-one underwent omega bypass and 37 classic RYGB. Follow-up endoscopy indicated no dysplastic changes in esophagogastric mucosa one year after the surgery. The number of patients with gastric intestinal metaplasia was 22 and 25 before and after the surgery, respectively, which was not a statistically significant increase.

Conclusion: Bariatric surgeries might not increase the risk of developing pre-cancerous lesions in the esophagogastric mucosa. Further epidemiological studies may help to establish this finding.

Keywords: Bariatric surgery, obesity, stomach neoplasms

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Introduction

Obesity has become one of the greatest healthcare concerns worldwide. According to the definition of obesity by the World Health Organization, people with a body mass index (BMI) greater than 30 are considered obese, and those with BMI greater than 40 are severely obese.[1] It is also predicted that the prevalence of obesity may increase more rapidly due to the recent global health crisis[2]. Many studies have established the role of obesity in developing various morbid conditions, including diabetes mellitus (DM), cardiovascular diseases (CVDs), and cancers. The association of obesity with the leading causes of death highlighted the impact of obesity on public health.[3] Among all proposed methods for weight loss, bariatric surgery has demonstrated promising results in individuals who were not successful in losing weight with other less invasive methods. Studies indicated that bariatric surgery could effectively cause permanent weight loss and resolve obesity-associated comorbidities such as DM and hypertension (HTN).[4] There is also a strong association between obesity and cancer. Excessive accumulation of adipose tissue could contribute to chronic low-grade systemic

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inflammation and hormonal disturbances, which are major risk factors for cancer development. Bariatric surgery could reduce the odds of developing cancer by causing weight loss.[5] Few studies have postulated that bariatric surgery may be associated with an increased risk of gastrointestinal malignancies. These reports are limited to case reports; however, assessing the role of bariatric surgery in the development of pre-cancerous and cancerous lesions in the gastrointestinal tract is supposed to be necessary regarding the growing number of obese population and the emerging role of bariatric surgeries.[6,7] In this study, we planned to assess the pathological alterations in gastric and esophageal mucosa in patients who underwent bariatric surgery. We prospectively evaluated patients by upper endoscopy and mucosal biopsies before the surgery and one year after.

Materials and Methods

Study design and participants

This prospective observational study was conducted from March 2020 to June 2021 in two centers affiliated with Isfahan University of Medical sciences. The study was approved by the institutional review board of Isfahan University of Medical science, Isfahan, Iran coded as IR.MUI.MED.REC.1401.045 on 2022-05-08.

Candidates for bariatric surgery referred to surgery clinics in two academic hospitals of Isfahan University of medical science were invited to participate in the study. We included patients aged 20–50 years without any history of prior malignancies and gastrointestinal surgery. The type of surgery was determined through patient and surgeon consultation regarding the patients' risk factors, surgery complications, and patients' personal preferences. The most common types of surgeries in our institution were classic Roux-en-Y gastric bypass (RYGB) and omega-loop gastric bypass (Omega); therefore, only patients undergoing these types of surgery were enrolled in the study. It is notable that regarding the recent literature, all patients with a history of Gastro-Esophageal Reflux Disease (GERD) were suggested to undergo classic RYGB.[8] After obtaining the written informed consent, patients were referred to the gastroenterology clinic for pre-operative upper endoscopy. Patients were excluded from the study if the result of pathologic evaluation of the first endoscopy was positive for mucosal dysplasia, Heliobacter pylori infection, or gastroesophageal malignancies. Before the surgery, patients' demographic information, anthropometric measurements, history of smoking, and concomitant comorbid conditions, including DM and HTN, were obtained.

Endoscopy and pathology study

Two experienced gastroenterologists evaluated all patients with the same endoscope (GIFXQ-20 Olympus—Tokyo, Japan). Endoscopy was performed in the left lateral position. 5% lidocaine throat spray was used as an anesthetic agent. Four quadrant biopsies were obtained every 5 mm at the squamous-columnar junction of the esophagus, and 2 biopsies were taken from the gastric antrum of each patient. Also, during the endoscopy, additional biopsies were taken from lesions without any suspicion of mucosal abnormality. The specimens were immediately fixed in 10% formalin and transported to the pathology laboratory. The samples were embedded in paraffin, and 5 μm slices were prepared from paraffin-embedded specimens. The specimens were stained with hematoxylin-eosin and alcian blue stain. Two expert pathologists independently performed the microscopic evaluations of the specimens, and any controversies were solved by discussion.

Bariatric surgery procedures

All surgical procedures were performed by the same team using laparoscopic devices of the same brands. Omega bypass consists of an approximately 60 ml gastric pouch with gastrojejunal anastomosis and a jejunal loop (omega-loop) of approximately 180 cm. RYGB consists of a longitudinal gastric pouch with a maximum length of 6 cm (30 ml) and an end-to-side gastro-jejunal anastomosis with a side-to-side jejunojejunal anastomosis creating an alimentary limb of 120 cm and a biliopancreatic limb of 60 cm. All patients received 40 mg of pantoprazole for six-months post-surgery.

Outcomes

Our primary outcomes were defined as the development of a new dysplastic lesion in the gastroesophageal epithelium. Secondary outcomes were determined as the development of new intestinal metaplasia and new-onset GERD.

Statistical analysis

We planned to analyze data from the participants who completed the study (complete record analysis). Quantitative variables were reported as mean ± SD, and qualitative variables were reported as absolute counts and percentages. Independent t-test was used to define the differences in baseline characteristics of patients divided by the type of surgery (classic and omega); likewise, Pearson's Chi-squared test was used for nominal variables. Paired sample t-test and Mcnemar test were used to identify the differences in pre- and one-year post-surgical variables (intestinal metaplasia, GERD, and H. Pylori). To identify the possible effect of different surgical methods on the development of gastric intestinal metaplasia, we separately analyzed the data from each group, and separate *P* values were reported for each group. The level of significance was defined as $P \leq 0.005$. All analyses were performed using IBM SPSS software version 24, IBM, USA.

Results

A total of 145 patients enrolled in the study, of which 6 refused to fill the consent form, 5 were positive for H. Pylori at the time of biopsy, 12 planned to undergo other types of surgery, and 14 refused to undergo follow-up endoscopy. Eventually, 108 patients were included in the analysis, of which 78.7% (N = 85) were females. Before the surgery, mean BMI of the total study population was 42.86 ± 2.33.

The mean post-surgery BMI of the total population was 30.04 ± 2.58. There was no significant difference between BMI change in males and females. A summary of patients' baseline characteristics and outcomes are reported in Table 1, divided by sex.

Table 2 summarizes the patients' baseline characteristics divided by the type of surgery (omega and classic bypass). There was no statistically significant difference in baseline characteristics, including age, sex, history of smoking, history of HTN, DM, and the difference in the mean BMI of patients undergoing classic and omega bypass surgery.

Results from pre-operative upper endoscopy also indicated no statistically significant difference in the prevalence of intestinal metaplasia in the two groups of patients.

The results from one-year post-surgery upper endoscopy and further pathologic studies [Table 3] indicated that the group undergoing classic bypass surgery had significant improvement in GERD symptoms; however, the prevalence of intestinal metaplasia increased in both groups of patients, but it was not statistically significant. Thus, no significant association between the prevalence of intestinal metaplasia and bariatric surgery could be deducted. Two patients undergoing omega bypass surgery developed GERD post-surgically though this was not statistically significant; moreover, no sign of mucosal dysplasia either in the endoscopic or in the results from pathology report was observed. Eight patients developed marginal ulcers, of which six underwent omega bypass $P = 0.031$, and two underwent classic bypass $P = 0.5$. None of the participants was using PPI at the time of follow-up endoscopy. Pathologic studies also indicated two positive cases of H. Pylori infection, which was not statistically significant. Figures 1 and 2 demonstrate endoscopic image and pathology specimen from two patients in the study.

Table 1: Baseline and post-surgical variables in patients divided by sex

	Sex		*P*
	Male	Fmale	
	Count (% of total population) or mean±SD		
Intestinal metaplasia before surgery	3 (2.8%)	19 (17.6%)	0.325
Intestinal metaplasia after surgery	4 (3.7%)	21 (19.4%)	0.461
GERD before surgery	2 (1.9%)	9 (8.3%)	0.790
GERD post-surgery	1 (0.9%)	2 (1.9%)	0.606
BMI before surgery	42.43±2.68	42.98±2.24	0.320
Change in BMI	13.44±3.32	12.65±2.82	0.252
Smoking	4 (3.7%)	10 (9.3%)	0.476
Hypertension	11 (10.2%)	31 (28.7%)	0.322
Diabetes mellitus	7 (6.5%)	40 (37%)	0.154

Discussion

The global age-standardized incidence of gastric cancer is 11 per 100,000 persons.[9] H. Pylori infection and chronic mucosal damage, such as what happens in GERD, are among the main underlying conditions leading to the development of cancerous lesions in the gastroesophagus. These factors contribute to the development of pre-cancerous lesions, mucosal metaplasia, and dysplasia by inducing chronic mucosal inflammation.[6,10,11] Despite gastric intestinal metaplasia being a relatively frequent finding (5–20%) in normal populations,[12] this finding is the precursor of low-grade mucosal dysplasia. Low-grade mucosal dysplasia could culminate in high-grade dysplasia and carcinoma.

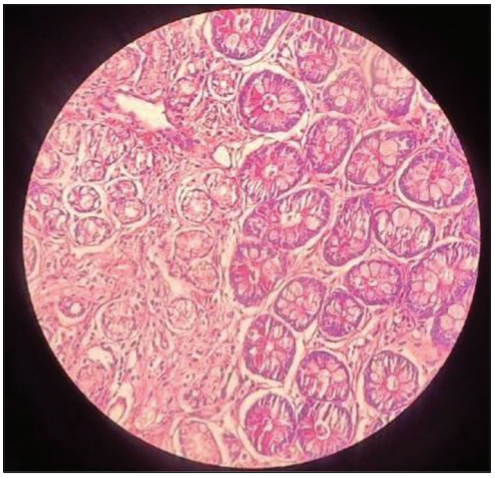

Figure 1: Hematoxylin-eosin staining of the specimen from the esophagogastric biopsy. The presence of columnar cells resembling gastric foveolar cells with no absorptive cell and neutral mucins and sulfomucins indicated incomplete intestinal metaplasia

Table 2: Baseline characteristics divided by the type of surgery

Baseline characteristics	Classic	Omega	*P*
Female *n* (%total population)	28 (25.2)	57 (59.8)	0.579
Smoking *n* (%total population)	6 (42.9)	8 (57.1)	0.47
Hypertension *n* (%total population)	15 (35.7)	27 (64.3)	0.8
Diabetes mellitus *n* (%total population)	14 (29.8)	33 (70.2)	0.39
GERD before surgery *n* (%total population)	11 (10.2)	0	0.000
Age Mean±SD	35.32±4.31	33.62±4.99	0.081
BMI before surgery Mean±SD	43.04±2.46	42.77±2.28	0.57
Intestinal metaplasia before surgery *n* (%total population)	7 (31.8)	15 (68.2)	0.78

Table 3: Summary of results from one-year post-surgery upper endoscopy

		Before surgery	After surgery	*P*
Intestinal metaplasia	Total	22	25	0.250
	Classic	7	9	0.5
	Omega	15	16	1
GERD	Total	11	3	0.039*
	Classic	11	1	0.002*
	Omega	0	2	0.5
H.Pylori	Total	0	2	0.5
	Classic	0	1	1
	Omega	0	1	1
Mucosal Dysplasia	0	0	0	-
Marginal Ulcer	Total	-	8	0.008*
	Classic	-	2	0.5
	Omega	-	6	0.031*

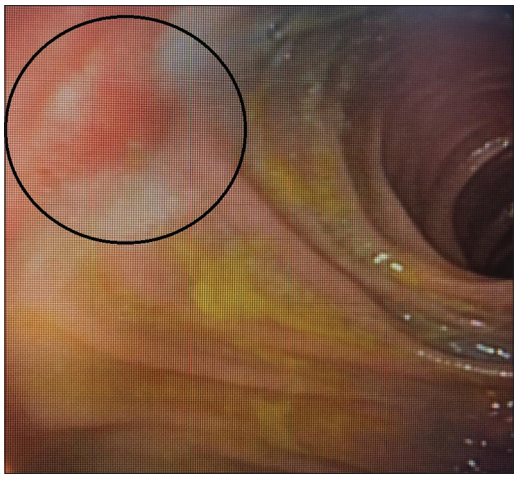

Figure 2: Marginal ulcer shown in the endoscopic image, a hyperemic region with inflammation surrounded by white mucosal pallor indicating mucosal disruption

Although metaplastic epithelium's cellular and molecular structure is not considered a cancerous lesion, patients with intestinal metaplasia are at six-fold increased risk of developing gastric cancer.[13] GERD is one of the main risk factors for the development of mucosal metaplasia. Obese people experience GERD more frequently and more severely compared to normal people.[14] Bariatric surgery could effectively improve GERD in about 80% of patients. However, studies have indicated that in a small number of patients (8%), especially those who undergo sleeve gastrectomy (SG), GERD may aggravate, or even de novo GERD may arise.[15] Although in our study population, GERD has decreased considerably after RYGB, two patients developed de novo GERD after omega bypass. Despite the fact that this finding is statistically non-significant, it raises the question of whether de novo GERD after bariatric could contribute to the development of gastroesophageal cancer?

Up to now, no study has directly assessed the pathological changes that may happen in esophagogastric mucosa following bariatric surgeries, and here in this study, we did not observe any findings in favor of gastroesophageal mucosal dysplasia one-year post-operation. According to the results of pre-operative upper endoscopy, the prevalence of gastric intestinal metaplasia was 14% (n = 15), and the prevalence of intestinal metaplasia one-year post-operation was around 16% (n = 17), both of which are the same as the normal population. It should be noted that, in order to omit the effect of H. Pylori infection, we only included patients with negative results for H. Pylori infection. Thus the slight increase in the number of patients with gastric intestinal metaplasia may be associated with H. Pylori infection after the surgery. Nevertheless, both differences in gastric intestinal metaplasia and H. pylori infection were insignificant.

Many studies have established the effect of bariatric surgery on cancer risk reduction in the morbidly obese population, although few studies have investigated the possibility that bariatric surgery could increase the odds of developing some gastroesophageal cancers. Mackenzie *et al*.[5] have indicated that compared to obese people who did not undergo bariatric surgery, those who underwent bariatric surgeries had a significantly lower risk for breast, endometrial, prostate, and other hormone-related cancers; however, the overall odds for colorectal cancer was 2.19 (CI = 1.21–3.96) in people undergoing bariatric surgery. Their results about esophageal cancer also showed a lower risk for patients who underwent bariatric surgery, but it was not statistically significant (CI = 0.15–1.66). Moreover, the odds of developing esophageal cancer were not statistically significant when dividing the study population by types of surgery. Studies also suggested that routine follow-ups in patients after bariatric surgery, especially in those experiencing de novo GERD, could prevent the development of end-stage esophagogastric cancers because the typical manifestations of these cancers such as weight loss, sense of abdominal fullness and early satiety, abdominal pain, and distension may be underlooked as the common complications of bariatric surgery.[16]

There are also few reports of gastric cancer in patients who underwent bariatric surgery. Orlando *et al*.[7] discussed 18 patients who had developed gastric cancer after bariatric surgery in a systematic review of case reports. The majority of tumors were reported to arise from the gastric pouch, but other regions were also reported, including excluded stomach and pylorus. The mean time of diagnosis was 8.6 years post-operative, and most patients had undergone RYGB; nevertheless, the authors did not extract the patients' data about pre-operative upper endoscopy and H. Pylori infection from the reports. Thus, it is not possible to conclude a direct link between bariatric surgery and the incidence of gastric cancer. In another systematic review by Chen *et al*.,[6] 17 patients who developed gastroesophageal cancer after SG were reviewed. The authors could not reach a clear conclusion about the role of SG in the development of GE cancer because four of the reported patients did not undergo pre-operative upper

endoscopy, nine were positive for H. Pylori infection test, and two had chronic gastritis before the surgery. Although they had primarily linked the risk of GE cancer to GERD as a complication of SG, a precise evaluation of the reported cases demonstrates no clear association between SG and the development of GE cancer.

Altogether, consistent with our results, bariatric surgery may not increase the odds of developing pre-cancerous lesions in the gastroesophageal mucosa after one year, but regarding that our results were collected from a one-year follow-up study, studies with longer follow-up durations may be needed to establish our understandings about the effect of bariatric surgery on the gastric mucosa. It is also noteworthy that more extensive population-based studies may define the odds of gastric cancers in patients undergoing different types of bariatric surgery more clearly.

Conclusion

In conclusion, we indicated that after one year, bariatric surgery does not induce the development of pre-cancerous lesions in gastroesophageal mucosa; however, we suggest that endoscopic follow-ups in this sort of patients may be very helpful for early diagnosis of gastrointestinal cancers in patients who underwent bariatric surgery.

Ethics approval and consent to participate

The study was approved by the institutional review board of Isfahan University of Medical science, Isfahan, Iran coded as IR.MUI.MED.REC.1401.045 on 2022-05-08.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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