Does Gastric Surgery (Such as Bariatric Surgery) Impact the Risk of Intestinal Inflammation?

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Key Words

Gastric bypass · Inflammatory bowel disease · Morbid obesity · Roux-en-Y gastric bypass · Sleeve gastrectomy

Abstract

Background: The prevalence of morbid obesity and inflammatory bowel disease (IBD) is on the rise in association with a Western lifestyle. Both conditions are characterized by chronic inflammation. Bariatric surgery (BS) is a recommended and widely used approach to address severe obesity and its related comorbidities. Roux-en-Y gastric bypass (RYGBP) and sleeve gastrectomy (SG) are the most frequently performed procedures worldwide. Evidence is scarce on outcomes of BS in IBD patients. **Summary:** Systemic and adipose-tissue inflammation seems to decrease following BS. Different studies observed decreased serum levels of inflammatory markers (CRP, IL-6, MCP-1, and TNF- α) along with a reduction of insulin resistance both after RYGBP and SG. Several authors documented postbariatric improvement of concomitant chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, gout, and psoriasis). There are only few retrospective case series on outcomes of BS in IBD patients. These studies reported safety and feasibility of BS and improvement in IBD status, manifested by prolonged disease remission and decreased use of pharmacotherapy. Weight loss outcomes were excellent and similar to those of

non-IBD patients. The preferred surgical approach for morbidly obese IBD patients is SG in order to avoid potential drawbacks of RYGBP, such as malabsorption, intestinal manipulation, and augmentation of technical difficulties for future IBD surgery. Seven cases of newly diagnosed IBD after BS have been reported, which are more likely to result from postoperative intestinal microbial dysbiosis than from directly induced inflammation. **Key Messages:** This review summarizes the outcomes of BS in IBD patients. SG is the preferable technique for morbidly obese IBD patients, who have potentially a double benefit from BS: weight loss and IBD remission. Further research is necessary to clarify the common pathophysiology of chronic inflammation in morbid obesity and in IBD. Postbariatric changes in gut microbiota should also be assessed to understand whether they promote IBD development or not.

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Introduction

Both metabolic syndrome (MS) and inflammatory bowel disease (IBD) are characterized by chronic inflammation and share common features in their pathology [1]. MS triggers inflammatory signals, and vice versa, IBD generates several metabolic changes. The prevalence of these conditions is on the rise in association with the pop-

ularity of a Western lifestyle [2, 3]. The clinical development of IBD starts with a defective mucosa facilitating the intestinal bacteria to cross the mucosal barrier and to induce an immune response mediated by proinflammatory cytokines along with diminished levels of immunosuppressive cytokines; consequently, chronic inflammation occurs [4]. In obesity, chronic inflammation originates from proinflammatory cytokines and adipokines such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and monocyte chemoattractant protein (MCP-1) secreted by adipocytes or by macrophages and lymphocytes that infiltrate the mesenteric fat, which is overexpressed in patients with active IBD [5].

Obesity affects over 640 million people worldwide, and if the present trends continue, the global obesity prevalence will reach 20% by 2025 [6]. Bariatric surgery (BS) is superior to lifestyle modifications alone (diet, sport, and medical treatment) in achieving body weight loss, and it is also effective in the treatment of obesity-related comorbidities, especially in type 2 diabetes mellitus (T2DM) [7, 8]. Currently, the most frequently performed BS procedures are the Roux-en-Y gastric bypass (RYGBP) and sleeve gastrectomy (SG) [9].

The incidence of IBD, defined as either Crohn's disease (CD) or ulcerative colitis (UC), is also continuously increasing along with a higher socioeconomic status which has been recently identified as an independent risk factor [10]. Obesity and overweight have become commonplace in adult IBD patients, with a prevalence of 32–52% in different European studies [11, 12]. Obesity is more frequently associated with CD than with UC [11].

It is the aim of this review to assess the impact of BS on systemic inflammation and discuss the outcomes of bariatric procedures in IBD patients against the background of the available evidence in the literature.

Common Bariatric Techniques and Outcome

RYGBP and SG are recommended and widely used in the treatment of severe obesity and its related comorbidities [13]. RYGBP consists of the creation of a small proximal gastric pouch (approximately 20 ml), which is connected to a jejunal (alimentary) limb with a length of 100–150 cm. A 50- to 80-cm biliopancreatic limb is anastomosed to the alimentary limb, and the small bowel distal to this anastomosis is called the common limb, which harbors the majority of intestinal absorption. In the long term, these anatomic changes in the digestive tract may lead to gastrointestinal complications (nausea, vomiting,

diarrhea, and dumping syndrome) and nutritional deficiencies (iron, vitamin A, vitamin B₁, vitamin B₁₂, vitamin D, folic acid, and zinc) or dehydration [14]. A recent meta-analysis demonstrated an association between RYGBP and an increased risk of kidney stones, contrarily to other BS procedures such as gastric banding or SG, which may decrease kidney stone risk [15].

During SG, the stomach is tubularized over a calibration bougie, and approximately 80% of its volume is resected parallel to the greater curvature. Like the RYGBP, the SG decreases gastric reservoir function and activates hormonal mechanisms such as increased GLP-1 hormone and decreased ghrelin [16]. The most frequent medical complication is gastroesophageal reflux disease, which might be promoted by both an increased postoperative gastroesophageal pressure gradient and the destruction of the angle of His during gastric sleeve formation. Further medical complications include recurrent aspiration pneumonia, dumping syndrome, and ketoacidosis [17]. Symptomatic cholelithiasis is rare (<5%); however, it was reported to be more likely to occur after SG than after RYGBP [18].

In experienced centers, both RYGBP and SG have an excellent safety profile with low perioperative morbidity and close-to-zero mortality [19]. Nevertheless, both procedures can lead to various late medical complications, as mentioned above. A meta-analysis found a similar rate of minor and major complications from 6 months to 3 years following the two procedures [17].

BS and Inflammation

To the best of our knowledge, there is no evidence indicating that BS may promote intestinal inflammation. On the contrary, systemic and adipose-tissue inflammation seems to decrease following bariatric procedures both at the biochemical and at the clinical level. These changes supposedly promote risk reduction in obesity-associated comorbid conditions including T2DM, cardiovascular diseases, infections, and cancer [20–23].

Viana et al. [20] demonstrated a significant decrease in systemic inflammatory cytokines (IL-6 and TNF- α) 1 year after RYGBP and SG. Sams et al. [21] found a significant and rapid increase in subcutaneous adipose anti-inflammatory cytokines (e.g. adiponectin) by enzyme-linked immunosorbent assay already 2 weeks following RYGBP, potentially contributing to systemic inflammation reduction. In the same study, insulin resistance was also found to be reduced, which could have an important

role in the amelioration of T2DM and, thus, in the reduction of long-term mortality. A study in adolescents undergoing RYGBP and SG also showed that the levels of IL-6, TNF- α , MCP-1, oxidized low-density lipoprotein cholesterol, and leptin significantly decreased while adiponectin increased, indicating a marked decrease in systemic inflammation and oxidative stress [22]. Consistently with the previously cited studies on RYGBP, Brethauer et al. [23] demonstrated a decrease in inflammatory cytokines and also a decrease in the levels of C-reactive protein, fasting insulin, and fibrinogen, along with an amelioration in arterial endothelial function, a further surrogate marker of cardiovascular risk reduction after RYGBP.

The impact of BS on systemic inflammation can also be observed by the postoperative improvement in concomitant chronic inflammatory diseases. Sparks et al. [24] reported a decrease in rheumatoid arthritis disease activity enabling lower medication use following SG. Romero-Talamás et al. [25] observed a decrease in psoriasis in 40% of patients following RYGBP and found that the remission correlated with the extent of excess weight loss. Yildiz [26] reported remission of psoriasis already 1 month after SG in 2 patients. Other studies showed improvement in gout (decreased uric acid levels 1 year after BS) and decreased immunosuppression medication requirements for systemic lupus erythematosus following BS [27, 28].

Abdominal Surgery in IBD Patients

Surgical management of IBD is complex and challenging [29]. In CD, the goal of surgery is to improve quality of life. It should be reserved for patients who develop medically unresponsive strictures, abscesses, or fistulas. In UC, proctocolectomy and ileo-anal pouch reservoir have become the preferred surgical management for advanced disease states. Surgery is required in 30–40% of patients with CD and 20–30% of patients with UC at some point during their lifetime [30]. Laparoscopy is the preferred approach for IBD operations due to faster intestinal function recovery, better cosmesis, less overall postoperative complications, and shorter inpatient stay [31]. Anatomic changes induced by obesity increase the technical complexity of these procedures, and obesity-related comorbidities might increase the risk of postoperative complications [32]. The American College of Surgeons National Surgical Quality Improvement Program Database showed that an increasing body mass index (BMI) adversely affected postoperative complications in

CD patients [32]. Nevertheless, a more recent retrospective cohort study found that obesity did not impact intraoperative variables, nor did it worsen postoperative complication rates in IBD patients [33].

Outcomes of BS in IBD Patients

IBD is a chronic condition with periods of remission and relapse. Accurate assessment of disease progression is based on the combination of clinical signs (weight loss, fatigue, quality and frequency of stools, abdominal discomfort) and endoscopic/histologic evaluation of mucosal healing [34]. Noninvasive methods for evaluating disease activity or predicting mucosal status also exist. A reliable surrogate marker of intestinal inflammation is the fecal calprotectin level, which correlates with IBD disease activity observed by capsule endoscopy [35]. This marker has not been studied after BS; however, the plasmatic calprotectin was measured in one study in non-IBD morbidly obese patients who underwent BS. Nijhuis et al. [36] found a significant decrease in serum calprotectin levels (in 11 out of 15 patients) from a mean of 119.6 ± 31.5 ng/ml to a mean of 93.9 ± 42.7 ng/ml ($p < 0.001$) 2 years postoperatively, suggesting a state of lower neutrophil activation following BS-induced weight loss. Theoretically, the decreased inflammatory state following BS might favorably impact the evolution of IBD; however, surgically induced malabsorption and abdominal surgery including intestinal manipulation might also adversely impact IBD patients [37–39]. The eventual complications that may be more frequent in IBD include anastomotic leak, fistula, abscess, bowel stricture, and bowel obstruction [40]. Furthermore, without any available evidence, Moum and Jahnsen [41] mention the potential risk of exacerbating intestinal inflammation and the increased risk of small-intestine neoplasia following RYGBP. As chronic steroid use is associated with increased morbidity and mortality after BS [42], operating on IBD patients with immunosuppressive treatment should be preceded by meticulous risk stratification.

The available literature is sparse on the outcomes of BS in IBD patients and is predominantly based on case reports or smaller case series. For example, Keidar et al. [37] presented a series of 9 morbidly obese IBD patients (7 CD and 2 UC) who underwent SG and of 1 CD patient who underwent gastric banding. Despite one staple line leak in a UC patient, the authors found that SG was safe and yielded satisfying weight loss-related results without a higher risk of postoperative complications or an in-

creased risk of postintervention IBD exacerbation. Furthermore, 3 patients were able to stop their 5-ASA treatment. Colombo et al. [38] reported successful BS procedures in 6 IBD patients with concomitant or deferred IBD surgery: SG in 5 CD and 1 UC and vertical banded gastroplasty in 1 CD patient. The authors observed only one perioperative complication (reoperation for staple line bleeding), effective BMI reduction, and absence of intestinal malabsorption. They concluded that BS in IBD patients offers a double benefit: on top of reducing systemic inflammation, the decrease in BMI reduces the pharmacological volume of distribution to the normal therapeutic range of immunosuppressive therapy. Aminian et al. [39] retrospectively identified 13 UC and 7 CD patients who underwent RYGBP, SG, or gastric banding in a large-volume bariatric center. Several early complications were reported, i.e. dehydration ($n = 5$), pulmonary embolism ($n = 1$), and wound infection ($n = 1$). Late complications occurred as well, i.e. pancreatitis ($n = 2$), ventral hernia ($n = 2$), and marginal ulcer ($n = 1$). Most patients experienced improvement in their IBD status, manifested by prolonged disease remission and decreased use of pharmacotherapy. Weight loss outcomes were excellent and similar to those of non-IBD patients. Lascano et al. [43] described a morbidly obese male UC patient who experienced clinical remission of UC with a reduction in medications following RYGBP. Moum and Jahnsen [41] presented a case of a CD patient who experienced an acute flare 5 weeks following RYGBP with increasing calprotectin levels in her feces. She responded well to high doses of infliximab, and 7 months later, she was in remission and achieved weight loss. An adverse outcome was presented by Tenorio et al. [44] who described the case of a UC patient who presented severe protein malnutrition after biliopancreatic diversion (BPD). Protein malnutrition is a frequent complication after BPD compared to RYGBP or SG, which is why BPD is only performed in low numbers in a few bariatric centers worldwide [45]. It is also not recommended in IBD patients who are already at an increased risk of malabsorption [46].

BS as a Risk Factor for IBD?

A few reports in the literature suggest that BS may be a potential risk factor for the development of CD. However, our literature review could identify only 6 patients from a total of 3 publications who have developed CD after BS [47–49]. Five patients had RYGBP and one had

a jejunio-ileal bypass – a historic weight loss operation that nowadays has been abandoned due to a high incidence of complications [50]. The time from surgery to the diagnosis of CD ranged from 2 months to 10 years. Papa-konstantinou et al. [51] reported 1 patient who developed UC and acute stroke 3 months after Mason's vertical banded gastroplasty. Although a causal link between BS and IBD has not been established, Janczewska et al. [48] theorized that changes in the intestinal flora promoted by RYGBP might lead to CD in genetically predisposed patients by triggering chronic intestinal inflammation. In fact, intestinal dysbiosis is a crucial component of CD potentially resulting from a combination of inflammation, antibiotic exposure, and dietary changes [52]. However, BS has also been shown to induce changes in gut microbiota. Palreja et al. [53] found an increased gut microbial diversity and an altered microbial composition already 3 months following RYGBP, and these changes were also present at 1 year. Diarrhea following RYGBP is most likely related to a higher fatty acid content of stools due to decreased fat absorption [54]. Nevertheless, CD might be kept in mind as a differential diagnosis for diarrhea and should be ruled out by endoscopy in postbariatric patients who present further alarming signs, such as abdominal pain and unintentional excess weight loss. In order to assess the real incidence of IBD following BS, Ahn et al. [47] planned to perform a prospective cohort study in the Boston Medical Center.

Recommendations on BS in IBD

MS and IBD share some common denominators, namely a triggered immune response, adipokine-mediated chronic inflammation, and elevated cardiovascular risk, but underlying mechanisms are not fully understood [55]. There are promising results from previously cited case series to support the beneficial effect of BS on IBD in morbidly obese individuals, at least in selected cases. However, the selection of the optimal bariatric procedure for a morbidly obese patient involves many considerations. As the IBD population is at risk for intestinal malabsorption, enteric fistulas, and bacterial overgrowth, most authors and 87% of the experts from the Fifth International Consensus Conference on current status of SG recommend the use of SG [37–39, 41, 56]. SG achieves satisfying metabolic results and involves the operation of the stomach only, which is in most of the cases free from IBD [37]. Also, SG presents a valid alternative to offset the arguments in disfavor of RYGBP.

Gastric bypass might predispose to bacterial overgrowth due to lack of gastric acidity, stasis in the afferent loop, and enterocyte toxicity via free bile acids resulting from microbial bile acid deconjugation after gastric diversion [47]. There is a potential risk of flare-up in patients with small-bowel CD in the operated segment of the small bowel after RYGBP, with an increased risk of stricture, abscesses, and fistulas [29]. As RYGBP alters the small-bowel anatomy, it can become the source of additional technical difficulties at the time of postbariatric IBD surgery, e.g. for the creation of an ileal pouch with a protective ileostomy after colectomy. Also, if later in the patient's life an intestinal resection becomes necessary due to the progression of CD, the common limb length might be shortened promoting malabsorption or mandating reversal of RYGBP anatomy. Therefore, Janczewska et al. [48] suggested that CD should be an absolute contraindication to RYGBP, and morbidly obese patients with a history of diarrhea and/or perianal abscess should be investigated for IBD as part of the standard preoperative workup.

Conclusions

BS is an effective treatment of morbid obesity and provides a decreased systemic inflammatory state, which results in the amelioration of concomitant chronic inflammatory diseases, a reduced risk of T2DM, cardiovascular disease, and other diseases. The literature is scarce on the impact of bariatric procedures in IBD patients. Based on the available evidence, SG seems to be the preferred bariatric technique for morbidly obese IBD patients in order to avoid intestinal manipulation or malabsorption following RYGBP. Few cases of CD after RYGBP have been reported, which are more likely to result from postoperative intestinal microbial dysbiosis than from directly induced inflammation.

Disclosure Statement

We have no conflicts of interest or financial ties to declare that are relevant to the subject of this review paper and any of the statements in it.

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