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Review Article

Bariatric Surgery and Crohn's Disease

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Abstract

Obesity is a chronic condition significantly associated with health disorders, including type-II diabetes, cardiovascular diseases and inflammation. Its prevalence has been on the rise for the last few decades, contributing to the World Health Organization's statement touting obesity as the pandemic of the millennium. In parallel, its incidence in patients with inflammatory bowel disease (IBD) is rising, with the prevalence of obesity among patients with IBD is similar to that of the general population ~20%-30%. The main common pathophysiological pathways which might link obesity to IBD include: disproportional accumulation of visceral fat, impaired release of adipokines, chronic inflammation, and disturbances in the gut microbiome. Large retrospective studies have shown that obesity is associated with an increased risk of Crohn's Disease (CD), a chronic, progressive, destructive condition whose incidence has been increasing as well (3-20 cases per 100,000). Bariatric surgery is a well-accepted, effective and safe option for significant and durable weight loss in individuals with morbidly obesity. Even though obesity is associated with higher rates of surgical complexities and postoperative complications (possibly further exacerbated in patients with IBD), data from case studies and multiple data analyses have demonstrated that bariatric surgery in patients with both morbid obesity and CD is safe and effective. Bariatric surgery infers marked improvement in weight-associated comorbidities, massive weight loss, as well as better quality of life, in this special patient population.

Keywords: Crohn's disease; Bariatric surgery; Inflammatory bowel disease; Obesity

1. Introduction

Obesity, which has reached pandemic proportions, is a chronic condition leading to complicated health outcomes. In parallel, the incidence of obesity among patients with inflammatory bowel disease (IBD) is also rising [1]. The main common pathophysiological pathways linking obesity to IBD include: disproportional accumulation of visceral fat, impaired release of adipokines, chronic inflammation, and disturbances in the gut microbiome. Crohn's disease (CD) is a chronic, progressive, destructive condition, falling under the spectrum of chronic idiopathic IBDs. Its incidence has been increasing, reaching 3-20 cases per 100,000 [2]. Studies have demonstrated that obesity was associated with an increased risk of CD [3]. Bariatric surgery (BS) is an effective, durable and safe option for weight loss in individuals with morbid obesity. However, it is generally associated with higher surgical complexities and rates of postoperative complications, including those causing IBD exacerbation [4]. It is for this reason, that IBD is considered a relative contraindication for BS. We herein review several case studies and data analyses which demonstrate the safety and efficacy of BS in patients with CD and morbid obesity. The incidence of de novo CD following BS will also be discussed.

2. Crohn's Disease

The pathogenesis of CD involves activation of the immune system and dysregulation of the intestinal immunity [5]. It is caused by stimulation of autoreactive Th-1 CD4+ lymphocytes to release pro-inflammatory cytokines including: Interleukin-12, 17 and 22, interferon-γ, tumor necrosis factor α (TNF- α), as well as other mediators [6, 7]. Risk factors for the development of CD include changes in the gut microbiome, disruptions to the intestinal mucosa, genetic factors, as well as environmental risk factors (such as smoking) [8]. The disease is characterized by a chronic intestinal inflammation of any part of the gastrointestinal tract (the distal small bowel and colon are mainly involved) causing strictures, fistulas, and abscesses of the intestine, leading to impairment of the intestinal function [9, 10]. Relapsing and remitting episodes are very common in CD. Symptoms of the disease include abdominal pain, diarrhea, fatigue, weight loss, low-grade fever, growth failure, anemia, recurrent fistulas, and symptoms of bowel obstruction [8, 10]. CD is usually a clinical diagnosis, supported by endoscopic, radiographic, and histologic criteria showing chronic intestinal inflammation [10, 11].

Its treatment depends on disease severity, location and subtype of the disease. The aim of the treatment is to achieve control of the inflammation. Medical therapy used includes antibiotics, anti-inflammatory and immune-modulating agents [10]. Various dietary manipulations have been suggested as adjuncts to medical therapy [12]. Approximately 30% of CD patients will require surgery within 5 years of diagnosis, and after 20 years of disease activity this number rises to 80%. However, since these procedures are not curative, many patients will require multiple surgeries during their life-span [9, 13]. Acute inflammation and other complications necessitate emergent interventions in 6-16% [14]. Surgery is indicated for stricturing CD with obstructive symptoms, complicated fistulae or perianal CD, failure of medical therapy, steroid dependence, dysplasia, or cancer [15]. Up to 80% of patients with CD will require hospitalization at some point during their clinical course, but the rate of hospitalization decreases in later years after

diagnosis. Management of CD is multidisciplinary including internists and surgeons as well as several allied health professionals [16].

3. CD and Obesity

Obesity is defined by the World Health Organization (WHO) as a body mass index of (BMI) ≥ 30 kg/m^2. It is a chronic condition leading to complicated health outcomes, which has become a worldwide epidemic affecting approximately 650 million people [17]. Obesity is closely associated with health disorders, including type-II diabetes, cardiovascular diseases and inflammation. It is increasingly related to cancers of the liver, breast, kidney and colon [18]. According to the WHO, the worldwide prevalence of overweight or obese individuals is approximately 35% [19]. In parallel with this obesity epidemic, its incidence in inflammatory bowel disease (IBD) patients is rising: 15-40% of adults with IBD are obese, and 20–40% are overweight, similar to that of the general population [1, 20]. Interestingly, "The Nurses' Health Study" conducted in the USA, as well as a Danish study of 75,000 women demonstrated that obesity was associated with an increased risk of CD but not ulcerative colitis [3, 21]. This was also shown in the works of Hemminki, Mendall and their co-workers [22, 23]. In contrast, the prospective cohort "EPIC" study conducted in 2013, including 300,724 patients from 10 European countries, did not find any association between obesity and the development of IBD [24].

Blain et al., reported that patients with obesity and CD (3% out of 2065 patients) presented different disease characterizations compared with those who were not obese: they were significantly older at diagnosis (32 versus 28 years), had a higher incidence of perianal disease, suffered from more relapses and were more frequently hospitalized [25]. Hass and colleagues, demonstrated that time to surgery in patients who were obese and had CD was shorter than that of patients with normal weight (24 months vs. 72 months, respectively) [26]. On the contrary, there is a lower rate of penetrating disease activity among individuals with CD who were obese, while no major difference was found in the rate of perianal disease or surgery between these populations [27]. Nevertheless, increased BMI was found to be associated with more subtle indicators of active IBD, including increased C-reactive protein (CRP) levels, as well as a significant decrease in IBD-related quality of life measures [28].

The interactions between obesity and IBD have been investigated and some potentially common pathophysiological pathways which might link both conditions have been suggested [29].

- Disproportional accumulation of visceral fat (VF)-Intra-abdominal fat is an important common characteristic of both obesity and CD [30]. When compared with healthy controls, fat distribution in patients with CD was disproportional with higher VF volume [31]. VF may play an important role in the initiation and chronic inflammatory processes in CD patients, due to its immune properties that could link the innate immune system to obesity-related metabolic disorders, specifically to gut inflammation [30]. Indeed, pro-inflammatory cytokines, such as TNF-α, were are overexpressed in both mesenteric and VF of patients with IBD [32].

- Adipokines have been proposed to activate the inflammatory process of IBD [32, 33]. There is impaired release of adipokines, such as leptin, adiponectin, and resistin, (produced by macrophages and lymphocytes that infiltrate mesenteric fat). These adipokines are overexpressed in the mesenteric fat of patients with IBD. Moreover, excess adiposity was found to be associated with intestinal permeability participating in CD pathophysiology [34].
- Chronic inflammation-higher levels of inflammation markers (e.g. TNF-α and CRP) were detected in the gastrointestinal tract of subjects with obesity, as measured by stool calprotectin [35]. Overexpression in the mesenteric fat and elevated serum levels of interleukin-6 and TNF-α, was found in patients with active IBD who were obese [32, 33].
- Disturbances in the gut microbiome-Obesity reduces gut microorganism diversity and causes abnormal gut bacterial translocation. This might lead to adipocyte activation, triggering pro-inflammatory cytokine production and alterations of on immune homeostasis [1]. The gut flora plays a profound role in maintaining human physiology and nutrition [36]. Alteration in the homeostasis of the gut microbiome results in a decrease of the bacterial population with anti-inflammatory properties and an increase in the proportion of bacteria with pro-inflammatory properties-defined as dysbiosis [37].

Other conditions linking obesity and CD include: changes in food-intake behavior, increased consumption of industrialized food and animal fat/protein, decreased dietary fiber intake as well as reduction in physical activity [38]. Treatments used for IBD, in particular corticosteroids and anti-TNF-α therapies, have been implicated in weight-gain [39]. On the other hand, data from various studies have suggested that the effect of TNF blocking is impaired in patients who are obese and suffer from CD [40, 41]. Higher BMI was also found to be associated with a lower response to anti-TNF agents in other auto-immune diseases, such as rheumatoid arthritis, psoriasis, and psoriatic arthritis [2]. Thus, obesity might be a risk factor for CD development due to its pro-inflammatory nature. Patients with CD could become obese due to the impairment of food digestion and adverse effects of the treatments. CD and obesity may result from similar risk factors.

4. CD and Bariatric Surgery

Obesity treatment options include lifestyle modification, various medications and invasive approaches. BS is an effective and safe option for weight loss in morbidly obese individuals. Indications for the surgery include a BMI >40 or >35 kg/m^2 with obesity-related comorbidities (e.g. type 2 diabetes, hypertension, sleep apnea, etc.) and the failure of previous conservative attempts to lose weight. The number of patients undergoing surgery for weight loss has increased dramatically over the last years [42, 43]. Different BS techniques have been described, with sleeve gastrectomy, Roux-Y gastric bypass (RYGB) and gastric banding being the most utilized in patients with IBD [42, 44]. Obesity is generally associated with higher rates of surgical complexities and postoperative associated complications [4]. These technical limitations and complications are further enhanced in obese patients with IBD. Patients with obesity and IBD who underwent surgery have longer operating times, as well as higher rates of postoperative morbidity. For non-bariatric procedures, Krane and co-workers found longer operative times,

increased blood loss and higher rates of conversion from laparoscopic to open surgery among patients with IBD and obesity, when compared to normal weight patients [44-46]. The inflammatory state in patients with morbid obesity raises concerns regarding impaired wound healing and recovery of bowel motility [47].

In a large retrospective surgical study of major abdominal surgeries, Causey et al., demonstrated a 10% higher rate of post-operative morbidity among patients with obesity and CD and a nearly two-fold rate of post-operative infection, when compared to non-obese subjects. Moreover, a nearly seven-fold post-operative infection rate was noted in individuals whose BMI was higher than 40 kg/m^2 [45]. Recent studies have shown that BS is safe and effective in this patient population. Moum et al., reported about a 40-year-old woman with CD and a BMI of 45 kg/m^2, who also suffered from type II diabetes mellitus and hypertension. Following RYGB and significant weight-loss, a remission in the CD was observed, and hypertension and diabetes were resolved [48]. Ungar and colleagues reported on 560 patients with CD, of which 13 had a BMI >35 kg/m^2. Four of these underwent sleeve gastrectomy. There were no reported leaks and only one patient suffered from post-operative bleeding. All four patients had a mean weight loss of 60% at 1 year following surgery [49]. Colombo et al., described 5 patients with morbid obesity and CD who underwent a BS. No post-operative complications were noted during the follow-up period of 4-5 years, and an improvement in the disease symptoms was observed [50].

Keidar and co-workers reported on a series of 10 patients with IBD who underwent BS, 8 of which had CD. Leak rate observed was 10% (1 patient) [43]. In a study of 20 patients with IBD (7 of which suffered from CD) and a BMI of 50.1 ± 9.0 kg/m^2 who underwent various types of BS, 2 had adverse post-operative events (dehydration, pulmonary embolism and pancreatitis). The mean weight loss one year following surgery was 11.3 ± 1.3 kg. The authors concluded that BS was a safe procedure in CD patients [51]. Similarly, Aelfers et al. reported on 45 patients with IBD (of which 29 were diagnosed with CD) who underwent BS. Two patients with CD had complications including during post-operative follow-up period, including anastomotic bleeding, pyelonephritis and pancreatitis [52].

In our medical center 8 patients with morbid obesity and CD (5 females) underwent laparoscopic sleeve gastrectomy between the years 2010-2018. The average age and BMI of the patients was 44.1 ± 2.4 years and 44.3 ± 2.4 kg/m^2, respectively. The average BMI decreased to 28.7 ± 1.3. One of the patients suffered from a leak and peritonitis immediately after the surgery, underwent laparoscopic washout and drainage and eventually resolved. His IBD symptoms nonetheless decreased. A second patient who had a very mild CD with rare attacks before the surgery, experienced a very severe relapse 10 months after the surgery, despite adequate weight-loss.

Bazerbachi et al., used the Nationwide Inpatient Sample data which was collected between the years 2011- 2013, in order to evaluate the safety and postoperative complications of BS in IBD patients. Out of 314,864 subjects who underwent various types of bariatric surgeries, 459 (0/14%) had CD. Patients without IBD who underwent BS served as a control group. A trend towards more bleeding events (which included: occurrence of intraoperative hemorrhage, postoperative hematoma formation, need for blood transfusion, and the occurrence of a gastrointestinal

bleed) was noted in the study group (7.1 vs. 3.34%; AOR, 2.2; 95% CI, 0.96-4.95; p=0.06). The authors concluded that BS in patients with IBD boasts an acceptable safety profile [53]. Using the same National Inpatient Sample database, Sharma et al, searched for patients with morbid obesity and IBD over the years 2004-2014. Out of 15,319 patients fulfilling this criteria, 9704 (63%) patients were diagnosis with CD, and only 248 of them (2.5%) underwent BS. These data revealed that renal failure, undernutrition, and fistulae were significantly lower in CD patients who underwent a BS in comparison to patients with obesity with no history of a surgical weight loss procedure (P=0.006). Patients with morbid obesity and IBD who underwent weight-loss surgery experienced a significantly lower hospitalization cost and shorter length of stay as compared to those who had not undergone weight loss surgery ($41607 ± 27,202 versus $42,030 ± 61,778; P < 0.001, and 2.3 ± 2.2 days versus 5.8 days ± 6.3; P < 0.001, respectively). Hence, BS appears to be safe and to reduce morbidity in obese patients with IBD. It is also worth mentioning that the BS has also led to a significant improvement in the outcomes of some additional inflammatory conditions, such as gout, psoriasis, and lupus [47].

It has been suggested that the common inflammatory state in obesity and IBD is the mechanism involved in the improved condition of obese IBD patients after BS. The weight loss is followed by a reduction in adipose tissue mass, thereby decreasing the release of pro-inflammatory cytokines resulting in the reduction of the IBD-associated complications and comorbidities. The improvement of the IBD symptoms might also occur due to the diminution in the pharmacological distribution volume of medical treatment, thus ameliorating their effect, reducing the required dose and the risk to induce adverse effects [50].

An additional interesting issue regarding CD and BS is the de novo development of the disease after the BS. The Guidelines for Clinical Application of Laparoscopic BS of the Society of the American Gastrointestinal and Endoscopic Surgeons, which was validated by the American Society for Metabolic and BS, stated that CD may be a relative contraindication to the RYGB procedure [54]. There are several case reports about the development of CD following gastrointestinal bypass surgery. For example, Janczewska et al., described 2 case reports in which CD developed post BS. The first was a 48 year old woman who suffered from watery diarrhea, fever, and vomiting 2 months after laparoscopic RYGB. At the time her BMI decreased to 30 kg/m^2. A diagnosis of CD was established following rigorous work-up including physical examination, laboratory tests, gastroscopy, sigmoidoscopy, colonoscopy, and pathological examinations of biopsies. The second was a 69 year old man with morbid obesity who underwent a jejunoileal shunt operation in 1999. He developed constant watery diarrhea and, later, signs of malabsorption. Workup included CT scan and colonoscopy with DiBiCol test, the latter demonstrating a pattern of 100% probability for CD.58 Dodell et al., reported on a 59 year old male referred to the gastroenterology clinic with new onset of diarrhea, fatigue and weight loss. His surgical history included RYGB 10 years earlier.

Laboratory tests, stool examination, colonoscopy and pathology evaluations were performed yielding a diagnosis of CD [55]. Korelitz et al., reported on 5 patients who developed IBD (3 of which were diagnosed with CD) following RYGB. All 5 suffered from symptoms of diarrhea and abdominal pain. The time of symptoms onset was 1month to 5 years following the bariatric intervention [56]. The Mayo Clinic and the Washington University School of

Medicine published data from a prospective database of 3709 patients who underwent various bariatric surgeries with a median follow up time of 5.1 years, and reported that the estimated incidence rate of de novo CD presentation after BS was 22.3 per 100,000 person-years. Bernstein et al., summarized the characteristics of patients who developed de novo CD after BS. The majority of the patients were female, aged 28-69, with onset of symptoms ranging from 2 months to 10 years after BS. The most common presenting symptoms were diarrhea, abdominal pain and unexpected weight loss, and the most common anatomical site was ileo-colonic [57]. Following BS, there have reports of bacterial overgrowth, with consequent alteration in microbial products which may lead to activation of the immune response, contributing to the development of CD [58]. Dysbiosis, mucosal barrier dysfunction, rapid fat tissue loss, as well as the introduction of partially digested nutrients into the small intestine could also lead to the onset of the disease [59].

5. Conclusions and Recommendations

Data from recent studies have demonstrated that bariatric procedures appear to be safe and effective in patients with morbid obesity and CD. The main advantageous outcomes of BS (massive weight loss, improvement/remission of comorbidities and improved quality of life) are achievable in patients with CD. There is no consensus about the preferred bariatric surgical technique for patients with IBD. Sleeve gastrectomy and RYGB have been utilized in this unique patient population. In those with CD, due to the possibility of future small bowel resection, it may be prudent to prefer a sleeve gastrectomy, rather than RYGB [54]. De novo CD after BS has been reported and is a concern. However, large, structured studies are needed to establish the role for routine BS in patients with both morbid obesity and CD.

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