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Obesity and novel management of inflammatory bowel disease

Kim JH *et al.* Obesity and IBD

Abstract

Obesity is prevalent within the inflammatory bowel disease (IBD) population, particularly in newly developed countries. Several epidemiological studies have suggested that 15%-40% of IBD patients are obese, and there is a potential role of obesity in the pathogenesis of IBD. The dysfunction of mesenteric fat worsens the inflammatory course of Crohn's disease and may induce formation of strictures or fistulas. Furthermore, obesity may affect the disease course or treatment response of IBD. Given the increasing data supporting the pathophysiologic and epidemiologic relationship between obesity and IBD, obesity control is being suggested as a novel management for IBD. Therefore, this review aimed to describe the influence of obesity on the outcomes of IBD treatment and to present the current status of pharmacologic or surgical anti-obesity treatments in IBD patients.

Key Words: Obesity; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core Tip: Obesity is prevalent within the inflammatory bowel disease (IBD) population, particularly in newly developed countries. The dysfunction of mesenteric fat worsens the inflammatory course of Crohn's disease and may induce formation of strictures or fistulas. Furthermore, obesity may affect the disease course or treatment response of IBD. Along with the increasing data that support pathophysiologic and epidemiologic relationship between obesity and IBD, attention is being focused on obesity control as a novel management of IBD. The main purpose of this review is to describe the influence of obesity on the outcomes of IBD treatment and to present the current status of pharmacologic or surgical anti-obesity treatments in IBD patients.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition with an unclear etiology and pathophysiology that remain to be fully elucidated^[1,2]. Obesity is a pathological condition in which there is an abnormal or excessive accumulation of body fat resulting from an imbalance between energy intake and consumption. In Western populations, a body mass index (BMI) exceeding 25 kg/m² is commonly classified as an overweight condition, and a BMI over 30 kg/m² is regarded as an obese condition. In Asian populations, the diagnostic thresholds for obesity and overweight have been established as BMIs of 25 kg/m² and 23 kg/m², respectively^[3]. Obesity is a clear risk factor for a spectrum of chronic diseases, including type 2 diabetes, cardiovascular disease, respiratory problems, and cancer. Moreover, obesity is also associated with the occurrence of autoimmune diseases such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus^[4].

The worldwide prevalence of obesity has nearly tripled since 1975^[5], and IBD has also shown a similar trend^[6]. This analogous increase is perhaps related to lifestyle changes caused by westernization and urbanization, including the lack of exercise and a westernized diet, which are common risk factors for obesity and IBD. Historically, it has been common for clinicians to associate IBD patients with a low or normal BMI due to the complications of IBD such as decreased food intake, malabsorption, weight loss, and nutritional deficiencies. However, obesity is increasingly being associated with IBD due to its overall pro-inflammatory effect. Several epidemiological studies have suggested that 15%-40% of IBD patients are obese^[7-11], and hypothesize that obesity contributes to the development of IBD. Furthermore, obesity may affect the disease course or treatment response of IBD. With the increasing data supporting pathophysiologic and epidemiologic relationship between obesity and IBD, research interest on interventions for obesity as a novel management of IBD is also increasing.

The present review aims to provide a comprehensive summary of the pathophysiology of obesity in IBD, the influence of obesity on IBD outcomes, the effect of obesity on IBD management, and the potential impact of obesity treatment

on IBD outcomes. Further, this review aimed to present the current status of anti-obesity treatments in IBD patients.

PREVALENCE OF OBESITY IN IBD PATIENTS

Previous studies have reported that 15%-40% of IBD patients are obese and 20%-40% are overweight^[7-11]. Additionally, severe obesity (BMI ≥ 40 kg/m²) is also reported in 2%-3.2% of IBD patients^[7]. The prevalence of obesity among IBD patients has been observed to increase over time, which appears to correspond with the global trend of rising obesity rates. A single-center study in France confirmed that the proportion of obesity among CD patients from 1974 to 2000 increased from 1.7% before 1981 to 4% after 1990^[12]. A single-center study in Korea, utilizing data from the Asan IBD Registry from 1989 to 2016, reported that out of 6803 patients diagnosed with IBD, 16 with CD and 27 with UC were classified as obese (BMI ≥ 30 kg/m²). The study did not reveal any clinically meaningful differences between the obese and non-obese patient groups^[13]. A analysis of 10282 CD patients enrolled in a randomized controlled clinical trial revealed a significant increase in mean BMI at enrollment, which rose from 20.8 kg/m² in 1991 to 27.0 kg/m² in 2008^[14].

RELATIONSHIP BETWEEN OBESITY AND IBD

Obesity as a precursor to the onset of IBD

Obesity may be a potential risk factor for developing IBD, particularly CD (Table 1). In the United States Nurses' Health Study, which followed around 110000 women, found that obesity at age 18 was a significant predictor for the development of CD but not UC, when compared to individuals with a normal BMI [adjusted hazard ratio (aHR) = 2.33; 95% confidence interval (CI): 1.15-4.69]^[15]. This study exhibited that a higher degree of weight gain (between the ages of 18 and enrolment) was linked with elevated risk of developing CD (weight gain > 13.6 kg vs < 2.3 kg; HR = 1.52; 95%CI: 0.87-2.65). The Copenhagen School Health Records Register cohort study investigated the potential association between BMI during the ages of 7 to 13 years and the onset of adult-onset IBD^[16]. Obesity in early adolescence has been shown to increase the risk of CD before the age of 30 years (HR = 1.2; 95%CI: 1.1-1.3)

while decreasing the risk of UC (HR = 0.9; 95% CI: 0.9-1.0). In a recent meta-analysis of five prospective cohort studies, obesity was found to be associated with an elevated risk of developing older-onset CD, while no significant association was found with UC^[17]. The analysis showed that obese patients had an increased risk of developing CD compared to those with a normal BMI (aHR = 1.34; 95% CI: 1.05-1.71; $I^2 = 0\%$). Moreover, every 5 kg/m² increase in baseline BMI was found to correspond to a 16% increase in the risk of CD (aHR = 1.16; 95% CI: 1.05-1.22; $I^2 = 0\%$). However, the European Prospective Investigation into Cancer and Nutrition-IBD study, which involved a large sample size, concluded no significant correlation between BMI and the incidence of IBD, showing contrasting results to previous studies^[18].

Obesity caused by IBD

Weight gain may occur during the treatment of IBD. Several preclinical data suggest that, in IBD patients, imbalance of gut microbiota and altered metabolic intestinal signaling mediated by hormones, bile acids, and satiety-related peptides have been implicated in the development of obesity and dysmetabolism^[19,20]. Smoking cessation as a lifestyle modification and utilization of corticosteroids could affect the weight gain in IBD patients^[21,22]. Additionally, there are a few studies investigating weight gain among IBD patients treated with biologic therapies, especially anti-tumor necrosis factor alpha (TNF)- α therapy. In 21 CD patients, total abdominal fat increased by 18% after 8 wk of infliximab induction therapy ($P = 0.027$)^[23]. A recent retrospective study examined the longitudinal changes in weight among patients with IBD receiving different biologic drugs including infliximab, adalimumab, vedolizumab and ustekinumab^[24]. The study revealed a statistically significant increase in body weight over time among patients receiving infliximab and vedolizumab, with the infliximab/vedolizumab group experiencing a greater degree of weight gain as compared to the adalimumab group. Moreover, observed weight gain among IBD patients undergoing biologic therapy was found to be linked with other clinical factors, such as male gender, high levels of C-reactive protein (CRP), and low serum albumin.

OBESITY AND IBD PATHOGENESIS

Obesity induces a chronic, low-grade inflammatory state, characterized by the release of multiple pro-inflammatory signaling molecules from hypertrophic adipocytes in mesenteric visceral adipose tissue (VAT)^[25-27]. Mesenteric VAT is characterized by the presence of M1 macrophages that secrete a variety of inflammatory cytokines and it has the potential to affect intestinal barrier function^[28,29]. Several studies have established a relationship between adipocyte mass and the degree of cytokine expression^[30]. Obesity has been shown to be positively associated with visceral adiposity, as determined by volumetric cross-sectional imaging analysis. Furthermore, in obese individuals, there is a direct correlation between visceral adiposity and circulating levels of interleukin-6 (IL-6). Additionally, BMI has been found to be linked with increased levels of CRP in this population^[31].

Other mechanisms of obesity in IBD include intestinal barrier dysfunction and alterations in the intestinal microbiota (Figure 1). Obesity and IBD are associated with dysbiosis along with a reduction in bacterial diversity^[32]. High fat diet during obesity decreases the diversity of the gut microbiota (dysbiosis), which, in turn, leads to the reduction of anti-inflammatory bacterial species or metabolites. These changes can trigger innate immune system by activation of pattern recognition receptors, including Nod-like receptors or Toll-like receptors, which are present on intestinal epithelial cells or dendritic cells. Pro-inflammatory cytokines secreted from innate immune system can also contribute to increased intestinal permeability, which may increase the risk of bacterial translocation^[17,25]. Numerous studies have demonstrated that impaired gut barrier function is a characteristic feature of obesity. This dysfunction permit increased bacterial translocation, leading to the subsequent initiation of systemic inflammation^[33,34].

Accumulating evidence suggests a connection between changes in the mesenteric fat and IBD, in particular CD^[27]. Intestinal barrier dysfunction and transmural inflammation may induce bacterial translocation to the surrounding mesenteric

adipose tissue, which subsequently leads to the adipocyte hypertrophy (red arrow, Figure 1). The hypertrophic adipocytes release pro-inflammatory cytokines, adipokines, and chemokines such as TNF- α , IL-6, leptin, resistin, and monocyte chemoattractant protein-1). These pro-inflammatory mediators can induce the infiltration of M1 macrophages and CD4+ T cell activation into T helper (Th) 1 and Th17 cells^[35]. This process may contribute to the development of hypertrophic mesenteric fat wrapping around the inflamed intestine, known as “creeping fat” that is pathognomonic of CD^[27]. Creeping fat itself is thought to be an intrinsic component of inflammatory dysregulation in the pathogenesis of CD. Compared to other VAT, creeping fat demonstrates greater immunological activity. Additionally, there is a significant correlation between the extent of creeping fat and the degree of histological inflammation, as well as the level of infiltration by lymphocytes or macrophages^[36]. In addition, the creeping fat formation may be induced by migration of preadipocytes from mesenteric VAT in response to the increased fibronectin signal released from activated muscularis propria smooth muscle cells in inflamed gut^[37]. The presence of creeping fat in CD patients has been associated with various pathological changes, including muscularis propria hyperplasia, transmural inflammation, and intestinal fibrosis. These alterations may contribute to the stricturing form of the disease^[37,38]. Notably, creeping fat has been found to contain higher levels of fibrotic tissue and T cells in the ileum, as compared to colonic fat from patients with either CD or UC^[39]. Creeping fat secretes a broad spectrum of pro-inflammatory and pro-fibrotic mediators such as adipokines, cytokines, fatty acids, and growth factors^[40]. Moreover, expression of leptin and adiponectin is elevated in the creeping fat of CD patients. The severity and activity of CD have been correlated with the levels of other adipokines, including resistin^[41]. A case-control study showed that the gene expression profile of creeping fat in CD patients was similar to that of VAT from obese patients, indicating a greater inflammatory state as compared to VAT obtained from non-obese individuals^[42].

IMPACT OF OBESITY ON THE NATURAL HISTORY AND OUTCOMES OF IBD

The effect of obesity on the disease phenotype of IBD remains uncertain. While a retrospective review has indicated that obesity may be a risk factor for perineal disease in IBD^[12], other studies have not found any differences in disease distribution or behavior between patients with UC or CD who are obese compared to those who are not^[8,43]. Obesity has been linked to increased disease activity and unfavorable clinical outcomes in several chronic inflammatory diseases, such as psoriasis and rheumatoid arthritis^[44,45]. However, evidence regarding the effect of obesity on outcomes in IBD is limited and inconclusive. A study of 581 IBD patients showed that obese individuals had significantly lower frequencies of hospitalization (42.1% *vs* 66.0%, $P < 0.001$) and a reduced likelihood of requiring surgical intervention (41.1% *vs* 61.1%, $P = 0.02$), when compared to those patients with normal BMI^[8]. However, in other population-based study for 143190 IBD patients, it was demonstrated that obesity was an independent predictor of higher rates of all-cause re-admission at both 30 d [18% *vs* 13%; adjusted odds ratio (aOR) = 1.16; $P = 0.005$] and 90 d (29% *vs* 21%; aOR = 1.27; $P < 0.0001$), in comparison with non-obese patients^[46]. A systematic review reported that there is no significant difference in the rates of corticosteroid usage, hospitalization, surgical intervention, or emergency room visits between obese and normal-weight individuals with IBD^[7]. This finding has been supported by a recent retrospective study conducted in South Korea, which found no significant differences in clinical features or treatment outcomes between obese and non-obese patients with IBD, as measured by the cumulative probabilities of receiving various treatments^[13].

In CD, many studies show that obesity may indeed have a beneficial effect. A previous report supports this hypothesis by showing that the small VAT adipocytes in CD patients exhibit higher anti-inflammatory genes, which implies a potential protective role of VAT in CD^[42]. A retrospective analysis of 221 patients with CD found that an increase of 1 kg/m² in BMI at diagnosis led to a 5% reduction in the risk of requiring surgical intervention in the future (HR = 0.95; 95%CI: 0.91-0.99).

Whereas, the risk of corticosteroid use or future hospitalization did not differ^[47]. The results of a retrospective study showed that obese patients with CD had lower frequencies of corticosteroid usage, anti-TNF treatment, hospitalization, and surgery in contrast to those with normal weight^[8]. However, there were also contrasting results. For instance, one study reported that obese patients with CD were more at risk of active disease (OR = 1.50; 95%CI: 1.07-2.11) or hospitalization (OR = 2.35; 95%CI: 1.56-3.52)^[12]. Alternatively, a prospective case-control study revealed no correlation between BMI and the risk of undergoing surgery or using corticosteroids in the future^[9].

In UC, several studies suggest that obesity may have a worse prognosis. In one population-based cohort study that included 267 patients with UC, each incremental increase in BMI by 1 kg/m² was associated with a 3.4% increase in the risk of hospitalization ($P = 0.052$) and a 6% increase in the risk of surgery ($P = 0.01$)^[47]. A recent population-based cohort of 417 UC patients, of whom 20.6% were obese, confirmed that obesity among individuals with UC may have unfavorable prognostic implication, particularly with regards to the subsequent hospitalization (HR = 1.72; 95%CI: 1.10-2.71; $P = 0.018$) and corticosteroid usage (HR = 1.026; 95%CI: 1.00-1.05; $P = 0.05$) in comparison to patients with normal weight^[48]. Moreover, an increase of 1 kg/m² in BMI was associated with a 5% escalation in the probability of subsequent hospitalization (HR = 1.05; 95%CI: 1.01-1.08; $P = 0.008$) and a 2.6% increase in the chance of requiring corticosteroid usage (HR = 1.026; 95%CI: 1.00-1.05; $P = 0.05$). However, the retrospective analysis of 284 UC patients showed that obese people displayed a reduced risk of developing complications^[8].

IMPACT OF OBESITY ON THE MANAGEMENT OF IBD

Medical management

There is evidence to suggest that obesity may be an adverse prognostic factor in a patient's response to drug therapy. The reason being obesity is considered a chronic inflammatory state and obesity can affect the pharmacokinetics of drugs. Obesity

may decrease drug half-life and trough levels due to an increase in drug clearance and volume of distribution.

Immunomodulators: Despite extensive clinical experience with thiopurine, few studies have evaluated clinical predictors of response to thiopurine in IBD. A retrospective study of 1176 IBD patients evaluating azathioprine responsiveness based on BMI found that a reciprocal association between BMI and outcomes in patients with UC and CD. More specifically, favorable outcomes were observed in UC patients with a BMI below 25 kg/m² and in CD patients with a BMI exceeding 25 kg/m²[49]. In a cohort of 132 patients with IBD treated with thiopurines dosed according to BMI, a study found that patients with obesity were less likely to reaching optimal therapeutic concentrations of the thiopurine metabolite, 6-thioguanine, which has been shown to correlate with remission of IBD[50].

Anti TNF- α therapy: Several data have suggested that obesity may induce a reduced response to anti-TNF- α agents[51]. The augmented clearance and expanded volumes of distribution associated with obesity can lead to lower trough levels, resulting in either a diminished response or a heightened risk of response loss to anti-TNF- α agents. For adalimumab, body weight has been shown to be the most significant predictor of drug clearance and volume of distribution in psoriasis patients[52]. In contrast to other rheumatoid conditions, studies examining the impact of obesity on anti-TNF therapy in IBD have produced inconsistent findings.

Obesity has been linked to an increased risk of failure of anti-TNF therapy, irrespective of the method of administration (subcutaneous *vs* intravenous) and dosing regimens (weight-based *vs* fixed-dose regimens). These results could imply that there is an intrinsic factor to obesity that reduces treatment response, regardless of drug level and mode of exposure. A recent meta-analysis found that obese patients with UC were at a greater risk of anti-TNF- α treatment failure (OR = 1.41; 95%CI: 1.01-1.98; *P* = 0.045) than non-obese patients, irrespective of whether they received fixed-dose or weight-based treatment regimens[53]. Furthermore, in another

study that evaluated 160 UC patients treated with various biologic agents, both weight-based (infliximab) and fixed-dose regimens (adalimumab, certolizumab, vedolizumab, and golimumab), regardless of the type of biologic used, an increase in BMI of 1 was associated with a 4% greater risk of treatment failure (aHR = 1.04; 95%CI: 1.00-1.08) for all patients^[54]. However, a pooled data analysis of over 1200 infliximab-treated IBD patients reported that BMI did not have a significant effect on clinical remission rate^[55]. A meta-analysis for multiple immune-mediated diseases showed that obesity was associated with anti-TNF therapy failure in several rheumatic diseases, but no such association was observed in IBD^[56]. However, in a recent meta-analysis including the newer 6 articles into the meta-analysis, obesity was associated with higher risk of failing anti-TNF therapy in UC patients, but not in CD patients^[53]. Although there are insufficient studies on the impact of obesity on safety of biologic agents, a cohort study of over 6000 biologic-treated IBD patients reported no association between obesity and an increased risk of serious infections^[57].

Vedolizumab: There is insufficient data regarding the potential impact of obesity on the therapeutic efficacy of vedolizumab in the management of IBD. Vedolizumab trough drug levels are known to be inversely proportional to body weight^[58]. A recent retrospective study showed that obesity was not significantly related to increased rates of dose escalation for vedolizumab therapy^[59]. However, a higher BMI was linked to reduced rates of vedolizumab discontinuation and CRP normalization, although not with endoscopic remission.

Ustekinumab: In chronic inflammatory conditions other than IBD, such as psoriasis and rheumatoid arthritis, obesity may negatively affect the clinical response to biological drugs. Of note, anti-interleukin drugs appear to be more strongly affected by BMI than anti-TNF α drugs. However, in IBD, there is very little research on the impact of obesity on treatment response with this drug. A post hoc analysis of IM-UNITI study, which evaluated the efficacy of ustekinumab for maintenance of CD,

revealed a statistically significant decrease in ustekinumab trough levels among obese patients (median 2.98 mcg/mL)⁶ compared to patients with overweight (4.84 mcg/mL; $P = 0.021$) and underweight or normal weight (4.43 mcg/mL; $P = 0.014$)^[60]. While BMI appeared to have an impact on ustekinumab drug levels, it was not found to be a significant predictor of clinical remission.

Tofacitinib: A pharmacokinetic profile of tofacitinib revealed that increased body weight had some effect on the drug's plasma concentrations, with higher body weight associated with lower peak and higher trough concentrations. However, these differences were considered to be not clinically significant^[61]. The evidence suggests that psoriatic arthritis patients with a baseline BMI over 35 kg/m² have lower rates of response to tofacitinib than those with lower baseline BMI^[62]. However, in a *post hoc* analysis of the OCTAVE studies, effectiveness and safety profile of tofacitinib in UC patients is not impacted by obesity^[63]. In the UC population, BMI was not identified as a significant predictor of outcomes, and no clear relationship between BMI and adverse events was observed.

Surgical management

It has been well established that obesity increase operative time and the risk for conversion to laparotomy^[64]. Obesity also may heighten the risk of short-term perioperative complications, such as surgical site infections and wound complications after abdominal surgery^[65]. Obesity also makes surgery for IBD more challenging, particularly those requiring pelvic exposure. A study involving 382637 inpatient hospitalizations for surgery in IBD patients revealed that obese patients had significantly higher rates⁴ of postoperative complications. Specifically, the study found that obese patients had increased odds of postoperative wound complications (OR = 1.35, $P = 0.01$), pulmonary complications (OR = 1.21, $P = 0.02$), infections (OR = 1.16, $P = 0.02$), and shock (OR = 1.30, $P = 0.02$)^[66]. A recent meta-analysis strongly supported the association between obesity and postoperative complications in IBD^[67].

Stoma creation and ileal pouch-anal anastomosis (IPAA) in obese patients are more difficult to perform and also appear to increase the risk of complications in IBD patients. Obesity has been identified as a risk factor for stoma-related complications^[68]. Additionally, it may increase the likelihood of postoperative complications, including pelvic sepsis, which has been shown to have a negative impact on long-term pouch function^[69]. However, several studies have indicated that overweight and obese patients who undergo a three-stage IPAA procedure with the utilization of a diverting stoma may achieve comparable long-term outcomes to non-obese patients^[64].

IMPACT OF OBESITY TREATMENT ON IBD OUTCOMES

Given the rising prevalence of obesity within the IBD population, there is a growing need to explore the effects of weight loss interventions on outcomes of IBD. It is widely recognized that weight loss can have a favorable influences on the outcome of numerous chronic diseases^[70]. Despite considerable evidence that obesity has a negative influence on the response to therapies for IBD, there is currently a lack of data regarding whether interventions aimed at treating obesity can improve outcomes in individuals with IBD. To date, no interventional studies have been conducted specifically to investigate the impact of intentional weight loss on IBD.

Current therapeutic strategies to obesity includes lifestyle modifications, pharmacologic treatment, bariatric surgery, and bariatric endoscopic applications, of which the intragastric balloon is the most widely used. The European Society for Clinical Nutrition and Metabolism (ESPEN)/United European Gastroenterology (UEG) guidelines suggest that the management of obesity in patients with IBD should involve a stepwise approach, starting with dietary and lifestyle interventions. If necessary, anti-obesity drugs or bariatric surgery can be considered as options (Table 2). However, the guidelines do not provide a one-size-fits-all approach and individualized care is recommended^[71].

Lifestyle and dietary interventions

A combination of dietary adjustments, physical exercise, and behavioral modifications as part of a lifestyle intervention is generally considered the preferred approach for achieving weight loss in the general population. Of course, IBD patients should also consider this approach, but there are special considerations in this cohort that require the advice of a certified dietitian. Specifically, individuals with active IBD may find it challenging to tolerate certain “healthy” foods, such as fruits and vegetables, which are commonly recommended as part of a healthy diet. Additionally, IBD patients, despite being overweight, may be vulnerable to the deficiency of various vitamins and micronutrients, and thus careful consideration of a balanced diet is essential. One study involving IBD patients showed improvements in body weight, waist circumference, and steatosis when a Mediterranean diet was prescribed^[72]. There is no available data to provide evidence on the impact of overall calorie intake or supervised dietary weight loss on outcomes in patients with IBD.

Moreover, exercise may have a positive effect on regulating IBD activity. Moderate-intensity exercise has been shown to have anti-inflammatory effects through a variety of mechanisms, such as reducing visceral fat, decreasing the secretion of inflammatory adipokines, and reducing stress-induced dysfunction of the intestinal barrier^[73]. A prospective study suggested that high levels of physical exercise may be associated with a lower risk of active disease in IBD patients^[74]. However, it should be noted that these studies have primarily relied on subjective measures of well-being and have not utilized specific objective indicators of disease activity.

Pharmacologic treatment

Currently, anti-obesity treatment is often recommended for patients with a BMI of 30 kg/m² or above, or a BMI of 27 kg/m² or higher in the presence of obesity-related comorbidities^[75]. There are several prescription drugs (orlistat, liraglutide, phentermine-topiramate and naltrexone-bupropion) available for weight loss, but there are no randomized controlled trials of these anti-obesity drugs in patients with IBD. The ESPEN/UEG guideline recommends that anti-obesity drugs may be

utilized in patients with IBD, provided they are indicated for such use, with the exception of orlistat. Orlistat should be avoided due to its mechanism of action and associated adverse effects. Notably, a case report demonstrated the use of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, in a patient with active CD and type 2 diabetes resulted in improved glycemic control and quality of life scores following a switch from insulin therapy^[76]. A recent cohort study of patients with both IBD and type 2 diabetes showed that treatment with GLP-1-based therapies was linked with a lower risk of adverse clinical events, defined as a composite of the need for oral corticosteroid treatment, TNF- α -inhibitor treatment, IBD-related hospitalization, or IBD-related major surgery, as compared to treatment with other antidiabetic therapies [adjusted incidence rate ratio (IRR) = 0.52, 95%CI: 0.42-0.65]^[77]. These observations suggest that GLP-1 based therapies may be a novel treatment option for IBD. Naltrexone and bupropion individually may have anti-inflammatory properties. Two small uncontrolled studies of IBD patients showed that naltrexone alone reduced disease activity and induced endoscopic response^[78]. The initiation of low-dose naltrexone in IBD patients has been found to result in a decrease in the prescription of several medications that are typically deemed crucial for the treatment of IBD^[79]. Bupropion has been associated with clinical improvement in case reports and case series in IBD patients^[80,81]. Phentermine-topiramate is a weight-loss drug that has demonstrated highly efficacy in promoting weight loss in obese individuals. While the precise mechanisms are still being investigated, preclinical studies have provided evidence supporting the anti-inflammatory properties of both topiramate and phentermine. Early experimental evidence indicated that topiramate could significantly reduce colonic tissue injury in animal models of IBD. However, these findings were not corroborated in a subsequent retrospective cohort study conducted in human subjects^[82,83]. A phase 2 clinical trial is currently in progress to investigate the effectiveness and safety of phentermine-topiramate in obese biologic-treated patients with UC (NCT04721873). Sodium-glucose linked transporter 2 inhibitor is the new glucose lowering drug, which has shown beneficial effects on the obesity and heart failure as well as type 2 diabetes^[84]. This drug significantly

improved acetic acid-induced IBD in animal models by activating autophagy signaling, inhibiting apoptosis and pro-inflammatory cytokines, lowering oxidative stress, and increasing wound healing^[85-87].

Bariatric endoscopic applications

Intragastric balloon therapies are a minimally invasive and temporary treatment for inducing weight loss in obese patients. While this approach has been used successfully in the management of obesity, there is limited research on the effectiveness and safety of intragastric balloon therapy in patients with IBD. Although a small series has examined the application of intragastric ballooning in patients with IBD, reports that detail the long-term outcomes associated with weight loss and complications are lacking. The use of intragastric balloon is currently contraindicated for IBD patients due to concerns about the potential for exacerbation of symptoms and complications. A case report demonstrated that the placement of an intragastric balloon for weight loss may exacerbate symptoms of UC^[88]. Further, there is currently a scarcity of high-quality evidence regarding the efficacy of other endoscopic procedures for weight loss in patients with IBD.

Bariatric surgery

For the general population, in obese patients with BMI ≥ 40 kg/m² or 35-39.9 kg/m² with obesity-related comorbidities and previously failed to achieve adequate weight reduction with non-surgical interventions, bariatric surgery is superior to lifestyle and diet interventions and reduces mortality^[89]. There are several different techniques for bariatric surgery, the most common being a Roux-en-Y gastric bypass (RYGB) and a sleeve gastrectomy (SG). These are now mainly performed laparoscopically.

Although data are sparse, bariatric surgery may be a viable, effective, and safe weight loss approach that could potentially result in improved outcomes for patients with IBD^[90-93]. In most cases revised from two systematic reviews, weight loss resulting from bariatric surgery can be beneficial in achieving remission, reducing disease activity, and decreasing medication dependence in patients with IBD^[92,94].

Bariatric surgery resulted in similar weight loss and risk of complications in IBD patients as in non-IBD patients. A case-control study that included 88 bariatric procedures performed on 85 IBD patients, matched 1:2 for age, sex, BMI, hospital of surgery, and type of bariatric surgery with non-IBD patients who underwent bariatric surgery, found that bariatric surgery was a safe and effective intervention for weight loss, producing similar results to those observed in the control group over a 2-year period^[93]. A case-control study involving 25 patients with IBD who received bariatric surgery, and matched with IBD patients who did not undergo bariatric surgery, found that the usage of rescue corticosteroids and the requirement for IBD-related surgery were less prevalent in the former group than in the controls^[95]. However, long-term effects of bariatric surgery in IBD patients are poorly understood.

Although conclusive findings have yet to be derived from randomized trials, current evidence suggests that SG may confer an advantage over RYGB in patients with IBD, as SG solely involves the stomach and thus may minimize the risk of small intestinal bacterial overgrowth^[90,96]. By avoiding anatomical alterations in the small intestine, the risk of complications such as strictures, abscesses, and fistulas may be reduced and future IBD-related surgeries may be simplified.

De-novo IBD after bariatric surgery

The development of *de-novo* IBD subsequent to bariatric surgery has been reported in several studies. The potential mechanisms underlying this association include exposure to viable toxins as a result of anatomical alterations, increased release of cytokines due to changes in adipose tissue, and alterations in the gut microbiome^[95,97]. A Danish nationwide population-based cohort study has reported that bariatric surgery is related to an increased risk of developing new-onset CD, but not UC^[98]. After bariatric surgery, the onset of IBD symptoms varied from 1 mo to 16 years^[97]. In a case series, it was found that 44 patients who had previously received bariatric surgery, with RYGB being the most common procedure, developed *de-novo* IBD after a median latency period of 7 years^[99]. Recent meta-analysis including

149385 patients reported that the pooled odds ratio for the *de-novo* IBD following bariatric surgery is 1.17^[100]. Thus, the possibility of *de-novo* IBD should be taken into account as a potential cause of symptoms such as abdominal pain and diarrhea in patients who have undergone bariatric surgery.

CONCLUSION

Both obesity and IBD are rapidly increasing in modern society, and the proportion of obesity among IBD patients is also reported to be higher now than that in the past. There are claims that obesity contributes to the pathogenesis of IBD or that there are common factors contributing to both diseases, such as dysbiosis, but it is still insufficient to know the causal relationship or direction between them. Although data to assess the effect of obesity on outcomes in IBD are sparse and inconclusive, obesity may have a protective effect in CD and a poorer prognosis in UC. Obesity can clearly affect the treatment of IBD or surgery. Therefore, clinicians need to be aware that obesity can affect the treatment response to drugs and increase surgical complications. Although there are few studies, obesity treatment appears to have the potential to have a relatively favorable effect on IBD outcomes. Bariatric surgery appears to be relatively safe and effective in obese IBD patients. Therefore, it is necessary to compare the benefits and side effects of bariatric surgery for IBD patients. Some patients develop new onset IBD, especially CD, after bariatric surgery, so clinicians are advised to keep this in mind.

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