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Impact of Obesity on Inflammatory Bowel Disease

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Abstract

Purpose of Review This review highlights recent work that evaluates the impact of obesity on inflammatory bowel disease (IBD) pathogenesis and management.

Recent Findings The impact of obesity on IBD prevalence, clinical course, and management, has been studied and described more so in recent years. Studies have shown that obesity increases IBD disease activity, leads to longer hospitalization courses, and increases the likelihood of the development of extraintestinal manifestations. Recent evidence has also suggested that obese IBD patients have a higher frequency of extended steroid treatment and increased use of antibiotics compared to non-obese IBD patients.

Summary The effect of obesity on patients with IBD is a topic that has garnered widespread interest in the last decade due to the increasing prevalence of both diseases. To date however, although there are still many unanswered questions. It is quite clear that obesity, and more specifically, visceral adiposity, affects numerous IBD-related outcomes in regard to pathogenesis, extra-intestinal manifestations, response to medical and surgical therapies, hospital length of stay, healthcare-related costs, and health-related quality of life. Future studies should include larger patient populations and evaluate additional factors that are altered in those with obesity including the gut microbiome, dietary patterns, and whether weight loss and/or degree of weight loss impact clinical outcomes.

Keywords Obesity · Crohn's disease · Ulcerative Colitis · Adipose tissue · Inflammatory bowel disease · Body mass index

Introduction

The global prevalence of obesity has dramatically increased over the last 50 years, affecting less than 1% of the world's population in 1975 to nearly 13% in 2016 [1]. In the United States, the Centers for Disease Control (CDC) reported overall prevalence increase from 30.5% to 42.4% over the past 20 years [2]. Once thought to be a disease only affecting high-income countries, the prevalence of overweight and obese adults is rapidly increasing in low- and middle-income countries [3]. Obesity is associated with a myriad of serious health conditions, including hypertension (HTN), type II diabetes mellitus (DM), sleep disorders, dementia, cardiovascular diseases, and various malignancies, and is associated with increased morbidity and mortality [4].

In parallel with the obesity epidemic, the incidence and prevalence of inflammatory bowel disease (IBD) is also rapidly increasing worldwide. It is hypothesized that this trend may be at least partly related to changes in dietary, lifestyle, and environmental factors associated with globalization [5]. Various additional factors may be implicated in the rise of IBD, including smoking and early exposure to parasitic infections and/or antibiotics [1]. While it is well-established that obesity negatively affects the disease course of other autoimmune conditions, the specific interplay between excessive body weight and the pathogenesis and clinical progression of IBD has yet to be fully elucidated [6]. In this review, we evaluate and discuss recent data pertaining to the epidemiology and pathophysiology of obesity in IBD, its effect on the disease course and management, and the

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influence obesity has on quality of life in those who suffer with IBD. Key findings from recently published literature are summarized in Table 1.

Epidemiology

To date, there is a paucity of large-scale studies evaluating the prevalence of obesity in those with IBD. Furthermore, the available data varies widely because of the heterogeneity of IBD. However, numerous IBD-related studies over the last decade, in both pediatric and adult populations, suggest that the current prevalence of overweight and obese IBD patients ranges from approximately 20–30%, similar to that of the general population [5]. In 2009, Steed *el al.* showed a significant increase in the percentage of IBD patients with obesity, reporting approximately 52% of their IBD patients as overweight or obese and similar rates of obesity amongst those with Crohn's Disease (CD) and Ulcerative colitis (UC) at 18% and 17.5%, respectively [16].

Whether obesity itself is a risk factor for the development of IBD is still widely debated. A large prospective study of U.S. women enrolled in the Nurses' Health Study II demonstrated that obesity and increased weight gain after the age of 18 were associated with a higher risk of developing CD; however, no association was identified amongst those with UC [17]. In contrast, a prospective study of 300,724 patients from the EPIC cohort (European Prospective Investigation into Cancer and Nutrition) reported that obesity had no influence on the development of CD or UC [18].

The rise in childhood obesity has closely mirrored the trends seen in the adult population over the past decade. Previously, children with IBD were often described as being malnourished and/or underweight. However, this association is becoming less common as there are increasing numbers of pediatric patients with IBD who are overweight or obese [19]. In a 2012 study of 1,598 children across the United States by Long et al., the overall prevalence of overweight or obese children was noted to be 20.0% in those with CD and 30.1% amongst those with UC or indeterminate colitis (IC), 35.2% in Hispanics, and 23.1% among non-Hispanics[20]. Similar to the findings from the Nurses' Health Study II from 1989 which focused on adult IBD patients, Jensen et al. demonstrated a positive association between risk of CD and BMI in those under the age of 30. Interestingly, the study also observed that being underweight in childhood was a risk factor for the development of UC later in life [17, 21].

Overall, there is a lack of recent and robust epidemiological data on the prevalence of obesity in IBD in both children and adults. Many of the studies available are cross-sectional, which often poses a significant challenge when trying to establish causality. Furthermore, many of the studies define underweight, normal weight, overweight and obese based on BMI, which may not be the optimal measure of total body composition or distribution of adipose tissue (visceral adiposity); the aforementioned measurements may have more profound effects than just BMI alone.

Pathophysiology of Obesity in Inflammatory Bowel Disease

The role of obesity in the development of IBD involves the complex interplay of multiple factors, some of which have yet to be elucidated. An in-depth analysis regarding the various pathogenic mechanisms in obesity that may contribute to IBD is beyond the scope of this review; however, a summary of the proposed mechanisms is depicted in Fig. 1.

Adipose tissue found in both subcutaneous and visceral fat can be considered a biologically active organ, composed of complex cells that continuously produce and secrete factors that lead to a chronic, low-grade state of inflammation [22]. These factors, termed "adipokines," are known to regulate metabolic homeostasis and important immune functions and include resistin, ghrelin, and leptin – all of which contribute to a pro-inflammatory state [5]. The adipokine known as "adiponectin" is decreased in obesity, which plays a permissive role in the continued production of pro-inflammatory molecules [23]. Insulin resistance is promoted by the interaction of tumor-necrosis-factor-alpha (TNF-α) and insulin receptors, which induces oxidative stress via increased production of free radicals [23]. Additionally, obesity is known to lead to alterations in the composition of the intestinal microbiome, contributing to dysbiosis [1]. Further, adipose tissue may affect the production of zonulin, a key mediator of intercellular tight junctions, and alter other components of intercellular tight junctions within the intestinal mucosa, which enhances the production of inflammatory adipokines, bacterial translocation, and T-cell infiltration [22]. These continued insults lead to a perpetual state of chronic, low-grade inflammation, which in turn enhances the production of several pro-inflammatory factors, including interleukins (IL-1, IL-6, IL-8, IL-10), cytokines and cytokine-related proteins (Interferon-gamma [IFN-γ], TNF-α), chemokines (monocyte chemoattractant protein [MCP-1], macrophage inflammatory protein 1 [MIP-1], macrophage migration inhibitor factor [MIF]), acute phase reactants (C-reactive protein), and the upregulation of pro-inflammatory signaling pathways (nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]) [22, 24]. Together, this results in the continued production of pro-inflammatory factors, facilitating the development of IBD [22, 23]. Whether obesity influences the disease phenotype (i.e., CD versus UC) remains unclear and is an area under active investigation.

Table 1 Summary of key literature findings regarding the effect of obesity on the clinical course, medical and surgical options, and quality of life in patients with IBD [7–15]

	Authors	Year	Study design	Population characteristics marker of obesity	Outcomes/Key	Findings
Obesity and the clinical course of IBD	Greuter et al	2020	Retrospective	3075 IBD patients -11% were obese	BMI ≥ 30 kg/m^2	Obese CD patients had significantly elevated CDAI and were less likely to be in remission based on CDAI < 100 and fecal calprotectin < 100 ug/g
	Nguyen et al	2019	Retrospective	10,256 IBD patients -50% were obese	Based on their ICD-9 code on admission (278.00, 278.01, or V85.30-V85.44)	Obese patients spent signifantly longer period of time in the hospital compared to non-obese patients, and had higher hospitalization-related costs
Obesity and IBD medical therapies	Losurdo et al	2020	Case–control	807 IBD patients—438 with CD, 369 with UC -6.9% were obese (BMI ≥ 30 kg/m^2) among those with IBD 378 patients without IBD -7.9% were obese (BMI ≥ 30 kg/m^2) among those without IBD	BMI > 30 kg/m^2	The frequency of extended systemic steroid treatment and use of antibotics were greater in obese patients compared to non-obese patients with IBD. No difference was found between groups in the use of biologics, mesalazine, or thiopurines
	Allin et al	2021	Prospective cohort	3,917,843 IBD patients—15,347 had a bariatric surgery	Not specified	Bariatric surgery was associated with increased risk for development of new-onset CD, but not for risk of new-onset UC
	McKenna et al	2020	Retrospective	31 IBD patients – 10 with CD, 20 with UC, 1 with IC	Not specified	Bariatric surgery was safe in IBD patients with no observed increase in infectious complications related to patients' IBD. Bariatic surgery also led to sustained weight loss at 6, 12, and 24 months, and found no IBD flares requiring surgery during the follow up period
	Braga Neto et al	2020	Case–control	47 IBD patients – 12 with CD, 13 with UC	Not specified	Compared IBD patients undergoing bariatric surgery to matched controls (IBD patients not undergoing bariatric surgery), and found that cases were less likely to require rescue corticosteroid usage and less likely to require IBD-related surgeries
	Heshmati et al	2019	Retrospective	54 IBD patients – 19 (8 with CD, 11 with UC) patients had RYGB, 35 (23 with CD, 12 with UC) had SG	Not specified	There was a significant difference in the proportion of patients with worsened CD (through increased IBD medication requirements) after RYGB and a greater rate of surgical complications after RYGB compared to SG
	McKenna et al	2019	Retrospective	758 CD patients who underwent ileocolonic resection -17% were obese	BMI ≥ 30 kg/m^2	Obese CD patients who had undergone ileocolonic resections were more likely to require conversion to open surgery and to have superficial surgical site infection, with obesity being an independent risk factor for superficial surgical site infections

Table 1 (continued)

	Authors	Year	Study design	Population characteristics marker of obesity	Outcomes/Key	Findings
Obesity and quality of life in IBD patients	Jain et al	2019	Cross-sectional	7,296 IBD patients—4,748 with CD, 2,548 with UC -19.5% of CD patients were obese -20.3% of UC patients were obese	BMI 30–34.9 kg/m^2 obesity class I, 35–39.9 kg/m^2 obesity class II	Obesity was found to be independently associated with higher anxiety, depression, fatigue, pain, and inferior social function scores in UC and CD patients at baseline. On longitudinal assessment, obese CD patients were also found to have worsened depression, fatigue, pain, and social function

Adipose tissue comes in a variety of biologically active forms, and is present in a unique form called "creeping fat," which is defined as pathological fat hyperplasia that is limited to areas of inflamed intestine in those with IBD [1]. Creeping fat is primarily observed in CD and is thought to be more immunologically active than other forms of adipose tissue [25]. Moreover, the extent of creeping fat correlates strongly with the severity of microscopic inflammation and degree of immune cell infiltration, fibrosis, and stricture formation [22, 25]. In addition, the expression of adipokines is increased in the hypertrophied mesenteric fat of patients with CD, further contributing to a state of perpetual inflammation [1].

Effect of Obesity on Inflammatory Bowel Disease Course

Obesity may be associated with an increased risk of IBD severity and IBD-related complications. However, more recent studies show conflicting results and may suggest that conditions that are commonly associated with obesity, such as metabolic syndrome, may have a more significant impact than just the presence of obesity itself.

Multiple studies identify an inverse relationship between disease activity in CD and BMI. One study found that patients with CD with a BMI > 25 kg/m^2 had less extensive disease activity than those with BMI < 25 kg/m^2. In addition, patients with a lower BMI were more likely to be described as having active disease, compared to those with a higher BMI. No correlation was found between BMI and duration of disease, perianal disease, endoscopic severity, history of small bowel resection, or use of biologics [26]. Similarly, one cross-sectional study found that patients with BMI ≥ 30 had lower risk of penetrating disease compared to those with a BMI < 25 (OR = 0.56, 95% CI 0.31–0.99), and no association was found between BMI and risk of perianal disease, stricturing disease, or IBD-related surgery [27]. Several studies have investigated whether colonic involvement in CD may be associated with obesity (particularly BMI ≥ 35), however results have been inconsistent [27–31]. On the contrary, a recent Swiss study used the Crohn's Disease Activity Index (CDAI) to objectively measure disease activity and showed that obese patients with CD had significantly elevated CDAI scores [7].

Among those with UC, recent studies suggest that obesity has an inverse relationship with disease severity [7, 8]. One study demonstrated that overweight patients were found to have less active disease compared to normal weight patients and a lower prevalence of pancolitis in obese patients compared to those with a normal BMI. This inverse relationship suggests that increased BMI may actually exert a protective effect on disease severity [31]. An alternative hypothesis may be that active disease prevents

the development of obesity secondary to malabsorption, diarrhea and decreased oral intake, thus lowering the apparent rate of obesity in those with severe IBD, rather than obesity itself being protective.

In studies investigating hospitalization of patients with IBD, data suggests an association between increasing BMI and more prolonged hospital length of stay (LOS) and healthcare costs. One study found that obese patients spent a median of eight days in the hospital per year, compared to five days in non-obese patients ($p < 0.01$), and had higher hospitalization-related costs [8]. Similarly, Singh et al. demonstrated that obese adults with CD and UC had prolonged hospital LOS compared to non-obese patients, and those with UC had higher rates of surgery and hospital LOS greater than seven days [32]. There is some evidence to suggest that certain comorbid conditions, particularly metabolic syndrome, play a key role in hospital LOS in obese patients with IBD as well [33].

Some researchers have hypothesized that obesity may influence systemic inflammatory markers (i.e. erythrocyte sedimentation rate (ESR) and/or CRP), but whether this is a true reflection of disease activity is unclear [26, 34]. In regards to the development of extra-intestinal manifestations (EIM), studies suggest that those with a greater BMI are more likely to have EIM such as arthralgias, erythema nodosum, and inflammatory arthritis ($p = 0.005$) [26].

Regarding disease onset, progression, and involvement, a case control study consisting of 807 patients published in 2020 by Losurdo et al. compared obese versus non-obese IBD patients and demonstrated that age of IBD onset was earlier in obese patients; however, no difference was found in regard to disease location as defined by the Montreal classification ($p = 0.004$) [9].

The Effect of Visceral Adiposity on IBD

While obesity is measured by overall BMI, visceral adiposity is measured by the ratio of visceral adipose tissue to subcutaneous adipose tissue on cross-sectional imaging. Data suggest that visceral adiposity is associated with an increased risk of complications and disease recurrence in those with CD after surgical resection [35, 36]. Additionally, further studies have found higher rates of post-operative complications in obese patients with CD when defining obesity by volumetric analysis rather than BMI stratification [37–39]. Therefore, consideration of visceral adiposity or central obesity, rather than BMI-based criteria, may be more accurate when evaluating the effects of obesity and metabolic syndrome on IBD-specific outcomes.

The Effect of Obesity on IBD Management

Medical Management

In general, pharmacokinetic studies have found that in patients treated with biologics, high body weight is a risk factor for increased drug clearance, shortened half-life, and low trough drug concentrations as a result of rapid proteolysis and a phenomenon referred to as "TNF sink," whereby increased levels of adipose-secreted TNF sequester anti-TNF agents [40–42].

Overall, data suggest that patients treated with anti-TNF agents, such as Infliximab (IFX) or Adalimumab (ADA), require dose escalation with increasing BMI. One study of 124 IBD patients treated with IFX found that obese patients were three to nine times more likely to have an IBD flare and require dose escalation when compared to patients with a normal weight [5]. Another study found that BMI was the only independent predictor for need for dose escalation in those with CD receiving ADA [43].

Other factors that may influence response to therapy are route of administration and weight-based dosing. Observational studies suggest that patients with CD who are treated with IFX have lower rates of IBD-related hospitalizations and abdominal surgeries compared to those treated with ADA or Certolizumab [32, 44]. One explanation is the variation in dosing and route of administration. IFX uses weight-based dosing and is administered intravenously, whereas other biologics (such as ADA) are administered subcutaneously in a fixed-dose manner. Similar findings have also been demonstrated in non-IBD autoimmune conditions, such as psoriasis [45]. Multiple studies have found that ADA is associated with need for dose escalation and lower trough levels in obese IBD patients, a finding that is not seen in those treated with IFX [46, 47]. Possible hypotheses include lower likelihood of obese patients receiving appropriately dosed therapy in a fixed-dosing regimen or poor absorption of medication via subcutaneous routes of administration compared with intravenous route. These findings however are not consistent throughout the literature. A retrospective cohort study evaluating biologic-treated UC patients found that regardless of whether patients were on weight-based or fixed-dose regimens, each 1 kg/m^2 increase in BMI was associated with 4% increase in the risk of treatment failure and 8% increase in risk of surgery and/or hospitalization [41]. However, another study found the opposite result, with no overall association between time to loss of response (LOR) and increasing weight among patients treated with anti-TNF agents [48].

Dreesen et al. retrospectively analyzed 179 patients with IBD treated with an integrin blocker, Vedolizumab (VDZ), another fixed-dose biologic. The study demonstrated that

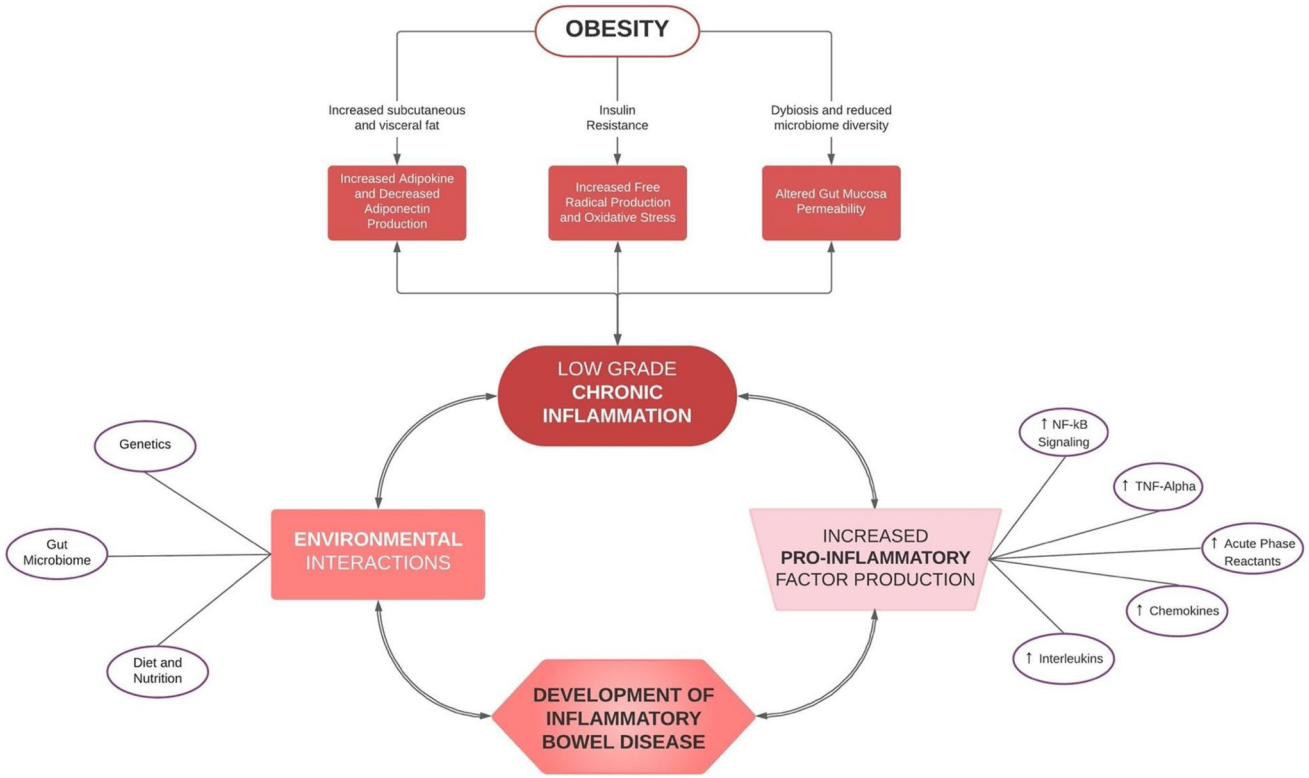

Fig. 1 Schematic displaying pathogenic factors that contribute to the intestinal inflammatory response in inflammatory bowel disease. The role of fat in obesity is hypothesized to involve the interaction of multiple complex mechanisms. Adipose tissue found in both subcutaneous and visceral fat can be considered a biologically active organ, as it continuously secretes and produces factors that lead to a chronic, low-grade state of inflammation [22]. These factors, termed 'adipokines,' include resistin, ghrelin, and leptin—all of which contribute to a pro-inflammatory state [5]. The adipokine, 'adiponectin,' is decreased in obesity, which plays a permissive role in the continued production of pro-inflammatory molecules [23]. Insulin resistance is promoted by the interaction of tumor-necrosis-factor-alpha (TNF-α) and insulin receptors, which leads to increased free radical production and oxidative stress [23]. Additionally, obesity is known to lead to alterations in the composition of the intestinal microbiome, contributing to dysbiosis [1]. Further, adipose tissue may alter components of the intercellular tight junctions within the intestinal mucosa, which enhances the production of inflammatory adipokines, bacterial translocation, and T-cell infiltration [22]. These continued insults lead to a state of low-grade inflammation, which in turn enhances the production of several factors including interleukins (IL-1, IL-6, IL-8, IL-10), cytokines and cytokine-related proteins (Interferon-gamma [IFN-γ], TNF-α), chemokines (monocyte chemoattractant protein [MCP-1], macrophage inflammatory protein 1 [MIP-1], macrophage migration inhibitor factor [MIF]), acute phase reactants (C-reactive protein), and the upregulation of pro-inflammatory signaling pathways (nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]) [22, 24]. Together, this results in the continued production of pro-inflammatory factors, facilitating the development of IBD [22, 23]. Figure shown was created based on several references

having a higher BMI during VDZ therapy initiation was associated with lower trough concentrations over a 30-week period and a lower probability of mucosal healing ($p < 0.05$) [49].

Lastly, one study evaluated the effect of obesity on treatment with non-biologic agents and found that frequency of extended systemic steroid treatment ($p = 0.02$) and use of antibiotics ($p = 0.05$) were greater in those with obesity [9]. Overall, there appear to be multiple hypotheses to suggest that response to medical treatment for those with IBD is altered in those who have obesity and may have future implications in deciding which therapies should be considered first-line in this patient population.

Surgical Management

Multiple studies in recent years have evaluated the effect of obesity on the need for IBD-related surgeries, operative characteristics, and post-operative complications; however, findings are inconsistent.

Data suggest that overweight patients require surgery significantly earlier compared to underweight patients. One study found that for patients with a BMI > 25 kg/m^2, the average time to first IBD-related surgery was 24 months, compared to 252 months for patients with BMI < 18.5 kg/m^2 ($p = 0.043$) [50]. However, the data are equivocal on the association between obesity and the lifetime need for surgery [27, 28]. A study of IBD patients in Scotland found an increased need for surgery among

overweight and obese patients with UC compared to non-obese patients; however, the same study found the opposite results in those with CD, with increased frequency of surgery performed in the normal-weight group [16].

For ileal pouch-anal anastomosis (IPAA), one study looked at short- and long-term post-operative complications in 909 UC patients. While no associations were observed for 1-stage IPAA, obese patients receiving 2- or 3-stage IPAA had greater estimated blood loss ($p = 0.005$ vs. $p < 0.0001$), longer operative times ($p = 0.02$ vs. $p = 0.0002$) and were less likely to receive laparoscopic surgery ($p < 0.0001$ for 2-stage IPAA vs. $p = 0.03$ for 3-stage IPAA). They also found that obese patients were more likely to have longer hospital LOS after 2-stage IPAA ($p = 0.009$) and an increased risk of superficial surgical site infections ($p = 0.003$), however there were no significant differences in long-term clinical outcomes (e.g., incontinence, frequency of bowel movements, pad usage, and pouchitis) in post-operative obese patients compared to non-obese patients [51].

Similarly, another study by the same group found that obesity was an independent risk factor in patients with CD who underwent ileocolonic resection for conversion to an open surgery, and was associated with increased development of superficial surgical site infections [51].

Other studies have found that measures of obesity other than BMI (i.e. calculated visceral/subcutaneous ratio) showed an increased correlation with post-operative complications in those with CD undergoing an elective ileocolectomy and a statistically significant association between higher visceral adiposity, operative and post-operative complications, and increased risk of recurrence of CD after surgical resection [36, 38, 39].

However, other studies suggest there is no difference in operative risk in obese patients compared to non-obese patients with IBD. One study analyzed the general perioperative and postoperative surgical outcomes in underweight, normal weight, overweight, and obese patients with IBD who underwent intestinal surgery and found no difference in laparoscopic conversion to open, estimated blood loss, intraoperative complications, or median operative time. Similarly, no difference was found in 30-day postoperative complications between the groups, including total complications, wound infections, or anastomotic leaks [52].

Given the reported complications associated with severe obesity in IBD, one potential solution is offering bariatric surgery. Studies examining the safety of bariatric surgery in obese patients with IBD have found bariatric surgery to be safe overall. One study observed sustained weight loss at 6, 12, and 24 months, with no IBD flares requiring surgery during the follow-up period (mean 2.7 years) [51]. Another case–control study found that IBD patients undergoing bariatric surgery were less likely than matched controls with IBD to require rescue corticosteroid usage or IBD-related surgeries, despite a higher BMI after bariatric surgery compared to controls who had not undergone bariatric surgery [10]. Another study comparing Roux-en-Y gastric bypass (RYGB) to sleeve gastrectomy (SG) found that RYGB is associated with worsened CD ($p = 0.016$) and a greater rate of surgical complications ($p = 0.02$) compared to SG, suggesting that SG may be a safer procedure in obese patients with CD [11].

Recently, there has been some data to suggest an increased risk of new-onset IBD following bariatric surgery. Allin et al. followed a cohort of over three million individuals and found an association between new-onset CD and those who had undergone bariatric surgery, but was not seen in those with UC [12].

Obesity and Quality of Life

While most IBD-related clinical studies focus on disease outcomes and efficacy of various treatments, the Food and Drug Administration (FDA) has recently advocated for the inclusion of health-related quality of life (HRQoL) measures in drug development clinical trials [53, 54]. HRQoL incorporates several domains, including patient perceptions of physical and psychosocial functioning, mental health, and general health [55]. Although these aspects provide meaningful insight to a patient's life beyond traditional clinical settings, the subjective nature of HRQoL is arguably a challenge to interpret, as patients with the same objective health status can report dissimilar HRQoL due to differences in coping abilities and expectations [56, 57].

In IBD, HRQoL is generally assessed by patient-reported outcomes obtained via the Short-Form 36 questionnaire or disease-specific scales, such as the Inflammatory Bowel Disease Questionnaire (IBDQ) [53]. These surveys inquire about distress, health anxiety, perceived stress, and the need for social support. While it is well-established that disease symptoms play an important role in HRQoL, even asymptomatic patients report lower HRQoL due to fear of pain and pain-specific catastrophizing [58]. In light of these findings, there have been more concerted attempts to bridge the gap between patient- and physician-specific experiences in managing patients with IBD. A 2020 meta-synthesis reported three essential themes that negatively impact the psychosocial well-being of IBD patients: 1) unpredictability of IBD, 2) the emotional turmoil of living with IBD, and 3) the difficulty of maintaining a normal life while managing IBD [59]. Patients also expressed a desire for increased physician training to shorten the path to diagnosis and greater integration of mental health support [60].

Obesity, independent of IBD, is strongly correlated with decreased HRQoL [61]. There are, however, IBD-related

HRQoL risk factors that overlap with those of obesity including female gender, lower socioeconomic status, and ethnicity [62]. Of note, there should be increased awareness of female IBD and obese patients' HRQoL, as studies suggest females are more likely to report concerns related to attractiveness and body image and worries about being treated differently because of their illness [63, 64]. Furthermore, obesity has been associated with higher anxiety, depression, fatigue and pain, as well as inferior social function scores compared with non-obese patients with IBD [13]. Obese patients with IBD also have a higher annual burden and cost of hospitalization compared with non-obese patients, further exacerbating financial stressors [8].

It is difficult to pinpoint a singular method to improve HRQoL in those with IBD. A 2015 Cochrane review found that Infliximab and Vedolizumab improve HRQoL in UC induction and maintenance therapy, respectively [65]. However, a more recent meta-analysis demonstrated that the placebo effect improves HRQoL in IBD patients, possibly related to expectations regarding the perceived increased effectiveness of biologics and intravenous/subcutaneous medications compared to oral treatments [66]. A recent study found that psychological intervention led to reductions in IBD symptoms and depression scores and that a personalized exercise program improved fatigue and HRQoL in those with quiescent disease [67]. Therefore, it is reasonable to suggest that a multimodal approach is required to mitigate HRQoL issues in these patients. Ultimately, HRQoL for obese patients with IBD is an important factor that is often underappreciated, and clinicians should consider a more holistic approach towards addressing this particular patient population.

IBD, Obesity, and Other Comorbid Conditions

The combined impact of obesity and IBD on other comorbidities has not been widely explored. While both obesity and IBD are pro-inflammatory conditions, there is a relative dearth of information regarding their combined effect on other disease processes such as colorectal cancer (CRC), thrombotic events and infertility, among others.

Studies suggest that both obesity and IBD are associated with an increased risk of the development of CRC (HR 1.16 and 1.88 respectively), although the risk varies depending on the IBD duration, intestinal involvement, and disease activity [68–70]. Current CRC screening guidelines do not take into account obesity as a risk factor, however this should be considered in future screening guidelines as more data become available.

Thrombotic events are another disease process that is seen more commonly in those with obesity and IBD. Obesity causes chronic inflammation (via adipokines, cytokines, tissue factor, and macrophages), impaired fibrinolysis (via increased plasminogen activator inhibitor-1 [PAI-1]), and venous stasis. Similarly, IBD causes episodic acute on chronic inflammation, impaired fibrinolysis (similarly via increased PAI-1 and decreased expression of tissue plasminogen activator [t-PA]), and malnutrition. The frequent use of corticosteroids in IBD may exacerbate this prothrombotic state by increasing fibrinogen and decreasing t-PA [71, 72].

There are currently no therapeutic approaches for preventing or managing thrombosis in obese patients, other than weight loss [73]. However, a consensus statement by the Canadian Association of Gastroenterology published guidelines on anticoagulation therapy after a venous thromboembolic event [74]. The guidelines suggest anticoagulant prophylaxis in patients with active IBD and minor gastrointestinal bleeding in those undergoing major surgery [75]. Second, if there is a history of venous thrombotic event(s) during a previous flare, then preventative anticoagulation is recommended during subsequent flares.

Infertility is another common problem in those with both obesity and IBD. In obesity, this is thought to be related to maladaptive changes in the hypothalamic-pituitary-ovarian (HPO) axis, menstrual cycle disturbance, and oligo-/anovulation. Furthermore, obese women are at an increased risk of maternal and perinatal complications [76]. Pregnant women with IBD are at an increased risk of complications as well, including venous thromboembolism, need for blood transfusions, antepartum hemorrhage, and need for cesarean section [1, 77]. There is an incomplete understanding of the exact mechanisms that underscore these associations, but they are thought to be related to the improper balance of estrogen and TNF signaling [78].

Conclusions and Future Directions

The prevalence of both obesity and IBD is on the rise and presents numerous therapeutic challenges in the management of patients with IBD. Studies have shown conflicting results, but seem to suggest that obesity increases IBD disease activity, leads to longer hospital length of stay, increases the likelihood of extraintestinal manifestations, and is associated with a higher frequency of prolonged steroid treatment and increased use of antibiotics compared to non-obese IBD patients. To date, although there are still many unanswered questions, it is quite clear that obesity, and more specifically, visceral adiposity, affects numerous IBD-related outcomes in regard to pathogenesis, extra-intestinal manifestations, response to medical and surgery therapies, hospital length of stay, healthcare-related costs, and

health-related quality of life concerns. Using BMI to define overweight and classes of obesity also presents a challenge because it does not account for those with visceral adiposity, which is often associated with metabolic syndrome, and seems to have a more significant impact on systemic inflammation, particularly in those with IBD.

Future directions for further study include investigating large cohorts of pediatric patients and young adults using various anthropometric measurements to determine a more precise contribution of obesity to IBD pathogenesis, prospective studies in both pediatrics and adults, and a more pronounced focus on risk factor mitigation and weight loss to determine if, and what degree of weight loss is required to improve disease activity, response to treatment, reduce risk of complications, and improve health-related quality of life in patients with IBD and obesity. Further, practice guidelines to help clinicians develop personalized nutrition plans for patients based on their food preferences and weight goals to prioritize foods rich in antioxidants and minimize pro-inflammatory foods may be helpful to help IBD patients maintain lean body mass and reduce the risk of future IBD flares.

Declarations

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Conflicts of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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