Obesity in inflammatory bowel disease: A review of its role in the pathogenesis, natural history, and treatment of IBD

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Abstract

In contrast to previous perceptions that inflammatory bowel disease (IBD) patients are generally malnourished and underweight, there is mounting evidence to suggest that rates of obesity in IBD now mirror that of the general population. IBD is an immune-mediated condition that appears to develop in individuals who have not only a genetic predisposition to immune dysregulation but also likely exposure to various environmental factors which further potentiate this risk. With the surge in obesity alongside the rising incidence of IBD, particularly in developing nations, the role that obesity may play, not only in the pathogenesis but also in the natural history of disease has become a topic of growing interest. Currently available data exploring obesity's impact on the natural history of IBD are largely conflicting, potentially limited by the use of body mass index as a surrogate measure of obesity at varying time points throughout the disease course. While there are pharmacokinetic data to suggest possible detrimental effects that obesity may have on the response to medical therapy, results in this realm are also inconsistent. Moreover, not only is it unclear whether weight loss improves IBD outcomes, little is known about the safety and efficacy of available weight-loss strategies in this population. For these reasons, it becomes increasingly important to further understand the nature of any interaction between obesity and IBD.

Keywords: Crohn's disease, inflammatory bowel disease, obesity, ulcerative colitis

INTRODUCTION

Obesity is on the rise in the IBD population with many estimates now citing that between 15% and 40% of these patients are obese.[1-5] Not only do these findings alter our prior conceptions about IBD patients being plagued by low body weight, but they spark numerous curiosities regarding the potential involvement of obesity in the pathogenesis of IBD, its impact on the natural history of disease, and how it may affect medical and surgical management for these patients.

It is increasingly recognized that obesity itself represents a low-grade inflammatory state and has been implicated as a risk factor for adverse outcomes in a number of other chronic inflammatory conditions.[6] While historically it had been thought that adipose tissue was simply an inert fat repository, it is now more widely appreciated that it serves as an active endocrine organ producing a large cytokine milieu, termed adipokines, some of which are proinflammatory (such as tumor necrosis factor [TNF] α or interleukin [IL]-6) and others

Access this article online	
Quick Response Code:	**Website:** www.saudijgastro.com
	DOI: 10.4103/sjg.sjg_30_21

How to cite this article: Johnson AM, Loftus EV. Obesity in inflammatory bowel disease: A review of its role in the pathogenesis, natural history, and treatment of IBD. Saudi J Gastroenterol 2021;27:183-90.

anti-inflammatory (adiponectin) in nature.[7] Additionally, the varying forms of adiposity each have unique biochemical profiles. For instance, the creeping fat associated with Crohn's disease (CD) yields a different cytokine milieu as compared to visceral or subcutaneous (SC) fat stores.[8,9] As a result, it has been hypothesized that overexpression of various adipokines in the visceral fat of obese IBD patients may potentiate the inflammatory cascade in IBD.

OBESITY AND IBD PATHOGENESIS

The incidence of IBD appears to be on the rise, particularly in developing nations where it was previously uncommon.[10] A major commonality among the geographic regions seeing a spike in the incidence of IBD is that of increasing westernization, a lifestyle shift which includes many environmental triggers hypothesized to contribute to the risk of *de-novo* IBD. This includes dietary changes, alterations in the microbiome, improved hygiene, and increased antibiotic use.[11] Dietary changes characteristic of modernized societies often includes heavier reliance on processed foods, an animal-sourced as opposed to plant-based diet, increased consumption of simple sugars and carbohydrates, and overall increased calorie consumption. While there are data to suggest that dietary factors may represent an environmental trigger in the pathogenesis of IBD,[12] we must also consider that the aforementioned dietary changes arguably result in a society with higher rates of obesity. It is well established that obesity has become a major global health issue in recent decades, and with this increased prevalence alongside the rising incidence of IBD in developing nations, obesity should also be considered as a risk factor in the pathogenesis of IBD.[13]

Studies attempting to review the true clinical impact that premorbid obesity has on the development of de-novo IBD are conflicting. One large cohort study suggested that obesity in early adolescence was associated with an increased risk of CD, with onset prior to the age of 30 years, but inversely associated with the risk of future UC diagnosis at any age.[14] Conflicting data from the European Prospective Investigation into Cancer and Nutrition cohort found no such association between body mass index (BMI) and future risk of ulcerative colitis (UC) or CD.[15]

OBESITY AND THE NATURAL HISTORY OF IBD

Given the data to support the detrimental effect that obesity may have on other immune-mediated conditions such as psoriasis and rheumatoid arthritis (RA),[6,16] it stands to reason that this relationship would be explored

in patients with IBD. While there are a few studies which have attempted to answer these questions, results have been inconsistent.

Ulcerative colitis

Very few studies have explored the role that obesity plays in UC-related outcomes. A retrospective analysis of 267 UC patients in Olmsted County, Minnesota, assessed the association between BMI at the time of IBD diagnosis and subsequent IBD-related complications and found that with each incremental increase in BMI by 1 kg/m², the risk of hospitalization and surgery rose by 3.4% and 5%, respectively.[17] In contrast to this, another retrospective review of 284 UC patients suggested that those who were overweight and obese had a lower risk of complications as a composite endpoint including anti-TNF use, colectomy, or hospitalization.[2] Finally, yet another review reported no difference in rates of corticosteroid use, hospitalization, surgery, or emergency department visits in obese versus normal-weight IBD patients.[1]

Crohn's disease

While there are more studies assessing the impact of obesity on CD outcomes, data are similarly sparse and inconclusive. Many of the studies reviewing the impact of obesity on CD outcomes seem to suggest that obesity may actually have a protective effect. A retrospective review of 221 CD patients from Olmsted County, Minnesota, demonstrated that the risk of future surgery decreased by 5% for each incremental increase in BMI by 1 kg/m² at the time of their CD diagnosis, while there was no difference in risk of future hospitalization or corticosteroid use.[17] Another retrospective study demonstrated that obese CD patients had lower rates of corticosteroid use, anti-TNF therapy, hospitalizations, and surgeries as compared to their normal-weight counterparts.[2] Lower rates of penetrating disease behavior have also been documented in obese CD patients.[3] On the other hand, others have reported no difference in rates of complications stratified by BMI.[1,4]

OBESITY AND THE MANAGEMENT OF IBD

Medical management

With the increasing prevalence of obesity within the IBD population, it becomes prudent to understand the impact that it may have on medical therapy. Several studies have suggested that obesity may be a negative prognostic factor in a patient's response to medical therapy, with multiple postulated mechanisms. As previously noted, obesity is thought of as a chronic inflammatory state, based on the idea that it potentiates a chronic low-grade activation of the

immune system resulting in increased levels of circulating cytokines, including TNF-α.[7] Additionally, it has been demonstrated that obesity may impact pharmacokinetics of drugs by increasing the volume of distribution and drug clearance, thereby resulting in shorter half-life and lower trough drug concentrations.[18,19] Finally, there is also a hypothesized phenomenon known as a "TNF sink," whereby monoclonal antibody clearance is more rapid due to unbound antigen targets "sopping up" antibody—which may be more pronounced with the higher inflammatory burden in obese patients.[20]

Antitumor necrosis factor α therapy

There are data to suggest that obesity may be a predictor of suboptimal response to anti-TNF-α agents.[21] Multiple mechanisms for this suboptimal response have been implicated. First of all, obesity has been demonstrated in pharmacokinetic studies to result in lower drug trough levels, likely related to increased volume of distribution and drug clearance.[18,19] A previous study of adalimumab in psoriasis patients revealed that body weight was the biggest predictor of drug clearance and volume of distribution.[22] Similar findings were also documented for certolizumab pegol use in CD patients, noting that increased body surface area resulted in increased drug clearance and volume of distribution.[23] The same has also been noted with use of intravenous (IV) anti-TNF, infliximab, in a variety of immune-mediated conditions.[24,25] The accelerated clearance and higher volumes of distribution in obesity appear to be associated with lower trough levels, resulting in either reduced response or increased loss of response to anti-TNF agents.

Some have theorized that these variations may lie in the altered pharmacokinetics of SC versus IV-based therapies.[26] In a retrospective review of CD patients treated with adalimumab or infliximab, obese patients on adalimumab experienced shorter time to loss of response and increased requirement for dose escalation, although the same was not true for those on infliximab.[27] In addition to the differing delivery mechanisms between adalimumab and infliximab, it has also been suggested that the fixed dosing of adalimumab, as opposed to the weight-based dosing scheme of infliximab, could reduce the likelihood that obese patients receive weight-appropriate therapy. However, a retrospective review of 1494 IBD patients demonstrated that as BMI increased, there was a significant decrease in the delivery of weight-appropriate dosing, and this was true for both IV and SC dosing.[1] Findings such as these have further supported the idea that there may be something intrinsic to obesity resulting in reduced treatment response, independent of drug levels.

There are multiple studies suggesting that obese patients may be at higher risk of anti-TNF failure regardless of the mode of administration and whether they are weight based or fixed dose.[28,29] However, there are data to contradict that idea, including a pooled analysis of data collected from the ACCENT-I, ACT-1, ACT-2, and SONIC trials of infliximab, suggesting that BMI had no impact on rates of clinical remission.[30] A recent meta-analysis by Singh and colleagues suggested that obesity was associated with a 60% higher odds of nonresponse to anti-TNF therapy across multiple immune-mediated conditions (OR, 1.60; 95% CI, 1.39–1.83), with each 1 kg/m^2 increase in BMI producing a 6.5% higher odds of failing anti-TNF therapy (OR, 1.065 [1.043–1.087], $I^2 = 5\%$).[31] This risk remained when comparing those treated with either weight-based or fixed-dose regimens. However, when IBD was evaluated independently (i.e., without inclusion of other immune-mediated conditions such as RA and psoriatic arthritis), obesity did not seem to have the same impact on loss of response.

Ustekinumab

Ustekinumab is the first and currently only clinically available inhibitor of IL-12 and 23, exerting its effect by binding the p40 subunit and interfering ultimately with production of the Th1-and Th17-dependent proinflammatory cytokines. As this drug is a more recent addition to the therapeutic armamentarium in IBD, there are far less data in regards to the impact obesity may have on treatment response. A post-hoc analysis of the IM-UNITI trial, which assessed ustekinumab for maintenance of CD, reviewed whether BMI had any influence of achievement of clinical or corticosteroid-free remission.[32] The investigators found that although ustekinumab trough levels were significantly lower in obese patients (median 2.98 mcg/mL) as compared to those who were considered overweight (4.84 mcg/mL; $P = 0.021$) or underweight/normal weight (4.43 mcg/mL; $P = 0.014$)—there were no differences in the rates of clinical remission.

Vedolizumab

Vedolizumab exerts its effect by inhibiting the alpha-4-beta-7 integrin receptor, resulting in its gut-selective anti-inflammatory mechanism of action. Similar to ustekinumab, there are sparse data regarding how obesity may impact vedolizumab's effectiveness in the treatment of IBD. Data are limited to a study of 83 patients including those with antibiotic-dependent or refractory pouchitis and CD of the pouch, in whom BMI was not predictive of clinical response.[33]

Immunomodulators

Both azathioprine (AZA) and 6-mercaptopurine are dosed according to weight. Consequently, obesity has been

suspected to be a detrimental risk factor for suboptimal weight-based dosing and therapeutic response, as we know that adequate levels of the thiopurine metabolite, 6-thioguanine (6-TGN), have been associated with improved outcomes in IBD.[34]

A retrospective review of 1176 IBD patients reviewed the impact of obesity on the effectiveness of immunomodulators, based on frequency of disease flares, defined as the initiation of or increase in corticosteroid use. The authors reported that UC patients with a BMI >25 kg/m² had reduced response to AZA as compared to those with a BMI <25 kg/m², while there were no differences noted in patients with CD. However, they noted that in CD patients who discontinued their AZA, those with BMI >25 were less likely to flare as compared to their normal-weight counterparts.[35]

Another retrospective analysis of an IBD cohort found that 6-TGN levels were reduced by 8% with each 5 kg/m² increase in BMI.[36] The natural assumption may be that obese patients simply were unable to achieve adequate weight-based therapy, but what was interesting is that these obese patients were more likely to have sub-therapeutic 6-TGN levels even when adjusting for the total dose of thiopurine relative to body weight, in that the average dose per kilogram of thiopurine was similar in the sub-therapeutic (1.70 mg/kg), therapeutic (1.63 mg/kg), and supra-therapeutic (1.81 mg/kg) groups ($P = 0.879$). Additionally, they noted that patients with BMI >30 seemed to have a skewed metabolism toward higher methylmercaptopurine nucleotide (MMPN) levels resulting in a higher MMPN: TGN ratio >11, which could not be accounted for by variations in thiopurine methyltransferase activity or dose per kilogram of body weight.[36] These differences were hypothesized to be secondary to either altered pharmacokinetics in obese individuals or potential alterations in thiopurine metabolism related to increased expression of a genetic transregulator known as Kruppel-like factor (KLF14) in adipose tissue.

Corticosteroids

Corticosteroids are a mainstay in the management of acute IBD flares. While they are quite efficacious in the short term for induction of remission, prolonged use is not recommended and often results in significant adverse effects. One of the more commonly reported side effects is that of weight gain, reported subjectively in approximately 70% of patients on chronic corticosteroids.[37]

A systematic review on the influence of glucocorticoids across a variety of inflammatory conditions concluded that evidence was lacking to suggest major alterations in energy intake and body weight or composition with short-term (<12 weeks) use of glucocorticoids; however, long-term (>12 weeks) use could impart clinically significant changes in body weight.[38] However, there was significant heterogeneity within this study regarding the disease indications and dosing regimen for corticosteroids, as well as the duration of use and primary outcome used to measure body composition. Whether obesity impacts the efficacy of corticosteroid use, or if weight gain associated with long-term corticosteroid use negatively influences IBD outcomes, is unclear.

SURGICAL MANAGEMENT

Despite the expansion of our armamentarium of IBD therapies over the years, a proportion of patients will ultimately require surgical management of their disease. It has been well documented that obesity may impart an increased risk of short-term perioperative complications in patients undergoing abdominal operations, namely, surgical site infections or wound complications.[39] Obesity also appears to increase intraoperative times, overall complexity of intra-abdominal operations, and the likelihood of conversion from laparoscopic to open procedures.[40] Technical challenges that obesity may generate with respect to commonly performed IBD-related operations of stoma formation and ileal pouch-anal anastomosis (IPAA) are worth special mention.

The formation of a stoma is commonplace in the surgical management of IBD, including either ileostomy or colostomy with the intent of temporary diversion, as well as those destined for more permanent use. Identifying an ideal location for stoma placement is paramount, a task which may pose added challenges in an obese patient due to a number of issues including altered abdominal contour, increased abdominal wall thickness, or large pannus. This can be further complicated when a stoma is necessary for an emergent indication and the typical preoperative planning is not possible or made more difficult due to the patient's tenuous clinical status or abdominal distention. In addition to confirming the technical feasibility of ostomy formation, it must be assured that the patient is able to readily access and visualize their stoma site, meaning that often for obese patients, a site above the umbilicus may be more realistic. Even with the best of attempts at identifying and creating a stoma in an ideal location, studies have demonstrated that likely as a result of increased abdominal adiposity, excessive stomal tension, and aforementioned technical challenges, obese patients remain at higher risk of stoma-related complications such as parastomal hernia, stomal prolapse or retraction, and mucocutaneous separation.[41,42]

In a subset of patients for whom an ileostomy is temporary, the intended destination for many is an IPAA, which can be significantly more challenging in the setting of obesity for a myriad of reasons. Often the mesentery of obese patients is increasingly fatty and ultimately foreshortened, making it sometimes difficult if not impossible to achieve the adequate length of bowel to extend to the pelvic floor for pouch construction. Obesity also creates challenges for the pelvic exposure necessary to perform restorative proctocolectomy with IPAA. While there are reports suggesting that these issues may increase the risk of postoperative complications such as pelvic sepsis, which can be an important predictor of long-term pouch function,[42] others have suggested that for obese patients who undergo three-stage IPAA with use of a diverting stoma in high-volume centers, long-term outcomes may be similar.[40] The potential added advantage of pursuing IPAA in three stages is that this may provide a window of opportunity following abdominal colectomy and ileostomy formation for the patient to pursue intensive weight-loss strategies prior to restoration of bowel continuity.

IMPACT OF WEIGHT LOSS ON IBD OUTCOMES

With how pervasive obesity has become within the IBD population, it has become increasingly important to understand what, if any, impact weight loss may have on IBD-specific outcomes. While it is well appreciated that weight loss favorably impacts outcomes in a multitude of chronic diseases, including other immune-mediated conditions like psoriasis,[43] the effect it may have on the natural history of IBD is largely unknown. A prospective trial assessing the impact of weight reduction on therapeutic response to TNF inhibitors in the psoriasis population found that patients who were randomized to low-calorie diet and lost an average of 12.9 kg had significantly higher rates of clinical improvement as compared to patients who were offered no dietary intervention and did not lose weight (85.9% vs. 59.3%, $P < 0.001$).[44] Results such as this generate further interest in exploring the impact weight loss may have in the IBD population.

Contemporary strategies for weight loss include lifestyle modifications, medications, bariatric surgery, and more recently bariatric endoscopy. The initial strategy recommended for weight loss in the general population is a comprehensive lifestyle intervention encompassing a combination of diet, physical activity, and behavioral modifications. Certainly, this approach should also be considered first-line in IBD patients, although it is likely advisable to have patients pursue such interventions under the direction of a certified dietician, as there may be some

special challenges inherent to this population that needs to be considered. Depending on the degree of intestinal inflammatory burden, it may not be feasible for patients with active disease to tolerate many "healthy" foods such as fruits and vegetables that are often part of a diet strategy. Moreover, this is a population who may be prone to a variety of vitamin and micronutrient deficiencies despite being overweight, so special attention should be paid to ensuring a well-balanced diet plan. Physical activity has documented favorable impact on not only physical but also psychological well-being in otherwise healthy individuals. There has been some interest in the potential positive effect exercise may have in modulating IBD activity, which may have some biologic rationale. Moderate-intensity exercise may impart an anti-inflammatory effect through a number of mechanisms, including the reduction of visceral fat and thereby reduced secretion of proinflammatory adipokines, as well as by diminishing stress-induced intestinal barrier dysfunction.[45] Several retrospective or survey-based clinical studies have found that IBD patients who exercise have improved sense of well-being and quality of life.[46,47] An additional prospective study utilizing the Crohn's and Colitis Foundation of America Partners internet-based cohort suggested that the risk of active disease in CD and UC patients was reduced in those with higher levels of exercise.[48] It is important to note, however, that these studies all focused on subjective measures of well-being, without any specific objective markers of disease activity.

While there are a handful of prescription medications available for weight loss, none have been studied in the IBD population. Similarly, with most endoscopic bariatric interventions being recent developments in the sphere of weight loss, there are no data on their use in IBD patients. A particular endoscopic modality worth mentioning includes intra-gastric balloon therapy, whereby a soft saline-filled balloon is inflated in the stomach to promote early satiation as well as possibly delayed gastric emptying, resulting in a restrictive-based weight-loss strategy. The temporary, reversible, and minimally invasive nature of this intervention could be an intriguing option in a subset of IBD patients. One may envision its potential for use in patients who require weight loss prior to pursing IPAA formation following the first stage of restorative total proctocolectomy. However, there are no formal studies reviewing the use of such balloons in CD or UC patients, and currently IBD is considered a contraindication for their use—further restricting options in this population.

For the general population, obese patients who have not achieved adequate weight reduction with the above interventions and who have a BMI either ≥40 kg/m² or

between 35 and 39.9 kg/m² with at least one obesity-related comorbid condition, bariatric surgery has been shown to be superior to diet and lifestyle interventions and also reduce mortality.[49] While IBD has classically been considered a relative contraindication to bariatric surgery, given the rising rates of obesity within this population, a few recent studies have attempted exploring the safety and feasibility of bariatric surgery in these patients. A cohort study of 719 IBD patients identified from the National Inpatient Sample found that while IBD patients had a higher risk of peri-operative small bowel obstruction as compared to non-IBD patients (adjusted odds ratio, 4.0; 95% CI, 2.2–74), the mortality risk and rates of other major postoperative complications were low—suggesting it is likely safe and feasible at least in the short term.[50] An additional smaller retrospective series reviewing 20 IBD patients demonstrated that not only was the performance of bariatric surgery safe, feasible, and an effective weight-loss strategy—but that it may have resulted in improved IBD outcomes. This was based on the finding that 9 of 10 patients on IBD pharmacotherapy reported significant improvement in their IBD symptoms postoperatively in follow-up.[51] Further supporting this idea was a case-control study including 25 IBD patients who underwent bariatric surgery, matched to IBD patients without bariatric surgery. During a median follow-up of over 7 years, they found that corticosteroid use and IBD-related surgery were less common in those who had bariatric surgery as compared to controls.[52]

There have also been a few case series describing the onset of de-novo IBD following bariatric surgery. For instance, Braga *et al.*[53] described new onset IBD in 44 patients who had previously undergone bariatric surgery, most commonly Roux-en-Y gastric bypass, after a median latency period of 7 years. With the very small numbers of reported cases, whether this is truly a causal relationship is unclear. Theorized mechanisms behind this potential association include the role of excess toxin exposure to the intestinal tract as a result of the altered anatomy, increased release of proinflammatory adipokines from shifts in adipose tissue, or alterations in the microbiome.[53,54]

Limitations and future directions

At this time, our understanding of the true impact that obesity has on the pathogenesis, natural history, and treatment of IBD is constrained by insufficient and contradictory data. A major limitation of the existing literature regarding the interaction of obesity and IBD is the dependence on BMI as a measure of obesity. As previously noted, the distribution of adipose tissue is separated into various compartments, which each encompass their own biochemical profile,

and is likely more clinically meaningful than BMI. BMI unfortunately is a crude measurement tool for accurately assessing adiposity, as it does not differentiate lean body mass from other tissue forms. Utilizing volumetric analysis of visceral fat via cross-sectional imaging studies would likely be the preferred means of assessing adiposity over BMI and may correlate more with IBD-related outcomes. As part of the randomized postoperative Crohn's endoscopic recurrence trial, investigators found that visceral adipose tissue, as measured on cross-sectional abdominal imaging, was an independent risk factor for endoscopic recurrence of CD following surgical resection of all macroscopic disease (relative risk, 2.1; 95% CI, 1.5–3.0; $P = 0.012$).[55] Another retrospective review found that in 143 CD patients who underwent ileocolectomy, the visceral-to-SC fat ratio was an independent predictor of postoperative morbidity, whereas BMI was not.[56]

In addition to the use of BMI as a surrogate measure of obesity, there is wide variation between available studies in the timing that BMI is measured. This is important, given it is not clear at what time point obesity may impart any impact it has on the natural history of IBD. For instance, is this established already in childhood years before disease onset, is the weight at the time of diagnosis important, or is obesity a fluid influence changing throughout the course of disease? Most available studies capture BMI at variable time points throughout the disease process, which also leaves these measurements susceptible to confounding factors such as corticosteroid exposure, tobacco use, or disease activity which may affect an individual's weight.

To further our understanding of the true influence obesity may have on the disease course of IBD, we would benefit from prospective studies utilizing measurements of visceral adipose tissue as a marker of obesity rather than BMI, as well as better adjustment for confounding factors such as smoking, corticosteroid use, and disease severity.

SUMMARY

The prevalence of obesity within the IBD population has risen considerably over time and now parallels that of the general population. While there are biologically plausible mechanisms to support a connection between obesity and IBD, epidemiological data are conflicting on any role obesity may play in the pathogenesis or natural history of the disease. Inherent limitations in study design, including the use of BMI as a surrogate measure, may contribute to some of the discrepancy, as visceral adiposity is more likely to be liable in promoting the inflammatory cascade and does not correlate well with BMI.

It is logical to surmise that obesity may impact the response to medical therapy by altering the pharmacokinetics of drug absorption, metabolism, and clearance—resulting in suboptimal drug levels which we know to be predictors of response. However, there are also data to suggest that obesity may negatively influence response to therapy independent of therapeutic drug levels, possibly related to a higher circulating burden of proinflammatory adipokines such as TNF-α due to increased visceral adiposity. With this in mind, some have argued that obese IBD patients may benefit from the use of weight-based medications such as infliximab along with more aggressive monitoring of drug levels throughout the course of their disease.

With the now pervasiveness of obesity within the IBD population, coupled with its potential negative prognostic implications, weight loss would seem to be an obvious goal as part of the management paradigm. However, we have very limited data to know whether weight loss positively impacts IBD outcomes. Moreover, many weight-loss strategies available to the general population have classically been relatively contraindicated or not studied within the IBD population. More recent data would suggest that bariatric surgery may be safe and feasible for IBD patients, particularly if performed in high-volume centers. The safety and effectiveness of varied weight loss interventions merit further study for a population which is now quite plagued with obesity, as aside from IBD outcomes, they would benefit from weight reduction for other health-related outcomes.

In conclusion, while there may certainly be an association between obesity and IBD in regards to disease pathogenesis, natural history, and response to therapy—our understanding of this relationship is limited. Further prospective studies utilizing measures of visceral adiposity as a proxy for obesity, as well as better control of confounding factors, are required to improve our understanding and ultimately management of obesity in this already complex patient population.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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