

Impact of Obesity on the Management of Inflammatory Bowel Disease

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Abstract: The worldwide prevalence of obesity has reached staggering proportions, and the inflammatory bowel disease (IBD) population has not been immune to this trend, with obesity rates estimated to be between 15% and 40%. With the concurrent rise in incidence of IBD itself, there are biologically plausible mechanisms that suggest a potential role of obesity in the pathogenesis of IBD, although epidemiologic data on this issue are conflicting. Similarly, studies exploring the impact that obesity may have on the natural history of disease have produced inconsistent results. Some studies suggest higher and others lower rates of surgery in obese Crohn's disease patients, other studies suggest a higher risk of surgery in obese ulcerative colitis patients, and yet other studies reveal no difference in outcomes regarding hospitalization or surgery for either group. Regardless of its impact on the pathogenesis or natural history of IBD, the rising prevalence of obesity in this population results in a need to better understand the effect it has on IBD management. Although pharmacologic data suggest that obesity may influence the absorption, distribution, and clearance of the available therapeutic agents, the actual clinical consequences that these differences have on disease management are less clear. Finally, it is possible that weight loss interventions for obesity could have an impact on the clinical course of IBD.

Along with the rising prevalence of obesity in the US population, a similar trend has been occurring in the inflammatory bowel disease (IBD) population,¹⁻⁶ a cohort that has historically been thought to experience malnourishment. With this rise in both obesity and IBD comes a surge of research gaps. For example, it is not yet clear if obesity plays a role in the pathogenesis of IBD. Whether obesity might impact the natural history of IBD also remains to be fully determined, and whether medical and surgical therapies for IBD are impacted by obesity is poorly understood. Finally, it is not known if weight loss strategies are safe and effective in the IBD population. This article summarizes the available literature on the intersection between obesity and IBD and identifies knowledge gaps in this relatively unexplored topic.

Keywords

Obesity, body mass index, inflammatory bowel disease, ulcerative colitis, Crohn's disease

Prevalence of Obesity in Inflammatory Bowel Disease Patients

The prevalence of obesity worldwide has risen to epidemic proportions and is one of the leading public health issues of the 21st century. Escalating obesity rates in the IBD population have been documented to parallel those in the general population. Data from cross-sectional and single-center cohorts suggest that the prevalence of obesity (body mass index [BMI], ≥ 30) in IBD patients is between 15% and 40%,¹ a proportion that increases further when overweight (BMI, 25 to <30) patients are also considered (Table).¹⁻⁶ In a population-based cohort of IBD patients from Olmsted County, Minnesota, the prevalence of overweight and obese patients rose from 24% and 12%, respectively, in 1990 to 1994 to 34% and 20%, respectively, in 2005 to 2010.⁷ This trend was corroborated in an analysis of 10,282 clinical trial participants with Crohn's disease (CD), where it was noted that the mean BMI at the time of enrollment increased from 20.8 in 1991 to 27.0 in 2008.⁸ These trends are not unique to the adult population, with rates of overweight and obese patients having similar increases in children.^{9,10}

Obesity and the Pathogenesis of Inflammatory Bowel Disease

With a coinciding upward trajectory of incident IBD cases across the globe,¹¹⁻¹⁵ particularly in geographic regions where IBD was previously uncommon, environmental triggers have been thought likely to contribute to the pathogenesis of this disease. Support of an environmentally based hypothesis includes studies that suggest an increased risk of de novo IBD in immigrants who move from low- to high-prevalence countries.¹⁶ Understanding the role of environmental exposures in the development of IBD has recently been identified as 1 of the 5 areas of research gaps in a Challenges in IBD research document sponsored by the Crohn's & Colitis Foundation.¹⁷ Several environmental factors associated with modernization have been implicated in this rising prevalence, including improved hygiene,¹⁸ increased antibiotic use,^{19,20} alterations in the intestinal microbiome,^{21,22} and dietary changes associated with an industrialized lifestyle.^{23,24} Obesity may be another important risk factor to consider, and it is also perhaps impacted by many of the aforementioned elements, although its role in the development of IBD has been arguably understudied despite its expanding presence worldwide.

The plausibility of obesity playing a pathogenic role in the development of IBD is centered around the idea that adipose tissue is not a biologically inert organ; rather, it is responsible for producing a repository of pro- and

anti-inflammatory cytokines (including tumor necrosis factor- α [TNF- α] and interleukin-6), many of which are central to the development of IBD.²⁵⁻²⁸ Moreover, it has been suggested that creeping fat itself is a distinct form of adiposity with unique biochemical properties, producing a different cytokine milieu compared to that of subcutaneous fat or even mesenteric fat in obese non-IBD patients.^{29,30} Additional postulated mechanisms include alterations in the intestinal microbiota²¹ as well as disrupted intestinal permeability resulting from zonulin production, a mediator of intercellular tight junctions, by visceral adipocytes.³¹

The few available epidemiologic studies on this topic are conflicting, and additional investigation is needed to clarify any role that obesity may play in the pathogenesis of IBD.³²⁻³⁴ A cohort of over 300,000 individuals from the Copenhagen School Health Records Register was studied to assess the relationship between BMI in the ages of 7 to 13 years and adult-onset IBD. For each incremental increase in BMI by 1 at all examined ages, there was an increased risk of CD before age 30 years (hazard ratio [HR], 1.2) and a decreased risk of ulcerative colitis (UC) diagnosis, irrespective of age (HR, 0.9).³⁴ In contrast, a large cohort study examining over 300,000 adults from the European Prospective Investigation Into Cancer and Nutrition study found no association between BMI and incident CD or UC.³² A notable difference between these 2 studies is that the former utilizes childhood BMI as a predictor while the latter focuses on obesity in adulthood, bringing into question whether exposure to obesity earlier in life is where the impact truly takes place. In summary, although biologic plausibility may be present to suggest a causative role of obesity in IBD patients, this remains speculative at best, and additional study is required.

Influence of Obesity on Inflammatory Bowel Disease Phenotype

Whether obesity influences the disease phenotype of IBD is unclear, as the few available studies exploring this issue have produced conflicting results (Table). A population-based cohort of 488 IBD patients demonstrated a nonsignificant trend ($P=.06$) for obese CD patients having higher rates of isolated colonic disease, but did not note any appreciable differences in disease behavior or presence of perianal disease in CD patients, nor differences in disease extent for patients with UC.³⁵ Although another retrospective review suggested that obese patients may have higher rates of anoperineal disease,³⁶ the remaining available studies have largely suggested no differences in disease distribution or behavior for CD or UC patients.^{2,5}

Table. Key Literature on the Prevalence and Impact of Obesity in IBD Patients

Authors	Study Design	Study Population	Key Findings
Lynn et al ^{7,35,39}	Retrospective review of a population-based cohort of IBD patients (N=488) Conducted in Olmsted County, Minnesota BMI: collected within 6 months of IBD diagnosis	Crohn's disease (n=221) • 31.7% overweight • 22.2% obese Ulcerative colitis (n=267) • 33.0% overweight • 25.5% obese	Crohn's disease • Trend toward obese patients having higher rates of isolated colonic disease (40.8%) compared to isolated ileal (36.7%) or ileocolonic involvement (22.4%) ($P=.06$). No difference in disease behavior or perianal involvement • With each incremental increase in BMI by 1, the risk of surgery decreased by 5% • No difference in the risk of future hospitalizations or corticosteroid use Ulcerative colitis • No difference in disease extent based on BMI • With each incremental increase in BMI by 1, the risk of surgery increased by 6% while the risk of hospitalization rose by 3.4%
Flores et al ²	Retrospective review of IBD patients from 2 centers (N=581) Conducted in Dallas, Texas BMI: mean value of all BMIs collected during follow-up period	Crohn's disease (n=297) • 33.3% overweight • 30.3% obese Ulcerative colitis (n=284) • 36.3% overweight • 35.2% obese	Crohn's disease • No difference in disease location, disease behavior, or presence of perianal disease • Lower rate of corticosteroid use in overweight (66.0%) and obese patients (62.2%) compared to normal- and underweight patients (81.0%) ($P=.007$) • Lower rate of anti-TNF- α therapy in overweight (36.0%) and obese patients (37.8%) compared to normal- and underweight patients (60.0%) ($P=.001$) • Fewer surgical procedures in overweight (n=102) and obese patients (n=70) compared to normal- and underweight patients (n=145) ($P=.006$) • Reduced rate of hospitalizations in overweight (43.0%) and obese patients (54.4%) compared to normal- and underweight patients (72.0%) ($P<.0001$) • Lower rate of composite endpoint (anti-TNF- α use, surgery, or hospitalization) in overweight (77.0%) and obese patients (73.3%) compared to normal- and underweight patients (94.0%) ($P<.0001$) Ulcerative colitis • No differences in disease extent or in corticosteroid exposure, anti-TNF- α use, or colectomy • Lower risk of hospitalization in overweight (44.0%) and obese patients (31.0%) compared to normal- and underweight patients (58.0%) ($P=.001$) • Lower rate of composite endpoint (anti-TNF- α use, colectomy, or hospitalization) in overweight (49.0%) and obese patients (40.0%) compared to normal- and underweight patients (67.0%) ($P=.001$)
Pringle et al ⁴	Single-center cross-sectional study of Crohn's disease patients Conducted in Boston, Massachusetts BMI: collected at study baseline	Crohn's disease (N=846) • 30.0% overweight • 16.0% obese	Crohn's disease • Compared to patients with BMI <25, obese patients had lower risk of penetrating disease (OR, 0.56; 95% CI, 0.31-0.99) • No significant differences in the risk of stricturing disease, perianal disease, or need for surgery based on BMI

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Table. (Continued) Key Literature on the Prevalence and Impact of Obesity in IBD Patients

Authors	Study Design	Study Population	Key Findings
Stabroth-Akil et al ⁶	Single-center retrospective review of ulcerative colitis patients Conducted in Cologne, Germany BMI: collection time frame unclear	Ulcerative colitis (N=202) • 26.7% overweight • 13.4% obese	Ulcerative colitis • Pancolitis was less common in overweight (53.7%) and obese patients (33.3%) compared to underweight (70.0%) and normal-weight patients (61.3%) (<i>P</i> =.03) • Overweight and obese patients had a lower proportion of years with chronic active disease compared to normal-weight patients (17.6% vs 23.9%; <i>P</i> =.05)
Seminerio et al ³	Single-center retrospective review of IBD study registry patients (N=1494) Conducted in Pittsburgh, Pennsylvania BMI: used the first, final, and mean BMI measurements during 2-year follow-up period	Crohn's disease (n=860) • 36.0% overweight • 27.0% obese Ulcerative colitis (n=634) • 34.0% overweight • 32.0% obese	All IBD patients • No association between higher BMI and corticosteroid use, emergency department visits, hospitalization, or surgery • Obesity was associated with use of lower weight-adjusted doses of purine analogues and biologics • Obesity was associated with diabetes mellitus, hypertension, hyperlipidemia, poor quality of life, and increased rates of C-reactive protein elevation
Nic Suibhne et al ¹	Single-center, prospective, case-control study of Crohn's disease patients with healthy controls matched by age, sex, and socioeconomics Conducted in Dublin, Ireland BMI: performed at study enrollment	Crohn's disease (N=100) • 23.0% overweight • 17.0% obese	Crohn's disease • Mean CDAI was significantly lower in overweight (71.1; 95% CI, 36.4-105.8) and obese patients (104.1; 95% CI, 48.1-160.0) compared to normal-weight patients (136.5; 95% CI, 101.0-162.8) (<i>P</i> =.029) • No significant differences in disease location, disease behavior, or perianal disease • No difference in rates of surgery or corticosteroid use between obese/overweight and normal-weight patients
Steed et al ³⁸	Retrospective review of population-based IBD cohort (N=489) Conducted in Tayside, Scotland BMI: single measurement within past 12 months	Crohn's disease (n=295) • 34.0% overweight • 18.3% obese Ulcerative colitis (n=194) • 44.0% overweight • 17.5% obese	Crohn's disease • Lower rate of surgery in overweight (18.0%) and obese (19.0%) patients compared to normal-weight patients (46.0%) Ulcerative colitis • 9.0% of overweight and 3.0% of obese patients required surgery compared to 5.0% of normal-weight patients
Hass et al ⁵	Single-center retrospective review of Crohn's disease patients Conducted in Philadelphia, Pennsylvania BMI: collected at diagnosis	Crohn's disease (N=148) • 32.4% overweight or obese	Crohn's disease • Patients with BMI >25 had shorter time to first surgery (24 months) compared to patients with BMI <18.5 (252 months) (<i>P</i> =.043) • Number of surgeries, escalation of therapy, and disease distribution did not differ when comparing patients with BMI >25 and those with BMI <25

BMI, body mass index; CDAI, Crohn's Disease Activity Index; IBD, inflammatory bowel disease; OR, odds ratio; TNF- α , tumor necrosis factor- α .

Impact of Obesity on the Natural History and Outcomes of Inflammatory Bowel Disease

Obesity has also been implicated as a potential detrimental risk factor in IBD-related outcomes, largely extrapolated from data associating obesity with worse clinical outcomes in other chronic inflammatory conditions, such as rheumatoid arthritis and psoriasis.^{26,37} Studies exploring the prognostic impact of obesity on IBD outcomes are limited and produce conflicting results (Table).

In a retrospective review of 581 IBD patients, obese individuals were less likely to be hospitalized (42.1% vs 66.0%; $P < .0001$) or undergo surgery (41.1% vs 61.1%; $P = .005$), compared to their normal- and underweight counterparts.² The reverse was demonstrated in a review of CD patients, which suggested a higher risk of developing active disease (odds ratio [OR], 1.50; 95% CI, 1.07-2.11) or requiring hospitalization (OR, 2.35; 95% CI, 1.56-3.52) for obese patients.³⁸ A single-center review of 148 CD patients revealed that those with a BMI of greater than 25 had a shorter time to first surgery compared to those with a BMI of less than 18.5 (24 vs 252 months; $P = .043$); however, the actual number of surgeries over time did not differ.⁵ A retrospective review of 221 CD patients followed for a median of 14.2 years found a 5% decreased risk of surgery with each incremental increase in BMI by 1 (HR, 0.95; 95% CI, 0.91-0.99), although there was no difference in the risk of future corticosteroid use or hospitalization.³⁹ A prospective case-control study found no association between BMI and future risk of surgery or corticosteroid use.⁴

In regard to UC, the data are similarly sparse and inconsistent. A population-based cohort of 267 UC patients demonstrated that with each incremental increase in BMI by 1, patients were at a 6% increased risk of future surgery ($P = .01$) and a 3.4% higher risk of hospitalization ($P = .052$).³⁹ Although a retrospective analysis of 1494 IBD patients did not demonstrate any association between obesity and rates of corticosteroid use, hospitalization, or surgery,³ other studies have reported either higher rates of surgery in overweight UC patients³⁸ or, conversely, a protective effect with a lower proportion of years with active disease in obese patients.⁶

Overall, due to the relative paucity of data, small patient cohorts, limited follow-up, and conflicting results, the effects that obesity may have on IBD-related outcomes are not well understood.

Impact of Obesity on the Management of Inflammatory Bowel Disease Patients

Medical Management

How obesity actually impacts the medical management of IBD remains unclear. It seems logical to surmise that

obesity may impact the absorption, distribution, and clearance of the current armamentarium of drugs, and a few pharmacokinetic studies have indeed produced data to suggest such an effect.^{40,41} Two commonly implicated factors by which obesity may impact response to biologic therapy in particular include the mode of drug administration (subcutaneous vs intravenous) and the issue of weight-based vs fixed-dose regimens.

Differences have been described in the pharmacokinetic profiles of subcutaneously vs intravenously administered medications,⁴² leading to the suggestion that obesity could potentially influence subcutaneous therapies more than intravenous ones. Bhalme and colleagues performed a retrospective review of CD patients treated with either infliximab or adalimumab, and found that patients who had a BMI of at least 30 experienced a shorter time to dose escalation due to loss of response while on adalimumab, but not infliximab.⁴³ Another postulated explanation for the reported difference seen in adalimumab- vs infliximab-treated patients has included the former's fixed-dosing schedule, resulting in obese patients being less likely to receive weight-appropriate therapy. However, a retrospective analysis of 1494 IBD patients compared the actual milligram per kilogram dose of medication that patients were receiving based on their BMI category. The analysis found that as BMI increased, the actual weight-based dose that patients received significantly decreased, which was true for both intravenously and subcutaneously delivered anti-TNF- α agents.³ For instance, the mean weight-based doses of infliximab and adalimumab were 3.96 mg/kg and 0.31 mg/kg, respectively, in patients with class III obesity, compared to 7.89 mg/kg and 0.62 mg/kg, respectively, in normal-weight patients ($P < .0001$).³ Findings were similar for oral immunomodulators.

Conflicting findings have suggested that obesity does not seem to play a role in the receipt of weight-appropriate therapy,⁴⁴ implying that obesity may have some intrinsic effect on treatment response, independent of drug levels or mode of exposure. Among the numerous mechanisms that have been postulated to play a role in altered pharmacokinetics are larger volumes of distribution and enhanced proteolysis, as well as obese patients simply having a more expansive repository of adipose tissue, producing a larger burden of TNF- α . A recent pooled meta-analysis reported that obese UC patients experienced higher odds of anti-TNF- α treatment failure (OR, 1.41; 95% CI, 1.01-1.98; $P = .045$), regardless of whether they received fixed-dose or weight-based treatment regimens.⁴⁵ Kurnool and colleagues performed a review of 160 UC patients treated with biologic agents, including both weight-based regimens (infliximab) as well as fixed-dose regimens (adalimumab, certolizumab pegol [Cimzia, UCB], vedolizumab [Entyvio, Takeda],

and golimumab [Simponi, Janssen]).⁴⁶ The authors found that each incremental increase in BMI of 1 was associated with a 4% increased risk of treatment failure (adjusted HR, 1.04; 95% CI, 1.00-1.08) for all patients, regardless of the type of biologic utilized.⁴⁶ Similar findings from Harper and colleagues demonstrated a 30% increased risk of UC flare (HR, 1.30; 95% CI, 1.07-1.58) and a 6% increased risk of CD flare (HR, 1.06; 95% CI, 1.02-1.11) with each incremental increase in BMI by 1.⁴⁷ Contrasting these findings is a pooled data analysis of 1205 infliximab-treated IBD patients from 4 landmark clinical trials (ACCENT-1, SONIC, ACT-1, and ACT-2), which did not identify any difference in clinical remission or response based on BMI.⁴⁸ These findings were supported by a systematic review and meta-analysis demonstrating that obesity was a risk factor for anti-TNF- α therapy failure in several rheumatic diseases, but not IBD.⁴⁹

Therefore, although there seem to be some data to suggest pharmacokinetic mechanisms by which obese patients may experience diminished response to therapy, the true clinical impact of these mechanisms on treatment outcomes is less clear and requires further study.

Surgical Management

Obesity has repeatedly been recognized as a risk factor for perioperative morbidity, largely driven by surgical site infections, but also by impaired wound healing, potentially increased thromboembolic complications, longer length of hospital stay, and need for short-term rehabilitation.⁵⁰⁻⁵³

For a myriad of reasons, obesity also creates technical challenges for IBD-related operations, particularly those requiring pelvic exposure. Not surprisingly, this greater complexity results in an increased risk of laparoscopic procedures that are converted to open procedures, as well as longer operative times.⁵¹ Two operative considerations of particular interest to the IBD population are related to issues with stoma creation and pouch construction. Obesity, particularly increased abdominal adiposity, not only makes creation of a stoma challenging, but also appears to increase the risk of postoperative complications such as stoma retraction, mucocutaneous separation, stomal prolapse, and parastomal hernia.⁵⁴ Additionally, obesity makes pouch construction cumbersome, if not impossible, in some cases due to foreshortening of the mesentery by mesenteric fat, which impedes the achievement of adequate pouch length and reach into the pelvis. A report cited obesity as a risk factor for increased pelvic sepsis,⁵⁵ which is a major predictor for pouch failure requiring excision. However, more contemporary data suggest that this may not be the case.⁵¹ This dichotomy is likely related to the idea that earlier research more frequently reported on outcomes of single-stage operations, and with the more contemporary use of a diverting stoma in 2- or 3-stage

operations, the risk of surgical complications has diminished. These findings suggest that pursuing 3-stage ileal pouch-anal anastomosis is the preferred strategy in obese patients, which may then also allow for an opportunity to achieve weight loss prior to eventual pouch construction and restoration of continuity. Moreover, patients need to be counseled appropriately on potential perioperative risks in the setting of obesity.

Although obesity appears to increase the risk of short-term perioperative complications as previously discussed, several studies have suggested that in high-volume centers, long-term pouch function in obese patients may be similar to that of their nonobese counterparts.^{50,51,55} Worth mentioning, however, is that these studies were largely done examining BMI at the time of restorative proctocolectomy. In a review of 846 IBD patients who underwent pouch surgery, those with postoperative weight gain were found to have increased risk for CD of the pouch (30.6% vs 18.5%; $P=.001$), mechanical or surgical pouch complications (18.4% vs 12.3%; $P=.049$), and postoperative pouch-related complications (21.1% vs 10.6%; $P<.001$).⁵⁶ Furthermore, excessive postoperative weight gain (defined as 15% increase in index body weight) led to higher rates of pouch failure (HR, 1.69; 95% CI, 1.01-2.84; $P=.048$) even after adjustments were made for postoperative immunosuppressive therapy, CD of the pouch, postoperative pouch-associated hospitalization, and mechanical or surgical pouch complications. Therefore, although elevated BMI at the time of restorative proctocolectomy may negatively impact perioperative outcomes, avoidance of significant postoperative weight gain should also be advised to prevent increased risk of future pouch complications.

Impact of Obesity on Cost and Quality of Life in Inflammatory Bowel Disease Patients

Outside of simply impacting medical and/or surgical outcomes of IBD patients, several studies suggest that obesity also negatively impacts overall quality of life, as well as the financial burden placed on IBD patients. A large Internet-based study of more than 7000 participants with IBD demonstrated that those who were obese were significantly more likely to have higher rates of anxiety, depression, fatigue, and pain and reduced social function both at baseline as well as over a 12-month follow-up, even after adjusting for disease activity.⁵⁷ Additionally, an analysis utilizing the Nationwide Readmissions Database 2013 demonstrated that obesity was associated with a significantly higher number of annual hospital days (8 vs 5 days; $P<.01$), more of which were preventable admissions, as well as a higher cost of hospitalization-related care (median, \$17,277 vs \$11,847; $P<.01$).⁵⁸

The IBD population already has a higher prevalence of anxiety and depression as well as reduced quality of life, independent of obesity.⁵⁹ Moreover, the cost burden of time away from work for flares, clinic visits, testing required for disease management, hospitalizations, and medical therapy is already substantial for these patients. It is, therefore, important to recognize that obesity may further exacerbate these issues, and could represent an opportunity to intervene via a modifiable risk factor to improve these metrics.

Impact of Obesity Treatment on Inflammatory Bowel Disease Outcomes

Regardless of the impact that obesity may have on IBD management, it is now a highly prevalent comorbidity among IBD patients, and what remains unclear is how to best manage it in this special population. Clinically available management options for obesity in the general population include lifestyle modifications, weight loss pharmacotherapy, novel endoscopic procedures, and bariatric surgery. Certainly, there is ample support to substantiate the benefits of weight loss for overall health and well-being, and even literature to suggest that weight loss may positively impact outcomes in other immune-mediated disorders, such as psoriasis.⁶⁰ However, data pertaining to the application of lifestyle management or clinically available weight loss pharmacotherapy in the IBD population are lacking, and obesity has classically been considered a relative contraindication to bariatric surgery. With the recent recognition that obesity is on the rise within this special population, there has been increased inquiry into the safety and feasibility of weight loss procedures in this cohort of patients.

Although data are sparse, studies have demonstrated that bariatric surgery is likely both feasible and safe in IBD patients.⁶¹⁻⁶³ Moreover, some researchers have even postulated that weight loss surgery may result in improved IBD outcomes.⁶³⁻⁶⁵ Drawing from conclusions citing improvement of other chronic inflammatory disorders, such as psoriasis⁶⁶ and systemic lupus erythematosus,⁶⁷ it has been presumed plausible that weight loss surgery may be advantageous in controlling disease activity in IBD patients. Multiple proposed explanations for this hypothesis exist, ranging from the reduction of excess visceral adiposity, which results in decreased generation of proinflammatory cytokines, to the reduction of the pharmacologic volume of distribution, which allows for a decrease in the required doses of IBD medications. The idea that weight loss may result in improved control of IBD is largely based off data from the aforementioned pharmacokinetic studies and clinical data reporting that higher BMI may be a predictor of earlier loss of response and need for dose escalation of anti-TNF- α therapy.^{47,68} Although clinical data remain

limited, in a case-control study of 25 IBD patients who underwent bariatric surgery and matched IBD controls who had not undergone bariatric surgery, investigators found that the surgical patients experienced a numerically lower number of IBD-related complications (specifically rescue corticosteroid use and IBD-related surgery) at 48% vs 72% in the control group (OR, 0.44; 95% CI, 0.1-1.6; $P=.27$).⁶⁵ However, although the surgical patients achieved a mean reduction in BMI of 12 following bariatric surgery, their postoperative BMI still remained higher than that of the control group.

On the other hand, there have been a few reports suggesting an increased risk of de novo IBD following bariatric surgery, proposing that such an operation in the context of a genetically predisposed individual may give rise to the development of IBD via changes in the microbiome, excess cytokine release by adipose tissue, or anatomic alterations resulting in variable toxin exposures to the intestinal tract.^{69,70} Braga Neto and colleagues performed a 2-center study describing what is currently the largest case series of 44 individuals who developed de novo IBD following bariatric surgery.⁶⁹ This development most commonly occurred in patients undergoing Roux-en-Y gastric bypass, followed by gastric banding and stapling, over a median latency period of 7 years between the operation and IBD diagnosis. However, a recently published analysis of the Explorys database suggested that the prevalence of de novo IBD was lower in obese patients treated with bariatric surgery (7.72/1000 patients) or weight loss medications (7.22/1000 patients) compared to obese patients who were not treated with those interventions (11.66/1000 patients).⁷¹ Although these findings are certainly intriguing, to date there are only approximately 60 reported cases of de novo IBD following bariatric surgery, and true causality of this relationship is not known. Certainly, these findings should not preclude the performance of weight loss surgeries, but they may prompt the inclusion of new-onset IBD in the differential diagnosis for diarrhea and abdominal pain in patients following bariatric surgery.

In summary, although bariatric procedures seem to be safe and effective, larger and more rigorous studies are required to establish the role of these procedures in this special patient population. At the present time, although IBD may not necessarily be a contraindication to bariatric procedures, they should be performed judiciously and only in the appropriate context under the direction of a multidisciplinary care team given the complexities involved.

Future Directions

Obesity is clearly an increasingly prevalent comorbid condition in the IBD population, although as previously outlined, its clinical relevance in the pathogenesis, natural

history, and treatment outcomes of IBD appears contradictory among the few available studies. There are several inherent limitations in the current literature that may contribute to this lack of clarity.

First of all, most accessible data come from retrospective studies measuring BMI at varying time frames throughout the disease course. Adiposity is a dynamic measurement and no doubt experiences a number of changes throughout an individual's disease course. If obesity does impact IBD outcomes, it is not clear when this effect is most influential (eg, obesity at the time of IBD diagnosis, weight gain throughout the course of disease, or presence of increased adiposity even years prior to the onset of IBD). Both the retrospective nature of the studies as well as the variable time frames at which obesity is assessed in the studies make it difficult to implicate causality. In addition, many studies neglect addressing potential confounding factors such as smoking status, corticosteroid use, or disease activity, all of which may impact weight status at a singular point in time.

Of important note is also that the overwhelming majority of existing studies utilize BMI as a surrogate measure of obesity. It remains unknown whether BMI is an accurate reflection of adipose stores, namely visceral adipose tissue (VAT), particularly given that one of the main hypotheses supporting the role of obesity in IBD patients involves the unique metabolic and biochemical properties of VAT as compared to subcutaneous adipose tissue (SAT). There are a few studies suggesting that VAT, but not BMI, might carry prognostic value in predicting postoperative outcomes and disease recurrence in CD patients.^{72,73} A prospective study showed that the ratio of VAT to SAT was associated with stricturing CD behavior as well as future serial fecal calprotectin and quality-of-life measurements, although the same was not true for BMI.⁷⁴ It is plausible, therefore, to consider that the inability of BMI to differentiate VAT from SAT may contribute to the conflicting results seen in the current literature.

For future studies, it would be beneficial to focus on prospective disease evaluation, improved control of confounding factors, and assessment of obesity utilizing measures that reflect VAT. Ideally, this involves cross-sectional imaging studies such as computed tomography, magnetic resonance imaging, or dual energy x-ray absorptiometry, all of which have been utilized in VAT assessment.

Conclusion

A growing body of evidence suggests that the IBD population is facing an obesity epidemic paralleling that of the general population. Interestingly, this is occurring alongside an increasing incidence of IBD, particularly in newly developed countries, bringing rise to questions regarding

the role of obesity in the pathogenesis of IBD. Although there are pathophysiologically sound theories to support a potential role of obesity in the development of IBD, robust epidemiologic data are lacking. Similarly, studies on the impact of obesity on the natural history of disease and IBD-related complications are conflicting.

Despite the aforementioned inconsistencies, management of these patients may warrant special consideration, as there are pharmacokinetic data to imply that obesity may not only adversely impact the achievement of adequate therapeutic drug levels, but even response to therapy independent of drug levels via mechanisms, including greater TNF- α burden or increased proteolysis and clearance. Although it should be noted that clinical data to this effect are inconclusive, in patients who are obese, clinicians may consider preferential use of weight-based therapies (if there are no other compelling clinical indications for fixed-dose regimens) and more vigilant monitoring with therapeutic drug levels to ensure adequate therapy for this particular population.⁷⁵ There are also special considerations to be made in the surgical management of these patients, particularly regarding stoma and pouch creation.

Particularly with patients who often identify their gastroenterologist as their primary care physician, it is increasingly important to remain cognizant of the fact that obesity should be addressed not only for the potential implications it may have on their IBD course, but also for the known adverse effects it may have on general health outcomes. Patients should be counseled and/or referred appropriately for weight management strategies, whether via lifestyle interventions, medications, or consideration of surgical or novel endobariatric procedures at experienced medical centers.

With the significant knowledge gap that exists regarding the impact of obesity on IBD management, additional study is needed to understand the implications of this ever-growing issue pervading this special population.

Disclosures

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