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Impact of Obesity on Response to Biologic Therapies in Patients with Inflammatory Bowel Diseases

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Abstract

Approximately 20–40% patients with inflammatory bowel diseases (IBD) are obese. Obesity is associated with inferior outcomes in patients with IBD, with lower rates of achieving remission, poor quality of life and higher burden of unplanned healthcare utilization. Multiple cohort studies in patients with immune-mediated inflammatory diseases, including IBD, treated with biologic agents like tumor necrosis factor-α antagonists have suggested that obesity is associated with inferior response to biologic therapy. One of the drivers of this impact obesity may be related to its negative impact on pharmacokinetics of biologic agents. Pharmacokinetic studies of multiple biologic agents have demonstrated the high body weight is associated with more rapid clearance and higher volume of distribution of biologic agents, which leads to low trough concentrations. Randomized trials in patients with psoriasis and psoriatic arthritis treated with biologic agents suggests that diet- or lifestyle-induced weight loss is associated with improve response to therapy. This provides an opportunity to explore intentional weight loss as adjunctive therapy in obese patients with IBD. However, diet- and lifestyle-intervention for weight loss are hard to implement in patients with IBD; hence, long-term therapy with weight loss agents (such as with phentermine-topirmate, naltrexone-bupropion) is attractive as adjunctive therapy in obese patients with IBD.

1. INTRODUCTION

The worldwide prevalence of obesity is increasing with predicament rates – approximately 39% adults are classified as overweight and 13% as obese.[1] An estimated 35% of the United States population is obese, leading to rising healthcare expenditure.[2, 3] Rates of

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inflammatory bowel diseases (IBD) are rising in parallel.[4] Obesity is an environmental exposure that has been implicated in these epidemiologic trends in IBD.[5] Obesity, which is linked to rising rates of immune-mediated inflammatory diseases like rheumatoid arthritis and psoriasis, has also been implicated in contributing to increased risk of developing Crohn's disease (CD).[6] In a pooled analysis of five prospective cohort studies with 601,009 participants, Chan and colleagues observed that obesity, based on body mass index (BMI) ≥30mg/kg^2, is associated with 34% higher risk of developing CD, compared with normal BMI; each 5kg/m^2 increase in BMI was associated with 16% higher risk of developing CD.[7] It is estimated that 15–35% patients with IBD are obese, and 20–40% may be overweight.[8] Obesity has also been linked to higher disease activity and poorer quality of life in patients with IBD. In cohort studies, obese patients with IBD were more likely to relapse and have difficult to treat disease, leading to higher rates of hospitalization, compared with non-obese patients.[8–11] Besides a direct impact on the natural history of IBD, obesity may also negatively impact treatment response and disease outcomes in patients with IBD.[8, 12]

The management of IBD, particularly of severe disease, involves the use of biologic agents, monoclonal antibodies (mAbs) such as tumor necrosis factor-α (TNFα) antagonists (infliximab, adalimumab, certolizumab pegol, golimumab), interleukin-23 (IL-23) antagonists (ustekinumab) and lymphocyte trafficking inhibitors (vedolizumab).[13] These drugs can effectively control the disease in 40–60% patients, but the response between individuals varies greatly. In this review, we will examine whether obesity associates with effectiveness and safety of biologics in patients with IBD, and whether intentional weight loss in obese patients can modify this association.

2. IMPACT OF OBESITY ON PHARMACOKINETICS AND PHARMACODYNAMICS OF BIOLOGIC AGENTS

Biologic agents exert their pharmacological effect when adequate drug concentrations are achieved at the drug's site of action. Inter- and intra-individual differences in bioavailability and pharmacokinetics may contribute to variability in treatment response. Several factors modify the pharmacokinetics of large mAbs and influence effectiveness.[14] Besides hypoalbuminemia, elevated inflammatory markers, anti-drug antibodies, and co-administration of immunosuppressive therapy, obesity has been a consistent factor that is associated with accelerated drug clearance and increased central volume of distribution, leading to unfavorable pharmacokinetics and low drug concentration at site of action.[8] In a population pharmacokinetic study of intravenous vedolizumab, albumin, and body weight were identified as predictors of clearance of vedolizumab with clinically meaningful impact observed at extremes of values.[15] This negative impact of body weight on drug clearance is seen regardless of whether fixed-dose or weight-based dosing regimens are used.[16] However, the magnitude of impact may vary by type of biologic, with higher impact seen with TNFα antagonists like infliximab and adalimumab, and may be less pronounced with vedolizumab and ustekinumab. Table 1 summarizes findings from key studies on impact of weight on pharmacokinetics of different biologic agents.

Additionally, obesity, particularly visceral fat, independently contributes to the higher systemic inflammatory burden, which may modify treatment effectiveness.[17] Adipokines like resistin and leptin are proinflammatory.[18] White adipose tissue also synthesizes different proinflammatory cytokines such as TNFα, IL-1β, and IL-18 and other adipocytokines that can cause gut inflammation. Compared with lean individuals, obesity causes elevation of TNF-α levels secreted by the fat tissue, causing increased pathogenesis of several inflammatory conditions and direct effect on trough level of anti-TNF agents.

3. IMPACT OF OBESITY ON TREATMENT EFFECTIVENESS OF BIOLOGIC AGENTS

Given this potential association between obesity and IBD disease activity, multiple studies have sought to examine how obesity may impact response to biologics in patients with IBD. Some consistent findings stand out. First, patients with obesity are more likely to require higher doses of the medication, through dose escalation.[9] In a prospective cohort of adalimumab-treated patients with CD, Bultman *et al* observed that over one-third of patients required adalimumab dose escalation (to every week dosing from every two weeks) within five months of starting therapy; higher BMI was the only independent factor predictive of dose escalation.[19] In another retrospective study, Bhalme *et al* observed that obese patients treated with adalimumab were almost two-times more likely to require dose escalation compared with patients with normal BMI.[20] Interestingly, morbidly obese patients may not receive their optimal dosing for weight-based therapies, frequently being underdosed. Seminerio and colleagues observed that the average dose of infliximab in patients with class III obesity was ~4mg/kg, compared to 7.9mg/kg in normal BMI and 6.4 mg/kg body weight in overweight patients.[21]

Second, obesity may impact treatment response to biologics independent of drug exposure. Kurnool *et al* observed that each unit increase in BMI was associated with a 4% increase in risk of treatment failure, 8% increase in risk of surgery or hospitalization, and 6% lower odds of achieving endoscopic remission in a cohort of 160 biologic-treated patients with ulcerative colitis, with comparable effects seen with fixed-dose therapies and weight-based agents.[22] In another study of infliximab-treated patients with IBD, obese patients were 3–9 times more likely to have an IBD flare and require biologic dose-escalation than normal-weight patients.[23] Each 1kg/m^2 increase in BMI was associated a 6% higher risk of CD flare (hazard ratio [HR], 1.06; 95% confidence intervals [CI], 1.02–1.11), and 30% higher risk of UC flare (HR, 1.30; 95% CI, 1.07–1.58). Secondary analyses of clinical trials, however, have not confirmed these observations. In a secondary analysis of clinical trials of infliximab in patients with ulcerative colitis, obesity was not associated with a risk of achieving remission or mucosal healing over a short term.[24] Similarly, in a post hoc analysis of 254 patients treated with ustekinumab in IM-UNITI, Wong and colleagues observed that at week 44, rates of clinical remission did not differ among those whose BMI was underweight (67.9%; 19 of 28 patients), normal (51.3%; 60 of 117), overweight (45.1%; 32 of 71), or obese (55.3%; 21 of 38) (p=0.89).[25]

While there is limited data in IBD, similar observations have been made in biologic-treated patients with other autoimmune diseases. In a prospective cohort of 89 infliximab-treated patients with rheumatoid arthritis, obese patients had lower rates of clinical response compared with non-obese patients. This effect persisted after adjustment for baseline disease activity and other prognostic factors (BMI>30kg/m^2 vs. 20–30kg/m^2 vs. <20kg/m^2: 50% vs. 75% vs. 84%).[26] Gremese *et al* similarly observed in that, at 12m, rates of clinical remission were lowest in obese patients, compared with overweight or normal BMI individuals (15% vs. 30% vs. 33%).[27] Likewise, in 557 patients with psoriatic arthritis (35% obese), the likelihood of achieving sustained minimal disease activity was lowest in obese (odds ratio [OR], 0.52; 95% CI, 0.40–0.67) and overweight (OR, 0.65; 95% CI, 0.50–0.85) patients, as compared to patients with normal BMI.[28] In a systematic review of 54 cohorts including 19,372 TNFα antagonist-treated patients with immune-mediated inflammatory diseases (23% obese), we observed that patients with obesity had 60% higher odds of failing therapy (OR,1.60; 95% CI, 1.39–1.83), with a dose-response relationship; each 1kg/m^2 increase in BMI was associated with 6.5% higher odds of treatment failure.[12]

Visceral adiposity, on top of overall obesity, may also influence response to biologics. In a retrospective cohort study of 176 TNFα antagonist-treated patients with IBD, Gu and colleagues observed that compared with patients with visceral fat index <0.33, patients with visceral fat index ≥ 0.67 had higher odds of surgery at 6 and 12 months.[29] Post hoc analysis suggested visceral adipose tissue volume may affect drug pharmacokinetics. Similarly, Lim and colleagues observed that higher visceral adipose tissue area was inversely associated with infliximab trough concentrations, and higher risk of secondary loss of response to adalimumab.[30]

4. IMPACT OF OBESITY ON TREATMENT SAFETY OF BIOLOGIC AGENTS

Obesity has been consistently associated with increased risk of surgical site infections.[31] Mechanistically, visceral adipose tissue is metabolically active and can modify the immune response through pro- and anti-inflammatory adipokines, cytokines and chemokines, which predisposes to infection. However, whether obesity modifies the risk of infections in patients with IBD, particularly those being treated with immunosuppressive agents, has not been well-studied. In a cohort study of approximately 6000 biologic-treated patients with IBD (8.8% obese), we observed that obesity is not associated with risk of serious infections.[32] On univariate analysis, risk of serious infections was comparable in obese vs. non-obese patients (8.8% vs. 8.5%). On Cox proportional hazard analysis, after adjusting for key covariates, obesity was not associated with increased risk of serious infections (HR, 0.74; 95% CI, 0.55–1.01).

5. WOULD INTENTIONAL WEIGHT LOSS IMPROVE RESPONSE TO BIOLOGIC AGENTS IN PATIENTS WITH IBD?

If obesity decreases the effectiveness of biologics, a natural question is whether intentional weight loss may make biologics more effective. Unfortunately, this is a key evidence gap. There are no trials examining intentional weight loss in obese patients with IBD. Trials examining diet and/or lifestyle-related weight loss suggest superior outcomes with

weight loss in patients with other immune-mediated inflammatory diseases.[8] In a meta-analysis of patients with overweight or obesity and psoriasis, patients receiving weight loss interventions were almost 3-times more likely to achieve significant clinical improvement, compared with standard of care.[33] Even 5% weight loss over baseline may be sufficient to experience benefits of weight loss. Di Munno *et al* compared low calorie or free-managed diet for weight loss in a 6-month randomized trial of 126 patients with psoriatic arthritis starting TNFα antagonist therapy, They observed that patients randomized to low-calorie diet noticed greater reduction in pain and inflammation, and were significantly more likely to achieve remission (low-calorie diet vs. free-range diet: 43% vs. 35%).[34] Interestingly, it wasn't the diet itself that resulted in benefit – patients who achieved greater weight loss regardless of specific intervention were significantly more likely to achieve favorable outcomes. Overall, 60%, 45%, and 23% patients with >10% weight loss, 5–10% weight loss, and <5% weight loss achieved remission, respectively. Patients with >5% weight loss were 4.2 times more likely to achieve remission compared with those who experienced <5% weight loss (OR, 4.20; 95% CI, 1.82–9.66).

Whether patients with obesity and IBD would experience similar benefits with weight loss is speculative. Case series have suggested that bariatric surgery may be performed highly selectively in morbidly obese patients with IBD with observed improvement in disease activity after weight loss.[35] In a case-control study involving 88 bariatric procedures (73 with sleeve gastrectomy) in 85 obese patients with IBD matched 1:2 on age, sex, BMI, hospital of surgery, and type of bariatric surgery with obese patients with IBD who underwent bariatric surgery, patients with IBD did not have any increase in the risk of perioperative complications, post-operative nutritional deficiencies or effectiveness in weight loss, over 2 years.[36] However, long-term consequences of major restrictive and malabsorptive procedures in patients with IBD are poorly understood. In a population-based cohort study, bariatric surgery was associated with increased risk of new-onset CD, but not UC.[37] Hence, risks and benefits of bariatric surgery should be very carefully weighed in selected patients with IBD. It is unclear whether minimally invasive or non-invasive approaches to weight loss may offer benefit.

Dietary interventions carry the lowest risk of adverse events, but adherence to a specific diet is limited. Intensive sustained lifestyle interventions are challenging in patients with IBD especially those with active disease. They offer only small average weight loss with commercial weight loss programs. That lost weight is frequently regained over time.[38] Weight loss achieved through pharmacological or endoscopic bariatric interventions may achieve the same effect on outcomes in autoimmune diseases but have not been studied. These medications typically result in 45–77% patients achieving >5% weight loss over placebo with a magnitude of average excess weight loss (over placebo) ranging from 2.6kg (with orlistat) to 8.8kg (phentermine-topiramate.[39] Orlistat, which works by inhibiting gastric and pancreatic lipases, reducing absorption of monoaclglycerides and free fatty acids, may not be appropriate in patients with IBD, especially those with active small Crohn's disease who may have chronic malabsorption syndrome.[40] Naltrexone and bupropion have been individually shown to induce weight loss through poorly understood central nervous system effects. The combination is believed to act in synergy to modulate the hypothalamic melanocortin system and the mesolimbic reward system to regulate both the intake of

food and body weight.[40] Two small trials have suggested that low-dose naltrexone may induce clinical and endoscopic response in patients with CD; it is unclear whether this effect is mediated by weight loss.[41] Case reports and case series have also suggested that bupropion may decrease IBD-related inflammation, by decreasing TNFα; it has also been shown to decrease fatigue and aide in smoking cessation which itself benefits CD.[42, 43] Phentermine-topiramate is a highly efficacious oral weight loss agent, which acts centrally to suppress appetite and increased satiety.[40] Preclinical data supports an anti-inflammatory role of both topiramate and phentermine. Using a novel computational approach for drug repositioning, Dudley *et al* observed that gene expression profiles of topiramate were very similar to those of corticosteroids.[44] Subsequent *in vivo* testing demonstrated that administration of topiramate for 7 days after trinitrobenzenesulfonic acid-induced colitis resulted in significant reduction in diarrhea and reduced pathologic inflammation. A phase 2 clinical trial of FDA-approved weight-loss medication, phentermine-topiramate in obese biologic-treated patients with UC is ongoing (NCT04721873).

6. CONCLUSION

In conclusion, the prevalence of obesity in patients with IBD is sizable, paralleling the general population, contrary to conventional beliefs that this patient population is malnourished. Obesity, in particular, visceral adiposity, may promote intestinal inflammation. Based on pharmacokinetic data, obesity appears to promote rapid clearance of biologic agents, regardless of drug dose. This translates into the inferior response to biological therapy in patients with obesity. This provides an opportunity for using treatment directed towards obesity, either through lifestyle, pharmacological or endoscopic interventions, as adjunctive therapy in obese patients with IBD, though prospective, interventional studies are lacking.

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This is a review of published literature, without generation of new data.

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KEY POINTS

- Approximately one-third patients with IBD are obese, which negatively impacts disease course.
- Obesity leads to more rapid clearance and low trough concentrations of biologic agents in patients with IBD.
- Obesity is associated with decreased treatment responsiveness to biologics.

Table 1.

Impact of obesity on pharmacokinetics of different biologics used for the management of IBD

Drug	Study design	Study objectives	Conclusion
Adalimumab[45]	Prospective observational multicenter study	Characterize the PK of adalimumab and identify clinically significant determinants of adalimumab clearance	• High lean body weight and positive antibodies to adalimumab were important predictors of adalimumab clearance
Golimumab[46]	3 phase II/III studies of golimumab in patients with UC	Characterize the PK and exposure-response relationship of golimumab in patients with UC	• Clearance of golimumab was explained by a 2-compartment model with first-order absorption and elimination • Clearance of golimumab increased when body weight increased from 25th percentile to 75th percentile.
Vedolizumab[47]	5 clinical studies in patients, including 1 phase I study in healthy volunteers, 1 phase II UC study, and 3 phase III UC/CD studies	Characterize the PK of vedolizumab and identify clinically significant determinants of vedolizumab clearance	• Clearance of vedolizumab was explained by a 2-compartment model with parallel linear and nonlinear elimination • Extreme values of body weight (>120kg) and albumin are clinically significant predictors of vedolizumab clearance
Ustekinumab[48] (Yan, et al. *J Clin Pharmacol* 2020)	2 phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter studies	Characterize the PK and exposure-response relationship of ustekinumab, in the treatment of moderately to severely active UC	• Observed serum concentration-time data of ustekinumab can be explained by a 2-compartment linear PK model with first-order absorption and first-order elimination. • Besides albumin, sex and antibodies to ustekinumab, body weight is a covariate that influences ustekinumab PK, but the magnitudes of this effects is likely not clinically relevant
Risankizumab[49]	Phase I and phase II study in patients with psoriasis vs. phase II study in patients with Crohn's disease	Characterize pharmacokinetics of risankizumab and evaluate covariates that affects exposure, in patients with psoriasis and Crohn's disease	• Clearance of risankizumab was explained by a two-compartment model with first-order absorption and elimination • Body weight and baseline albumin are significant covariates that explain variability in risankizumab exposure

Abbreviations: CD = Crohn's disease, PK = pharmacokinetics; UC = ulcerative colitis