Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes

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Abstract | Incidence of IBD is rising in parallel with overweight and obesity. Contrary to conventional belief, about 15–40% of patients with IBD are obese, which might contribute to the development of IBD. Findings from cross-sectional and retrospective cohort studies are conflicting on the effect of obesity on natural history and course of IBD. Most studies are limited by small sample size, low event rates, non-validated assessment of disease activity and lack robust longitudinal follow-up and have incomplete adjustment for confounding factors. The effect of obesity on the efficacy of IBD-related therapy remains to be studied, though data from other autoimmune diseases suggests that obesity results in suboptimal response to therapy, potentially by promoting rapid clearance of biologic agents leading to low trough concentrations. These data provide a rationale for using weight loss interventions as adjunctive therapy in patients with IBD who are obese. Obesity also makes colorectal surgery technically challenging and might increase the risk of perioperative complications. In this Review, we highlight the existing literature on the epidemiology of obesity in IBD, discuss its plausible role in disease pathogenesis and effect on disease course and treatment response, and identify high-priority areas of future research.

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With an estimated 2.1 billion adults worldwide overweight (BMI ≥25 kg/m²), of which 600 million are obese (BMI ≥30kg/m²), the prevalence of overweight and obesity has reached epidemic proportions[1]. From 1980 to 2013, the proportion of overweight adults has increased 28% in developed countries and nearly 60% in developing countries, with no country reporting a decrease in prevalence during the same period[1]. In the USA, more than one-third (35.7%) of adults are obese, with the estimated annual medical costs of a patient with obesity being US$1,429 higher than individuals of a normal weight[2].

In parallel with the obesity epidemic, the incidence and prevalence of IBD is rising globally. In a systematic review of 260 population-based studies, the estimated annual incidence of IBD ranged from 10–30 cases per 100,000 persons in the Western world; an estimated 0.5% of adults in the West suffer from IBD[3]. A time-trend analysis suggests that incidence of IBD has increased over time, particularly in newly industrialized countries[4,5]. Various environmental exposures have been implicated in these epidemiological trends in IBD, including smoking, improving hygienic standards, infections and antibiotics and dietary factors such as high-fat or low-fibre diets. A potentially understudied

factor might be obesity, which has been associated with an increased risk of several autoimmune diseases such as rheumatoid arthritis, psoriasis and psoriatic arthritis[6,7]. Beyond the potential epidemiological association, the rising prevalence of obesity implies that a substantial proportion of patients with IBD would be obese. Obesity negatively affects disease course and treatment response in other autoimmune diseases, but there is limited synthesis of data on the effect of obesity in IBD.

In this Review, we discuss the epidemiology and pathophysiology of obesity in IBD, the potential effect of obesity on disease course and complications, treatment response and surgical outcomes in patients with IBD, and whether treatment of obesity could modify disease course in patients with IBD.

Epidemiology

Prevalence of obesity in IBD. Cross-sectional studies in patients with IBD show that about 15–40% of adults with IBD are obese, and an additional 20–40% are overweight[8–14]. In a population-based study of 489 patients with IBD conducted in Scotland, 18% of patients were obese (compared with 23% of the general population), and 38% of patients were overweight; this proportion

Key points

- ~20–40% of patients with IBD in Western countries are obese
- Premorbid obesity, in particular visceral adiposity, might increase the risk of developing Crohn's disease
- Obesity might contribute to the pathogenesis of IBD through dysbiosis, mucosal barrier dysfunction with bacterial translocation and activation of adipocytes
- Risk of complications, such as surgery, hospitalization and infection, might be increased in patients with IBD who are obese
- Obesity is associated with rapid clearance of biologic agents, resulting in low trough concentrations, and could result in suboptimal response to biologics
- Treating obesity could be a potential adjunct therapeutic target in patients with IBD who are obese

was comparable between patients with Crohn's disease (18% obese) or ulcerative colitis (17.5% obese)[15]. By contrast, only 3% of patients with Crohn's disease and 0.5% of patients with ulcerative colitis were underweight (BMI <18.5 kg/m²). Large US-based, single-centre adult cohort studies have observed similar rates of obesity (TABLE 1).

A similar trend has also been observed in paediatric patients with IBD. In two North American multicentre inception cohorts of paediatric patients with IBD formed between 2000 and 2002, about 9–10% of children with Crohn's disease and 20–34% of children with ulcerative colitis had a sex-specific BMI-for-age above the 85th percentile at diagnosis[16]. In another multiple-site registry of 1,598 children with IBD, Long and colleagues[9] observed 23.6% of children were above the 85th sex-specific BMI-for-age percentile (20.0% patients with Crohn's disease, 30.1% patients with ulcerative colitis), including 9.5% children who were above the 95th percentile; by contrast, only 2.9% of children were below the 5th percentile at diagnosis. A greater proportion of Hispanic children with IBD were obese or overweight than non-Hispanic children with IBD (35.2% versus 23.1%, $P = 0.02$). These rates of obesity in patients with IBD are not different from rates observed in the general population.

This rise in the prevalence of obesity in patients with IBD seems to parallel the global obesity epidemic. In an early single-centre study conducted in France including 2,065 patients with Crohn's disease seen between 1974 and 2000, the prevalence of obesity was 3%, gradually rising from 1.7% of patients diagnosed with Crohn's disease before 1981 to 4% of patients diagnosed with Crohn's disease after 1990 (P for trend <0.01)[17]. By contrast, contemporary cohorts estimate the prevalence of obesity in IBD at 15–40%, as discussed earlier. On analysing 40 trials of 10,282 patients with Crohn's disease conducted between 1991 and 2008, an increase in trial participant weight was observed over time[18]. The minimum mean weight of participants increased from 57.1 kg in 1997 to a maximum mean weight of 89.1 kg in 2008.

Premorbid obesity and IBD risk.
Besides a high prevalence of obesity in patients with IBD, premorbid obesity has also been associated with a risk of developing Crohn's disease, but not ulcerative colitis, though this relationship has not been consistently observed[19–21] (TABLE 2). In the Danish National Birth Cohort of over 75,000 women, prepregnancy obesity was associated with a 1.9-fold increase in risk of developing Crohn's disease (hazard ratio (HR) 1.88, 95% CI 1.02–3.47), but not ulcerative colitis (HR 0.77, 95% CI 0.48–1.25)[20]. Similar effect estimates were observed in the Nurses' Health Study, with BMI at age 18 years being predictive of risk of Crohn's disease (BMI >30 versus normal BMI: HR 2.33, 95% CI 1.15–4.69) but not ulcerative colitis (HR 1.17, 95% CI 0.54–2.52)[19] (FIG. 1). Interestingly, in the Danish National Birth cohort, the association between premorbid BMI and risk of Crohn's disease was U-shaped, as women with a BMI <18.5 were also at increased risk of developing Crohn's disease compared with women of a normal BMI (HR 2.57, 95% CI 1.30–5.06)[20]. The effect of obesity on risk of developing IBD might be age-dependent, with obesity in teenage or young adulthood associated with higher risk of developing Crohn's disease than obesity at later ages. Using the population-based Swedish Hospital Discharge Register, Hemminki et al.[22] observed that among patients hospitalized with a primary diagnosis of obesity, the relative incidence of Crohn's disease is highest when obesity is diagnosed before 30 years of age (standardized incidence rate (SIR) 1.92, 95% CI 1.17–2.96), and decreases with increasing age at obesity diagnosis (SIR for Crohn's disease when obesity diagnosed between 40–49 years of age 1.04, 95% CI 0.37–2.28). Additionally, magnitude of weight gain after age 18 years has also been associated with increased risk of Crohn's disease, but not ulcerative colitis. In the Nurses' Health Study, women who gained >13.61 kg (30 lbs) between age 18 years and enrolment in the cohort had a 1.5-fold higher risk of developing Crohn's disease, as compared with women who remained within 2.27 kg (5 lbs) of their weight at age 18, in a dose-dependent manner[19] (FIG. 1).

Of the several compartments of body fat, visceral adiposity is now well recognized to be the metabolically active fraction[23], and might be more predictive of the risk of developing IBD than overall obesity as determined by BMI. Patients with IBD have higher visceral fat volumes than those without IBD[24]. In a prospective cohort study, Khalili and colleagues[19] observed a trend towards increased risk of Crohn's disease, but not ulcerative colitis, in patients with a high waist–hip ratio (WHR). Among patients with Crohn's disease, participants with a premorbid WHR ≥0.83 had a 1.6-fold higher risk of developing Crohn's disease than those with a WHR ≤0.73 (HR, 1.58, 95% CI 0.78–3.21, $P = 0.14$) (FIG. 1). Beyond obesity, obesity-related lifestyle factors such as physical activity might also modify risk of IBD. In the Nurses' Health Study, high level of physical activity (recreational or occupational) was associated with decreased risk of developing IBD[25,26].

Can IBD contribute to obesity?
The high prevalence of obesity in patients with IBD might also suggest an independent effect of IBD on the risk of obesity development. Although current epidemiological data is unable to accurately assess the directionality of this association, preclinical data suggests that dysbiosis and altered metabolic gut signalling induced by IBD and acting through

hormones (including incretins such as gastric inhibitory polypeptide and glucagon-like peptide), satiety-related peptides (such as ghrelin and peptide YY) and bile acids might contribute to development of obesity and dysmetabolism in patients with IBD[27,28]. In addition, smoking cessation and use of corticosteroids could contribute to weight gain in patients with IBD; in the general population, the average magnitude of weight gain with smoking cessation and corticosteroid use is 3–5 kg; ~11% of patients who quit smoking and ~24% of patients on corticosteroids for >1 year gain >10 kg body weight[29–31].

Limitations of current literature. Most of the available epidemiological data on prevalence of obesity in IBD is cross-sectional, which limits the ability to infer causality or even directionality of the association (that is, whether obesity contributes to IBD pathogenesis, or vice versa).

A limited number of prospective cohort studies (Nurses' Health Study, Danish National Birth Cohort and European Prospective Investigation into Cancer and Nutrition study) have measured BMI in adulthood (generally in the 3rd to 5th decades of life) and subsequent development of IBD in an older population. These studies might not be representative of the general IBD population. Moreover, the Nurses' Health Study and the Danish National Birth Cohort have only studied women, and it is not possible to study whether obesity would have a similar effect on risk of developing IBD in men. Finally, given the increasing understanding of the metabolically active nature of visceral fat, overall obesity measured using BMI probably does not adequately capture the association with IBD; current studies have included limited assessment of visceral fat and its effect of development of IBD, usually through a surrogate measure like WHR.

Table 1 | **Key studies on obesity epidemiology and its effect on disease course and complications in IBD**

Study	Study characteristics	Patient characteristics	Prevalence of obese and overweight	Key findings	Refs
Flores *et al.* (2015)	• Two-centre retrospective cohort study • Conducted in Dallas, Texas, USA, 2000–2012 • Median follow-up 5.2 years	Crohn's disease: • $n = 297$, 31% female • Mean disease duration 15 years • Ileocolonic disease in 47% • Penetrating disease in 20% • Biologic use in 45% Ulcerative colitis: • $n = 284$; 24% female • Mean disease duration 12 years • Extensive disease in 59% • Biologic use in 16%	Crohn's disease: • 30.3% obese • 33.3% overweight (based on mean BMI of each patient during the study period) Ulcerative colitis: • 35.2% obese • 71.5% overweight (based on mean BMI of each patient during the study period)	Crohn's disease: • No differences between Crohn's disease phenotype (age at onset, location, behaviour) in patients who were obese vs overweight vs normal or underweight • Lower rates of a composite endpoint of Crohn's-disease-related surgery or hospitalization and/or initiation of anti-TNF therapy in patients who were obese (73%) and overweight (77%) than patients who were normal weight or underweight (94%) Ulcerative colitis: • No differences in disease extent (age at onset, location, behaviour) in patients who were obese vs overweight vs normal or underweight • Lower rates of a composite endpoint of ulcerative-colitis-related surgery or hospitalization and/or initiation of anti-TNF therapy in patients who were obese (40%) and overweight (49%) than patients who were normal weight or underweight (67%)	8
Seminerio *et al.* (2015)	• Single-centre, retrospective cohort study • Conducted in Pittsburgh, Pennsylvania, USA, 2009–2011 • Median follow-up not reported	• $n = 1,494$ with IBD (860 with Crohn's disease, 634 with ulcerative colitis), 51% female • Mean disease duration ~16 years	• 31.5% obese, 4.4% of whom severely obese (BMI ≥ 40 kg/m^2) • 40% overweight (based on average BMI of each patient during the study period)	• No difference in risk of IBD-related surgery, hospitalization, emergency department use in patients who were obese vs overweight vs normal BMI • Obesity, in particular BMI ≥ 35 kg/m^2, associated with poorer IBD-related quality of life and higher frequency of elevated CRP compared with normal BMI patients • Actual dose of prescribed medication for weight-based therapies lower than anticipated based on body weight (for example, mean infliximab dose in patients with class III obesity was 3.96 mg/kg and that of azathioprine was 1.1 mg/kg) • Increasing BMI associated with increased rates of diabetes mellitus, hypertension and hyperlipidaemia	12
Pringle *et al.* (2015)	• Single-centre cross-sectional study • Conducted in Boston, Massachusetts, USA, 2004–?	• $n = 846$ with Crohn's disease, 55% female • Mean disease duration 12 years • Penetrating disease in 29% • Biologic use in 56%	• 16% obese • 30% overweight (at Crohn's disease diagnosis)	• Compared with adults with BMI <25 kg/m^2, patients who were obese had lower prevalence of penetrating disease (OR 0.56, 95% CI, 0.31–0.99), but comparable rates of perianal and stricturing disease and prior surgery • Genetic predisposition did not seem to modify the effect of obesity on Crohn's-disease-related complications	10
Hass *et al.* (2006)	• Single-centre, retrospective cohort study • Conducted in Philadelphia, Pennsylvania, USA, 1997–2002	• $n = 138$ with Crohn's disease, 59% female • Mean disease duration 13 years • Perianal disease in 10% • Biologic use in 45%	32% overweight or obese (at Crohn's disease diagnosis)	• No difference in the number of Crohn's-disease-related surgeries or escalation of medical therapy in patients with BMI ≥ 25 kg/m^2 vs BMI <25 kg/m^2 • No difference in the time to first surgery between patients who were overweight vs normal weight, although time to first surgery was shorter in those overweight vs underweight (2 years vs 21 years, respectively, $P = 0.04$)	77

CRP, C-reactive protein; OR, odds ratio.

Table 2 | **Key studies on the association between pre-morbid obesity and risk of developing incident IBD**

Study	Study characteristics	Patient characteristics	Key findings	Refs
Khalili *et al.* (2014)	US population-based cohort of 111,498 women (Nurses' Health Study II) followed over 18 years	Incident Crohn's disease and ulcerative colitis in 153 and 229 participants, respectively	• 2.3-fold higher risk of developing Crohn's disease in women with obesity compared with women with normal BMI at age 18 (HR 2.33, 95% CI, 1.15–4.69), after adjusting for key confounding variables including physical activity • A greater magnitude of weight gain (from age 18 to age at enrolment) associated with increased risk of developing Crohn's disease (weight gain >13.6 kg vs <2.3 kg: HR 1.52, 95% CI 0.87–2.65) • No association between obesity during young adulthood (or weight change since young adulthood) and risk of developing ulcerative colitis (obese vs normal BMI at age 18: HR 1.17, 95% CI, 0.54–2.52) • Association between overweight or obese body habitus (but not slender or thin body habitus) during young adulthood and development of Crohn's disease but not ulcerative colitis	18
Harpsoe *et al.* (2015)	Danish National Birth Cohort study of 75,008 women (median 30 years of age at cohort entry), followed over median 11 years	Incident Crohn's disease and ulcerative colitis in 138 and 394 participants, respectively	• Women who were obese (based on prepregnancy body weight) had a 1.9-fold higher risk of developing Crohn's disease (OR 1.88, 95% CI 1.02–3.47) • No association between prepregnancy obesity and risk of developing ulcerative colitis (OR 0.77, 95% CI 0.48–1.25)	19
Chan *et al.* (2013)	Nested case–control study within the European Prospective Cohort Study of 300,724 participants, from 23 centres in 10 countries	Incident Crohn's disease and ulcerative colitis in 75 and 177 participants, respectively	No association between obesity and risk of developing Crohn's disease (obese vs normal BMI: OR 0.85, 95% CI 0.29–2.45) or ulcerative colitis (obese vs normal BMI: OR 1.15, 95% CI 0.62–2.12)	20

The ideal study to evaluate the association between obesity and risk of developing IBD would involve creating a prospective cohort of paediatric or young adult patients with assessment of overall obesity and visceral adiposity at multiple time points, through both anthropometry as well as more sophisticated methods (such as the ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue on cross-sectional imaging), and subsequent close follow-up for the development and accurate phenotyping of IBD. However, as IBD would be expected to be observed in only 1 in 200 participants, such a study would involve following a large number of participants over many years, and would be cost prohibitive. As an intermediary step, prospective identification of patients with IBD in diverse historical cohorts established decades ago, similar to efforts from the Nurses' Health Study and the European Prospective Investigation into Cancer and Nutrition study, might help understand the association between obesity and risk of developing IBD.

Obesity in the pathogenesis of IBD

Increasingly, obesity is recognized as a perpetual state of chronic low-grade inflammation[32]. Whether via the systemic and paracrine increase in levels of cytokines, chemokines and adipokines, the expression of innate immune receptors on preadipocytes and adipocytes or the conversion of preadipocytes to macrophages, adipose tissue is integrally involved in the regulation of inflammation.

Role of adipose tissue. Subcutaneous and visceral adipose tissue compartments display distinct metabolic and immunological profiles. Mesenteric VAT has a predominance of pro-inflammatory M1 macrophages that secrete several inflammatory cytokines, including TNF and IL-1. In addition, adipocytes also produce

other pro-inflammatory cytokines such as IL-6, chemokines such as C-C motif chemokine 2 (also known as chemoattractant protein-1) and adipokines such as leptin and resistin. These adipokines affect satiety and lipid metabolism, and regulate the effects of insulin and glucose metabolism through a network of interactions with cytokines[33]. In obesity, this altered network of adipokine and cytokine interactions contributes to impaired adipocyte metabolism; animal models and humans with obesity have increased levels of circulating cytokines, which can induce innate immune responses and influence the expression of several inflammatory mediators[34]. As low-grade inflammation is involved in the pathophysiology of obesity, circulating cytokines have been named as potential therapeutic targets for the treatment of obesity.

Patients with IBD show a unique locally restrictive form of VAT — creeping fat — whereby mesenteric fat hyperplasia is limited to areas of inflamed bowel[35,36]. Predominately seen in Crohn's disease, creeping fat is thought to be more immunologically active than other VAT, and the extent of creeping fat correlates closely with the extent of histological inflammation and degree of lymphocyte or macrophage infiltration[23]. In a case–control study, Zulian and colleagues[36] observed that the gene expression profile of omental VAT, which is distant from unhealthy mesenteric depots, from patients with Crohn's disease was similar to that of VAT adipocytes from IBD-free individuals with obesity, with high expression of pro-inflammatory genes, and was distinct from VAT adipocytes in healthy, normal-weight individuals. Furthermore, expression of leptin and adiponectin has been demonstrated to be increased in the hypertrophied mesenteric fat of patients with Crohn's disease, and specific risk alleles (such as *ATG16L1*) associated with alterations in adiponectins have also been
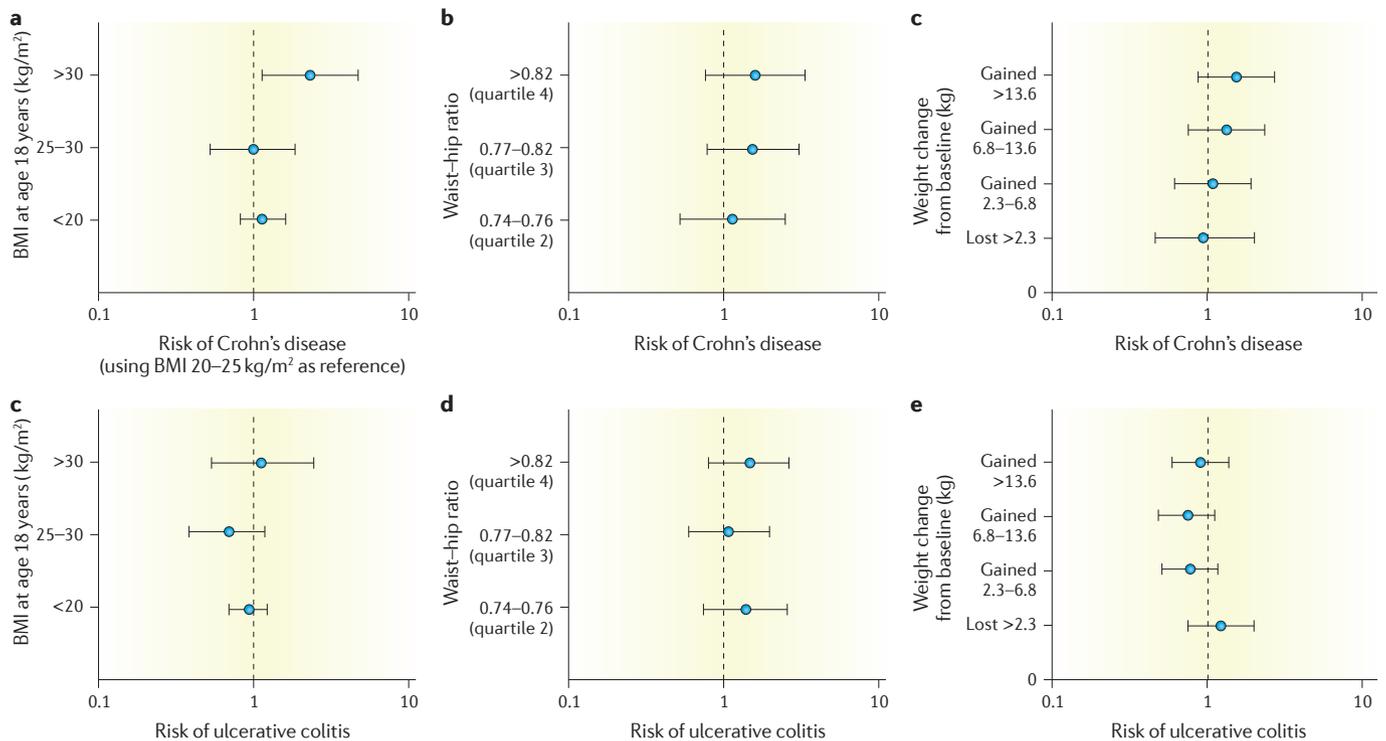
Figure 1 | **Association between premorbid obesity, waist–hip ratio and weight gain since age 18 years and IBD risk.** Data from the Nurses' Health Cohort[18] showing the relationship between premorbid obesity at 18 years of age, waist–hip ratio and weight gain since age 18 years on the risk of developing Crohn's disease and ulcerative colitis.

associated with an increased risk of developing Crohn's disease. Levels of other adipokines, such as resistin, also correlate with Crohn's disease severity and disease activity, further supporting the interaction of adipokines and cytokines to promote mucosal inflammation[37].

Role of dysbiosis. Central to the pathogenesis of IBD is mucosal barrier dysfunction, bacterial translocation and loss of intestinal immune homeostasis[38]. Translocation of bacteria has been linked to adipocyte and preadipocyte activation, with ensuing alterations in pro-inflammatory cytokine expression and immune homeostasis[28,35,38–60] (FIG. 2). Increased gut bacterial translocation is pertinent given its independent links to both obesity and Crohn's disease; both conditions have a reduction in bacterial diversity with accompanying dysbiosis[61]. A colonic-mucosa–bacteria–adipose-tissue feedback loop is then slowly established and reinforced by alterations in motility and immunoendocrine axes[62,63]. High-fat diet (both directly and by contributing to obesity) has been associated with an increased risk of Crohn's disease in preclinical models, with effects mediated through dysbiosis and altered gut permeability[64–66]. Epidemiological studies have also reported an association between a diet rich in omega fatty acids and saturated, monounsaturated and polyunsaturated fats and risk of developing Crohn's disease and/or ulcerative colitis[67].

Studies in Crohn's disease have identified genetic polymorphisms in enteroendocrine transcription factors (*PHOX2B*) as well as autoantibodies to specific cell components[68,69]. This finding, coupled with alterations in the levels of enteroendocrine hormones such as PYY, GLP-1 and GLP-2 (REF. 70), suggests a possible role for enteroendocrine cells in the propagation of inflammation in IBD. Treatment with GLP-2, an epithelial growth factor with anti-inflammatory properties, reduces the severity of injury in animal colitis models[71], and its use as a treatment option for Crohn's disease is currently under investigation[72]. Circulating PYY levels correlate with Crohn's-disease-related nausea and anorexia[73], and evidence has demonstrated that enteroendocrine cells might be key producers and mediators of pro-inflammatory cytokines, such as IL-17 (REF. 74). With evidence demonstrating an adipose-tissue–colon feedback loop between substance P, adipocytes and IL-17, alterations in neuroendocrine cells and hormones could play into and further strengthen this feedback mechanism to further promote inflammation. Hence, through a combination of paracrine, enteroendocrine and microbial factors, obesity — in particular visceral adiposity — could contribute to development and perpetuation of inflammation in IBD, particularly Crohn's disease.

Effect of obesity on IBD course

Obesity has been associated with high disease activity and worse clinical outcomes in several autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis[75,76]. Studies in patients with Crohn's disease suggest that overall obesity (as measured by BMI) is not consistently associated with an increased prevalence of IBD-related complications. In a cross-sectional study of 846 patients with Crohn's disease, Pringle and

colleagues[10] observed a lower prevalence of penetrating disease complications in patients who were obese (odds ratio (OR) 0.56, 95% CI 0.31–0.99), but comparable risk of stricturing and perianal complications, compared with adults of a normal BMI. In another cross-sectional study of 297 patients with Crohn's disease (30.3% obese), there was no difference in the prevalence of penetrating (20% versus 22%) or stricturing complications (17% versus 22%) between individuals who were obese or those of a normal weight[8]. Obesity, in particular class II (BMI ≥35 kg/m^2) or class III obesity (BMI ≥40 kg/m^2) might be associated with increased prevalence of colonic involvement with Crohn's disease, but this finding has not been consistently observed[8,10,11,13,14]. Similarly, in patients with ulcerative colitis, obesity has not been associated with disease severity. In a cohort of 202 patients with ulcerative colitis (13.4% of whom were obese), Stabroth-Akil and colleagues[14] observed a lower prevalence of pancolitis in patients who were obese than in patients of a normal BMI (33% versus 61%, respectively).

Longitudinal studies show variable effects of obesity on IBD disease course and the development of complications (TABLE 1). Inferior IBD-related quality of life and a higher frequency of elevated levels of serum C-reactive protein (an inflammatory marker) have been observed in patients with obesity (particularly class II or III obesity) compared with patients of normal weight; however, there was no statistically significant difference in the risk of IBD-related surgery, hospitalization or emergency department use between patients who were obese, overweight or a normal BMI[12]. A shorter time to first surgery in those who were overweight or obese versus undernourished individuals (2 years versus 21 years,

respectively) has also been found, although there were no differences in the number of surgeries related to Crohn's disease or escalation of medical therapy in patients with BMI ≥25 kg/m^2 versus BMI <25 kg/m^2 (REF. 77). By contrast, Flores and colleagues[8] observed a lower risk of IBD-related surgery (41% versus 52% versus 61% for patients who were obese, overweight, or normal or underweight, respectively), hospitalization (42% versus 44% versus 66%) and initiation of anti-TNF therapy (25% versus 26% versus 43%), both in patients with Crohn's disease and ulcerative colitis. Outcomes during an index hospitalization are generally worse among patients with IBD who are obese compared with non-obese patients with IBD. In a cross-sectional study using the Nationwide Inpatient Sample, we observed that among 6,742 hospitalized patients with ulcerative colitis, adults who are obese have higher rates of surgery (23.1% versus 14.2%), severe hospitalization (need for surgery or hospital stay >7 days: 35.3% versus 26.2%) and longer hospital stay (mean 6.0 versus 5.4 days) than patients who are not obese[78].

Contribution of visceral adiposity. Although overall obesity has not been consistently associated with more severe disease activity and progression to disease complications, visceral adiposity has been independently associated with increased risk of IBD-related complications. In a cross-sectional study, Erhayiem and colleagues[79] observed that patients with complications of Crohn's disease had a higher CT-measured visceral fat area and a higher visceral to subcutaneous fat area ratio (mesenteric fat index) than patients with inflammatory Crohn's disease; on multivariate analysis, mesenteric fat index was
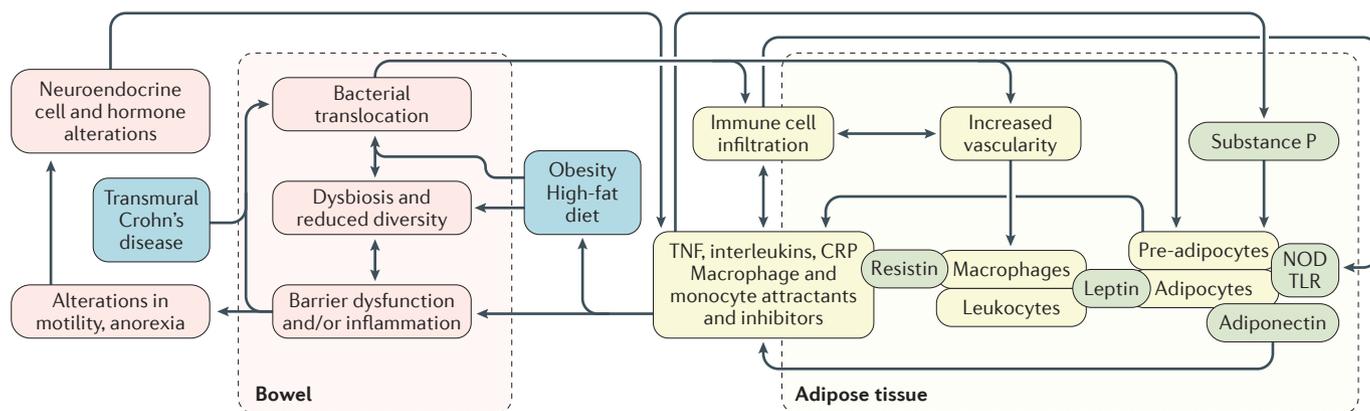
Figure 2 | **Postulated pathogenesis and feedback loop between visceral adipose tissue and intestinal inflammation in IBD.** In patients with IBD, the T-cell compartment shifts from a homeostatic regulatory environment consisting of M2 macrophages, natural killer cells and CD4$^+$ T$_{reg}$ cells toward a pro-inflammatory environment characterized by M1 macrophages, CD4$^+$ T$_H$1 and CD8$^+$ cytotoxic subtypes. Leptin, a member of the IL-6 protein family, is produced by adipocytes in proportion to fat mass. Leptin increases synthesis of pro-inflammatory cytokines in monocytes and macrophages, and is involved in T-cell-mediated immune responses. Adiponectin, produced by adipocytes in an inverse proportion to fat mass, functions as an insulin sensitizer and anti-inflammatory adipokine in patients who do not have IBD. However, in IBD, and in particular in Crohn's disease, evidence supports its role as a

pro-inflammatory adipokine that results in increased cytokine secretion and epithelial cell proliferation. Macrophages and monocytes are the main source of resistin, the expression of which is induced by pro-inflammatory cytokines (IL-1, IL-6 and TNF), and circulating levels correlate with acute-phase reactants (C-reactive protein, CRP). Resistin can promote expression of TNF and IL-6. Evidence from the past decade has demonstrated the existence of an adipose-tissue–colonic-mucosa feedback loop, in which preadipocytes release IL-17A in response to substance P; the colonic mucosa from these individuals shows an increase in IL-17A receptors. Obesity and a high-fat diet, as well as transmural inflammation in Crohn's disease, results in impaired mucosal barrier function through alterations in tight-junction proteins, thereby promoting bacterial translocation. TLR, Toll-like receptor.

independently associated with Crohn's disease complications. In a retrospective cohort study of 114 paediatric patients with IBD (101 with Crohn's disease), high VAT volume was associated with increased risk of penetrating or stricturing Crohn's disease complications (OR 1.7, 95% CI 1.1–2.9), Crohn's-disease-related hospitalization (OR, 1.9, 95% CI 1.2–3.4), shorter time interval to surgery (HR 1.4, 95% CI 1.0–2.0) and moderate–severe disease activity scores (OR 1.8, 95% CI 1.1–3.1), after adjusting for age and BMI[24]. High visceral fat area has also been associated with increased risk of recurrence of Crohn's disease after surgical resection (endoscopic recurrence: HR 8.6, 95% CI 1.6–47.1; clinical recurrence: HR 2.6, 95% CI 1.0–6.7)[80]. Likewise, the metabolic consequences of obesity, in particular of visceral adiposity, have also been associated with IBD-related disease severity. In a single-centre retrospective cohort study of 868 patients with Crohn's disease (19.0% of whom were obese), an increased incidence of IBD-related hospitalization was observed in the 4% of the cohort with metabolic syndrome (defined as >3 of the following features: obesity, diabetes mellitus, hypertension, high levels of circulating triglycerides and low levels of circulating HDL cholesterol), compared with those without metabolic syndrome (incidence rate ratio 1.79, 95% CI 1.06–3.00). However, on evaluating different components of metabolic syndrome, presence of diabetes mellitus, high circulating triglyceride levels and low HDL cholesterol levels, but not obesity, were associated with increased incidence of IBD-related hospitalization[81]. In another retrospective cohort study of 240 patients with Crohn's disease (12.5% of whom were obese), although obesity was identified as a risk factor for surgery on univariate analysis (OR 2.2, 95% CI 1.0–4.8), it was not an independent predictor of surgery after adjustment for confounding variables. On the other hand, diabetes mellitus (which affected 6.7% of cohort) was a strong independent predictor of surgery, even after adjustment for corticosteroid use (OR 5.4, 95% CI 1.7–17.6)[82]. Patients with diabetes also had lower quality of life and higher clinical disease activity than individuals without diabetes.

Limitations of current literature. Current studies on the association between obesity and natural history of IBD have several limitations, and need to be interpreted carefully. Cross-sectional and cohort studies are retrospective in nature, which limits the ability to make causal inference given the dynamic nature of weight as well

as IBD activity. This approach is limited by confounding by disease severity, wherein patients with severe disease activity (and at higher risk of disease-related complications) are likely to lose weight, resulting in potential misclassification of their BMI. On the other hand, patients with mild disease activity are more likely to maintain (or might gain) weight, as is the trend in the general population[83]; in these patients, obesity or overweight might be a manifestation rather than the aetiology of a mild disease course. Additionally, most studies failed to adjust for other potential confounding factors such as smoking and corticosteroid use. Smoking cessation might improve Crohn's disease course, and could also result in weight gain causing a misclassification of obesity category. Similarly, use of corticosteroids, often prescribed to patients with more severe disease, is frequently associated with weight gain, potentially resulting in misclassification of BMI categories. Moreover, single tertiary-centre retrospective cohort studies have low event rates with limited follow-up, hence the independent effect of overweight and obesity on IBD course and development of complications has not been comprehensively studied. Design considerations for a more robust observational study of the relationship between IBD and obesity are described in BOX 1.

Given the increasing recognition of metabolic differences in visceral (and mesenteric) and subcutaneous adiposity, overall BMI might not adequately capture the association between obesity and IBD. As observed in several studies, measurement of visceral fat (through VAT area or volume, or at least measurement of central obesity using surrogate measures such as WHR) could help us better understand the true effect of obesity on IBD.

Obesity and IBD-related therapy

Observational comparative effectiveness studies in Crohn's disease suggest that infliximab is associated with lower rates of IBD-related hospitalization and abdominal surgery than adalimumab and certolizumab pegol[84,85]; these observations are also supported by indirect treatment comparison network meta-analyses[86]. These differences could be due to differences in systemic drug exposure related to body weight; infliximab dose is weight-based and intravenously administered, whereas other agents are administered subcutaneously in a fixed dose. For example, in a single-centre retrospective cohort study, Bhalme *et al.*[87] observed — in adalimumab-treated but not infliximab-treated patients — a higher likelihood of dose escalation in patients who were obese than in patients who were not obese (BMI >35 kg/m² versus BMI <25 kg/m², 40% versus 20%, respectively). In an exploratory analysis of trials of adalimumab in patients with psoriasis, the response rate decreased progressively with increasing quartile of weight, from 74–79% in the lowest quartile to 62–71% in the highest quartile[88]. By contrast, in a pooled analysis of three randomized controlled trials of infliximab in psoriasis, the response rates were comparable in patients who were normal weight, overweight and obese (78% versus 78% versus 74%, no statistically significant difference

between groups)[88]. Importantly, patients who are obese, particularly those who are morbidly obese, are less likely to receive optimal weight-appropriate therapy. Seminerio and colleagues[12] observed that the average dose of infliximab in patients with class III obesity was ~4 mg/kg body weight, compared with 7.9 mg/kg body weight in those with normal BMI and 6.4 mg/kg body weight in patients who were overweight. Similarly, the usual per kilogram body weight dose of immunomodulators was lower in patients with class III obesity than in patients with normal BMI (azathioprine dose 1.1 mg/kg body weight per day versus 1.7 mg/kg body weight per day, respectively, and 6-mercaptopurine dose 0.7 mg/kg body weight per day versus 1.2 mg/kg body weight per day, respectively).

However, obesity might affect treatment response to biologics independent of drug exposure. Population pharmacokinetic studies of all biologic agents approved for use in IBD, including anti-TNF agents (infliximab[89], adalimumab[90], certolizumab pegol[91], golimumab[92],) and anti-integrin agents (vedolizumab)[93], have identified high body weight as a risk factor associated with increased drug clearance, resulting in short half-life and low trough drug concentrations. This effect might be related to rapid proteolysis[94] and to a 'TNF sink' phenomenon in patients with obesity, whereby increased levels of adipose-secreted TNF sequester anti-TNF agents. In a retrospective cohort study of 124 infliximab-treated patients with IBD, patients with obesity were 3–9 times more likely to have an IBD flare and require biologic dose escalation than normal weight patients[95]. Each unit increase in BMI was associated with a 6% higher likelihood of Crohn's disease flare (HR 1.06, 95% CI 1.02–1.11) and 30% higher likelihood of ulcerative colitis flare (HR 1.30, 95% CI 1.07–1.58). In another single-centre prospective cohort of 199 patients with Crohn's disease treated with adalimumab and followed over a median of 1 year, over one-third of patients were dose-escalated to weekly adalimumab within a median 5 months of initiating therapy, and BMI was the only independent predictor of dose escalation[96]. However, these findings have not been consistent. In a prospective, single-centre experience, no statistically significant association was observed between BMI and infliximab or adalimumab trough levels[97].

Although data on obesity and treatment response in IBD is limited, similar observations have been made in biologic-agent-treated patients with other autoimmune diseases. In a prospective cohort of 89 patients with rheumatoid arthritis treated with infliximab, patients who were obese had lower rates of clinical response (measured using Disease Activity Score in 28 joints) than patients with a normal BMI, even after adjustment for baseline disease activity and anti-citrullinated protein antibody status (BMI >30 kg/m² versus BMI 20–30 kg/m² versus BMI <20 kg/m², 50% versus 75% versus 84%, respectively)[98]. Similarly, in a prospective cohort of 641 patients with rheumatoid arthritis (10.3% of whom were obese), the cumulative rate of clinical remission at 12 months after treatment initiation was lowest in patients with obesity, compared with individuals who were overweight or normal BMI (15.2% versus 30.4% versus 32.9%, respectively)[99]. Likewise, in 557 patients

with psoriatic arthritis (35.4% of whom were obese), likelihood of achieving sustained minimal disease activity was lowest in patients who were obese (OR 0.52, 95% CI 0.40–0.67) and overweight (OR 0.65, 95% CI 0.50–0.85), compared with patients with normal BMI[100].

Besides biologic therapy, obesity might also modify response to immunomodulator therapy in IBD. Among 132 patients with IBD treated with thiopurines dosed according to body weight, patients who were obese were less likely to achieve therapeutic 6-thioguanine nucleotide concentrations, with thiopurines instead preferentially metabolized via the 6-methyl mercaptopurine nucleotide pathway[101].

Effect of obesity on IBD-related surgery

Intra-abdominal surgeries in patients with obesity are both technically challenging and are usually associated with higher rates of postoperative complications than surgeries in patients with a normal BMI[102]. In a systematic review of 33 studies on the effect of obesity on perioperative outcomes with laparoscopic colorectal resection for any aetiology, Makino and colleagues[103] observed longer operative times and an increased likelihood of conversion to open procedure in patients who were obese. Compared with patients who were not obese, patients with obesity had more comorbidities, a higher risk of postoperative complications (in particular wound infection) and a longer length of hospital stay. In a cohort of patients undergoing colorectal cancer surgery, increased perioperative mortality, higher rates of surgical complications, increased hospital costs and more frequent need for discharge to short-term rehabilitation facilities were observed in those with obesity compared with those who were not obese.

Key studies on the effect of obesity on surgical outcomes in patients with IBD are summarized in TABLE 3. In a nationwide US study of 382,637 inpatient hospitalizations for surgery in patients with IBD (using the Nationwide Inpatient Sample), Jain and colleagues[105] observed that patients with obesity had increased rates of postoperative wound complications (OR 1.35, $P = 0.01$), infections (OR 1.16, $P = 0.02$), pulmonary complications (OR 1.21, $P = 0.02$), and shock (OR 1.30, $P = 0.02$). No difference in the risk of cardiovascular complications (OR 1.09, $P = 0.52$), perforations (OR 1.04, $P = 0.71$), venous thromboembolism (OR 1.18, $P = 0.40$) or death (OR 0.73, $P = 0.07$) was observed between obese and non-obese IBD surgeries. Two aspects of surgery that might be particularly challenging in patients with IBD merit special mention. First, obesity makes creating a stoma challenging, as it tends to retract, and is associated with higher rates of stoma-related complications such as parastomal hernia, mucocutaneous separation and stoma prolapse[106,107]. Second, the mesentery of patients with obesity tends to be foreshortened by the mesenteric fat, making it more challenging to create a J-pouch in patients with ulcerative colitis. Obesity increases risk of short-term postoperative complications in patients undergoing ileal pouch–anal anastomosis, although long-term outcomes might be comparable to those in patients without obesity in experienced centres[108,109].

Table 3 | **Key studies on the effect of obesity on surgical outcomes in patients with IBD.**

Study	Study characteristics	Patient characteristics	Obesity rate	Key findings	Refs
Krane *et al.* (2013)	• Single-centre, retrospective cohort study • Conducted in Chicago, Illinois, USA, 2002–11	626 patients (all with BMI >18.5 kg/m²) undergoing laparoscopic colorectal resection	• 13.6% obese (mean BMI 35.1 kg/m²) • 46.5% overweight or obese	• Longer operative time in patients overweight and obese compared with normal weight patients • Higher rate of conversion to open surgery in patients overweight (10.7%) and obese (12.9%) vs normal weight (8.3%) patients, predominantly related to visceral obesity • Overall rate of intraoperative and post-operative complications comparable between groups, except a higher rate of incisional hernia in patients with obesity vs normal weight patients	124
Causey *et al.* (2011)	Multi-centre, retrospective cohort study (National Surgical Quality Improvement Program), USA, 2005–2008	2,319 patients undergoing abdominal surgery for Crohn's disease (25% performed laparoscopically)	16% obese (2% morbidly obese)	• Longer operative time in patients who were obese (177 min) vs non-obese (164 min) • Higher perioperative morbidity in patients who were obese vs non-obese (32% vs 22%, respectively, OR 1.9) • Higher rate of postoperative complications in patients who were obese vs non-obese, particularly wound infection (OR 1.7, increasing to 7.1 when BMI >40 kg/m²)	125
Klos *et al.* (2014)	• Single-centre retrospective cohort study • Conducted in St Louis, Missouri, USA, 1990–2011	178 patients with ulcerative colitis undergoing IPAA	42% obese	• Higher rate of complications in patients who were obese (80%) vs non-obese (64%) • Higher rate of pouch-related complications in patients who were obese vs non-obese (61% vs 26%, respectively), including anastomotic/pouch strictures (27% vs 6%, respectively), inflammatory pouch complications (17% vs 4%, respectively) and pouch fistulae (12% vs 3%, respectively)	108

IPAA, ileal pouch–anal anastomosis.

Beyond overall obesity, visceral adiposity might be an independent predictor of surgical outcomes and complications in patients with IBD. Using analytic morphomics (the application of machine learning to biomedical images to derive patient-specific biomarkers), Stidham and colleagues observed that a high visceral to subcutaneous fat ratio, and not high BMI, is associated with increased risk of infectious complications after surgical resection for Crohn's disease[110]. In another retrospective cohort of 164 patients undergoing primary Crohn's disease-related surgery, a high visceral fat area (≥130 cm²) was independently associated with a 2.7-fold increased risk of overall postoperative complications[111].

Besides surgery, an area that merits discussion in patients with IBD who are obese is medical imaging. Two types of abdominal imaging, CT and MRI, are frequently used in patients with IBD, and can impose special challenges in patients who are morbidly obese[112]. Equipment-specific issues include table weight limit, gantry width and tube capacity; imaging via MRI brings greater equipment-specific issues, as the standard MRI table weight capacity is 350 lbs (158.8 kg) and the standard machine bore diameter is 60 cm, limiting the ability to place patients in the scanner. Image-quality issues are also present, as a result of photon starvation, reduced contrast-to-noise ratio and truncation artefacts[112]. Owing to difficult intravenous access and risk of extravasation, and the need for weight-based contrast administration, there can be issues with intravenous contrast in patients who are obese. Additionally, claustrophobia and patient discomfort are substantial concerns when using MRI. Hence, despite inherent limitations, CT might be the best and easiest way to image larger patients. Specific solutions during imaging and post-image processing might be implemented to optimize image quality in patients who are obese.

Obesity treatment and IBD outcomes

Although there is considerable evidence that obesity adversely affects response to IBD-related therapy, there is a paucity of data on whether treating obesity can favourably affect outcomes in patients with IBD. No interventional studies of interventional weight loss in IBD exist; however, trials of diet and/or lifestyle-induced weight loss in other autoimmune diseases suggest improvement in outcomes with this form of adjunctive therapy. In a meta-analysis of five studies in patients with psoriasis who were obese or overweight, those randomized to weight loss intervention were 2.9 times more likely to achieve 75% reduction in Psoriasis Area and Severity Index score, compared with those not receiving the weight loss intervention (OR 2.92, 95% CI 1.39–6.13)[113]. Achieving as little as 5% weight loss is associated with favourable outcomes. In a 6-month randomized trial comparing a low-calorie or a free-managed diet (comprising dietary advice but no calorific restriction) in 126 patients with psoriatic arthritis starting anti-TNF therapy, Di Munno and colleagues[114] observed a greater reduction in levels of pain and inflammatory markers, and higher likelihood of achieving minimal disease activity, in patients receiving a low-calorie diet (42.9% versus 34.9% of patients achieved minimal disease activity on low-calorie diet versus free-managed diet, respectively). Importantly, regardless of the intervention, magnitude of intentional weight loss was associated with improvement in outcomes: the proportion of patients attaining minimal disease activity in those achieving >10% weight loss, 5–10% weight loss and <5% weight loss was 59.5%, 44.8% and 23.1%, respectively. Patients who achieved at least 5% weight loss were 4.2 times more likely to achieve minimal disease activity compared with those who experienced <5% weight loss (OR 4.20, 95% CI 1.82–9.66).

Whether similar benefits would be observed among patients with IBD who are obese is speculative. Although bariatric surgery is technically feasible in patients with IBD, long-term consequences of major restrictive and malabsorptive procedures in these individuals are poorly understood. Case series have suggested that these procedures are safe in highly selected patients who are morbidly obese and have IBD, and have also anecdotally observed improvement in disease activity after weight loss[115,116]. However, short of bariatric surgery, other weight loss interventions would also probably be beneficial. Although dietary interventions carry low risk of adverse events, adherence to specific diets is limited, and despite intensive lifestyle interventions remaining the cornerstone of initial obesity management, their long-term effectiveness in a real-world setting is limited by small average weight loss with commercial weight-loss programmes and frequent regain of lost weight over time[117]. Weight loss achieved through pharmacological or endoscopic bariatric interventions might achieve the same effect on outcomes in IBD as in other autoimmune diseases, but has not been studied. With five weight-loss medications now approved by the FDA for long-term management of obesity, with average excess weight loss (over placebo) ranging from 2.6 kg (with orlistat) to 8.8 kg (phentermine–topiramate), and an estimated 44–75% of patients achieving the threshold of at least 5% weight loss, it is very appealing to consider pilot trials of the efficacy and safety of these medications as adjunct therapies in patients with IBD who are obese[118]. Two medications in particular merit attention: phentermine–topiramate and naltrexone–bupropion. Both of these medications result in statistically and clinically significant weight loss (mean 8.8 kg and 5.0 kg excess weight loss over placebo, respectively, and 75% and 50% patients achieving at least 5% weight loss, respectively), with low rates of serious adverse events. Preclinical data supports an anti-inflammatory role of both topiramate and phentermine. Using a novel computational approach for drug repositioning, Dudley and colleagues[119] systematically compared the gene expression profiles of a compendium of 164 drug compounds in human cell lines to the gene expression signature of IBD derived from public microarray data of patient biopsy samples. On the basis of this analysis, they predicted that topiramate is very likely to be effective against both Crohn's disease and ulcerative colitis. Subsequently, *in vivo* testing of topiramate was performed in a 2,4,6-trinitrobenzenesulfonic acid (TNBS) rat model of IBD, with three independent validations. Administration of topiramate for 7 days after TNBS-induced colitis resulted in markedly reduced diarrhoea and reduced pathological inflammation. Similarly, several lines of evidence have shown that noradrenaline might regulate intestinal mucosal immune responses mediated by intraepithelial lymphocytes via β1-adrenoreceptors[120]. The individual components of naltrexone–bupropion have also shown favourable effects in IBD. One 12-week trial of low-dose naltrexone (4.5 mg per day) in 40 patients with Crohn's disease found higher rates of clinical and endoscopic remission in the intervention group than the placebo group; at this low dose, this observed benefit might be mediated through naltrexone's anti-inflammatory effect rather than through weight loss[121]. Preclinical studies have suggested that bupropion might have an anti-TNF effect, with small case series reporting the effectiveness of this medication in inducing clinical remission[122,123].

Conclusions

The prevalence of obesity in patients with IBD is sizeable and parallels rates in the general population, contrary to conventional beliefs that patients with IBD are malnourished. Although from a pathophysiological perspective, obesity, and in particular visceral adiposity, seems to promote intestinal inflammation, epidemiological studies implicating obesity in the development of IBD are limited. Understanding of the effects of obesity on cross-sectional disease severity and development of disease complications is incomplete, with studies conducted to date (with flawed designs and inherent limitations) showing conflicting results. On the basis of pharmacokinetic data, obesity seems to promote rapid clearance of biologic agents, regardless of drug dose. The effect of obesity on response to therapy remains to be studied, though data from other autoimmune diseases suggests that obesity is an independent predictor of poor response to medical therapy. This association provides an opportunity for using treatment directed towards obesity, either through lifestyle, pharmacological or endoscopic interventions, as adjunctive therapy in patients with IBD who are obese.

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