REVIEW

Interaction of obesity and inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of unknown etiology that is thought to result from a combination of genetic, immunologic and environmental factors. The incidence of IBD has been increasing in recent decades, especially in developing and developed nations, and this is hypothesized to be in part related to the change in dietary and lifestyle factors associated with modernization. The prevalence of obesity has risen in parallel with the rise in IBD, suggesting a possible shared environmental link between these two conditions. Studies have shown that obesity impacts disease development and response to therapy in patients with IBD and other autoimmune conditions. The observation that adipose tissue produces pro-inflammatory adipokines provides a potential mechanism for the observed epidemiologic links between obesity and IBD, and this has developed into an active area of investigative inquiry. Additionally, emerging evidence highlights a role for the intestinal microbiota in the development of both obesity and IBD, representing another potential mechanistic connection between the two conditions. In this review we discuss the epidemiology of obesity and IBD, possible pathophysiologic links, and the clinical impact of obesity on IBD disease course and implications for management.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Obesity; Body mass index

Core tip: Epidemiologic studies have shown a parallel rise in the prevalence of obesity and immune-mediated conditions, including inflammatory bowel disease (IBD). This association may be related to share dietary or environmental exposures that exert their effect through changes in the intestinal microbiota. Several lines of evidence demonstrate that obesity is a pro-inflammatory condition that impacts the incidence, disease course and response to therapy in patients with IBD. Exploring the mechanisms of interaction between obesity and IBD advances our understanding of IBD

and opens up a potential role for weight loss and weight maintenance strategies in the management of IBD.

Figure 1 Proposed etiologic links between obesity and inflammatory bowel disease.

INTRODUCTION

Obesity - the chronic medical condition defined generally as excessive body fat mass leading to deleterious health outcomes - has emerged as one of the leading global public health issues of the 21st century. In the United States, according to data from the National Health and Nutrition Examination Survey (NHANES), approximately 30% of adults are obese, as defined by having a body mass index (BMI) greater than 30 kg/m^2[1]. World Health Organization estimates of the prevalence of overweight or obese individuals (BMI > 25 kg/m^2) approximate 35% of the global population, with increases over time demonstrated in both developed and developing nations[2]. The global cost of treating obesity and its resultant health complications may be as much as $2 trillion (US)[3]. Although obesity was once considered uncommon in IBD, the prevalence of obesity in IBD has risen in parallel with the general population. Several lines of evidence support a biologically plausible connection between adiposity and IBD (Figure 1). Understanding the interaction between obesity and IBD with regard to disease pathogenesis, phenotypic disease expression and response to therapy has important implications for management.

EPIDEMIOLOGY OF IBD AND OBESITY

Temporal trends have demonstrated an increase in IBD incidence across the globe over the latter half of the 20th century[4]. A number of environmental factors have been postulated to be associated with this, concordant with the long-noted observation that IBD is more prevalent in developed, as opposed to developing, nations. These disparate factors have included smoking (for Crohn's disease incidence)[5], improved levels of hygiene[6], alterations in the intestinal microbiome[7,8], and dietary changes associated with an industrialized lifestyle, including increased intake of linoleic acid, increased intake of animal fat/protein and decreased dietary fiber intake[9-11]. Given the rising incidence of both IBD and obesity - as well as the interplay between some of the aforementioned risk factors common to both conditions-an epidemiologic interaction between the two conditions has been postulated. To date there
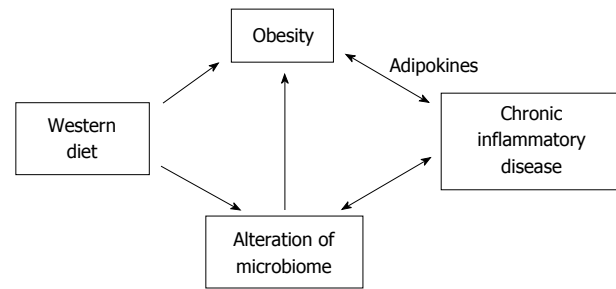
is a relative paucity of population-level studies reporting the prevalence of obesity among individuals with IBD, but reports from various IBD cohorts in both pediatric and adult populations would suggest that the current prevalence of overweight and obese IBD patients approximates that of the general population, being approximately 20%-30%[12-15]. Furthermore, when looking at the weight distribution of individuals recruited to participate in clinical trials for Crohn's disease, there has been a clear trend in increasing weight over the past two decades, from a minimum mean BMI of 20.8 kg/m^2 in 1992, to a maximum mean BMI of 27.0 in 2001, and a weakly positive linear trend (r^2 = 0.14) of increasing BMI among study participants throughout this period of time[16].

As to whether or not obesity - as reflected by the body mass index-is an intrinsic risk factor for the development of *de novo* IBD, a large prospective cohort (EPIC) of European adults demonstrated no such association, after adjustment for smoking status, physical activity and total caloric intake as assessed by food frequency questionnaire. Among those individuals with incident IBD in this cohort, BMI was not associated with phenotypic disease expression (Crohn's *vs* ulcerative colitis), nor disease location/extent[17]. An earlier retrospective cohort of incident IBD diagnoses in adults, compared to an older (age 50-70 years) non-IBD control cohort, suggested a higher rate of obesity at diagnosis in the IBD patients (OR = 2.0, P = 0.01)[18]. More recently published data from the Nurses' Health Study demonstrated a greater than two-fold increased risk of developing Crohn's disease among obese women; furthermore, an association was also observed between body morphology (as reflected by participants' waist-hip ratio as adolescents) and future development of Crohn's disease in this cohort. No such relationship between BMI or anthropometric measurements of obesity was seen with incident UC in this same study[19]. Another cohort of women recruited in Denmark also demonstrated an increased risk of Crohn's disease among obese individuals, with no such relationship seen with ulcerative colitis[20]. Perhaps accounting for the discrepancy between the data from the EPIC study and the Nurses' Health study is the fact that the EPIC cohort described above was much

Table 1 Clinical impact of obesity on inflammatory bowel disease

Medical therapy	Surgical therapy	Natural history and disease complications
Decreased clinical response to azathioprine[77]	Earlier time to 1st surgery[15]	Conflicting data:
Lower 6-thioguanine levels on treatment with azathioprine[78]	Higher rate of perioperative complications[112,114,119-121]	Higher prevalence of perianal disease[22]
Decrease likelihood of response to adalimumab[83]	Increased need for conversion from laparoscopic to open surgery[113,118]	Lower prevalence of penetrating disease[24]
Shorter time to loss of response to infliximab[92]		Increased hospitalization[22]
		Decreased IBD-related quality of life[23]
		Decreased healthcare utilization[14]

IBD: Inflammatory bowel disease.

older (median age 52) compared to the American and Danish cohorts (median age 35 and 30 respectively), and of course, the American and Danish cohorts were entirely female, as compared to a roughly equal sex distribution in the EPIC cohort. If there is in fact an increased risk of developing IBD intrinsic to obesity, this risk may interact with age and sex. Adding to the biologic plausibility of an etiologic link between adiposity and IBD, other studies have demonstrated that obesity is associated with an increased risk of developing other autoimmune conditions such as rheumatoid arthritis and psoriasis, that share similar genetic and immunologic mechanisms with IBD[21,22].

RELATIONSHIP BETWEEN OBESITY AND IBD OUTCOMES

There are mixed data regarding the impact of obesity on IBD-related health outcomes (Table 1). Co-morbid obesity has been linked to an earlier time to first surgery among patients with Crohn's disease in one retrospective registry, with no difference noted in the overall number of surgeries or the need to escalate medical therapy over time between groups[15]. In a retrospective study of French IBD patients, obese individuals with Crohn's disease were suggested to have a higher rate of perianal disease, and a more frequent need for hospitalization[23]. A more recent retrospective cohort of IBD patients, approximately 40% of whom had UC, showed no association between BMI and need for surgery, hospitalization or medication escalation across BMI categories, after adjustment for obesity-related health conditions such as hypertension or diabetes. However, increased BMI was associated with more subtle indicators of active disease, including increased C-reactive protein levels (which was controlled for in this analysis in regard to IBD outcomes) as well as a significant decrement in IBD-related quality of life measures[24]. Another recent study of a mixed IBD (CD + UC) population showed conflicting results with decreased rates of surgery or hospitalization, as well as decreased use of anti-TNF biologic therapy, among obese IBD patients[14]. In this study, however, underweight patients were grouped together with normal weight patients for the analysis,

which may have obscured the association between obese and normal weight patients by including sicker patients in the comparator group. Data from a prospective registry of Crohn's patients showed a lower rate of penetrating disease activity among obese individuals with Crohn's disease, after adjustment for factors such as smoking, age, baseline inflammatory activity and genetic risk profile; this same study showed no major difference in the rate of perianal disease or surgery among obese *vs* non-obese Crohn's patients[25]. Among patients with ulcerative colitis, retrospective cohort data has been published suggesting that overweight (BMI > 25 kg/m^2) patients may have a less complicated clinical course than normal-weight or underweight (BMI 18-24 kg/m^2 and < 18 kg/m^2 respectively) patients[26]. In a prospectively recruited cohort of IBD patients in Ireland, obese patients with Crohn's disease were on average found to be older, less physically active, to have lower CDAI scores and higher C-reactive protein levels than their non-obese counterparts. Smoking status, age at diagnosis, need for surgery and corticosteroid use did not differ between groups[27].

Special mention should be made about the potential interaction between diabetes and inflammatory bowel disease independent of obesity, given the strong and well-described association between obesity and type 2 diabetes. Individuals with IBD (UC specifically) may be at higher risk of developing *de novo* diabetes according to a large UK cohort, even after adjustment for concurrent glucocorticoid usage and baseline BMI[28]. Co-morbid diabetes among IBD patients has been associated with higher rates of infection on immunomodulatory therapy, hospitalization and need for surgery over time[29-31].

All of the aforementioned studies have used body mass index as the surrogate marker of adiposity, and as yet, we have much less data about the interaction between other markers of obesity, such as volumetric analysis of visceral fat, and IBD outcomes. One small retrospective study of individuals with Crohn's disease demonstrated that individuals with higher relative amounts of mesenteric fat, as defined by the ratio between their visceral and subcutaneous fat area on cross-sectional imaging, had significantly higher

Table 2 Immunologic effect of adipokines

Adipokine	Levels in obesity	Immunologic effects	Overall effect
Adiponectin	Decreased	Decreases TNF-α, IFNγ, IL-6 Inhibits VCAM-1, ICAM-1 expression Increases IL-10, IL-1RA Promotes proliferation of Tregs Antagonizes NF-κB pathway	Anti-inflammatory
Leptin	Increased	Increased activation and proliferation of monocytes and macrophages Increased IL-6, TNF-α, IL-12 Activates NK cells Activates NF-κB pathway Promotes Th1-differentiation Inhibits proliferation of Tregs	Pro-inflammatory
Resistin	Increased	Increases IL-6, IL-12, TNF-α	Pro-inflammatory

TNF-α: Tumor necrosis factor-α; NF-κB: Nuclear factor-κB; IFNγ: Interferon γ.

rates of fibro-stenotic or penetrating disease behavior. This observation differs from the aforementioned finding of less penetrating disease among obese IBD patients when solely BMI is used to define obesity[32]. Prospective data are lacking with regard to the potential interaction between obesity and IBD complications that are independently associated with both conditions, such as venous thromboembolism; cholelithiasis and hepatic steatosis; cardiovascular disease; and, perhaps most importantly, colorectal cancer[33-36]. Also confounding the relationship between obesity and IBD outcomes is the observation that increased visceral adiposity may be associated with a higher risk of irritable bowel syndrome[37]. This interaction could confound the interpretation of studies that suggest that obese IBD patients have a less complicated clinical course, if some of their symptoms over time are in fact accounted for by a higher prevalence of co-morbid functional bowel disease, which should be associated with less need for medication escalation or surgery.

DEFINITION OF OBESITY

One of the ongoing challenges in trying to elucidate the interaction between obesity and health outcomes has been the lack of consensus regarding a standardized definition of obesity. For its ease of use, the body mass index (BMI), a simple adjusted ratio of weight to height, has been used as the operational definition of obesity when it exceeds 30 kg/m^2. As an isolated measure, the BMI does predict broad health outcomes such as all-cause mortality at higher categories of obesity (such as BMI > 35 or 40 kg/m^2), but performs poorly (and may indicate lower all-cause mortality) when it is considered among individuals presently defined as "overweight" (*i.e.,* BMI > 25 kg/m^2)[38,39]. Multiple studies have demonstrated that various anthropometric measurements of obesity - such as the waist-to-hip circumference ratio or volumetric analysis of abdominal fat *via* cross-sectional imaging-perform

better than BMI as predictors of adverse health outcomes[40-42]. A glaring deficit in the current literature regarding IBD and obesity has been the general reliance on the BMI as the sole marker of obesity, and lack of validation of the standard BMI categories of overweight or obesity as clinically relevant cutoffs in IBD. As addressed in this review in later sections, it may be that adipose distribution is more clinically significant than overall body size. As such, incorporation of multiple domains of obesity to reflect the differences between health outcomes and body fat distribution, would help elucidate the interaction of obesity and IBD by minimizing the confounding effect of individuals with elevated lean body mass who happen to have BMI values that may place them in the operational categories of "overweight" or even obese, or whose adipose distribution is predominantly intra-abdominal, *vs* peripheral, fat.

OBESITY AS A PRO-INFLAMMATORY STATE

Far from being an inert repository of excess calories, adipose tissue is responsible for the secretion of a number of pro- and anti-inflammatory cytokines, some of which are unique to this tissue type and which have been labeled adipokines (Table 2). A full discussion of the complex relationship between adipokines and autoimmune conditions including IBD is beyond the scope of this discussion, but some intriguing points are worth reviewing.

Adiponectin is a 30 kD protein produced almost exclusively by adipocytes and has complex interactions with multiple inflammatory pathways; interestingly, it shares some degree of structural homology with tumor necrosis factor-alpha (TNF-α), a cytokine intrinsically involved in the pathogenesis of IBD[43]. Adiponectin appears to exert anti-inflammatory effects, with evidence of antagonism of pathways that TNF-α promotes, such as the nuclear factor-κB pathway[44]. Interestingly, increased expression of adiponectin

has been found in the so-called "creeping fat" of patients with active Crohn's disease when compared to mesenteric fat from patients with UC and with colonic adenocarcinoma; however, adiponectin concentrations were found to be lower in the mesenteric fat of CD patients with internal (*e.g.,* entero-enteral) fistulas compared to individuals with non-fistulizing disease[45]. In one study, circulating adiponectin levels appear to be increased among UC patients as compared to both CD patients and healthy controls[46]. Another study demonstrated reduced circulating levels of adiponectin in individuals with both active and inactive IBD compared to healthy controls; curiously, this same study demonstrated that hyperinsulinemia in the absence of hyperglycemia was independently associated with a higher likelihood of clinical remission in IBD patients (in tandem with decreased circulating adiponectin levels)[47]. Circulating adiponectin levels in patients with IBD treated with infliximab do not seem to be affected pre- and post-treatment[48].

Leptin was one of the originally identified adipokines, and appears to have a number of pro-inflammatory effects; it is also one of many adipokines that plays a role in appetite modulation and energy homeostasis. Increased serum leptin levels are directly associated with total body fat mass, and leptin in general has a pro-satiety effect on appetite centers in the hypothalamus[49]. Leptin appears to increase the secretion of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α, and synergistically, pro-inflammatory cytokines promote leptin expression in inflamed tissue[50,51]. Several studies have demonstrated lower serum leptin levels, when adjusted for body weight, in patients with IBD compared to healthy controls, in both pediatric and adult populations[46,52]. Treatment with infliximab in patients with IBD does not appear to modify circulating serum leptin levels[48].

Resistin is another adipokine with complex relationships with inflammatory pathways: in humans, it is produced by adipocytes as well as by cells in the reticuloendothelial system (*e.g.,* splenic monocytes/macrophages). As with leptin, studies have demonstrated that resistin stimulates the production of pro-inflammatory cytokines such as TNF-α and IL-12, and that in turn, pro-inflammatory cytokines appear to induce resistin expression[53,54]. Multiple studies have demonstrated elevated serum resistin levels in patients with IBD (both UC and CD)[38,40,55]. Unlike with adiponectin or leptin, serum resistin levels are seen to decrease in humans with IBD treated with infliximab[42,56].

Mesenteric fat itself, along with producing both pro- and anti-inflammatory adipokines, is also a source of multiple pro-inflammatory cytokines that are integral to the inflammatory cascade involved in IBD, such as TNF-α and IL-6. In obese individuals, visceral adiposity as assessed by volumetric cross-sectional imaging analysis directly correlates with circulating IL-6 levels, and BMI is associated with C-reactive protein levels[57]. The "creeping fat" associated with Crohn's disease

has received increasing attention as an intrinsic component of the inflammatory dysregulation that predisposes to transmural inflammation, rather than an epiphenomenon coincidental to this process. For instance, TNF-α gene expression can be demonstrated in the mesenteric fat of patients with active Crohn's disease, whereas this expression is not demonstrated in healthy controls[58]. Pre-adipocytes isolated from mesenteric fat from individuals with IBD also express IL-17 upon binding of substance P to the neurokinin-1 receptor, as compared to healthy controls[59]. Mesenteric adipose tissue is also a source of circulating C-reactive protein in patients with Crohn's disease[60,61]. Furthermore, when compared to healthy controls, relative to overall body size, individuals with Crohn's disease may have a predilection for accumulation of intra-abdominal fat relative to subcutaneous fat, seen in association with reduced serum growth hormone levels[62]. In a small randomized clinical trial of pediatric patients with Crohn's disease on corticosteroids, supplemental growth hormone was associated with improved PCDAI scores and quality of life indices, with an apparent corticosteroid-sparing effect as well, but with no significant effect noted on rates of mucosal healing[63]. Another small trial looking at adult patients with Crohn's disease suggested clinical benefit as measured solely by the CDAI in individuals receiving supplemental growth hormone, as compared to individuals receiving customary care[64]. To date, no studies have addressed the question as to whether changes in mesenteric fat distribution over time- or with targeted interventions designed to reduce mesenteric fat accumulation-lead to improved clinical outcomes in patients with IBD.

OBESITY AND THE MICROBIOME

The importance of the human fecal microbiome has come to the forefront in multiple fields of medicine, with IBD being a particularly robust demonstration of the link between the intestinal bacterial (and fungal/viral) population, and human health. More recent attention has been paid to the possible links between the microbiome and human obesity. The gut bacteria are capable of salvaging undigested foods to sources of calories usable by their human hosts, and the permeability of the gut mucosa to bacterial products of metabolism has been associated with multiple chronic medical conditions. Using pairs of mono- and dizygotic twins, it has been shown that obese *vs* lean individuals vary according to the diversity of their bacterial populations, with enrichment in the obese individuals of bacterial gene products associated with metabolism of carbohydrates[65]. Another study including a large number of twins demonstrated that host genetic profiles seem to interact with the microbiome, leading to the selection of a more "obesogenic" bacteriologic profile; identification of obesity-attenuating bacterial species, and colonization of germ-free mice with

those bacteria then leads to attenuated weight gain in those same mice[66]. Individuals with reduced colonic bacterial diversity-which is a state associated with IBD in general - also seem to be predisposed to obesity[67,68]. Furthermore, specific bacteria shown to exert an anti-inflammatory effect on the gut-such as *Faecalibacterium prausnitzii*-have been shown to be lacking in obese individuals without IBD[65,69].

While the specific association between mesenteric fat distribution and IBD at the level of the microbiota remains largely undescribed, it is intriguing to postulate that many of the epidemiologic associations with IBD such as diet and exposure to antibiotics could be modulated in part through interactions on the gut microbiome. This area represents a specific deficiency in our understanding of the pathogenesis of IBD, and is a ripe area for future investigation.

OBESITY AND IBD PHARMACOLOGY

Despite the increasing prevalence of obesity in IBD, and the seemingly logical differences in pharmacokinetics that may be expected in obese *vs* non-obese individuals, the influence of obesity on drug absorption, distribution, metabolism and excretion remain poorly understood, and discussion of the pharmacokinetic effects of obesity is beyond the scope of this review.

If there are inter-individual differences in drug effect that are impacted by obesity, pharmacodynamic differences likely account for the majority of these, perhaps by virtue of some of the pathophysiologic changes seen at the level of pro- and anti-inflammatory pathways described earlier that would interact with IBD-specific drugs. In fact, when considered by class, there are multiple studies that suggest that obesity does influence the efficacy of specific drugs commonly used to treat IBD. The following paragraphs will review this data by drug class.

A retrospective study of individuals with UC and CD showed a differential response to azathioprine administration and discontinuation according to BMI: individuals with UC whose BMI was > 25 kg/m^2 at initiation had a higher likelihood of exacerbation (as defined by initiation or increase in corticosteroid dosage over time) compared to individuals whose BMI was in the normal range. Among patients with CD in this study, after discontinuation of azathioprine, individuals whose BMI was > 25 kg/m^2 had a lower rate of subsequent flare than their counterparts whose BMI was in the normal range[70]. A more recently published retrospective study demonstrated that obese individuals had mean 6-thioguanine (6-TG) levels that were significantly lower than their non-obese counterparts, when adjusted for the total dose of azathiopurine or mercaptopurine they were receiving relative to total body weight. The rate of sub-therapeutic 6-TGN levels (as defined according to standard parameters) in individuals whose BMI

was > 25 kg/m^2 or > 30 kg/m^2 was nearly two-fold higher than normal BMI individuals, with only about 30%-40% having levels in the therapeutic or supra-therapeutic range[71].

To date, there have been no studies addressing whether or not obesity influences the efficacy of methotrexate in treating IBD or in other similar autoimmune conditions, but there have been multiple studies that have shown that obesity and obesity-related comorbidities increase the likelihood of developing derangement in hepatic transaminases on chronic low dose methotrexate therapy in individuals with rheumatoid arthritis, sometimes requiring discontinuation of the medication[72,73]. Co-morbid diabetes has been associated with accelerated histologic fibrosis in individuals with psoriasis treated with long-term low dose methotrexate[74,75].

The effects of obesity on the response to anti-TNF therapy have also been investigated, with several studies in both the IBD and non-IBD populations that use these medications suggesting a possible interaction, although this has not been universally demonstrated. Among the subcutaneously-dosed anti-TNF agents, retrospective data have suggested that, along with prior non-response to infliximab and after adjustment for multiple co-variates, BMI is a negative predictor of response to adalimumab at initiation[76]. This has been confirmed by another retrospective analysis, showing a roughly two-fold increase in loss of response to adalimumab among individuals whose BMI is > 30 kg/m^2 compared to normal weight individuals[77]. In a post-hoc analysis of CLASSIC-II data, individuals whose BMI was less than 29 kg/m^2 were found to have higher rates of remission at week 56 than individuals whose BMI was greater than that[78]. BMI has also been demonstrated to be a negative predictor (albeit not a particularly strong one) of adalimumab trough levels at 28 wk into therapy for individuals with Crohn's disease[79]. Improved response to adalimumab in patients with psoriasis has also been demonstrated when stratified by BMI, with a roughly 20% decrease in partial response rates seen among individuals whose BMI > 30 kg/m^2 compared to their non-obese counterparts[80]. There are limited data to suggest an interaction between BMI and the other available subcutaneous anti-TNF therapies for IBD: in the PURSUIT-M trial, the relative effect of golimumab in maintaining response/remission did not appear to differ by body weight (BMI was not reported per-patient), and no interaction between BMI and maintenance response or remission rates were reported for certolizumab in the PRECISE-2 trial[81,82]. A trial of weight-based intravenous golimumab induction dosing was halted for lack of efficacy: at all weight-based doses selected, mean trough golimumab concentrations were lower than corresponding subcutaneous dosing regimens, however, limiting any inferences that could be made about a weight-based approach to dosing of this particular agent[83].

The relationship between BMI and infliximab - to date the only anti-TNF agent whose dosing is adjusted based upon total body weight - has been evaluated among both IBD and non-IBD populations. From a pharmacokinetic standpoint, infliximab primarily distributes in the vascular space, and concordant with this observation, the apparent volume of distribution of infliximab in patients with ulcerative colitis (per data from the ACT 1 and 2 trials) does increase in proportion to body weight (not BMI, as height data was not reported for those studies). This observation could explain the need for increased absolute doses given to individuals of higher body weight to maintain therapeutic drug concentrations[84]. In one of the aforementioned studies showing an attenuation of response to adalimumab over time in obese individuals, no such effect was seen with infliximab according to BMI strata[74]. Contrary to that finding, we published a retrospective analysis of individuals naïve to infliximab therapy that demonstrated a nearly three-fold increase in loss of response to infliximab - as primarily reflected by a need for dose escalation-among obese patients with Crohn's disease compared to their non-obese counterparts, after adjustment for co-variates such as smoking and corticosteroid usage at initiation of biologic therapy. A similar relationship was suggested for patients with UC, but due to small sample numbers, the effect size magnitude was likely over-stated, and the observation did not meet statistical significance. Moreover, changes in absolute weight/BMI over time (either increases or decreases) also correlated with loss of response to IFX over time in this same analysis[85]. Infliximab trough levels were not available for the majority of individuals in this study; interestingly, a more recently published study demonstrated that BMI was not associated with lower trough levels of infliximab or adalimumab (although there was a trend toward lower trough adalimumab levels in obese patients), suggesting any differential response among obese patients on anti-TNF therapy would be a pharmacodynamic, as opposed to pharmacokinetic, interaction[86]. Impaired responses to infliximab among obese patients have also been demonstrated in individuals with rheumatoid arthritis, psoriasis and with inflammatory spondyloarthropathy[87-89]. Furthermore, obese patients with rheumatoid arthritis may respond less well to a second-line anti-TNF agent than their non-obese counterparts; no such comparable data yet exist for IBD patients[90].

In individuals with psoriasis, rheumatoid arthritis and inflammatory spondyloarthropathy, weight gain is fairly consistently observed after initiation of anti-TNF therapy, driven primarily by gains in fat mass as opposed to lean body mass when this has been analyzed[91-94]. This should not be surprising, given that TNF-α is a potent anorexigen with multiple central- and peripheral effects on weight management and caloric intake/expenditure[95]. In one small open label study of infliximab in Japanese patients with Crohn's disease -

all of whom were normal or underweight at enrollment according to standard BMI criteria - a mean BMI increase of about 1 kg/m^2 was seen over the course of treatment, and the magnitude of the increase in BMI was directly correlated with the likelihood of clinical response and remission[96]. Among children with IBD, early use of anti-TNF therapy has been shown to lead to more significant catch-up growth than the use of other classes of therapy[97]. While gains in weight among under- or normal-weight individuals would be a desirable outcome in individuals with IBD, we have no information about the effect of anti-TNF therapy among already overweight or obese IBD patients.

No data are available about the effects of obesity on the efficacy of anti-integrin therapies in IBD. The major IBD clinical trials of natalizumab and vedolizumab did not stratify response rates according to body weight[98-100]. In patients with multiple sclerosis, natalizumab levels have been demonstrated to be lower in individuals of larger body weight[101]. In the vedolizumab trials for both UC and CD, there was a definite dose-response relationship observed with vedolizumab trough levels and likelihood of response and remission in the induction phase; a similar dose-response relationship was not demonstrated in the maintenance phases. Further research is necessary to determine whether individuals with sub-optimal early response to anti-integrin therapy-perhaps driven in part by sub-optimal drug levels as a function of differences in body size and composition-would benefit from a weight-based induction dosing schedule.

Finally, special mention should be made concerning the glucocorticoids (GCs) and obesity. Although the pharmacologic use of glucocorticoids is often blamed for unintended weight gain, the true obesogenic effect of glucocorticoid therapy is difficult to determine, due to substantial heterogeneity in the studies that have objectively assessed this question. The studies vary in terms of the indication for GC therapy, the duration and dose of therapy, and the definition of obesity (*e.g.,* changes in body weight or anthropometric changes) as an outcome measure. Looking at multiple short- and long-term (defined generally as < 8 wk *vs* > 8 wk of continuous use) studies, variable effects of GC use on caloric intake, energy expenditure, changes in body weight and changes in fat- and fat-free mass have been demonstrated[102]. Subjectively, weight gain is reported in about 70% of individuals on chronic GC therapy, and is the most frequent self-reported complication of chronic GC therapy among patients[103]. To the extent that they exist, the short term metabolic effects of GCs may be mitigated by the use of GCs with high first pass metabolism: over 8 wk of use, the mean weight gain among patients on once daily budesonide at a dose of 9 mg was 1 kg compared to 2 kg mean weight gain among individuals on 40 mg prednisolone. The rate of developing abnormal fat distribution as reflected by a Cushingoid facial appearance was also about three-fold higher among prednisolone-treated

patients compared to patients treated with ileal-release budesonide[104]. Whether obesity alters the efficacy or risks of GC therapy remains largely unknown; furthermore, whether accumulation of intra-abdominal fat in IBD patients on chronic GC therapy would lead to worsened long-term outcomes is also unknown, but would be an intriguing question to investigate.

OBESITY AND IBD-RELATED SURGERY

Multiple retrospective studies have demonstrated a higher rate of post-operative morbidity in obese patients undergoing abdominal and non-abdominal operations, particularly driven by a higher rate of post-operative infectious complications. Post-operative mortality, however, does not appear to be significantly affected by obesity after adjustment for co-morbid diseases[105]. Obesity has also been shown to be a risk factor for conversion from laparoscopic to open surgery in patients undergoing colorectal surgery in general[106].

Specific to the IBD population, multiple lines of evidence suggest that obesity may negatively influence surgical outcomes, specifically when obesity is defined according to volumetric analysis of fat distribution, rather than solely BMI. When looking solely at BMI categories to define obesity, a large retrospective surgical registry demonstrated a 10% higher rate of post-operative morbidity among obese Crohn's patients, driven by a nearly two-fold higher rate of post-operative infection (nearly seven-fold higher in individuals whose BMI was greater than 40 kg/m^2)[107]. This same registry also demonstrated similar findings for obese individuals-not specific to the IBD population-undergoing laparoscopic colectomy[108]. Two smaller single-center retrospective series did not demonstrate a higher risk of peri-operative morbidity among obese Crohn's patients when stratified by BMI criteria[109,110]. Another single center study using BMI strata demonstrated longer operative times, blood loss and conversion from laparoscopic to open surgery among obese individuals with IBD, with no significant differences in overall post-operative morbidity and mortality[111].

Several more recently published retrospective studies described a higher rate of post-operative complications among obese Crohn's patients when obesity was defined by volumetric analysis, and in some cases, specifically noted that BMI stratification did not predict post-operative outcomes when morphologic assessment of fat distribution was taken into account[112-114]. Looking solely at visceral fat area as defined by cross-sectional imaging, one study has also demonstrated a higher rate of endoscopic disease recurrence in individuals with Crohn's disease with higher amounts of visceral/mesenteric fat at 6 mo post-operatively[115].

To date, although benefits have been seen in nutritional optimization of malnourished IBD patients before elective surgery[116], there are no studies addressing the role of weight loss in obese IBD patients in advance of elective non-bariatric surgery. Until such data become available, it would be premature to recommend any such approach given the nutritional stresses that occur after major abdominal surgery, and given that the most common metric to define obesity (*i.e.*, BMI) does not reliably differentiate lean body mass from fat mass, and that losses in the former would not be desirable before or after major IBD-related surgery.

MEDICAL AND SURGICAL WEIGHT LOSS AND IBD

Although multiple studies have investigated the interaction of diet with IBD at the level of relative macronutrient content (*e.g.,* high fat *vs* low fat diets), to date, no data exist regarding the effects of overall caloric intake or supervised dietary weight loss on outcomes in IBD patients[117]. Epidemiologic studies have suggested that regular physical activity may exert a protective effect on the development of IBD, although the confounding effects of decreased physical activity as a result of as-yet undiagnosed inflammatory bowel disease could confound this observation. Non-controlled studies, as well as a single randomized controlled trial, have demonstrated that physical activity generally leads to improved health-related quality of life in IBD patients, with no significant changes noted in markers of inflammation in the few studies that specifically report those measures pre- and post-intervention[118,119]. To date, no prospective or retrospective data are available to address the question of whether or not targeted medical weight loss in obese patients with IBD affects clinical outcomes or response to therapy. In patients with chronic plaque psoriasis-a condition in which an association with obesity is consistently demonstrated-multiple randomized controlled trials have shown a beneficial effect of medical weight loss in obese individuals. This effect has been specifically demonstrated among individuals on cyclosporine and biologic (*e.g.,* anti-TNF and anti-IL 12/23) therapy[120-123].

For patients with morbid obesity (*e.g.,* BMI > 40 kg/m^2), particularly in those who have significant co-morbidities such as diabetes, bariatric surgery has been shown to lead to reductions in all-cause mortality, and is more effective than routine medical care in the treatment of obesity-related complications such as diabetes[124-126]. There is a marked paucity of data in the literature about the safety or efficacy of bariatric surgery among patients with IBD patients. Due to concerns about the potential for increased complications among patients with Crohn's disease undergoing any elective form of bowel surgery, IBD has been considered a relative contraindication to bariatric surgery. However, small case series-each containing fewer than 10 patients - have been

published suggesting that weight loss surgery in carefully selected patients with IBD is technically feasible and theoretically safe[127-130]. In these limited series, the weight loss achieved post-surgery was comparable to what would be expected for non-IBD patients undergoing these operations, and in some cases, improvements were also noted in the underlying inflammatory bowel disease post-operatively. Case reports have described *de novo* IBD diagnosed after bariatric surgery, but the significance of this remains unclear given the extremely small number of such cases reported[131-134].

CONCLUSION

The prevalence of both obesity and IBD are increasing worldwide, and several lines of evidence suggest that these conditions may be linked through shared environmental risk factors, and mediated through alterations in the intestinal microbiome. Adipose tissue represents a metabolically and hormonally active organ, producing adipokines that exert a pro-inflammatory effect that drives disease activity in patients with immune-mediated diseases, including IBD. Studies reporting the influence of obesity on IBD disease course and response to medical therapy have described a mixed but largely detrimental impact. Lack of a standard definition of obesity hampers interpretation of the current literature, and establishing a clinically relevant measure of adiposity is essential to advancing our understating of the interplay between obesity and IBD. Future studies are required to establish whether weight loss, either medical or surgical, is safe or effective in IBD patients and whether this may have a beneficial impact on IBD or general health outcomes. Additionally, future investigations should address the value of individualizing drug dosing in IBD patients based on BMI or other measures of adiposity, but such an approach would be premature currently.

In summary, obesity has emerged as yet another important piece in the intricate puzzle of autoimmune diseases, such as IBD. Future studies that advance our understanding of the complex interactions between IBD and obesity are required to optimize patients' health outcomes.

REFERENCES

1   **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; **311**: 806-814 [PMID: 24570244]
2   **Ng M**, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766-781 [PMID: 24880830]
3   **Dobbs R**, Sawers C, Thompson F. Overcoming obesity: An initial economic analysis. McKinsey Global Institute, 2014
4   **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864]
5   **Calkins BM**. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989; **34**: 1841-1854 [PMID: 2598752]
6   **Baron S**, Turck D, Leplat C, Merle V, Gower-Rousseau C, Marti R, Yzet T, Lerebours E, Dupas JL, Debeugny S, Salomez JL, Cortot A, Colombel JF. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut* 2005; **54**: 357-363 [PMID: 15710983]
7   **Joossens M**, Huys G, Cnockaert M, De Preter V, Verbeke K, Rutgeerts P, Vandamme P, Vermeire S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. *Gut* 2011; **60**: 631-637 [PMID: 21209126]
8   **Shaw SY**, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 2687-2692 [PMID: 20940708]
9   **Tjonneland A**, Overvad K, Bergmann MM, Nagel G, Linseisen J, Hallmans G, Palmqvist R, Sjodin H, Hagglund G, Berglund G, Lindgren S, Grip O, Palli D, Day NE, Khaw KT, Bingham S, Riboli E, Kennedy H, Hart A. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. *Gut* 2009; **58**: 1606-1611 [PMID: 19628674]
10 **Ananthakrishnan AN**, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Korzenik JR, Fuchs CS, Willett WC, Richter JM, Chan AT. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology* 2013; **145**: 970-977 [PMID: 23912083]
11 **Jantchou P**, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. *Am J Gastroenterol* 2010; **105**: 2195-2201 [PMID: 20461067]
12 **Long MD**, Crandall WV, Leibowitz IH, Duffy L, del Rosario F, Kim SC, Integlia MJ, Berman J, Grunow J, Colletti RB, Schoen BT, Patel AS, Baron H, Israel E, Russell G, Ali S, Herfarth HH, Martin C, Kappelman MD. Prevalence and epidemiology of overweight and obesity in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 2162-2168 [PMID: 21910178]
13 **Steed H**, Walsh S, Reynolds N. A brief report of the epidemiology of obesity in the inflammatory bowel disease population of Tayside, Scotland. *Obes Facts* 2009; **2**: 370-372 [PMID: 20090388]

14   **Flores A**, Burstein E, Cipher DJ, Feagins LA. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. *Dig Dis Sci* 2015; **60**: 2436-2445 [PMID: 25799938]

15   **Hass DJ**, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 482-488 [PMID: 16616354]

16   **Moran GW**, Dubeau MF, Kaplan GG, Panaccione R, Ghosh S. The increasing weight of Crohn's disease subjects in clinical trials: a hypothesis-generatings time-trend analysis. *Inflamm Bowel Dis* 2013; **19**: 2949-2956 [PMID: 23945182]

17   **Chan SS**, Luben R, Olsen A, Tjonneland A, Kaaks R, Teucher B, Lindgren S, Grip O, Key T, Crowe FL, Bergmann MM, Boeing H, Hallmans G, Karling P, Overvad K, Palli D, Masala G, Kennedy H, vanSchaik F, Bueno-de-Mesquita B, Oldenburg B, Khaw KT, Riboli E, Hart AR. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). *Am J Gastroenterol* 2013; **108**: 575-582 [PMID: 23318483]

18   **Mendall MA**, Gunasekera AV, John BJ, Kumar D. Is obesity a risk factor for Crohn's disease? *Dig Dis Sci* 2011; **56**: 837-844 [PMID: 21221790]

19   **Khalili H**, Ananthakrishnan AN, Konijeti GG, Higuchi LM, Fuchs CS, Richter JM, Chan AT. Measures of obesity and risk of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2015; **21**: 361-368 [PMID: 25563694]

20   **Harpsøe MC**, Basit S, Andersson M, Nielsen NM, Frisch M, Wohlfahrt J, Nohr EA, Linneberg A, Jess T. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. *Int J Epidemiol* 2014; **43**: 843-855 [PMID: 24609069]

21   **Lu B**, Hiraki LT, Sparks JA, Malspeis S, Chen CY, Awosogba JA, Arkema EV, Costenbader KH, Karlson EW. Being overweight or obese and risk of developing rheumatoid arthritis among women: a prospective cohort study. *Ann Rheum Dis* 2014; **73**: 1914-1922 [PMID: 25057178]

22   **Mahé E**, Beauchet A, Bodemer C, Phan A, Bursztejn AC, Boralevi F, Souillet AL, Chiaverini C, Bourrat E, Miquel J, Vabres P, Barbarot S, Bessis D, Eschard C, Hadj-Rabia S. Psoriasis and obesity in French children: a case-control, multicentre study. *Br J Dermatol* 2015; **172**: 1593-1600 [PMID: 25363889]

23   **Blain A**, Cattan S, Beaugerie L, Carbonnel F, Gendre JP, Cosnes J. Crohn's disease clinical course and severity in obese patients. *Clin Nutr* 2002; **21**: 51-57 [PMID: 11884013]

24   **Seminerio JL**, Koutroubakis IE, Ramos-Rivers C, Hashash JG, Dudekula A, Regueiro M, Baidoo L, Barrie A, Swoger J, Schwartz M, Weyant K, Dunn MA, Binion DG. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015; **21**: 2857-2863 [PMID: 26241001]

25   **Pringle PL**, Stewart KO, Peloquin JM, Sturgeon HC, Nguyen D, Sauk J, Garber JJ, Yajnik V, Ananthakrishnan AN, Chan AT, Xavier RJ, Khalili H. Body Mass Index, Genetic Susceptibility, and Risk of Complications Among Individuals with Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2304-2310 [PMID: 26181430]

26   **Stabroth-Akil D**, Leifeld L, Pfützer R, Morgenstern J, Kruis W. The effect of body weight on the severity and clinical course of ulcerative colitis. *Int J Colorectal Dis* 2015; **30**: 237-242 [PMID: 25392256]

27   **Nic Suibhne T**, Raftery TC, McMahon O, Walsh C, O'Morain C, O'Sullivan M. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. *J Crohns Colitis* 2013; **7**: e241-e248 [PMID: 23040290]

28   **Dregan A**, Charlton J, Chowienczyk P, Gulliford MC. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. *Circulation* 2014; **130**: 837-844 [PMID: 24970784]

29   **Ananthakrishnan AN**, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Diabetes and the risk of infections with immunomodulator therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2015; **41**: 1141-1148 [PMID: 25864945]

30   **Fitzmorris PS**, Colantonio LD, Torrazza Perez E, Smith I, Kakati DD, Malik TA. Impact of metabolic syndrome on the hospitalization rate of Crohn's disease patients seen at a tertiary care center: a retrospective cohort study. *Digestion* 2015; **91**: 257-262 [PMID: 25833139]

31   **Harper JW**, Welch MP, Sinanan MN, Wahbeh GT, Lee SD. Co-morbid diabetes in patients with Crohn's disease predicts a greater need for surgical intervention. *Aliment Pharmacol Ther* 2012; **35**: 126-132 [PMID: 22074268]

32   **Erhayiem B**, Dhingsa R, Hawkey CJ, Subramanian V. Ratio of visceral to subcutaneous fat area is a biomarker of complicated Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 684-687.e1 [PMID: 21642015]

33   **Yuhara H**, Steinmaus C, Corley D, Koike J, Igarashi M, Suzuki T, Mine T. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**: 953-962 [PMID: 23550660]

34   **Gizard E**, Ford AC, Bronowicki JP, Peyrin-Biroulet L. Systematic review: The epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2014; **40**: 3-15 [PMID: 24815622]

35   **Singh S**, Singh H, Loftus EV, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 382-93.e1: quiz e22 [PMID: 23978350]

36   **Tandon K**, Imam M, Ismail BE, Castro F. Body mass index and colon cancer screening: the road ahead. *World J Gastroenterol* 2015; **21**: 1371-1376 [PMID: 25663756 DOI: 10.3748/wjg.v21.i5.1371]

37   **Lee CG**, Lee JK, Kang YS, Shin S, Kim JH, Lim YJ, Koh MS, Lee JH, Kang HW. Visceral abdominal obesity is associated with an increased risk of irritable bowel syndrome. *Am J Gastroenterol* 2015; **110**: 310-319 [PMID: 25583325]

38   **Flegal KM**, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007; **298**: 2028-2037 [PMID: 17986696]

39   **Flegal KM**, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013; **309**: 71-82 [PMID: 23280227]

40   **Petursson H**, Sigurdsson JA, Bengtsson C, Nilsen TI, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS One* 2011; **6**: e26621 [PMID: 22028926]

41   **Yusuf S**, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005; **366**: 1640-1649 [PMID: 16271645]

42   **Zhang C**, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation* 2008; **117**: 1658-1667 [PMID: 18362231]

43   **Shapiro L**, Scherer PE. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Biol* 1998; **8**: 335-338 [PMID: 9512423]

44   **Ouchi N**, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 2000; **102**: 1296-1301 [PMID: 10982546]

45   **Yamamoto K**, Kiyohara T, Murayama Y, Kihara S, Okamoto Y, Funahashi T, Ito T, Nezu R, Tsutsui S, Miyagawa JI, Tamura S, Matsuzawa Y, Shimomura I, Shinomura Y. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. *Gut* 2005; **54**: 789-796 [PMID: 15888786]

46   **Karmiris K**, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalis EA. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. *Inflamm Bowel Dis* 2006; **12**: 100-105 [PMID: 16432373]

47   **Valentini L**, Wirth EK, Schweizer U, Hengstermann S, Schaper L, Koernicke T, Dietz E, Norman K, Buning C, Winklhofer-Roob BM, Lochs H, Ockenga J. Circulating adipokines and the protective effects of hyperinsulinemia in inflammatory bowel disease. *Nutrition* 2009; **25**: 172-181 [PMID: 18849144]

48   **Karmiris K**, Koutroubakis IE, Xidakis C, Polychronaki M, Kouroumalis EA. The effect of infliximab on circulating levels of leptin, adiponectin and resistin in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2007; **19**: 789-794 [PMID: 17700265]

49   **Auwerx J**, Staels B. Leptin. *Lancet* 1998; **351**: 737-742 [PMID: 9504534]

50   **Grunfeld C**, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, Feingold KR. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *J Clin Invest* 1996; **97**: 2152-2157 [PMID: 8621806]

51   **Zumbach MS**, Boehme MW, Wahl P, Stremmel W, Ziegler R, Nawroth PP. Tumor necrosis factor increases serum leptin levels in humans. *J Clin Endocrinol Metab* 1997; **82**: 4080-4082 [PMID: 9398717]

52   **Aurangzeb B**, Leach ST, Lemberg DA, Day AS. Assessment of nutritional status and serum leptin in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2011; **52**: 536-541 [PMID: 21407117]

53   **Kaser S**, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. *Biochem Biophys Res Commun* 2003; **309**: 286-290 [PMID: 12951047]

54   **Silswal N**, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochem Biophys Res Commun* 2005; **334**: 1092-1101 [PMID: 16039994]

55   **Konrad A**, Lehrke M, Schachinger V, Seibold F, Stark R, Ochsenkühn T, Parhofer KG, Göke B, Broedl UC. Resistin is an inflammatory marker of inflammatory bowel disease in humans. *Eur J Gastroenterol Hepatol* 2007; **19**: 1070-1074 [PMID: 17998831]

56   **Waluga M**, Hartleb M, Boryczka G, Kukla M, Zwirska-Korczala K. Serum adipokines in inflammatory bowel disease. *World J Gastroenterol* 2014; **20**: 6912-6917 [PMID: 24944482 DOI: 10.3748/wjg.v20.i22.6912]

57   **Park HS**, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract* 2005; **69**: 29-35 [PMID: 15955385]

58   **Desreumaux P**, Ernst O, Geboes K, Gambiez L, Berrebi D, Müller-Alouf H, Hafraoui S, Emilie D, Ectors N, Peuchmaur M, Cortot A, Capron M, Auwerx J, Colombel JF. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. *Gastroenterology* 1999; **117**: 73-81 [PMID: 10381912]

59   **Sideri A**, Bakirtzi K, Shih DQ, Koon HW, Fleshner P, Arsenescu R, Arsenescu V, Turner JR, Karagiannides I, Pothoulakis C. Substance P mediates pro-inflammatory cytokine release form mesenteric adipocytes in Inflammatory Bowel Disease patients. *Cell Mol Gastroenterol Hepatol* 2015; **1**: 420-432 [PMID: 26543894]

60   **Peyrin-Biroulet L**, Gonzalez F, Dubuquoy L, Rousseaux C, Dubuquoy C, Decourcelle C, Saudemont A, Tachon M, Béclin E, Odou MF, Neut C, Colombel JF, Desreumaux P. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. *Gut* 2012; **61**: 78-85 [PMID: 21940721]

61   **Vermeire S**, Van Assche G, Rutgeerts P. The role of C-reactive protein as an inflammatory marker in gastrointestinal diseases. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 580-586 [PMID: 16327837]

62   **Katznelson L**, Fairfield WP, Zeizafoun N, Sands BE, Peppercorn MA, Rosenthal DI, Klibanski A. Effects of growth hormone secretion on body composition in patients with Crohn's disease. *J Clin Endocrinol Metab* 2003; **88**: 5468-5472 [PMID: 14602791]

63   **Denson LA**, Kim MO, Bezold R, Carey R, Osuntokun B, Nylund C, Willson T, Bonkowski E, Li D, Ballard E, Collins M, Moyer MS, Klein DJ. A randomized controlled trial of growth hormone in active pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2010; **51**: 130-139 [PMID: 20453679]

64   **Slonim AE**, Bulone L, Damore MB, Goldberg T, Wingertzahn MA, McKinley MJ. A preliminary study of growth hormone therapy for Crohn's disease. *N Engl J Med* 2000; **342**: 1633-1637 [PMID: 10833209]

65   **Turnbaugh PJ**, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480-484 [PMID: 19043404]

66   **Goodrich JK**, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, Spector TD, Clark AG, Ley RE. Human genetics shape the gut microbiome. *Cell* 2014; **159**: 789-799 [PMID: 25417156]

67   **Dubinsky M**, Braun J. Diagnostic and Prognostic Microbial Biomarkers in Inflammatory Bowel Diseases. *Gastroenterology* 2015; **149**: 1265-1274.e3 [PMID: 26284597]

68   **Le Chatelier E**, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, Bork P, Wang J, Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013; **500**: 541-546 [PMID: 23985870]

69   **Quévrain E**, Maubert MA, Michon C, Chain F, Marquant R, Tailhades J, Miquel S, Carlier L, Bermúdez-Humarán LG, Pigneur B, Lequin O, Kharrat P, Thomas G, Rainteau D, Aubry C, Breyner N, Afonso C, Lavielle S, Grill JP, Chassaing G, Chatel JM, Trugnan G, Xavier R, Langella P, Sokol H, Seksik P. Identification of an anti-inflammatory protein from Faecalibacterium prausnitzii, a commensal bacterium deficient in Crohn's disease. *Gut* 2016; **65**: 415-425 [PMID: 26045134]

70   **Holtmann MH**, Krummenauer F, Claas C, Kremeyer K, Lorenz D, Rainer O, Vogel I, Böcker U, Böhm S, Büning C, Duchmann R, Gerken G, Herfarth H, Lügering N, Kruis W, Reinshagen M, Schmidt J, Stallmach A, Stein J, Sturm A, Galle PR, Hommes DW, D'Haens G, Rutgeerts P, Neurath MF. Significant differences between Crohn's disease and ulcerative colitis regarding the impact of body mass index and initial disease activity on responsiveness to azathioprine: results from a European multicenter study in 1,176 patients. *Dig Dis Sci* 2010; **55**: 1066-1078 [PMID: 19513841]

71   **Poon SS**, Asher R, Jackson R, Kneebone A, Collins P, Probert C, Dibb M, Subramanian S. Body Mass Index and Smoking Affect Thioguanine Nucleotide Levels in Inflammatory Bowel Disease. *J Crohns Colitis* 2015; **9**: 640-646 [PMID: 25968584]

72   **Schmajuk G**, Miao Y, Yazdany J, Boscardin WJ, Daikh DI, Steinman MA. Identification of risk factors for elevated transaminases in methotrexate users through an electronic health record. *Arthritis Care Res* (Hoboken) 2014; **66**: 1159-1166 [PMID: 24470205]

73 **Kent PD**, Luthra HS, Michet C. Risk factors for methotrexate-induced abnormal laboratory monitoring results in patients with rheumatoid arthritis. *J Rheumatol* 2004; **31**: 1727-1731 [PMID: 15338491]

74 **Langman G**, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. *J Gastroenterol Hepatol* 2001; **16**: 1395-1401 [PMID: 11851839]

75 **Malatjalian DA**, Ross JB, Williams CN, Colwell SJ, Eastwood BJ. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. *Can J Gastroenterol* 1996; **10**: 369-375 [PMID: 9193771]

76 **Bultman E**, de Haar C, van Liere-Baron A, Verhoog H, West RL, Kuipers EJ, Zelinkova Z, van der Woude CJ. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Aliment Pharmacol Ther* 2012; **35**: 335-341 [PMID: 22191671]

77 **Bhalme M**, Sharma A, Keld R, Willert R, Campbell S. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur J Gastroenterol Hepatol* 2013; **25**: 543-549 [PMID: 23337170]

78 **Chiu YL**, Rubin DT, Vermeire S, Louis E, Robinson AM, Lomax KG, Pollack PF, Paulson SK. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 1112-1122 [PMID: 23584130]

79 **Lie MR**, Peppelenbosch MP, West RL, Zelinkova Z, van der Woude CJ. Adalimumab in Crohn's disease patients: pharmacokinetics in the first 6 months of treatment. *Aliment Pharmacol Ther* 2014; **40**: 1202-1208 [PMID: 25263077 DOI: 10.1111/apt.12969]

80 **Cassano N**, Galluccio A, De Simone C, Loconsole F, Massimino SD, Plumari A, Dattola S, Puglisi Guerra A, Donato L, Cantoresi F, De Pita O, Fenizi G, Altamura V, Congedo M, Pellicano R, Vena GA. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. *J Biol Regul Homeost Agents* 2008; **22**: 233-237 [PMID: 19036225]

81 **Schreiber S**, Khaliq-Kareemi M, Lawrance IC, Thomsen OØ, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007; **357**: 239-250 [PMID: 17634459]

82 **Sandborn WJ**, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Colombel JF, Reinisch W, Gibson PR, Collins J, Järnerot G, Rutgeerts P. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014; **146**: 96-109.e1 [PMID: 23770005]

83 **Rutgeerts P**, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Zhang H, Colombel JF, Reinisch W, Gibson PR, Sandborn WJ. Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. *Aliment Pharmacol Ther* 2015; **42**: 504-514 [PMID: 26119226]

84 **Fasanmade AA**, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, Davis HM, Zhou H. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol* 2009; **65**: 1211-1228 [PMID: 19756557]

85 **Harper JW**, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 2118-2124 [PMID: 23863401]

86 **Bond A**, Asher R, Jackson R, Sager K, Martin K, Kneebone A, Philips S, Taylor W, Subramanian S. Comparative analysis of the influence of clinical factors including BMI on adalimumab and infliximab trough levels. *Eur J Gastroenterol Hepatol* 2016; **28**: 271-276 [PMID: 26657455]

87 **Ottaviani S**, Gardette A, Tubach F, Roy C, Palazzo E, Gill G, Meyer O, Dieudé P. Body mass index and response to infliximab in rheumatoid arthritis. *Clin Exp Rheumatol* 2015; **33**: 478-483 [PMID: 25962513]

88 **Spertino J**, Lopez-Ferrer A, Vilarrasa E, Puig L. Long-term study of infliximab for psoriasis in daily practice: drug survival depends on combined treatment, obesity and infusion reactions. *J Eur Acad Dermatol Venereol* 2014; **28**: 1514-1521 [PMID: 25493314]

89 **Gremese E**, Bernardi S, Bonazza S, Nowik M, Peluso G, Massara A, Tolusso B, Messuti L, Miceli MC, Zoli A, Trotta F, Govoni M, Ferraccioli G. Body weight, gender and response to TNF-α blockers in axial spondyloarthritis. *Rheumatology* (Oxford) 2014; **53**: 875-881 [PMID: 24407233]

90 **Iannone F**, Fanizzi R, Notarnicola A, Scioscia C, Anelli MG, Lapadula G. Obesity reduces the drug survival of second line biological drugs following a first TNF-α inhibitor in rheumatoid arthritis patients. *Joint Bone Spine* 2015; **82**: 187-191 [PMID: 25619156]

91 **Briot K**, Gossec L, Kolta S, Dougados M, Roux C. Prospective assessment of body weight, body composition, and bone density changes in patients with spondyloarthropathy receiving anti-tumor necrosis factor-alpha treatment. *J Rheumatol* 2008; **35**: 855-861 [PMID: 18381782]

92 **Brown RA**, Spina D, Butt S, Summers GD. Long-term effects of anti-tumour necrosis factor therapy on weight in patients with rheumatoid arthritis. *Clin Rheumatol* 2012; **31**: 455-461 [PMID: 22009196]

93 **Hmamouchi I**, Roux C, Paternotte S, Kolta S, Dougados M, Briot K. Early increase of abdominal adiposity in patients with spondyloarthritis receiving anti-tumor necrosis factor-α treatment. *J Rheumatol* 2014; **41**: 1112-1117 [PMID: 24737911]

94 **Mahé E**, Reguiai Z, Barthelemy H, Quiles-Tsimaratos N, Chaby G, Girard C, Estève E, Maccari F, Descamps V, Schmutz JL, Begon E, Bravard P, Maillard H, Boyé T, Beauchet A, Sigal ML. Evaluation of risk factors for body weight increment in psoriatic patients on infliximab: a multicentre, cross-sectional study. *J Eur Acad Dermatol Venereol* 2014; **28**: 151-159 [PMID: 23279264]

95 **Amaral ME**, Barbuio R, Milanski M, Romanatto T, Barbosa HC, Nadruz W, Bertolo MB, Boschero AC, Saad MJ, Franchini KG, Velloso LA. Tumor necrosis factor-alpha activates signal transduction in hypothalamus and modulates the expression of pro-inflammatory proteins and orexigenic/anorexigenic neurotransmitters. *J Neurochem* 2006; **98**: 203-212 [PMID: 16638016]

96 **Nakahigashi M**, Yamamoto T. Increases in body mass index during infliximab therapy in patients with Crohn's disease: an open label prospective study. *Cytokine* 2011; **56**: 531-535 [PMID: 21820319]

97 **Walters TD**, Kim MO, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, Baldassano R, Crandall W, Rosh J, Pfefferkorn M, Otley A, Heyman MB, LeLeiko N, Baker S, Guthery SL, Evans J, Ziring D, Kellermayer R, Stephens M, Mack D, Oliva-Hemker M, Patel AS, Kirschner B, Moulton D, Cohen S, Kim S, Liu C, Essers J, Kugathasan S, Hyams JS. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. *Gastroenterology* 2014; **146**: 383-391 [PMID: 24162032]

98 **Ghosh S**, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, Vyhnálek P, Zádorová Z, Palmer T, Donoghue S. Natalizumab for active Crohn's disease. *N Engl J Med* 2003; **348**: 24-32 [PMID: 12510039]

99 **Sandborn WJ**, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369**: 711-721 [PMID: 23964933]

100 **Feagan BG**, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A, GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for

ulcerative colitis. *N Engl J Med* 2013; **369**: 699-710 [PMID: 23964932 DOI: 10.1056/NEJMoa1215734]

101 **Foley J**, Metzger R, Hoyt T. The effect of dosing interval extension and patient weight on long term natalizumab pharmacokinetics. *Neurology* 2015; **84** Suppl 3: 258

102 **Berthon BS**, MacDonald-Wicks LK, Wood LG. A systematic review of the effect of oral glucocorticoids on energy intake, appetite, and body weight in humans. *Nutr Res* 2014; **34**: 179-190 [PMID: 24655484]

103 **Curtis JR**, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, Kovac SH, Spettell CM, Saag KG. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; **55**: 420-426 [PMID: 16739208]

104 **Campieri M**, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997; **41**: 209-214 [PMID: 9301500]

105 **Doyle SL**, Lysaght J, Reynolds JV. Obesity and post-operative complications in patients undergoing non-bariatric surgery. *Obes Rev* 2010; **11**: 875-886 [PMID: 20025695]

106 **Masoomi H**, Moghadamyeghaneh Z, Mills S, Carmichael JC, Pigazzi A, Stamos MJ. Risk factors for conversion of laparoscopic colorectal surgery to open surgery: does conversion worsen outcome? *World J Surg* 2015; **39**: 1240-1247 [PMID: 25631940]

107 **Causey MW**, Johnson EK, Miller S, Martin M, Maykel J, Steele SR. The impact of obesity on outcomes following major surgery for Crohn's disease: an American College of Surgeons National Surgical Quality Improvement Program assessment. *Dis Colon Rectum* 2011; **54**: 1488-1495 [PMID: 22067176]

108 **Mustain WC**, Davenport DL, Hourigan JS, Vargas HD. Obesity and laparoscopic colectomy: outcomes from the ACS-NSQIP database. *Dis Colon Rectum* 2012; **55**: 429-435 [PMID: 22426267]

109 **Guardado J**, Carchman E, Danicic AE, Salgado J, Watson AR, Celebrezze JP, Medich DS, Holder-Murray J. Obesity Does Not Impact Perioperative or Postoperative Outcomes in Patients with Inflammatory Bowel Disease. *J Gastrointest Surg* 2016; **20**: 725-733 [PMID: 26696530]

110 **Canedo J**, Pinto RA, Regadas S, Regadas FS, Rosen L, Wexner SD. Laparoscopic surgery for inflammatory bowel disease: does weight matter? *Surg Endosc* 2010; **24**: 1274-1279 [PMID: 20044772]

111 **Krane MK**, Allaix ME, Zoccali M, Umanskiy K, Rubin MA, Villa A, Hurst RD, Fichera A. Does morbid obesity change outcomes after laparoscopic surgery for inflammatory bowel disease? Review of 626 consecutive cases. *J Am Coll Surg* 2013; **216**: 986-996 [PMID: 23523148]

112 **Connelly TM**, Juza RM, Sangster W, Sehgal R, Tappouni RF, Messaris E. Volumetric fat ratio and not body mass index is predictive of ileocolectomy outcomes in Crohn's disease patients. *Dig Surg* 2014; **31**: 219-224 [PMID: 25277149]

113 **Stidham RW**, Waljee AK, Day NM, Bergmans CL, Zahn KM, Higgins PD, Wang SC, Su GL. Body fat composition assessment using analytic morphomics predicts infectious complications after bowel resection in Crohn's disease. *Inflamm Bowel Dis* 2015; **21**: 1306-1313 [PMID: 25822011]

114 **Ding Z**, Wu XR, Remer EM, Lian L, Stocchi L, Li Y, McCullough A, Remzi FH, Shen B. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery. *Colorectal Dis* 2016; **18**: 163-172 [PMID: 26391914]

115 **Li Y**, Zhu W, Gong J, Zhang W, Gu L, Guo Z, Cao L, Shen B, Li N, Li J. Visceral fat area is associated with a high risk for early postoperative recurrence in Crohn's disease. *Colorectal Dis* 2015; **17**: 225-234 [PMID: 25307174]

116 **Spinelli A**, Allocca M, Jovani M, Danese S. Review article: optimal preparation for surgery in Crohn's disease. *Aliment Pharmacol Ther* 2014; **40**: 1009-1022 [PMID: 25209947]

117 **Lee D**, Albenberg L, Compher C, Baldassano R, Piccoli D, Lewis JD, Wu GD. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 2015; **148**: 1087-1106 [PMID: 25597840]

118 **Bilski J**, Mazur-Bialy AI, Wierdak M, Brzozowski T. The impact of physical activity and nutrition on inflammatory bowel disease: the potential role of cross talk between adipose tissue and skeletal muscle. *J Physiol Pharmacol* 2013; **64**: 143-155 [PMID: 23756389]

119 **Klare P**, Nigg J, Nold J, Haller B, Krug AB, Mair S, Thoeringer CK, Christle JW, Schmid RM, Halle M, Huber W. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. *Digestion* 2015; **91**: 239-247 [PMID: 25823689]

120 **Jensen P**, Zachariae C, Christensen R, Geiker NR, Schaadt BK, Stender S, Hansen PR, Astrup A, Skov L. Effect of weight loss on the severity of psoriasis: a randomized clinical study. *JAMA Dermatol* 2013; **149**: 795-801 [PMID: 23752669]

121 **Naldi L**, Conti A, Cazzaniga S, Patrizi A, Pazzaglia M, Lanzoni A, Veneziano L, Pellacani G. Diet and physical exercise in psoriasis: a randomized controlled trial. *Br J Dermatol* 2014; **170**: 634-642 [PMID: 24641585]

122 **Gisondi P**, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *Am J Clin Nutr* 2008; **88**: 1242-1247 [PMID: 18996858]

123 **Al-Mutairi N**, Nour T. The effect of weight reduction on treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. *Expert Opin Biol Ther* 2014; **14**: 749-756 [PMID: 24661040]

124 **Adams TD**, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; **357**: 753-761 [PMID: 17715409]

125 **Sjöström L**, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; **357**: 741-752 [PMID: 17715408]

126 **Schauer PR**, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE, Kashyap SR. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. *N Engl J Med* 2014; **370**: 2002-2013 [PMID: 24679060]

127 **Aminian A**, Andalib A, Ver MR, Corcelles R, Schauer PR, Brethauer SA. Outcomes of bariatric surgery in patients with inflammatory bowel disease. *Obes Surg* 2015; **26**: 1-5

128 **Colombo F**, Rizzi A, Ferrari C, Frontali A, Casiraghi S, Corsi F, Sampietro GM, Foschi D. Bariatric surgery in patients with inflammatory bowel disease: an accessible path? Report of a case series and review of the literature. *J Crohns Colitis* 2015; **9**: 185-190 [PMID: 25518054]

129 **Keidar A**, Hazan D, Sadot E, Kashtan H, Wasserberg N. The role of bariatric surgery in morbidly obese patients with inflammatory bowel disease. *Surg Obes Relat Dis* 2015; **11**: 132-136 [PMID: 25547057]

130 **Lascano CA**, Soto F, Carrodeguas L, Szomstein S, Rosenthal RJ, Wexner SD. Management of ulcerative colitis in the morbidly obese patient: is bariatric surgery indicated? *Obes Surg* 2006; **16**: 783-786 [PMID: 16756744]

131 **Ahn LB**, Huang CS, Forse RA, Hess DT, Andrews C, Farraye FA. Crohn's disease after gastric bypass surgery for morbid obesity: is there an association? *Inflamm Bowel Dis* 2005; **11**: 622-624 [PMID: 15905716]

132 **Janczewska I**, Nekzada Q, Kapraali M. Crohn's disease after gastric bypass surgery. *BMJ Case Rep* 2011; **2011**: bcr0720103168

133 **Papakonstantinou AS**, Stratopoulos C, Terzis I, Papadimitriou N, Spiliadi C, Katsou G, Hadjiyannakis E. Ulcerative colitis and acute stroke: two rare complications after Mason's vertical banded gastroplasty for treatment of morbid obesity. *Obes Surg* 1999; **9**: 502-505 [PMID: 10605911]

134 **Manguso F**, Picascia S, Balzano A. Ulcerative colitis exacerbating after placement of intragastric balloon for the treatment of obesity. *Inflamm Bowel Dis* 2008; **14**: 872-873 [PMID: 18240281]

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