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THE IMPACT OF PHYSICAL ACTIVITY AND NUTRITION ON INFLAMMATORY BOWEL DISEASE: THE POTENTIAL ROLE OF CROSS TALK BETWEEN ADIPOSE TISSUE AND SKELETAL MUSCLE

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Crohn's disease and ulcerative colitis are both chronic inflammatory bowel diseases (IBDs) characterized by a cyclical nature, which alternates between active and quiescent states, ultimately impairing a patients' quality of life. The etiology of IBD is not known but it likely involves a combination of genetic predisposition and environmental risk factors. Physical exercise has been suggested to provide protection against the onset of IBD, but there are inconsistencies in the findings of the published literature. Current research recommends exercise to help counteract some IBD-specific complications and preliminary studies suggest that physical activity may be beneficial in reducing the symptoms of IBD. Obesity is becoming more prevalent in patients diagnosed with IBD and may be associated with higher disease activity. There is evidence that adipokines are involved in the inflammatory and metabolic pathways. Hypertrophy of the mesenteric white adipose tissue has been long recognized as a characteristic feature of Crohn's disease; however its importance is unknown. Recent data suggest that dysregulation of adipokine secretion by white adipose tissue is involved in the pathogenesis of Crohn's disease. Skeletal muscle was shown to produce biologically active myokines, which could be a important contributor to the beneficial effects of exercise. There is mounting evidence for the bi-directional endocrine cross talk between adipose tissue and skeletal muscle. The objective of the present review is to explore the role of exercise and its impact on IBD. Also, we discuss how current discoveries regarding the importance of adipokines and myokines and their cross talk expand our view of the pathological changes and the therapeutic options for IBD.

Key words: *exercise, nutrition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, adipose tissue, adiponectin, myokines, irisin, tumor necrosis factor-like weak inducer of apoptosis*

INTRODUCTION

The term inflammatory bowel disease (IBD) covers a group of chronic, relapsing, and remitting intestinal disorders, which includes Crohn's disease (CD) and ulcerative colitis (UC), characterized by rectal bleeding, severe diarrhea, abdominal pain, fever, and weight loss. The chronic diseases have a cyclical nature that alternates between active and quiescent states, ultimately impairing a patients' quality of life. Biopsies obtained from patients with active disease revealed the presence of a large inflammatory cell infiltrate parallel to extensive mucosal and transmural injury including edema, loss of goblet cells, decreased mucous production, crypt cell hyperplasia, erosions, and ulcerations. The inflammatory process in CD is typically transmural, involving the small and/or large intestine, often resulting in the formation of fistulas and strictures, while UC affects only the colon and is limited to the mucosa and superficial submucosa. Anorexia, malnutrition, altered body composition, and development of mesenteric white adipose tissue (mWAT) hypertrophy (accumulation of intra-abdominal mWAT), are other well-known features of inflammatory bowel diseases, specifically CD (1). Although progress has been made in understanding the mechanism of IBD, its etiology is still unknown. The accepted theory suggest that a combination of environmental agents and a dysfunctional mucosal immune system in genetically susceptible individuals could lead to the development of either CD or UC (2, 3).

IBD affects several million worldwide and places a heavy burden on populations because it reduces the quality of life and capacity for work and increases disability. The role of lifestyle factors in inflammatory bowel diseases seems to be crucial. Epidemiological studies have indicated that the incidence and prevalence of IBD rapidly increased particularly in developed countries and the rise observed in the rest of the world closely correlates with adopting a Western lifestyle (4). Moreover, children of individuals immigrating from countries with low prevalence of IBD to those with a higher prevalence are at an increased risk of developing IBD (4). It is interesting that the incidence of CD appears to be increasing at a faster rate than that of UC (5). Recent epidemiological studies indicated a marked

rise across different ethnicities and a reduction in familial disease in pediatric IBD, and a decrease in monozygotic twin concordance rates from 46% to 13% compared to earlier studies. These findings confirm an important and increasing role that environmental factors play in the pathogenesis of the disease (4). In most countries, peoples' lifestyle changed substantially leading to serious modifications in dietary habits, physical inactivity and obesity (6). Those changes in lifestyle may have a bearing on the course of the disease. In this review we will inspect consecutively the role of exercise and obesity in IBD.

PHYSICAL ACTIVITY AND INFLAMMATORY BOWEL DISEASE

The potential benefits of exercise and physical activity on the gastrointestinal tract have generated some interest. Intensive exercise such as long distance running and triathlons commonly cause gastrointestinal discomfort including nausea, heartburn, diarrhea, or even gastrointestinal bleeding. Marathon runners suffer from 'runner's ischemic colitis', involving bloody diarrhea, fatigue and fever (7). However there is overwhelming evidence

Table 1. Studies assessing the impact of physical activity on onset of IBD.

Reference	Number of patients	Study description	Outcome
Sonnenberg, 1990 (30)	12 014	Retrospectively reviewed Social Security statistics of people with IBD in Germany	Occupations that involved physical activity were protective against the onset of IBD.
Persson *et al*.,1993 (31)	152 CD 145 UC 305 controls	Postal questionnaire in Sweden (Stockholm county)	The relative risk (RR) of Crohn's disease but not UC was inversely related to regular physical activity and estimated at 0.6 (95% CI: 0.4–0.9) and 0.5 (95% CI: 0.3–0.9) for weekly and daily exercise, respectively.
Boggild *et al*., 1996 (34)	2 273 872	A cohort, comprising male and female Danes aged 20-59 years on 1 January 1986 were followed up for hospitalizations due to chronic inflammatory bowel disease until 31 December 1990	Sedentary lifestyle may increase the risk of inflammatory bowel disease
Klein *et al*., 1998 (32)	55 UC 33 CD 76 population 68 clinic controls	Pre-illness life style was studied in patients in Israel with recent onset of IBD and in matched population and clinic controls	IBD patients had lower levels of physical activity during their pre-illness period than clinic patients but not population controls
Cucino *et al*., 2001 (33)	2399 CD 2419 UC	The numbers of deaths from Crohn's disease and ulcerative colitis were retrieved from the computerized 1991–1996 data files of the National Center for Health Statistics (USA) and individuals occupation was examined	IBD mortality is low in occupations associated with manual work and relatively high in sedentary occupations. CD and UC show a similar distribution
Halfvarson *et al*. 2006 (35)	Discordant twin pairs 102 CD 125 UC	Population-based Swedish-Danish twin cohort using the co-twin control method Denmark through a postal questionnaire	No significant difference found in physical activity between twins
Chan *et al*., 2013 (36)	300 724	European Prospective Investigation into Cancer and Nutrition study. The cohort was monitored, and identifying participants who developed either CD or UC.	No association was found between physical activity and onset of IBD
Hlavaty *et al*., 2013 (37)	190 CD 148 UC 355 controls	Case-control study in Slovakia (questionnaire)	CD and UC associated with less than two sporting weekly activities in (odds ratio, OR 2.7, 95% CI 1.5–5.0; $p<0.001$) and (OR 2.0, 95% CI 1.1–3.5, $p=0.02$), respectively.

that physical activity reduces the risk of colon cancer (8) but the preventive effect of physical activity on inflammatory bowel disease is less understood. It was documented that self-reported physical activity or physical performance is correlated inversely with systemic low-level inflammation, suggesting that the anti-inflammatory activity induced by regular exercise may exert some of the beneficial health effects of exercise in patients with chronic diseases (9). Most recently, the potential role of physical activity in IBD patients has raised some interest (10-13).

BENEFITS OF EXERCISE FOR INFLAMMATORY BOWEL DISEASE PATIENTS

The disease of ankylosing spondylitis (AS) has been associated with IBD. It is of interest that 0.9–8% of IBD patients developed AS and 4% to 18% of IBD have been diagnosed with asymptomatic sacroilitis (14). The effectiveness of exercise therapy has been shown to improve flexibility (especially in the spinal column), strength, and for pain reduction in the joints (15).

About half of CD patients are diagnosed with osteopenia and a further 13% progress to osteoporosis (16). In healthy individuals, exercise alone has been associated with increased bone mineral density and its role in the prevention of osteoporosis in IBD patients has been proposed (17-19). A study by Robinson *et al.* (17) suggested that physical exercise can increase bone mineral density (BMD) in CD and may reduce the risk of osteoporotic fracture.

A decrease of muscle mass, strength and endurance as well as growth retardation in children are common in IBD (1, 20, 21). It was observed that the prevalence of sarcopenia is high particularly in young CD patients and strongly related to osteopenia (22). Although no studies on osteopenia involving UC patients have been published, it is likely that these patients experience decreased muscle performance, because they suffer from similar symptoms and they would require similar treatment. Resistance exercise can prevent and even reverse the progression of sarcopenia (23). It has been demonstrated to acutely increase muscle protein synthesis and translational efficiency, acutely increase satellite cell proliferation and chronically increase the satellite cell number and subsequently increase the number of myonuclear domains per myofiber (23). Exercise can also ameliorate the severity of CD and accompanying anorexia while modifying the release of adipokines and ghrelin (24).

Fatigue is a commonly observed symptom in CD, even in quiescent state of disease and a role of cytokines in this phenomenon has been suggested (25). Patients with CD were reported to have a reduction in aerobic capacity (21). Exercise could reduce perceived fatigue in these patients as it has been shown in those with chronic fatigue syndrome (26).

Stress has both short- and long-term effects on the functions of the gastrointestinal tract and can lead to deterioration of IBD symptoms. (27) IBD patients have higher levels of daily stress and a lower quality of life comparing with healthy subjects but also comparing with patients with other chronic disease (28, 29) and it's possible that exercise may improve their overall quality of life.

PHYSICAL ACTIVITY AND INFLAMMATORY BOWEL DISEASE

The effect of lifestyle on the onset of IBD was studied in several studies (*Table 1*) and physical activity in the pre-illness period was protective against the onset of IBD (30-33), but this associations was stronger for CD than for UC (31). However a prospective Danish study, which followed two cohorts, each of with more than 2.3 million individuals, for five or 10 years, found only a small association between sedentary occupations and the onset of IBD (34).

Halfvarson *et al.* (35) studied environmental factors in a population-based Swedish-Danish twin cohort using the co-twin control method and found no significant differences between the twins in physical exercise before the diagnosis of IBD in the co-twin. Most recent a European prospective study has shown that physical activity was not associated with the development of incident UC or CD (36). On the other hand a new case-control study, which included 338 patients (190 CD, 148 UC) and 355 controls have shown that CD and UC were associated with a lack of consistent childhood sports activities (37).

The effect of exercise on IBD involving mainly patients with a quiescent state of disease has not been extensively studied (*Table 2*). Studies on the sedentary patients with inactive or mildly active CD have shown that moderate exercise like walking program or yoga lead to significant improvement in the measures of the quality of life and stress levels (38-40). Those studies also revealed that moderate-intensity exercise is well tolerated by IBD patients who are in remission. In a study by D'Inca (41) authors also observed that moderate aerobic exercise did not elicit subjective symptoms or changes in intestinal permeability and lipoperoxidation. It was confirmed by a larger study in which the daily physical activity and physical exercise levels were measured prospectively for CD patients in remission, and for healthy subjects (42). Moderate aerobic exercise has no significant effect on the gastrointestinal parameters examined. Ploeger *et al.* (43) tested the effect of moderate intensity continuous exercise and high intensity intermittent exercise in youth with CD and concluded that such patients can engage in distinctly different types of exercise without a significant exacerbation of the disease. Almost 1000 IBD patients (54% with CD and 46%with UC) from UK completed the online survey. The results of the survey have shown that majority of respondents were undertaking regular exercise, and exercise was found to be beneficial for the symptoms of IBD. However, most of the respondents were requested to stop exercising at some point because of the severity of their symptoms (44, 45).

OBESITY

Obesity has been linked to the development of a number of chronic diseases including cardiovascular disease, type 2 diabetes mellitus, chronic liver disease, and certain types of cancer (46).

Adipocyte hypertrophy in obesity leads to the secretion of inflammatory cytokines and chemokines, similar to those elevated in patients with IBD (47-49). Obesity was also shown to be associated with increased markers of bowel inflammation (50) and intestinal permeability (51). Recent research has suggested that obesity and metabolic syndrome may be associated with profound changes in microbiota (52).

While substantial weight loss is a characteristic feature of CD affecting about 80% of patients during the active state, however, there is evidence that the CD epidemiology may be changing (53). Obesity in inflammatory bowel disease especially in CD, has previously been considered very rare (3%) but prevalence of obesity is rising in CD, paralleling its increased prevalence in the whole population (54). Sousa (55) observed that 32% of CD patients in quiescent state were overweight and 8% were obese. A prevalence of 18% of obesity in IBD population in comparison to approximately 23% of the Scottish population on a whole was recently reported, suggesting that obesity per se is not a risk factor for CD (56). There were

significantly more obese men and women with CD than with UC. On the other hand, recent study have shown that in patients with stable CD the prevalence of overweight/obesity was 40% and being underweight was rare in this setting (42). In a large study of children with newly diagnosed CD, most (66–69%) were in the normal range for their Body Mass Index (BMI) and 10% were classed as overweight or at risk for becoming overweight (57).

Recently, a prospective cohort study, which investigated the association between obesity and the development of IBD on a total of 300,724 participants, found that obesity as measured by BMI, and was not associated with the development of incident UC or CD (36). It should be mentioned that the current definition of obesity is anthropometric and based on the BMI and does not take into account body composition, *i.e.* fat-free mass and fat mass. It is very likely that in future research, other indicators of obesity should be used, particularly those connected with abdominal adiposity.

Obesity alone is associated with several physical limitations followed by a decline in the quality of life and it's also considered to be an exacerbating agent in the course of several chronic diseases. Present knowledge indicates that obese IBD patients also have other additional risks that affect their treatment, and their surplus of adipose tissue may act as a pathogenic agent (58, 59).

ADIPOKINES AS INFLAMMATORY MEDIATORS IN INFLAMMATORY BOWEL DISEASE

The intestinal mucosa even under physiological conditions exhibit continuous, low-grade, nonpathogenic inflammation, caused by the constant exposure to a antigenic load from several dietary and microbial antigens, and a large variety of Toll-like receptor (TLR) ligands (60). The intestinal epithelial barrier and specialized immune cell types are under normal physiological

Table 2. Studies examining the impact of exercise on IBD.

Reference	Number of patients	Study description	Outcome
Robinson *et al*., 1998 (17)	117 CD patients	Home based low impact exercise program of increasing intensity focused on the hip and lumbar regions	Bone mineral density increased in compliant patients in the lumbar spine and the hip.
D'Inca *et al*., 1999 (41)	6 CD patients in remission 6 control	Exercise at 60% VO_2max (cycle ergometer)	Exercise did not elicit subjective symptoms or changes in intestinal permeability and lipoperoxidation..
Loudon *et al*.,1999 (38)	12 patients with inactive or mildly active CD	A thrice-weekly, 12-wk walking program. Subjects walked an average of 2.9 sessions/wk, at an average of 32.6 min/session, and for an average distance of 3.5 km/session	Physical health, general well-being, stress diminished and quality of life improved without disease exacerbation.
Elsenbruch *et al*., 2005 (45)	30 patients with inactive UC 30 patients control	Stress management program, light exercise	Improvement in quality of life in patients with UC in remission, while no effects of therapy on clinical or physiological parameters were found.
Ng *et al*., 2007 (39)	16 patients with inactive UC 16 patients control	Low-intensity walking 30min at 60% of maximum heart rate, 3 times per week during 3 months	Improvement in the quality of life and reductions in CD symptoms.
Ploeger *et al*., 2001 (43)	15 pediatric CD patients 15 controls	30 min of cycling at 50% of peak mechanical power (PMP) and 6 bouts of 4x15-s of cycling at 100% PMP	Responses in patients were similar compared with controls; youth with CD can engage in distinctly different types of exercise without a significant exacerbation of the disease
Robbins *et al*., 2012 (44)	About 1000 IBD patients (54% CD and 46% UC)	UK online survey	Majority of respondents were undertaking regular exercise and exercise was found to be beneficial for the symptoms of IBD. Most of the respondents had to stop exercising at some point because of the severity of their symptoms

conditions, and are responsible for the differentiation between harmful antigens and harmless dietary components or beneficial commensal bacteria. In contrast, the development of IBD is associated with a disruptions in these homeostatic mechanisms and recognition of the normal microbiota as pathogenic bacteria (60). The possible mechanism of the pathogenesis of IBD is that overly aggressive acquired (T cell) immune responses to luminal bacterial antigens develop in genetically susceptible hosts, and environmental factors induce the onset of disease (3, 61). In both CD and UC, patients activated innate (macrophage, neutrophil) and acquired (T and B cell) immune responses and the loss of tolerance to enteric commensal bacteria were demonstrated (62). Also antibody-neutralization studies have suggested role of TNF-α in the pathogenesis of CD (63).

T helper (Th) cells differentiate into Th1 and Th2 cells, and produce different sets of cytokines (64). CD and UC show distinct differences in terms of cytokine production (4, 29). CD related inflammation is associated with marked production of Th1 cytokines (*e.g.*, interferon), UC seemed to be a Th2 cytokine-mediated disease characterized by increased production of interleukin (IL)-5 production and normal IFN-γ production (65-67). Studies on UC verified have shown that UC was associated with increased IL-13 production (but not IL-4 production) by natural killer T (NKT) cells, rather than by conventional T cells (68). There are also a group of additional cytokines, such as TNF-α, IL-1β, and IL-6, that are associated with both forms of IBD with a index of disease activity expressed to a lesser or greater degree (65). Each of these cytokines activate dNF-κB and the mitogen-activated protein kinases (MAP kinases), and thereby inducing various "downstream" proinflammatory effects. These cytokines serve as the immediate precursors of tissue and organ pathology in IBD. In addition, TNF-α enhances the reciprocal production of IL-12, a function that might account for the particular association of this cytokine with Th1 responses (65). Recently the role of TNF-like weak inducer of apoptosis (TWEAK) TNF superfamily (TNFSF) member that controls many cellular activities has emerged as a new player in the inflammatory processes and its crucial role in IBD has been postulated (56, 57). Its actions are mediated by binding to fibroblast growth factor-inducible 14 (Fn14), a highly inducible cell surface receptor that has been linked to several intracellular signaling pathways, including the nuclear factor-κB (NF-κB) pathway (56). The TWEAK-Fn14 axis normally regulates various physiological processes, in particular it seems to play an important role and posses a beneficial effect in the mechanism of tissue repair following acute injury, as well as playing an important role in pathological tissue remodeling (69). TWEAK may promote the pathogenesis of IBD by signaling through Fn14, and functions in parallel to TNF-κ (69). Fn14 present on intestinal epithelial cells (IEC) can be up regulated due to their exposure to microbial products or cytokines. This contributes to a failure of the mucosal barrier; causing the induction of IEC-derived mediators that promote chronic inflammation and shifts gut immunity against commensal bacteria (70). The accumulated evidence indicates that the, expression of Fn14 is up regulated in CD patients. Moreover, the TWEAK/Fn14 pathway plays a pathological role in mouse models of CD by inducing an inflammatory response and regulating intestinal epithelial cell turnover (71). On the other hand, anti-TWEAK mAb treatment of wild-type mice, causing the TWEAK or Fnl4 deficiency resulted in reduced clinical disease index and accompanying inflammation, and colon epithelial damage and crypt abnormality (72).

Adipose tissue consist not only of adipocytes but also a connective tissue matrix, nerve tissue, stromovascular cells and immune cells (73). In obesity, both hypertrophy and hyperplasia of adipocytes occurred, but hypertrophy was predominant only during the initial stages of the development of obesity. This is because the capacity to hypertrophy is limited, and once adipocytes reach a critical size neo-adipocyte differentiates the action of growth factors secreted by the hypertrophied adipocytes is observed (74). Obesity is characterized by the progressive infiltration of adipose tissue by macrophages - enlarging adipocytes secrete macrophage chemoattractant protein 1 (MCP-1), which attract macrophages. An additional source could be the transdifferentiation of preadipocytes to macrophages (75).

We know presently that obesity represents a low-grade chronic inflammatory state characterized by abnormal cytokine production, increased synthesis of acute-phase reactants, such as C-reactive protein (CRP), and the activation of pro-inflammatory signalling pathways (76). Our understanding of adipose tissue has been altered and now we see adipocytes as new members of the immune system, as they produce a number of proinflammatory cytokines and molecules associated with the innate immune system (*Fig. 1*).

Peroxisome proliferator-activated receptor gamma (PPARγ), known for its significant role in adipogenesis, has been recently described as being a gene for the susceptibility to IBD as the NOD2/CARD15 gene (77). PPARγ is involved in the regulation of inflammation, and its agonists strongly ameliorate experimental colitis (*Fig. 2*). A deficit of PPARγ in patients with UC has been highlighted, and this could in part explain the acute inflammation in human CD patients. In addition, bacteria, including those of the commensal flora, are able to positively express and regulate PPARγ (77).

Recently, the differential expression of TNF-superfamily member B cell activating factor of the TNF family (BAFF), a proliferation inducing ligand (APRIL), and TWEAK in adipocytes was reported, and its actions was mediated by its binding to Fn14, a highly inducible cell surface receptor that has been linked to several intracellular signaling pathways, including the nuclear factor-κB (NF-κB) pathway (78). The activation of the pro-inflammatory transcription factor NF-κB in monocytes and adipocytes is a consistent common finding in obese patients (79). Recently, an increase of TWEAK and Fn14 gene expression in adipose tissue of severely obese patients was reported and inflammatory stimuli *in vitro* differentially increased the expression of TWEAK in macrophages and Fn14 in adipocytes (80). Finally, preadipocytes and adipocytes express a broad spectrum of functional Toll-like receptors and can convert into macrophage-like cells (81, 82). Circulating free fatty acids are associated with enhanced pro-inflammatory cytokine production by a number of cells including macrophages (83).

Abdominal adiposity is associated with a pro-inflammatory state and especially mWAT, which has been implicated in a wide range of gastrointestinal disorders from fatty liver to acute pancreatitis and to GI cancers (84). Recent reports suggest that macrophages infiltrate adipose tissue in the obesity enhancing production of additional inflammatory mediators (85). The adipose tissue depots can be altered due to inflammatory pathologies such as CD (86). Visceral adipose tissue (VAT) is generally considered to be more inflamed than other fat depots, generating pro-inflammatory GI substances and thus has been considered as the key regulator of systemic inflammation in obesity (87) (*Fig. 2*). Visceral adipose tissue is also strongly associated with nonalcoholic fatty liver disease (NFLD). VAT is thought to provide an immediate source of free fatty acid and proinflammatory cytokines such as TNF-α, IL-6, and IL-1β delivered, to the liver *via* the portal vein, which contribute to the progression of hepatic inflammation. Based on research in animal models, some authors suggested that interactions between inflammatory changed mesenteric fat and the intestinal mucosa could trigger and worsen

inflammation in adipose tissue. This would place adipose tissue cross - talk with the intestine as a key pathogenic tissue in obesity of induced metabolic disorders (87) (*Fig. 2*).

The natural course of CD while not necessarily being associated with obesity, it is characterized by marked changes in mesenteric adipose tissue behavior. Fat wrapping and mesenteric adipose tissue hypertrophy are consistent features recognized on surgical specimens in patients with CD (88). Recent research suggests that the hypertrophied fat could contribute actively to disease severity and may have an impact on the development of complications (89). Localization of mucosal ulcers in CD patients, which contrary to that observed in infectious diseases, is most marked along the mesenteric attachments, and may indicate a causal link between the mesenteric adipose tissue and the mucosal changes. Mesenteric WAT confirmed by a histopathological examination of biopsies from CD patients is characterized by fibrosis, perivascular inflammation, intimal and medial thickening of vessels, significant infiltration of inflammatory cells and an increase in the number of adipocytes (90). Massive infiltration of intestinal mucosa by inflammatory cells, mainly CD68- and CD3-positive T lymphocytes have indicated that the pathologically changed mucosa and its adjacent mesentery share a common inflammation in CD (*Fig. 2*). The hypertrophied mWAT is a key source of the increased TNF-α, IL-6 and other circulating proinflammatory cytokines in CD patients, which contribute to the debilitating systemic symptoms seen in this disease. In these patients, a selective enlargement of fat depots around the diseased lymph nodes is observed and over 50% of the intestinal surface is covered by adipose tissue (91). A recent study has shown that fat wrapping is present in all patients with CD undergoing ileal resection that correlates significantly with the degree of acute and chronic

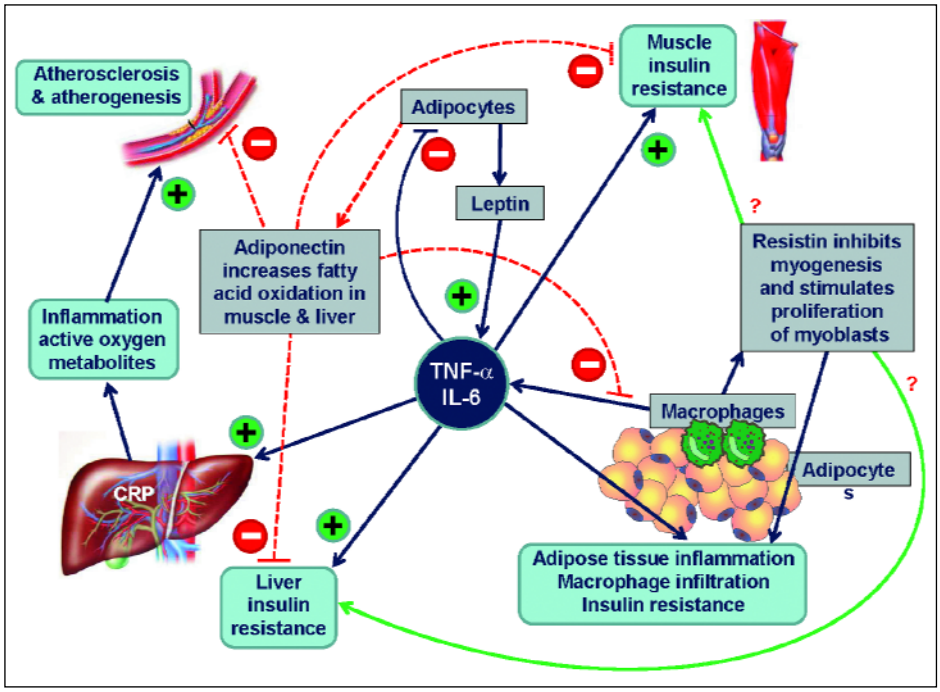

Fig. 1. Central role of proinflammatory cytokines released from white adipose tissue (WAT) infiltrated by macrophages in obese individuals. The infiltrated macrophages and adipocytes release a variety of cytokines such as leptin, TNF-α, IL-6 and resistin responsible for insulin resistance. Resistin inhibits myogenesis and stimulates proliferation of myoblasts in skeletal muscle. On contrary, the expression and plasma levels of "protective" adiponectin are decreased during obesity. Adiponectin inhibits liver insulin resistance and promotes fatty acid oxidation in skeletal muscle and liver. Adiponectin is known to suppress pro-inflammatory effects of TNF-α and attenuates the development of arteriosclerosis and atherogenesis.

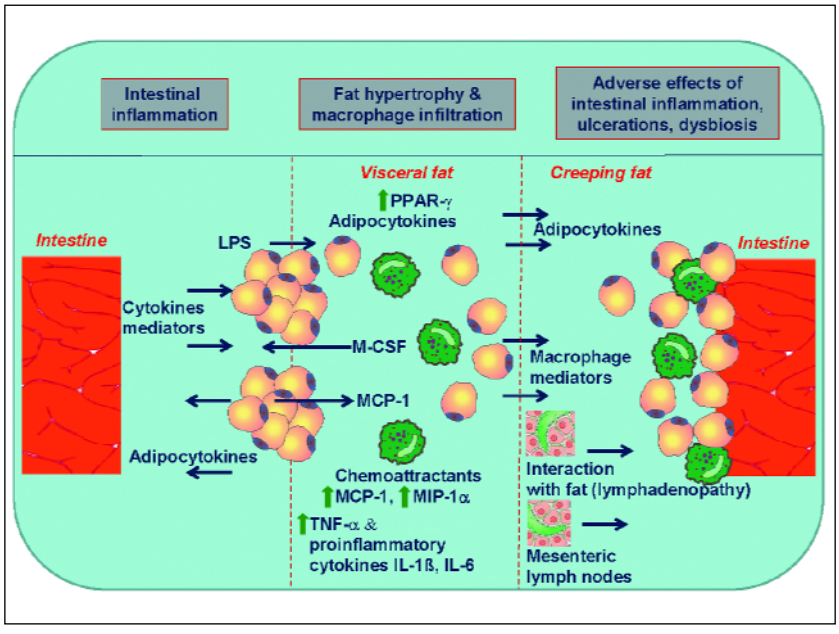

Fig. 2. Network of cytokines and inflammatory mediators in IBD including Crohn's disease (CD). The intestinal inflammation process leads to a sustained release of inflammatory cytokines (TNF-α, IL-1β, leptin, chemoattractant protein-1 (MCP-1), MIP-1α and IL-6). PPARγ and adipocytokines are overexpressed by mesenteric adipocytes in CD patients promoting the hypertrophy of mesenteric white adipose tissue. Adiponectin secrete by small adipocytes exerts antiinflammatory effects resulting in an inhibition of TNF-α activity. Macrophage accumulation in adipocytes leads to release of inflammatory mediators that may enhance chronic inflammation. The increased infiltration of the visceral adipose tissue by macrophages and adipocytokines leads to an inflammatory transformation of the visceral adipose tissue into creeping fat and adverse effects such as formation of mucosal ulcerations along the mesenteric border, dysbiosis, fat and intestinal translocation of bacteria.

inflammation. Moreover fat wrapping correlates well with the extent of transmural inflammation in the form of lymphoid aggregates (91). Hypertrophied mWAT is observed from the very beginning of the disease and it is associated with an overexpression of TNF-α, leptin and other adipokines. A significant correlation of these cytokines with the severity of the disease was observed, suggesting a key role for adipose tissue in the intestinal inflammatory process in CD (92). It is of interest that intestinal luminal leptin, a cytokine produced by adipocytes, is increased in CD and can upregulate NFκB expression in colonic epithelial cells (93). It was suggested also that leptin may serve as useful predictive marker of inflammation in IBD (94). Cytokines, especially produced by mesenteric adipocytes, have a important role in the longevity and over-reactivity of *lamina propria* T lymphocytes (LPL-T) in IBD (95). Adipokines such as adiponectin and leptin are produced mainly by adipocytes, but unlike adiponectin, leptin is considered to be a pro-inflammatory cytokine and it possesses structural similarity to other pro-inflammatory cytokines such as IL-6, IL-12 and granulocyte colony - stimulating factor (96) (*Fig. 1*). Leptin directly regulates production of several cytokines, particularly those triggered due to an activation of T cells. It increases IL-2 and IFN production, while decreasing IL-4 levels (97). An overexpression of leptin mRNA in mWAT was reported in IBD patients, indicating that leptin might participate in the inflammatory process by enhancing mesenteric TNF-α expression (98). Studies in leptin-deficient, ob/ob mice further support a role for adipokines as direct modulators of colonic inflammation. In these studies, it was shown that leptin infusion worsened colitis and that leptin-deficient mice developed less severe experimental colitis than wild-type controls (99). The protective effect of the ob/ob genotype was abolished by leptin infusion, suggesting that leptin, not obesity per se, increased damage caused by experimental colitis.

Interestingly, adiponectin exhibits a structure similarity to TNF-α, and antagonizes the effects of TNF-α by reducing secretion, and attenuating the biological actions of this cytokine by competing for the receptor (25) (*Fig. 1*). Adiponectin's production is enhanced in hypertrophied mWAT of CD patients and this overexpression is higher than in UC patients and patients undergoing surgery for colon cancer (100). A somewhat ambiguous situation exists for the feeding stimulant, ghrelin. It is the endogenous ligand for the growth hormone secretagogue receptor 1a (GHS-R1a). Although GHSRla is mainly expressed at central neuroendocrine tissues, a wide spread pattern of expression has also been demonstrated in a stomach and neuronal cells of the gut (101). A major focus of research with ghrelin has been primarily related to the regulation of food intake and its accompanying endocrine functions. Ghrelin and its receptor for mRNA expression were shown to be upregulated in experimental colitis. Furthermore, ghrelin stimulated IL-8 promoter activity and the activation of the NF-κB/IκB pathway in the human colonic epithelial cell line (101). Administration of ghrelin in an experimental colitis model significantly decreased damage and the induction of proinflammatory cytokine induction in experimental colitis (102, 103). However, in human colonic cell lines, ghrelin increases TNF-α-induced proinflammatory interleukin-8 production and activates NF-κB (48).

Mesenteric fat is also an important source of CRP in CD. Its production by mesenteric adipocytes may be triggered by local inflammation and bacterial translocation to mesenteric fat, providing an another mechanism by which mesenteric fat hyperplasia may contribute to the inflammatory response in CD (89). It is likely that the mesenteric fat in CD is exposed to gut microbial antigens. Adipocytes express Toll-like receptors (TLRs) and CD14, which can interact with these antigens activating NF-κB pathways (104). About 95% of the total viable bacteria cultured from mesenteric tissues are normally located in adipocytes and only 5% are translocated to the mesenteric lymph nodes, indicating that adipocytes might be a main reservoir of bacteria in the mesentery. Interestingly, obesity is associated with reduced microbial diversity in a similar pattern to that seen in CD (105, 106). All these observations fuelled speculation about the potential roles of mesenteric mWAT in the development of Crohn's disease by reacting to the microbial environment and by initiating and/or promoting local inflammatory reactions by autocrine and/or paracrine modulation of adipocytes (89).

The possibility of another link between adipose tissue and adipokines and IBD has come from research demonstrating that ATG16L1- deficient mice show a strongly enhanced expression of both adiponectin and leptin in epithelial cells. ATG16L1is a component of a large protein complex essential for autophagy and mutations in the ATG16L1 gene, which was linked to CD (106). Autophagy not only plays a key role in intestinal inflammation, but also it is involved in the regulation of lipid metabolism (103).

Another recently identified pathway in IBD is that of endoplasmic stress/XBP1, which regulates fatty acid synthesis and facilitates adipogenesis and adipocyte differentiation. X-box binding protein 1 (XBP1), is a protein that is encoded by the XBP1 and is part of the endoplasmic reticulum stress response, which is the unfolded protein response (UPR). Abnormalities in XBP1 have led to a heightened ER stress and subsequently could cause an increased susceptibility for IBD (109). An association of XBP1 variants with both forms of human IBD (CD and UC) was identified and it was suggested that XBP1 could possibly link intestinal inflammation with the pathological changes in mWAT in CD (107, 108).

Anorexia is another feature present in CD which could be explained by adipokine overproduction by mesenteric fat (97). It is generally accepted that reduced food intake in IBD is responsible for adverse symptoms such as abdominal pain, fear of diarrhea, incontinence, surgery, nausea, depression and a feeling of general unwellness, but the specific disorder of appetite control has not been investigated. It is believed that satiety control in IBD is also probably modulated by the availability of inflammatory cytokines like leptin, which is known to suppress appetite and reduces the motivation to eat (109-111). Leptin levels have been shown to be significantly higher in mesenteric adipose tissue from CD patients, than in patients with non-inflammatory diseases of the gut (93, 96). Experimental colitis in rats resulted in elevated circulating leptin levels, which correlated to the degree of inflammation and the development of anorexia (112).

A number of mechanisms could underlie the association of obesity, general or local, with IBD. In genetically obese mice, an increased intestinal permeability has been reported, a defect that has been observed in both CD and UC (113). It is interesting that being infiltrated with macrophages and lymphocytes (more so in the obese), preadipocytes can respond to a number of stimuli to produce pro-inflammatory cytokines thus perpetuating inflammation, and they can additionally change their phonotype differentiating into macrophages (114, 115).

CROSS TALK BETWEEN SKELETAL MUSCLE AND ADIPOSE TISSUE

Evidence suggests that the protective effect of exercise may to some extent be attributed to its the anti-inflammatory effects. Exercise may exert its anti-inflammatory effect *via* a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each cycle of exercise. Such effects may in

part be mediated *via* muscle-derived peptides, so-called "myokines". Contracting skeletal muscles release myokines *via* a endocrine fashion, mediating direct anti-inflammatory effects, and/or specific effects on visceral fat. By mediating anti-inflammatory effects in the muscle itself, myokines may also counteract TNF-driven insulin resistance. A exercise-induced increase in myokines appears to be involved in mediating both systemic as well as local anti-inflammatory effects (116, 117). If the endocrine and paracrine functions of the muscle including myokines are not stimulated through contractions, this will cause dysfunction of several organs and tissues of the body as well as an increased risk of chronic inflammatory diseases (116, 117). Presently identified myokines which exert endocrine, paracrine or autocrine effects are LIF, IL-6, IL-7, BDNF, IGF-1, FGF-2, FSTL-1 and irisin (118) (*Fig. 3*).

The prototype myokine, IL-6, appears to be able to mediate metabolic effects as well as anti-inflammatory effects. A number of studies have revealed that in response to muscle contractions both type I and type II muscle fibres express the myokine IL-6, which subsequently exerts its effects both locally within the muscle and in several organs in a hormone-like fashion (119). Until recently, it was accepted that an observed rise in the IL-6 level during exercise was a consequence of the immune response to local damage (*Fig. 3*). Today it is known that muscle is unique in its ability to produce IL-6 during contraction in a completely TGF-independent mode, which suggests a major involvement of this cytokine in a regulation of metabolism, which is not considered to be a inflammatory mediator (120). It was shown that IL-6 released by muscle during exercise could mediate release of GLP-1 from intestinal L cells (and from pancreatic A cells), which in turn acts as a incretin causing insulin release, providing evidence that there is possible cross talk between adipocytes, muscle, and the pancreas that is responsible for energy homeostasis (121) (*Fig. 3*). Exercise dramatically increased the level of IL-6 in mice and induced a parallel marked rise in GLP-1. The role of IL-6 was confirmed by experiments *in vitro* where incubation of the L-cells and α-cells with IL-6 caused the release of GLP. Additionally, administration of IL-6 augmented glucose-stimulated insulin release in mice fed a regular or high fat diet, as well as in ob/ob (lacking leptin) and db/db (nonfunctional leptin receptor) mice, but not after pretreatment of db/db mice antibodies to IL-6, thereby blocking the effects of endogenous IL-6 (121).

IL-15 is expressed in human skeletal muscle, and has been identified as an anabolic factor in muscle growth, and appears to also play a role in lipid metabolism (116, 122). Therefore, IL-15 has been suggested to be involved in muscle-fat crosstalk. It was demonstrated that IL-15 mRNA levels were upregulated in human skeletal muscle following a course of strength training, suggesting that IL-15 may accumulate within the muscle as a consequence of regular training (123). When IL-15 was overexpressed in murine muscle, a decrease in visceral fat mass, but not subcutaneous fat mass was observed. Also elevated circulating levels of IL-15 resulted in significant reductions in body fat and increased bone mineral content (124). Although IL-15 has been suggested to play a role in muscle-adipose crosstalk, its secretion from muscle cells has so far not been described and it is premature to call JL-15 a true myokine.

The depletion of muscle mass and impaired muscle function, as well as reduced height velocity in children are characteristic manifestations of IBD (1, 20). The IBD-related growth failure and decreased muscle mass have been attributed to a variety of mechanisms including decreased nutrient intake, malabsorption of ingested nutrients, increased metabolic rate, and the inhibitory effects of inflammation on the growth hormone (GH)/insulin-like growth factor (IGF)-I axis (125). Both plasma IGF-I and muscle IGF-I are decreased in response to diverse inflammatory insults, which are consistent with the acceleration of the loss of muscle protein (126). The function of the GH-insulin-like growth factor (IGF)-I axis depends on a finely tuned mechanisms, which can be impaired by inflammatory cytokines released from pathologically modified mWAT. Inflammatory cytokines, notably TNF-α, reduce liver GH receptor numbers and seems responsible for hepatic GH resistance and decrease of circulating IGF-I level that leads to growth inhibition and decrease of lean body mass (LBM) (127, 128). Recent evidence indicates that TWEAK cytokine mediates skeletal the muscle

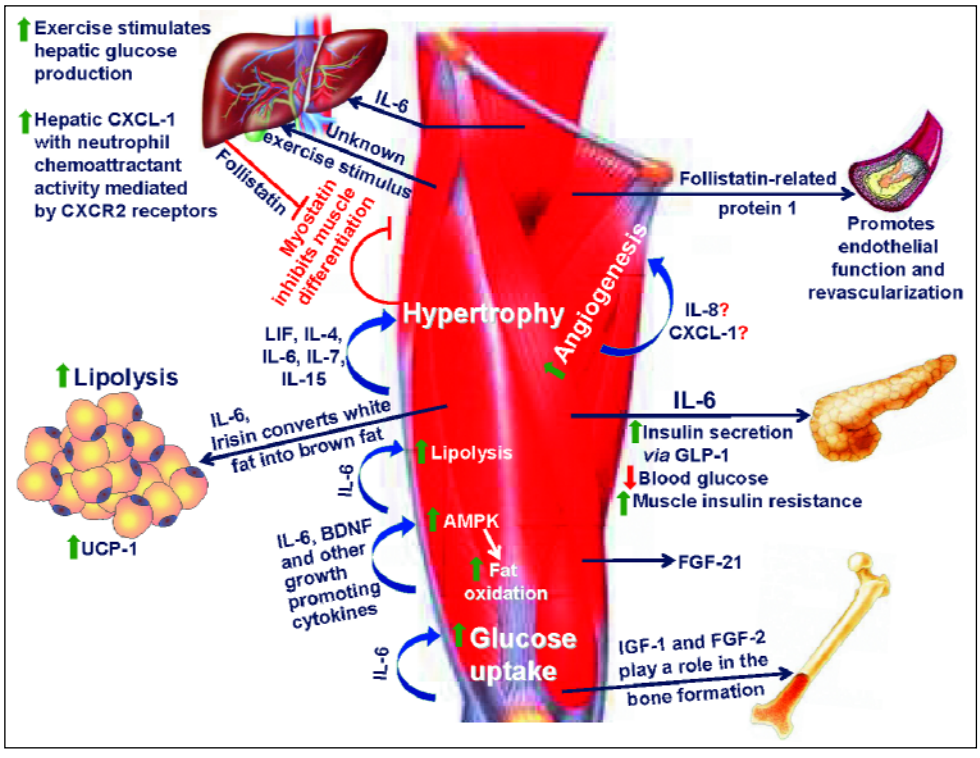

Fig. 3. Pleiotropic role of IL-6 in metabolic alterations associated with exercise in skeletal muscles and white adipose tissue. Besides the local effect, IL-6 can exert fat oxidation, an increase in insulin-stimulated glucose uptake and mediate a inter-organ cross talk between liver, adipose and pancreatic tissues. Muscles synthesize and release of myokines that might counteract the harmful effects of pro-inflammatory adipokines. New myokine irisin released during exercise exhibits a direct effects on 'browning' of white fat leading to burning of excess calories. Discovery of irisin therefore raised expectations of potential for developing new therapies for metabolic diseases (modified from Pedersen BK and Febbraio MA [ref. 118]).

atrophy in a variety of clinical settings (129-131). Studies performed on rats with experimental colitis have demonstrated an inhibitory effect of the inflammation on IGF-I generation and on linear growth (4). Impaired function of satellite cells is another link between impaired insulin/IGF-I signaling and muscle protein loss (20). It has been suggested that muscle catabolism is multifactorial, being caused by the reduced protein synthesis and the increased protein degradation, as well as a mitochondrial component. In muscle wasting, apoptosis as well as autophagy have been implicated. The therapeutic strategies resulted in an increased mitochondrial capacity within the muscle suggesting that mitochondrial dysfunction plays a critical role in muscle loss (132, 133). A key player controlling mitochondrial function is the peroxisome proliferator-activated receptor coactivator α (PGC-1α), a master regulator of mitochondrial biogenesis (6). In skeletal muscle, PGC-1α can also prevent muscle wasting by regulating autophagy (134). The health promoting effects of increased PGC-1α expression in skeletal muscle has been addressed, which could be shown in different experimental mouse models within the affected muscles (134-137). In a recent study, Bostrom *et al.* (138) identified a new myokine, which they named irisin. Irisin is released during exercise and cause the transformation of white fat cells into brown-in-white, or brite cells - white fat cells with a phenotype similar to that of brown fat cells (138) (*Fig. 3*). In humans, plasma levels of irisin after 10 weeks of regular endurance training were markedly increased. It was suggested that irisin could be therapeutic for human metabolic disease, obesity and other disorders in which exercise is beneficial (139).

FURTHER RECOMMENDATIONS

The recognition of the active role of mWAT in pathology of IBD leads to a number of potential therapeutic approaches that reduce adipose tissue depots. Several drugs used in the treatment of insulin resistance and hypercholesterolemia have been shown to have beneficial circulating adipokine levels, however, their impact on IBD is not fully understood. (75). Synthetic ligands of PPAR-γ such as the glitazones are commonly used in the treatment of type 2 diabetes. Their beneficial effects observed in obese rats include a decrease in circulating levels of TNF-α and leptin and, a significant rise in adiponectin level (75). In animal models of IBD, glitazones have been demonstrated to decrease the intestinal tissue injury and they were proposed to exert a beneficial influence on the course of CD and UC (139-141). Recent discovery of the "muscle hormone" irisin (138), and its ability to modify adipose tissue metabolism, constitutes a breakthrough in our understanding of muscle-fat crosstalk and metabolic disorders (118) (*Fig. 3*). This myokine could lead to a innovative therapeutic perspective and may contribute to the creation of a "exercise pill", which could also be helpful in IBD by reverting the changes in mesenteric adipose tissue (142). However, because exercise causes a very complex reaction within the body, and has direct and indirect benefits on the whole body, it would be extremely difficult to introduce a drug on the market which totally mimics the full effects of exercise.

Previous studies have shown that low-intensity exercise has no negative effects and is well tolerated in IBD patients. The current evidence seems to indicate beneficial effect on the course of the disease. In guidelines accepted in 1998, specifically for IBD patients, physical exercise was recommended for general health, to counteract muscle wasting, and improve bone density (89). Aerobic activity for 20 min to 60 min two to five days every week, accompanied by resistance exercise at least two times per week was recommended. The guidelines however were not based on actual research. In a recent review, authors proposed similar recommendations and suggested that two main types of physical interventions that should be recommended: aerobic activity and muscular resistance training (12).

CONCLUSIONS

Although previous research suggest that exercise may be beneficial for IBD patients, further studies are necessary to confirm these conclusions and to find out whether all patients would benefits from physical activity. It is also necessary to evaluate the effectiveness of different types of exercise, as well as the duration and intensity of the exercise program in order to find a optimal level for patients. Weight training programs could be beneficial for IBD patients, specifically as a means to counteract the adverse changes in muscle and bones. Regular physical activity has also been connected to enhanced psychological well-being, a better general health and quality of life. Taken together, this leads to the conclusion that physical exercise may be beneficial in the prevention of IBD and ameliorating its symptoms but further studies are definitely required to achieve a final conclusion regarding its role in the management of IBD, and to establish appropriate recommendations for exercise regimens.

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