

Exercise and Inflammatory Bowel Disease



Insights into Etiopathogenesis and Modification of Clinical Course

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KEYWORDS

- Inflammatory bowel disease • IBD • Exercise • Inflammatory disorders
- Physical activity

KEY POINTS

- There is a growing appreciation that regular exercise regimens are essential for patients suffering from chronic inflammatory disorders, including IBD.
- Low- to moderate-intensity exercise for IBD patients in remission and those with mild active disease, improves quality of life of these patients and helps counteract IBD-related complications.
- A regular exercise regimen may also exert a beneficial modifying effect on disease course, improving inflammatory parameters, psychological status and quality of life in patients with IBD.
- Exercise may help counteract IBD-related complications such as improving bone mineral density, immunologic response, psychological health, weight loss, and stress management ability.

INTRODUCTION

Exercise and physical activity are crucial for maintaining health and well-being. A sedentary lifestyle contributes to and complicates a multitude of chronic illnesses, often resulting in multiple comorbidities. Although there are recommendations regarding exercise to maintain health in the general population, there is sparse information regarding exercise and inflammatory bowel disease (IBD). Furthermore, the importance of regular exercise in the optimal management of IBD has not received

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attention in guidelines and is often overlooked by practitioners. This review summarizes evidence regarding health benefits of exercise, guidelines regarding exercise in the general population and chronic inflammatory disorder populations, limitations regarding exercise capacity in patients with IBD, the association of lack of exercise with IBD pathogenesis, the role of exercise in beneficially modulating IBD clinical course, and extraintestinal benefits of exercise in patients with IBD.

HEALTH BENEFITS OF EXERCISE: HISTORICAL INFORMATION FROM THE GENERAL POPULATION AND INFLAMMATORY DISORDERS

The 2008 Physical Activity Guidelines for Americans identifies 2 types of physical activity that should be performed on a weekly basis: aerobic and muscle-strengthening exercises.¹ It is recommended that adults perform 150 minutes of moderate physical activity such as brisk walking every week as well as muscle-strengthening activities on at least 2 days of the week to work all major muscle groups including legs, hips, chest, abdomen, shoulders, and arms. If patients choose to perform vigorous-intensity activity (instead of moderate physical activity), such as jogging, running, swimming laps, or playing tennis or basketball, they need 75 minutes per week instead of the 150 minutes.¹ Similarly, these patients should conduct muscle-strengthening activities on at least 2 days of the week to work all major muscle groups.

Regular exercise regimens have been associated with improved cardiovascular status, stamina, and overall well-being. Exercise, which can be limited to as little as 10 minutes of sustained activity per day, has been associated with a decreased lifetime risk of developing ischemic heart disease, hypertension, diabetes, breast cancer, Alzheimer disease, dementia, frailty, and neurodegenerative progression in Parkinson disease.²⁻⁷ Exercise has been shown to decrease serum levels of C-reactive protein (CRP), a biomarker of inflammation and cardiovascular disease risk. In patients with rheumatoid arthritis, exercise programs have uniformly showed benefit regarding improved functional status, emotional status, and quality of life, with no detrimental effects on disease activity.⁸⁻¹⁰

In asthma, a chronic inflammatory disorder of the airways, exercise is a known precipitant of flares in a subset of patients (ie, exercise-induced asthma). Historically, this triggering mechanism prompted recommendations to avoid physical activity in asthmatic children to avoid exertional dyspnea. However, more recent investigation of training programs to promote physical conditioning in children and adolescents with asthma has revealed opposite findings, suggesting that exercise can be safe and well tolerated in most children with asthma, which may potentially improve overall asthma management as well as associated general health benefits.¹¹ Although exercise did not change the overall occurrence or degree of exercise-induced asthma, physical conditioning was tolerated with the use of a bronchodilator before exercise, which led to improvements in aerobic fitness, quality of life, and psychological status.

EXERCISE AND INFLAMMATORY BOWEL DISEASE

Despite the known beneficial effects of exercise on quality of life and psychological status, which overlap with treatment goals in the management of IBD, there has been limited investigation regarding the role of exercise in IBD care. One of the first recommendations advocating regular exercise for patients with IBD was published by Ball in 1998.¹² This single-investigator article suggested patients with IBD target 20 to 60 minutes of aerobic activity for 2 to 5 days a week in addition to resistance training at least twice per week.¹² The basis for this recommendation came from an extrapolation of exercise guidelines for the general population with the creation of

tailored IBD-specific goals, which included improving overall health, preventing muscle weakening, and helping to improve bone mineral density.

The European Crohn's and Colitis Organization's consensus guidelines regarding the management of Crohn disease and ulcerative colitis have identified a beneficial role for exercise in the symptomatic treatment of axial arthropathy associated with IBD, as well as isotonic exercise in patients suffering from reduced bone density.¹³ To date, there have been no formal guidelines regarding specific exercise regimens for patients with IBD that target overall improved health, quality of life, and improved psychological status that have been proposed by consensus panels. The reason for this lack of emphasis is likely the result of limited prospective evidence supporting a beneficial role of exercise in the specific IBD patient population.

Patients with IBD with severe disease activity and/or complications from their illness may find exercise challenging. Extraintestinal manifestations of disease, such as arthralgias/arthritis and the common symptoms of diarrhea, fatigue, and tiredness, can limit the ability of a patient with IBD to exercise. Much of the focus regarding medical management of IBD has been on achieving and maintaining control of gut inflammation, management of bowel symptoms, and surveillance regarding the emergence of dysplasia/neoplastic complications. Guidelines regarding management for both Crohn disease and ulcerative colitis have historically not included recommendations regarding sleep hygiene, diet, and exercise, all of which are essential for optimal health. Even patients with IBD who have achieved remission may experience difficulties with exercise, as recent investigation has demonstrated a diminished capacity for muscle function as compared with healthy controls. Wiroth and colleagues¹⁴ showed that muscle strength and endurance, especially in the lower limbs, were decreased in patients with Crohn disease who were in remission when compared with matched healthy controls. The exact etiologic mechanism for this difference in muscle function is not clear, but appeared to be independent of cumulative glucocorticoid use, disease duration or severity, and presence of current inflammation. Similarly, it was shown that patients with IBD have decreased muscle function peak power and reduced peak oxygen uptake.¹⁵

EXERCISE AS AN ENVIRONMENTAL FACTOR INFLUENCING THE ETIOPATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

Several environmental factors play a critical role in the development and course of IBD. Cigarette smoking is the best-defined environmental risk factor in IBD; it increases the risk for developing Crohn disease and will worsen the clinical trajectory of patients with established disease.¹⁶ Conversely, cigarette smoking has a diametrically opposite effect in ulcerative colitis, whereby it protects against the development of disease and smoking cessation appears to be a risk for the emergence of disease. Given the common association between cigarette smoking and lack of physical fitness, a possible synergy of these 2 environmental factors may play a role in Crohn disease pathogenesis, but this has not been fully explored.

Several studies have investigated whether pre-illness exercise regimens play a protective role against the development of IBD. The results of earlier studies were inconclusive, but the quality of these studies was problematic, as numerous confounding environmental factors made definitive statements problematic.^{17–21} More recent retrospective epidemiologic studies have failed to define a protective or causative relationship between pre-illness exercise regimens and the development of IBD.^{22,23} Perhaps the strongest prospective study assessing the impact of physical activity on IBD etiopathogenesis was performed by Khalili and colleagues,²⁴ which

used the Nurses' Health Study cohort. The Nurses' Health Study has tracked 121,700 female nurses from 1976, and the Nurses' Health Study II has tracked 116,000 female nurses from 1989 to prospectively assess risk factors for cancer and cardiovascular disease in women's health. These are the largest epidemiologic cohort studies into risk factors for major chronic disease in women ever conducted, and during 3,421,972 person-years of follow-up, there were 284 incident cases of Crohn disease and 363 cases of ulcerative colitis documented.²⁴ Comparing women with the highest quintile of physical activity with the lowest quintile demonstrated a 44% reduction (hazard ratio 0.56, 95% confidence interval 0.37–0.84) in the risk of developing Crohn disease compared with women with sedentary lifestyles. Physical activity was not associated with risk of ulcerative colitis. Age, smoking, and body mass index in the cohort did not significantly modify the association between physical activity and the risk of ulcerative colitis or Crohn disease. These investigators concluded that in 2 large prospective cohorts of US women, physical activity was inversely associated with risk of Crohn disease but not ulcerative colitis.²⁴ The impact of physical fitness on the risk of IBD in young men has been assessed by Melinder²⁵ in a comprehensive epidemiologic study from Sweden. In a study of 240,984 Swedish military conscripts during late adolescence from 1969 to 1976, 986 individuals developed Crohn disease and 1878 were diagnosed with ulcerative colitis. Stratification of recruits by quintiles of physical fitness demonstrated a protective effect of exercise against the development of both forms of IBD. Low fitness in young men was associated with a raised risk of IBD with unadjusted hazard ratios (and 95% confidence intervals) of 1.62 (1.31–2.00) for Crohn disease and 1.36 (1.17–1.59) for ulcerative colitis. Melinder²⁵ further evaluated this cohort by adjusting for socioeconomic conditions in childhood, physical fitness, body mass index, and erythrocyte sedimentation rate measured during adolescence and subsequent diagnosis of IBD. When results were attenuated by adjustment for prodromal disease activity, there was a reduction in the hazard ratios to 1.32 (1.05–1.66) for Crohn disease and 1.25 (1.06–1.48) for ulcerative colitis. Melinder²⁵ concluded that the inverse association of physical fitness with IBD risk is consistent with a protective role for exercise; however, these findings were tempered by the fact that evidence of disease activity before diagnosis was present in adolescence, suggesting that some or all of the associations between fitness and IBD may be due to prodromal disease activity reducing exercise capacity and therefore fitness.

In a recent study, Cook and colleagues²⁶ sought to characterize mechanisms linking the beneficial effects of exercise and IBD by characterizing the impact of exercise on the gut microbiome. Given the increasing appreciation regarding an altered microbiome/intestinal dysbiosis with the emergence of chronic gut inflammation, these investigators evaluated the effects of moderate exercise on the regulation of intestinal immune function. In a series of studies, Woods and colleagues²⁷ demonstrated that there are differential effects of exercise that are modulated by the psychological context under which the training is performed. The investigators established that the microbiome differed among mice that were sedentary, those that had access to voluntary wheels, and those that were forced to run on a treadmill, which was paralleled by differential alterations in gut immune function, cytokine production, and oxyradical generation. It was concluded that exercise results in a change in the microbiome, which may be the reason behind its beneficial role in the treatment and prevention of IBD.²⁷

CAN EXERCISE MODULATE CLINICAL COURSE IN INFLAMMATORY BOWEL DISEASE?

Exercise has been shown to improve health-related quality of life in patients with chronic diseases, such as rheumatoid arthritis, cancer, heart failure, and depression.^{28–32}

In humans, it has been shown that low-intensity to moderate-intensity exercise and physical activity for patients with IBD in remission and those with mild active disease improves quality of life of these patients and helps counteract IBD-related complications, without negatively impacting disease activity.²²

Studies pertaining to the effect of exercise on IBD were mainly conducted in patients with Crohn disease who were either in remission or had mildly active disease. In one study, patients with Crohn disease remained at their same disease status immediately and 6 months after a single 60-minute session of cycling.³³ The quality of life, stress levels, and body mass index and aerobic capacity of patients with Crohn disease improved significantly after a 3-month walking regimen.³⁴ Similar results with improvements in psychological and physiologic health were demonstrated when a low-intensity walking intervention was introduced to patients with Crohn disease.³⁵ A study by Jones and colleagues³⁶ showed that higher levels of exercise were protective against active disease at 6 months among patients with Crohn disease who were in remission. Although a protective effect was seen among patients with ulcerative colitis, this was not statistically significant.³⁶ In a different study, however, patients with ulcerative colitis were found to experience improvements in their quality of life without interruption of their disease activity when they were subjected to a 10-week 6-hour training program that was composed of moderate exercise as well as stress management, Mediterranean diet, behavioral techniques, and self-care strategies.³⁷

Klare and colleagues³⁸ conducted a prospective randomized controlled trial examining the effects of a 10-week moderate physical activity program on health-related quality of life in patients with IBD. In this study, patients with mild to moderate IBD were recruited and randomized into an intervention group (supervised moderate-intensity running program 3 times a week) or no intervention. Results demonstrated that patients with moderate severity IBD were able to perform symptom-free regular endurance exercise. Although there was a mean increase in quality of life score between before and after the exercise program, this was not significantly different from the mean increase noted in the control group. There was, however, a significant difference in improvements in the social well-being of patients who were enrolled in the exercise intervention program when compared with the control patients. Patients with Crohn disease who had higher exercise levels were less likely to experience a flare of their IBD at 6 months.³⁹ Also, those patients who exercised had a better mood, maintained their weight, and had fewer bone mineral disturbances.

Exercise was also found to promote healing in colitis models due to protective myokines released from skeletal muscles.³⁹ It has been demonstrated that a single bout of moderate-intensity exercise in healthy individuals inhibited monocytic intracellular tumor necrosis factor (TNF) production via beta-2 adrenergic activation. This in turn may protect against conditions associated with low-grade inflammation.⁴⁰ Similar to healthy human data, TNF expression was decreased in the intestinal lymphocytes of mice undergoing voluntary exercise training.⁴¹

Cook and colleagues⁴² further examined different exercise training intensities in mice. In this study, mice with dextran sulfate sodium-induced colitis were randomized to a sedentary lifestyle, voluntary wheel running, or moderate forced treadmill running. Mice in the longer duration and more intense forced treadmill running group had exacerbated colitis symptoms, inflammation, and higher cytokine expression, whereas mice in the voluntary wheel-running group attenuated inflammatory gene expression and symptoms.⁴²

Similar to animal models, despite the positive effects of exercise on disease course, it is important to know that exercise may lead to increase of proinflammatory cytokine release and in turn transiently exacerbate IBD symptoms.

EXTRAIESTINAL BENEFITS OF EXERCISE IN INFLAMMATORY BOWEL DISEASE

In addition to promoting good health, exercise may help counteract IBD-related complications, such as improving bone mineral density, immunologic response, psychological health, weight loss, and stress management ability. Exercise and physical activity also may help patients cope with and minimize symptoms related to extraintestinal manifestations of IBD. Further research, however, is needed to make recommendations regarding exercise regimens for patients with IBD.

Bone Health

Approximately 40% of patients with Crohn disease have bone mineral density loss, with some reports reaching up to 80%.^{43–53} Metabolic bone disease among patients with IBD is multifactorial and could be related to an individual's age or genetic predisposition, precipitated by the inflammatory disease process itself, use of glucocorticoids, malabsorption, weight loss, and lifestyle changes, such as decreased exercise. The inflammation associated with active IBD contributes to high circulating cytokine levels, such as interleukin-1, interleukin-6, and TNF- α . This increase in cytokines in turn augments the normal bone-remodeling process by increasing osteoclastic and decreasing osteoblastic functions.⁴³ The resulting reduced bone mineral density is observed in patients with IBD, namely patients with Crohn disease, even before the institution of steroid therapy, indicating that the cytokines play a role in altered bone density independent of steroid use.⁵⁴ Additionally, it was shown that bone turnover markers normalized in patients with Crohn disease as early as 8 weeks after treatment with anti-TNF- α therapy, regardless of clinical remission, because of its effect on circulating cytokines.⁵⁵ Not only do cytokines alter bone morphology, they have been found to negatively affect muscle mass.^{56–59}

In healthy individuals, exercise and physical activity improve bone strength by a “muscle-pull” effect that causes an osteogenic stimulus as the muscles undergo a contraction pull on their bony attachments, resulting in a local deformation.^{60,61} Another important mechanism in which exercise promotes bone health is via weight-bearing activities that cause a direct compression and more deformation on the bone that similarly results in an osteogenic stimulus. Studies have shown that muscle mass and bone health go hand-in-hand among healthy patients.⁶²

Lee and colleagues⁴³ reported that patients with Crohn disease benefited from high-impact exercises because of their effect on muscle mass, skeletal health, and osteogenic stimuli, and also because they helped increase patients' body weight. The increased weight in turn increases the mechanical loading during activity and will lead to a positive effect on bone health. In a study by Robinson and colleagues,⁶³ 117 patients with Crohn disease were randomized to a control group or an intervention group that entailed a 12-month low-impact exercise program. Although bone mineral density increased among the intervention group compared with the control group, this increase was not statistically significant. It is possible that if the exercise was more intense, then a significant difference may be achieved. Despite the results, it is noted that among patients with Crohn disease, exercise and physical activity play an important role in preventing and treating disturbed bone mineral density (osteopenia and osteoporosis) and also result in increased muscle mass and muscle strength.

Ankylosing Spondylitis

Ankylosing spondylitis has been closely linked with IBD. One percent to 8% of patients with IBD develop ankylosing spondylitis, and as many as 18% are found to have asymptomatic sacroiliitis that is incidentally diagnosed on imaging.⁶⁴ Studies have

shown that exercise plays an important role in improving joint flexibility of patients with ankylosing spondylitis, specifically the spinal column, and that exercise further increases muscle strength and leads to less joint pain.^{65–67}

Psychological Benefit of Exercise

Exercise has been shown to help in stress reduction, which subsequently positively impacts IBD symptoms and overall quality of life.^{68,69} Different exercises have been investigated, including walking, running, swimming, and yoga, all of which have had a significant impact on stress reduction. Stress itself is a trigger for active disease, so elimination and minimization of stress may play a role in prolonging periods of disease remission among patients with IBD. Stress reduction also decreases symptoms of anxiety and leads to improved quality of life.⁷⁰

Immune Response

Low-intensity and moderate-intensity exercise has been shown to improve the immune system.⁷¹ High-intensity exercises and prolonged periods of exercise, however, tend to negatively impact the immune system. By exercising in moderation, an individual's immune system is naturally boosted, subsequently leading to a "healthier" body.

Maintaining Normal Weight

In the past, patients with IBD were thought to be underweight and cachectic; however, more recently, with the obesity epidemic, up to 40% of patients with IBD are found to be obese.⁷² Obesity is a proinflammatory state, and exercise helps individuals lose weight that in turn aids in the reduction of proinflammatory cytokines that are associated with obesity. Seminerio and colleagues⁷³ showed that obesity was more commonly encountered among patients with ulcerative colitis rather than patients with Crohn disease. Additionally, obese patients were found to have comorbid conditions, such as diabetes mellitus, hypertension, and hyperlipidemia, and these patients had a poor quality of life and elevated biochemical inflammatory markers (CRP). The poor quality of life and elevated CRP, however, were not independently correlated with obesity.⁷³ Additionally in that study, obesity was not found to be a predictor of high health care utilization. Results of the study by Seminerio and colleagues⁷³ were different from prior literature that demonstrated that obese patients with Crohn disease had higher hospitalization rates than normal-weight patients with Crohn disease.⁷⁴ Older literature demonstrated that obese patients with Crohn disease were more likely to have anoperineal complications within a shorter time frame, require surgery within a shorter time frame, and had higher instances of active disease.^{74,75} Similarly, poor outcomes were noted among obese patients with ulcerative colitis, especially in terms of worse surgical outcomes with higher chance of pelvic sepsis and perioperative morbidity when compared with nonobese patients with ulcerative colitis.⁷⁶ The effect of obesity on IBD medications has not been clearly investigated, but it has been noted that obese patients have rapid clearance of biologic agents and, as a result, have sub-optimal response to therapy. Exercise helps obese patients reach their ideal weight, thus limiting complications from the obesity, decreasing the proinflammatory state, and also improving response to therapy, particularly biologic therapy.

SUMMARY

Regular exercise is essential for maintaining a healthy lifestyle, improving physical endurance, preventing frailty, and improving quality of life and psychological status. There is a growing appreciation that regular exercise regimens are essential for

patients suffering from chronic inflammatory disorders, including IBD. Although data are limited, an emerging signal suggests that regular exercise early in life may help to prevent the development of Crohn disease. Mechanistic studies suggest benefits of moderate exercise on both mucosal immune function and maintaining a healthy gut microbiome. Maintaining a regular exercise regimen also may exert a beneficial modifying effect on disease course, improving inflammatory parameters, psychological status, and quality of life in patients with IBD.

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