

Exercise and Crohn's disease: Speculations on potential benefits

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Crohn's disease (CD) is a chronic inflammatory bowel disease that affects nearly one million people in the United States and Canada. While current pharmaceutical treatments are effective in controlling symptoms, patients continue to experience a reduced quality of life (QOL). Based on preliminary studies, QOL in CD patients may be improved by engaging in physical activity. Exercise may decrease CD activity and reduce psychological stress. Current research also suggests that low-intensity exercise does not exacerbate gastrointestinal symptoms and does not lead to flare-ups. Furthermore, exercise appears to reduce CD symptoms and improve QOL. In summary, physical activity may be beneficial to certain patient groups, but more studies are needed before broad recommendations can be made.

Key Words: *Crohn's disease; Exercise; Quality of life*

Crohn's disease (CD) affects close to one million people in the United States and Canada. While the traditional therapeutic goal has been to induce long-term remission, this does not necessarily indicate that a patient is asymptomatic and enjoys a high quality of life (QOL). On the contrary, QOL is reduced in both symptomatic CD patients and patients in remission (1).

QOL is a complex term to define. When considering inflammatory bowel disease (IBD) specifically, Irvine (2) perceived QOL to be the impact of a chronic illness on a patient's function, behaviour or performance, and reflecting the patient's perceptions, beliefs and attitude. Both physiological and psychological components affect QOL in CD patients, and each deserves attention from the clinician. Low QOL, arising from both disease activity and psychological distress, has been well documented in the literature (3-12).

The role of exercise in CD has not been well studied. The benefits of physical activity for good health have been widely shown in the general population (13-16). In other chronic illnesses, such as rheumatoid arthritis, exercise has been recommended to improve general health, as well as reduce or prevent disease activity. The present review examines preliminary studies on the impact of exercise on CD, effects of exercise on gastrointestinal (GI) symptoms, and the potential for exercise to improve bone mineral density (BMD) and psychological health. Recommendations are made concerning future areas of research.

L'exercice et la maladie de Crohn : Les spéculations quant à ses bienfaits potentiels

La maladie de Crohn (MC) est une maladie inflammatoire de l'intestin dont près d'un million de personnes sont atteintes aux États-Unis et au Canada. Les traitements pharmaceutiques sont efficaces pour contrôler les symptômes, mais les patients continuent d'avoir une qualité de vie (QV) réduite. D'après des études préliminaires, la QV des personnes atteintes de la MC peut s'améliorer grâce à l'activité physique. L'exercice pourrait réduire l'activité et le stress psychologique de la MC. Les recherches courantes indiquent également que l'exercice de faible intensité n'exacerbe pas les symptômes gastro-intestinaux et n'entraîne pas de récives. De plus, l'exercice semble réduire les symptômes de MC et améliorer la QV. Bref, l'activité physique peut être bénéfique à certains groupes de patients, mais plus d'études s'imposent avant qu'on puisse formuler des recommandations plus généralisées.

EXERCISE EFFECTS ON GI SYMPTOMS AND CD

Currently, a recommendation for exercise does not exist for CD patients. The American College of Sports Medicine states that the goals of exercise training for individuals with chronic illnesses include, counteracting the detrimental physiological effects of bed rest or previous sedentary living patterns, and optimizing patient's functional capacity within the physiological limitations of the disease (17). With this principle in mind, the task is to find an exercise intensity that is safe and beneficial to the individual.

In the past, studies of the effect of exercise on the GI tract have involved healthy athletes (18-21). Consequently, these have focused on high-intensity activities, which not surprisingly produced GI symptoms and disturbances. Baska et al (18) hypothesized that during exercise, luminal agents such as bile, pancreatic secretions and bacteria can cross tight junctions in the small intestine and cause a local immune response. Further research by Pals et al (19) and Travis and Menzies (20) used the lactulose-to-rhamnose ratio method to determine intestinal permeability. They found an increase in the lactulose-to-rhamnose ratio at 80% aerobic capacity peak exercise, indicating that there was an increase in paracellular transport through leaky tight junctions in the small intestine. However, this phenomenon was not found during low-intensity exercises such as at 40% peak aerobic capacity.

Another common GI disturbance during exercise is the urge to defecate. Rao et al (21) found that there was an

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TABLE 1
Potential undesirable symptoms that may occur during exercise in the Crohn's disease patient population

Patient should stop exercising and consult a physician if:

- Gastrointestinal symptoms increase
- General feeling of unwell or malaise
- Fainting
- Dizziness
- Chest pains
- Significant shortness of breath

intensity-dependent decrease in the number of pressure waves and the area under the curve in pressure waves in the gut. The decrease in colonic phasic activity may offer less resistance to colonic flow and a decreased transit time, leading to the urge to defecate. In the case of the diarrhea-prone CD patient, this is an unwanted side effect. Table 1 lists some potential undesirable symptoms that may occur during exercise in the CD patient population.

The study of the effect of exercise on IBD was first reported when Sonnenberg (22) examined the incidence of IBD in individuals by their occupation. He found that workers whose jobs involved the outdoors and physical activity were less likely to develop IBD than those who worked in air conditioned, indoor working conditions. In another important epidemiological study, Persson et al (23) found that the relative risk of CD was inversely related to physical activity. These two studies suggest that exercise may have a protective effect against CD.

There have only been two small studies that have evaluated the effects of exercise on CD. In one study, Loudon et al (24) looked at the effects of a low-intensity group walking program on CD patients. Twelve subjects participated in the program; however, there was no control group. At the completion of the three-month program, the IBD Questionnaire, IBD Stress Index and the Harvey-Bradshaw Index all showed statistical improvements (pre- and postexercise scores = 172 ± 27 and 189 ± 12 , 29.2 ± 15.4 and 19.5 ± 10.8 , and 5.9 ± 5.0 and 3.6 ± 3.1 , respectively; $P < 0.05$). Furthermore, the maximum aerobic capacity and body mass index both improved, indicating that the potential for improvement in fitness and physical health exists. Together, the findings from this small study suggest that exercise may improve general well-being, fitness and QOL. The low-intensity walking program did not exacerbate GI symptoms and the disease condition did not deteriorate in this patient group.

In another study, D'Inca et al (25) investigated the effects of a one time bout of moderate-intensity exercise on CD patients in remission. Similarly, this study did not include a control group. On a cycle ergometer, research participants cycled at an incremental load to exhaustion. They were then allowed to rest for approximately 1 h before carrying out the exercise protocol of 60% maximum aerobic capacity for 1 h. In this study, D'Inca et al (25) did not observe any increased symptoms during or immediately after the protocol. Furthermore, there was no increase in the frequency of relapse at a period of six months after the exercise bout. Therefore, although more research is needed, a moderate-intensity exercise program is probably safe for some CD patients.

POTENTIAL FOR EXERCISE TO IMPROVE BMD

Currently, poor BMD in patients with CD is an active area of research. It has been reported that osteopenia occurs in 40% to 50% of IBD patients and approximately 15% develop osteoporosis (26-30). Low BMD may expose patients to a high risk of bone fractures (31-33). Causes of low BMD are multifactorial, with nutrient deficiencies and corticosteroid and inflammatory substance use being contributors (34,35).

In patients with rheumatoid arthritis who take corticosteroids, there is a 100% increase in the risk of fractures (36,37). In studies more specific to IBD, the magnitude of the risk of corticosteroid-related fractures was related to the daily corticosteroid dose. The risk of fractures increased shortly after the start of oral corticosteroid treatment and reversed toward baseline levels after the discontinuation of oral corticosteroids, indicating a strong relationship between steroid dose and fracture risk in CD patients (38,39). Further studies (40-42) have shown that the total dose of corticosteroids is inversely associated with BMD. In addition, corticosteroid use has been shown to increase protein oxidation (43). The muscle is a large storage site of protein, and corticosteroid use may induce muscle loss and contribute to decreased muscle strength and endurance. Both aerobic and resistance exercises may be beneficial by inducing muscle hypertrophy and conditioning, and by offsetting the effects of corticosteroids.

It has also been postulated that the inflammatory effect of CD is a potential contributor to low BMD. Inflammatory cytokines such as interleukin-1 may induce the receptor activator of nuclear factor-kappa B ligand in the bone metabolism pathways and promote bone resorption (44,45). In addition, reduced bone formation in CD patients can further contribute to a low BMD (46).

Low BMD is a significant health risk and may contribute to a poor QOL, leading to fractures, and limiting work and participation in social activities. Osteopenia, common in children with IBD, may have ramifications on growth patterns into puberty and beyond (47). Aside from pharmaceutical and nutrient supplementation, the best treatment for low BMD is exercise. For years, the importance of exercise as a major vehicle to develop bone integrity has been stressed. The mechanical loading of the muscles acting on the bone causes an anabolic effect and results in osteogenesis (48). The prevention of osteopenia and/or treatment of low BMD can potentially have a positive effect on the QOL of the CD patient by reducing the risk of fractures and enabling a more active social life. However, before commencing an exercise program, the BMD of the CD patient should be known. A physical activity prescription should be tailored to the baseline health status of the patient. In patients with bone demineralization, injuries and fractures, including stress fractures, are a concern and, therefore, a supervised program of low-intensity, weight-bearing exercises is the most appropriate activity to begin an active lifestyle.

Robinson et al (49) studied the impact of low-intensity exercise on the risk of osteoporosis and on BMD in CD patients. The study focused on low-impact exercises to improve BMD and demonstrated a slight improvement in BMD directly related to the number of exercise sessions completed, suggesting a dose response. A control group was present in the study. BMD, measured in the greater trochanter, increased an average of 8% ($P = 0.02$) after the exercise program

and patients did not experience any exacerbations in GI symptoms.

POTENTIAL FOR EXERCISE TO IMPROVE PSYCHOLOGICAL HEALTH

In addition to the potential benefits on BMD, exercise may also improve psychological health (16). The clinical goal of the physician is to bring the CD patient into a state of disease remission. However, the patient may continue to have psychological distress. For example, in a study by Minderhoud et al (11), 42% of CD patients in remission fulfilled the Rome II criteria for diagnosis of irritable bowel syndrome, a percentage considerably higher than the normal 10% to 20% found in the general population. Therefore, the irritable bowel syndrome, symptoms of diarrhea, anxiety, urgency, foul flatulence and varying degrees of abdominal pain can undoubtedly affect the psychological profile of the patient. While pharmaceutical treatment may be effective for physical symptoms, exercise can be used to positively influence psychological health. Exercise has been shown to be successful in improving the psychological health of individuals, as well as in patients with chronic diseases such as cancer and rheumatoid arthritis (50-66). While Loudon et al (24) found that low-intensity group exercise improved the QOL scores, this was not specific to psychological health. More research is merited in this area especially because Guthrie et al (67) have argued that psychological factors and disease activity independently affect QOL in IBD patients.

REFERENCES

- Martin A, Leone L, Fries W, Naccarato R. Quality of life in inflammatory bowel disease. *Ital J Gastroenterol* 1995;27:450-4.
- Irvine EJ. Review article: Patients fears and unmet needs in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20(Suppl 4):54-9.
- Mitchell A, Guyatt G, Singer J, et al. Quality of life in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1988;10:306-10.
- Drossman DA, Patrick DL, Mitchell CM, Zagami EA, Appelbaum MI. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns. *Dig Dis Sci* 1989;34:1379-86.
- Drossman DA, Leserman J, Mitchell CM, Li ZM, Zagami EA, Patrick DL. Health status and health care use in persons with inflammatory bowel disease. A national sample. *Dig Dis Sci* 1991;36:1746-55.
- Irvine EJ. Quality of Life – Measurement in inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1993;199:36-9.
- Porcelli P, Zaka S, Centonze S, Sisto G. Psychological distress and levels of disease activity in inflammatory bowel disease. *Ital J Gastroenterol* 1994;26:111-5.
- Porcelli P, Leoci C, Guerra V. A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scand J Gastroenterol* 1996;31:792-6.
- Irvine EF, Grace E, Kerr GD, et al. Non-disease related factors affecting health related quality of life (HRQOL) in inflammatory bowel disease (IBD). *Gastroenterology* 1998;114:1002A. (Abst)
- Isgar B, Harman M, Kaye MD, Whorwell PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983;24:190-2.
- Minderhoud IM, Oldenburg B, Wismeijer JA, van Berge Henegouwen GP, Smout AJ. IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior. *Dig Dis Sci* 2004;49:469-74.
- Simren M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Björnsson ES. Quality of life in inflammatory bowel disease in remission: The impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;97:389-96.
- Paffenbarger RS Jr, Hyde RT, Wing AL, Steinmetz CH. A natural history of athleticism and cardiovascular health. *JAMA* 1984;252:491-5.
- Ellington T, Conn VS. Exercise and quality of life in elderly individuals. *J Gerontol Nurs* 2000;26:17-25.
- Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995;122:327-34.
- Weyerer S, Kupfer B. Physical exercise and psychological health. *Sports Med* 1994;17:108-16.
- American College of Sports Medicine. Guidelines for Exercise Testing and Prescription, 4th edn Philadelphia: Lea and Febiger, 1991.
- Baska RS, Moses FM, Graeber G, Kearney G. Gastrointestinal bleeding during an ultramarathon. *Dig Dis Sci* 1990;35:276-9.
- Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;82:571-6.
- Travis S, Menzies I. Intestinal permeability: Functional assessment and significance. *Clin Sci (Lond)* 1992;82:471-88.
- Rao SS, Beaty J, Chamberlain M, Lambert PG, Gisolfi C. Effects of acute graded exercise on human colonic motility. *Am J Physiol* 1999;276:1221-6.
- Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut* 1990;31:1037-40.
- Persson PG, Leijonmarck CE, Bernell O, Hellers G, Ahlborn A. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;22:268-72.
- Loudon CP, Corroll V, Butcher J, Rawsthorne P, Bernstein CN. The effects of physical exercise on patients with Crohn's disease. *Am J Gastroenterol* 1999;94:697-703.
- D'Inca R, Varnier M, Mestriner C, Martines D, D'Odorico A, Sturniolo GC. Effect of moderate exercise on Crohn's disease patients in remission. *Ital J Gastroenterol Hepatol* 1999;31:205-10.
- Bernstein CD. Calcium and bone tissues in inflammatory bowel disease. *Gastroenterol Int* 1997;10:71-7.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Medical advances have produced a variety of pharmaceutical options for CD patients. Even so, CD patients continue to suffer physical and psychological symptoms that affect their QOL. The research thus far has shown that low-intensity exercise has no negative effects on either physiological or psychological health. The evidence seems to point toward a beneficial effect to both physiological and psychological health, which ultimately improves QOL. BMD, QOL, body mass index and muscle mass show improvement secondary to exercise programs. All of these parameters are commonly diminished in CD patients.

While preliminary studies suggest exercise may be beneficial to CD patients, further research is warranted to confirm these observations and define whether all patient groups would benefit. Higher intensities and longer durations of exercise studies are also needed to establish a potential upper tolerable limit for physical activity in CD patients.

Other forms of exercise such as swimming and cycling could be used to evaluate any potential benefits. Anecdotal evidence based on patients' personal accounts suggests that cycling causes fewer GI symptoms than running or brisk walking because the person is stationary. Therefore, patients with CD could potentially respond better to cycling. Other types of exercises may also be used, such as a weight training program, which may be of most benefit to CD patients with low BMD because the mechanical loading of muscles promotes osteogenesis.

27. Compston JE. Review article: Osteoporosis, corticosteroids and inflammatory bowel disease. *Aliment Pharmacol Ther* 1995;9:237-50.
28. Robinson RJ, al-Azzawi F, Iqbal SJ, et al. Osteoporosis and determinants of bone density in patients with Crohn's disease. *Dig Dis Sci* 1998;43:2500-6.
29. Fries W, Dinca M, Luisetto G, Peccolo F, Bottega F, Martin A. Calcaneal ultrasound bone densitometry in inflammatory bowel disease – A comparison with double x-ray densitometry of the lumbar spine. *Am J Gastroenterol* 1998;93:2339-44.
30. Silvennoinen JA, Karttunen TJ, Niemela SE, Manelius JJ, Lehtola JK. A controlled study of bone mineral density in patients with inflammatory bowel disease. *Gut* 1995;37:71-6.
31. Pigot F, Roux C, Chaussade S, et al. Low bone mineral density in patients with inflammatory bowel disease. *Dig Dis Sci* 1992;37:1396-403.
32. Robinson RJ, Iqbal SJ, Abrams K, Al-Azzawi F, Mayberry JF. Increased bone resorption in patients with Crohn's disease. *Aliment Pharmacol Ther* 1998;12:699-705.
33. Bernstein CN, Seeger LL, Sayre JW, Anton PA, Artinian L, Shanahan F. Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. *J Bone Miner Res* 1995;10:250-6.
34. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Bone mineral density in patients with inflammatory bowel disease: A population-based prospective two-year follow-up study. *Scand J Gastroenterol* 2004;39:145-53.
35. Bischoff SC, Herrmann A, Goke M, Manns MP, von zur Muhlen A, Brabant G. Altered bone metabolism in inflammatory bowel disease. *Am J Gastroenterol* 1997;92:1157-63.
36. Hooyman JR, Melton LJ III, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. *Arthritis Rheum* 1984;27:1353-61.
37. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995;54:49-52.
38. Jahnsen J, Falch JA, Aadland E, Mowinckel P. Bone mineral density is reduced in patients with Crohn's disease but not in patients with ulcerative colitis: A population based study. *Gut* 1997;40:313-9.
39. Bernstein CN, Blanchard JF, Metge C, Yogendran M. The association between corticosteroid use and development of fractures among IBD patients in a population-based database. *Am J Gastroenterol* 2003;98:1797-801.
40. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;20:1487-94.
41. Compston JE, Judd D, Crawley EO, et al. Osteoporosis in patients with inflammatory bowel disease. *Gut* 1987;28:410-5.
42. Abitbol V, Roux C, Chaussade S, et al. Metabolic bone assessment in patients with inflammatory bowel disease. *Gastroenterology* 1995;108:417-22.
43. Al-Jaouni R, Schneider SM, Piche T, Rampal P, Hebuterne X. Effect of steroids on energy expenditure and substrate oxidation in women with Crohn's disease. *Am J Gastroenterol* 2002;97:2843-9.
44. Schulte CM. Review article: Bone disease in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20(Suppl 4):43-9.
45. Moschen AR, Kaser A, Enrich B, et al. The RANKL/OPG system is activated in inflammatory bowel disease and relates to the state of bone loss. *Gut* 2005;54:479-87.
46. Vestergaard P, Krogh K, Rejnmark L, Laurberg S, Mosekilde L. Fracture risk is increased in Crohn's disease, but not in ulcerative colitis. *Gut* 2000;46:176-81.
47. Cowan FJ, Warner JT, Dunstan FD, Evans WD, Gregory JW, Jenkins HR. Inflammatory bowel disease and predisposition to osteopenia. *Arch Dis Child* 1997;76:325-9.
48. Turner CH, Robling AG. Exercise as an anabolic stimulus for bone. *Curr Pharm Des* 2004;10:2629-41.
49. Robinson RJ, Krzywicki T, Almond L, et al. Effect of a low-impact exercise program on bone mineral density in Crohn's disease: A randomized controlled trial. *Gastroenterology* 1998;115:36-41.
50. Brown DW, Brown DR, Heath GW, et al. Associations between physical activity dose and health-related quality of life. *Med Sci Sports Exerc* 2004;36:890-6.
51. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. *Med Sci Sports Exerc* 2001;33(Suppl 6):587-97.
52. Tsai JC, Chan P, Wang CH, et al. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. *J Intern Med* 2002;252:448-55.
53. McMurdo ME, Burnett L. Randomised controlled trial of exercise in the elderly. *Gerontology* 1992;38:292-8.
54. Schroll M. Physical activity in an ageing population. *Scand J Med Sci Sports* 2003;13:63-9.
55. Courneya KS. Exercise in cancer survivors: An overview of research. *Med Sci Sports Exerc* 2003;35:1846-52.
56. Burnham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. *Med Sci Sports Exerc* 2002;34:1863-7.
57. Dunn AL, Garcia ME, Marcus BH, Kampert JB, Kohl HW, Blair SN. Six-month physical activity and fitness changes in Project Active, a randomized trial. *Med Sci Sports Exerc* 1998;30:1076-83.
58. King AC, Haskell WL, Young DR, Oka RK, Stefanick ML. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years. *Circulation* 1995;91:2596-604.
59. Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. *Med Sci Sports Exerc* 1998;30:475-8.
60. Belza B, Topolski T, Kinne S, Patrick DL, Ramsey SD. Does adherence make a difference? Results from a community-based aquatic exercise program. *Nurs Res* 2002;51:285-91.
61. Durak EP, Harris J, Ceriale SM. The effects of exercise on quality of life improvements in cancer survivors: The results of a national survey. *JEPonline* 2001;4:21-28.
62. Kull M. The relationships between physical activity, health status and psychological well-being of fertility-aged women. *Scand J Med Sci Sports* 2002;12:241-7.
63. Stephens T. Physical activity and mental health in the United States and Canada: Evidence from four population surveys. *Prev Med* 1988;17:35-47.
64. Farmer ME, Locke BZ, Moscicki EK, Dannenberg AL, Larson DB, Radloff LS. Physical activity and depressive symptoms: The NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol* 1988;128:1340-51.
65. Stewart AL, Hays RD, Wells KB, Rogers WH, Spritzer KL, Greenfield S. Long-term functioning and well-being outcomes associated with physical activity and exercise in patients with chronic conditions in the Medical Outcomes Study. *J Clin Epidemiol* 1994;47:719-30.
66. Martinsen EW. Physical activity and depression: Clinical experience. *Acta Psychiatr Scand Suppl* 1994;377:23-7.
67. Guthrie E, Jackson J, Shaffer J, Thompson D, Tomenson B, Creed F. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. *Am J Gastroenterol* 2002;97:1994-9.




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