Original Article

Exercise Improves Clinical Symptoms, Pathological Changes and Oxidative/Antioxidative Balance in Animal Model of Colitis

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Abstract

Background: Ulcerative colitis is one of the major phenotypic forms of inflammatory bowel diseases. The present study aimed to investigate the effect of force swimming exercise on clinical symptoms (disease activity index; DAI), colon histopathology, inflammation and fibrosis, and oxidant/antioxidant balance in dextran sulfate sodium (DSS)-induced colitis mice. **Methods:** Male C57BL6 mice were randomly divided into five groups (n = 6 each): control, exercise, colitis, colitis + sulfasalazine, and colitis + exercise. Exercise was performed by forced swimming six weeks before and during the experiment. Colitis was induced by 1.5% DSS in drinking water. The animals were evaluated for body weight changes and DAI (including changes of body weight, stool consistency, rectal bleeding, and prolapse) during the induction of colitis and treatment. At the end of experiment, colons and spleens were evaluated by H and E and Masson Trichrome stainings. Oxidant (Malon dialdehyde; MDA), and antioxidant markers [total thiol groups, superoxide dismutase (SOD), and catalase activity] were also measured in colon tissue. **Results:** Results indicated that exercise in colitis mice significantly improved DAI, colon length, spleen weight, and histological injury score and alleviated fibrotic changes in colon tissue that were comparable to sulfasalazine group. Exercise also restored the oxidant/antioxidant balance in colitis mice by reducing MDA and increasing antioxidative markers including total thiol groups, SOD, and catalase activity. **Conclusions:** Taken together, aerobic exercise could improve clinical symptoms and colonic inflammation through, at least, the balancing the oxidative stress markers. Thus, it can be considered in management of colitis patients as effective method.

Keywords: *Colitis, dextran sulfate, exercise, inflammatory bowel diseases*

Introduction

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are a group of gastrointestinal tract diseases that are accompanied by diarrhea, abdominal pain, malnutrition, and rectal bleeding.[1] Despite the fact that IBDs are idiopathic, the recent hypothesis for their pathogenesis is that there is an interaction between genetic and environmental factors, and changes in the microbial intestinal flora, which cause disruption in intestinal barrier, resulting in exaggerated immunological responsiveness to normal bacteria in the gut lumen.[2] Immune system in gut is normally in a state of homeostasis, but in IBD, immunological control is disrupted, resulting in an imbalance between pro- and antiinflammatory processes, which cause the intestinal immune system to stay chronically engaged and, hence, inflamed.[2] Chronic inflammation is a pathological hallmark of IBD in humans and animals.[3] Dysbiotic gut microbiota, which is frequently reported in IBD patients,[4] suggests that changes in composition of gut microbiom in Westernized diets may also play a role in IBD etiology.[4]

Regular, moderate exercise has been indicated to benefit in some tissues, including heart, adipose tissue, muscle and brain, as well as reducing the risk of metabolic and inflammatory disease.[5] Exercise training has also been shown to impact the gut and its related gut microbiota in animals in recent studies.[6-8] Moreover, changes in the gut microbiome during exercise have been linked to changes in some physiological factors, such as changes in metabolism, behavior, and immunology.[9,10] These data show that physical exercise and/or changes in gut microbiom may have beneficial effects in

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colitis development, while the underlying mechanism(s) is still unknown. Regular physical activity, as a result of intricate interactions between interrelated physiological mechanisms, has been shown to have significant effects on overall wellbeing.[2]

Although evidence exists that low intensity exercise training protects against oxidative damage of colonic tissue in animal model of colitis induced by dextran sodium sulfate (DSS),[11] it seems that the most overall benefits of exercise are seen when the sedentary patients become mild or moderately active,[12] it is unclear whether recommendation for current moderate intensity exercise are effective. Therefore, this study aimed to investigate the effect of 6-weeks force swimming exercise on clinical symptoms and histopathological changes associated in animal model of colitis.

Materials and Methods

Chemicals

Dextran sulfate sodium (DSS; molecular weight: 40 kDa, purity: 98%) was purchased from Sigma Co. (CA, USA) and dissolved in usual drinking water. All other reagents and chemicals were purchased from Cayman Co. All suspensions were freshly prepared before use.

Animal ethics statement

Male C57BL6 mice (weighing between 22 and 24 g) were purchased from the Pasteur Institute of Iran and kept with a normal temperature of between 22 and 25°C, and relative humidity of 50% to 60%, with a regular 12h light-dark cycles with free access to tap water and standard diet for one week before the experiments. All experimental protocols were approved and conducted according to the Guidelines for the Use of Laboratory Animals by the by the Ethical Committee of Mashhad University of Medical Sciences (Ethical code: IR.MUMS.MEDICAL.REC.1399.685). The animals were sacrificed under anesthesia by sodium pentobarbital (30 mg/kg, intraperitoneally).

Animals and study design

Mice were randomly divided into five groups as follow: Group I: control, Group II: exercise, Group III: Colitis, Group IV: colitis + sulfasalazine (colitis + Sulfa) as standard treatment in UC, and Group V: colitis + exercise (n = 6 each). A schematic presentation of study protocol is shown in Figure 1. a. Exercise was performed for six weeks and then in colitis groups (groups III, IV, and V), the DSS were dissolved in drinking water [1.5% (w/v)] for one week and other groups (groups I and II) were used as a vehicle control and received usual drinking water during the study. This model of colitis was established as previously described.[13] Groups IV received sulfasalazine, as a standard therapy (100 mg/kg; oral gavage)[1] in last 7 days. Exercise was continued throughout the experiment for groups II and V and other groups had a sedentary life.

Table 1: The disease activity index (DAI) scoring parameters

Disease activity index				
Score	**Rectal bleeding**	**Stool consistency**	**Rectal prolapse**	**Lose weight**
0	None	Normal	None	<5%
1	Red	Soft	Sign of prolapse	5-10%
2	Dark red	Very soft	Clear prolapse	10-15%
3	Gross bleeding	Diarrhea	Extensive prolapse	>15%

Swimming exercise

In this study, we used a weight-unloaded swimming training which described previously.[14] Swimming was performed in a 120 cm glass container, 80 cm depth, filled with water and maintained at 34–37°C. The animals were acclimatized to the swimming pool one week before starting the experiment. Then, the mice were trained for about 15–20 min, 5 days/week for 6 weeks. Then, in colitis groups, DSS administration began and swimming was continued during the study.

Animals follow up and sampling

During the study, disease activity index (DAI) was measured and scored every day after starting DSS administration. DAI score was calculated according to a method previously described[13] to assess the disease severity and checked daily based on changes of body weight, rectal bleeding, stool consistency and rectal prolapse and the highest DAI index in experimental groups was reported. At the end of study, mice were weighted and sacrificed. The spleen was harvested for photo'ing and weighing. In addition, colon was dissected and colon length (from cecum to rectum) was measured. Then, colons were longitudinally cut, washed with cold normal saline and removed from fecal residue and weighted. A part of isolated distal colon was stored in formalin 10% solution for histopathological staining and analysis. The middle part of colon was dissected and saved at -20°C for measurement of oxidative (malondialdehyde: MDA) and antioxidative stress markers (total thiol groups, catalase and superoxide dismutase, SOD, activity).

Histopathologic evaluations

The harvested colon tissues were put in neutralized formalin (10%) and embedded in paraffin. Then, they were sectioned (5 μm thickness), and mounted on poly lysine covered slides. Then, they were deparaffinized and the sections stained with hematoxylin and eosin (H&E). Each sample was observed at 4 and ×10 magnifications. The degree of histological score change was recorded as previously described[1] according to: the degree of inflammation (0–3), crypt loss (0–4), pathological changes (0–4) and mucosal damage (0–3). Total number of these score was considered as histological score [Table 2]. The sections were also stained by Mason trichrome for evaluation of tissue collagen content. The stained slices were observed at 4 and ×10

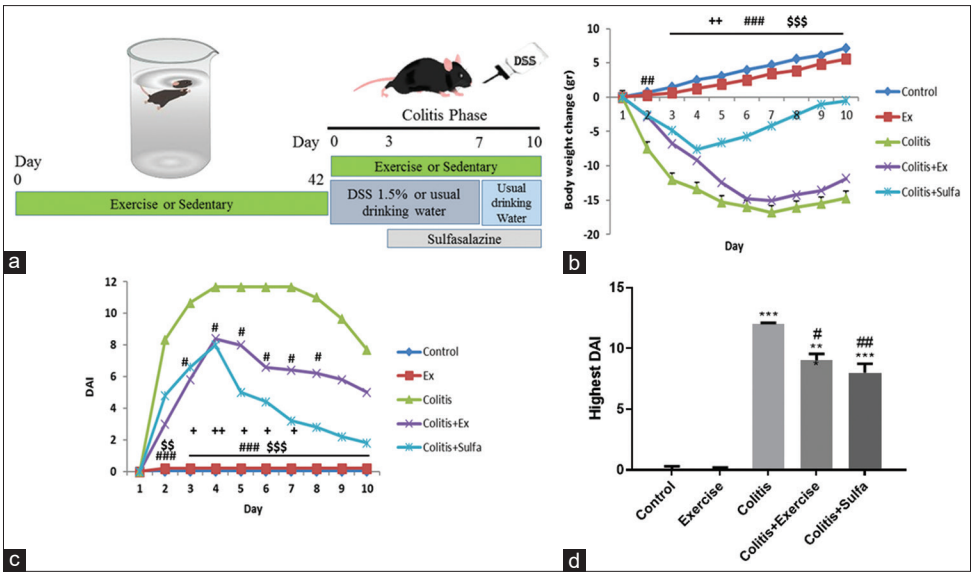

Figure 1: The colitis clinical symptoms ameliorated with exercise. (a) Schematic presentation of the experimental protocol of colitis model and exercise. (b) daily changes of body weight during colitis. (c and d) The effects of exercise on daily disease activity index (DAI) (c) and highest DAI (d). ***P < 0.001 vs. control. #*P* < 0.05, ##P < 0.01 and ###P < 0.001 vs. colitis group. $$P < 0.01 and $$$ P < 0.001 vs. colitis + exercise group. +P < 0.05 and ++P < 0.01 vs. colitis + sulfa group. Data are reported as Mean ± SE. (n = 6 each)

magnifications under an optical microscope (Nikon, E 100) and percent of fibrosis was analyzed using image J software. Tissue histology was recorded from 10 independent measurements on five different sections in each specimen by two independent pathologists.

Measurement of catalase activity

By measuring the changes of absorbance measured at 240 nm by a spectrophotometer, catalase activity in the supernatants of colon homogenates was determined by its ability to decompose hydrogen peroxide (H_2O_2).[15]

Measurement of MDA in colon tissue

One of the indicator of lipid peroxidation is Malon dialdehyde (MDA) which was measured using the thiobarbituric acid (TBA) assay as previously reported.[15] Absorbance was read at 535 nm, and the results were reported as nmol/g tissue.

Evaluation of total thiol groups

Total thiol groups levels in colon homogenates were measured using 5,5′-dithiobis 2-nitrobenzoic acid (DTNB) reagent.[15] The optical density of the colored product was recorded and the results were reported as μmol/g tissue.

Evaluation of SOD activity

By measuring the ability of SOD in inhibition of the autooxidation of pyrogallol, SOD activity in colon homogenate was determined, as previously described.[15] In this method, the amount of enzyme needs for 50% inhibition of auto oxidation of pyrogallol in one minute considers as one unit of SOD. The change in absorbance at 420 nm was determined every one minute for three times and the results were reported as U/g tissue.

Table 2. Colonic histopathological scoring parameters

Score	0	1	2	3	4
Inflammation	None	Mild	Moderate	Severe	
Mucosal damage	None	Mucus layer	Submucosa	Muscular and serosa	
Crypt loss	None	1/3	2/3	100% + intact epithelium	100% with epithelium lose
Pathological change range	None	1-25%	26-50%	51-75%	76-100%

Statistical analysis

SPSS version 20 software was used for Statistical analysis. *P* Value less than 0.05 was considered as statistically significant. Data were reported as the means ± standard error (SE). Intergroup differences were analyzed using one-way ANOVA or two-way ANOVA with Tukey's *post hoc* test where appropriate.

Results

Effects of exercise on body weight and DAI in colitis

Figure 1: b illustrates the body weight change during the experiment. The control and exercise groups showed a steady increase in body weight. On the first 4 days after DSS administration, the body weight of animals in colitis groups was reduced, however, after that, the body weight in sulfasalazine-treated group gradually increased, although it did not reach to body weight of control group. DSS-alone treatment and Exercise + DSS groups had a significant reduction in body weight gain.

Evaluation of DAI including changes of body weight, rectal bleeding, stool consistency and rectal prolapse indicated that the animals who received DSS-alone (colitis group) had high DAI and experienced higher DAI during the study [Figure 1. c and d]. Treatment by sulfasalazine significantly increased body weight and reduced DAI in colitis groups. Exercise also significantly lowered the increased DAI compared with colitis group. These results indicated that exercise effectively relieved DSS-induced colitis symptoms.

Effects of exercise on Colon Length and colon weight/length ratio

Previous studies showed that the colon length was negatively correlated with the severity of colitis.[16,17] As shown in Figure 2, evaluation of colon length revealed that the colitis group exhibited significantly shorten colon and reduced colon length compare to control group ($p < 0.01$). Colon weight to length ratio which is a marker of inflammation was significantly higher in colitis group compare with control group ($p < 0.05$). Exercise training and treatment of colitis animals with sulfasalazine increased colon length and significantly reduced colon weight to length ratio ($p < 0.01$) [Figure 2c and d].

Effects of exercise on spleen weight

The spleen is an important immune organ, and its size can reflect the levels of inflammation.[18] The image of spleen and spleen weight are shown in Figure 2. b, e and f. We found colitis group had significant spleen weight and spleen/body weight ratio. Sulfasalazine administration and exercise training significantly reduced spleen weight in colitis group suggesting that the inflammation was successfully established.

Histopathological changes

As shown in Figure 3, the control and exercise groups revealed intact colonic structure, epithelial cells and normal crypt structure and abundant goblet cells. Colitis group showed severe epithelial lesions, crypt loss, loss of epithelial cells in colon tissue, and marked increased in leukocyte infiltration and inflammation score compare with the control group. In comparison with the colitis group, the colons of exercise in colitis mice showed significantly improvement in colonic structural damage, exhibited less crypt loss and inflammatory cell infiltration and attenuated histological injury scores caused by DSS [Figure 3, a-e] ($p < 0.01$). Histological evaluation of colon tissue stained by Masson trichrome indicated that colitis group had higher collagen tissue than control [Figure 4]. Exercise and sulfasalazine significantly ameliorated collagen content in colon tissue [Figure 4. b]. Taken together, the results indicated that exercise significantly improved DSS-induced tissue morphological changes.

Measurement of oxidant/antioxidant markers

Measurement of MDA, an oxidative stress marker, and antioxidant markers including SOD and catalase activity and total thiol groups in colon homogenates revealed higher MDA and lower antioxidant markers in colitis group

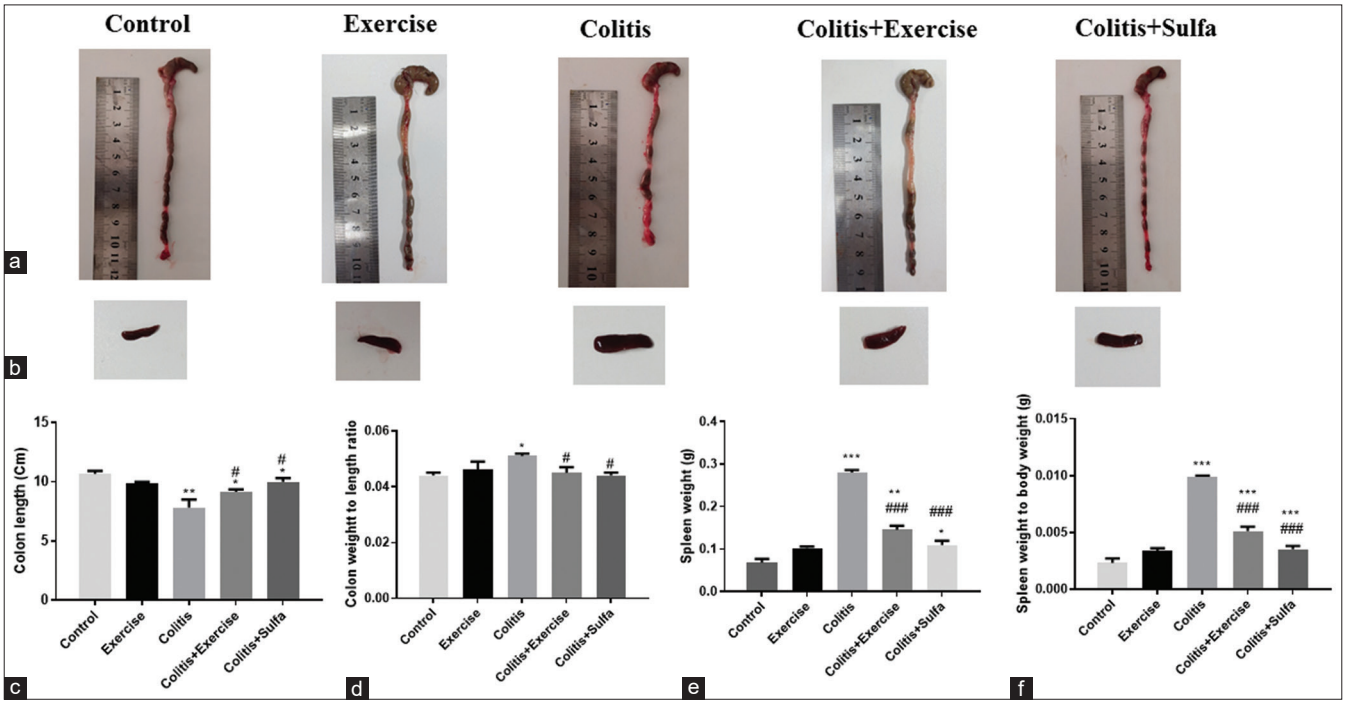

Figure 2: Exercise improved colon and spleen changes on DSS-induced colitis. Effect of exercise on colon and spleen macroscopic image (a and b), (c) Colon length, (d) Colon weight to length ratio, (e) Spleen weight and (f) Spleen weight to body weight. *P < 0.05, **P < 0.01 and ***P < 0.001 vs. control. #P < 0.05 and ###P < 0.001 vs. colitis group. Data are reported as Mean ± SE. (n = 6 each group)

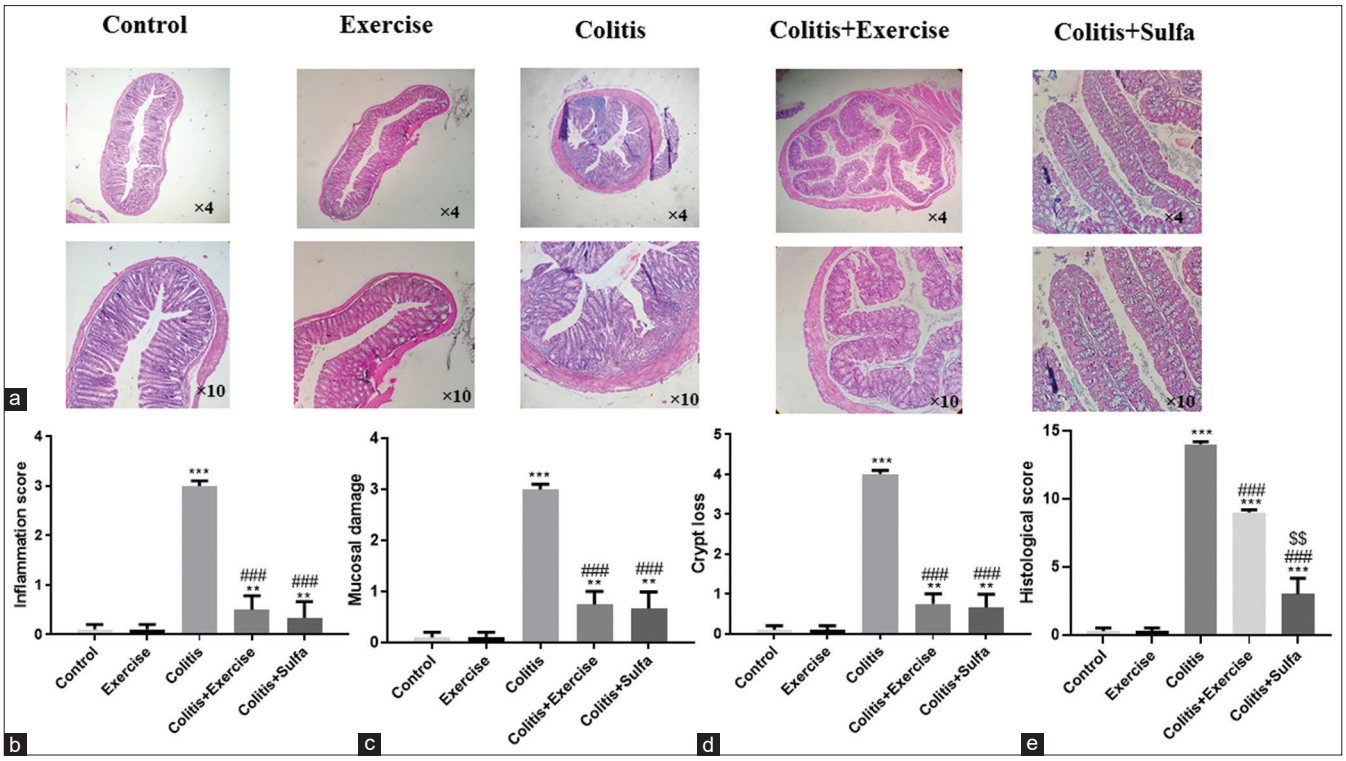

Figure 3: Exercise improved histological damage to colon tissue in murine colitis model. (a) Representative histopathology images of colon stained by H and E. (b) Inflammation score. (c) Mucosal edema. (d) Crypt loss and (e) histological changes of different groups Asterisks indicate inflammation. **P < 0.01 and ***P < 0.001 vs. control. ###P < 0.001 vs. colitis group. $$P < 0.01 vs. colitis + exercise group. Data are reported as Mean ± SE. (n = 6 each group)

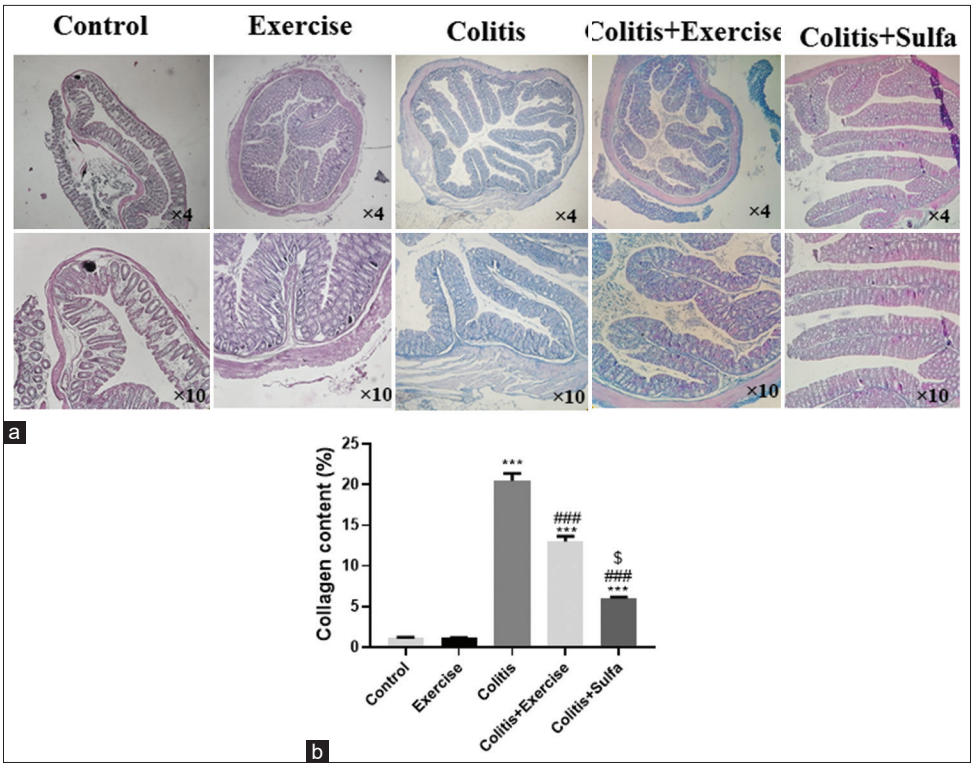

Figure 4: Exercise improved DSS-induced collagen deposition in colon tissues. (a) Representative histopathology images of colon stained by Masson Trichrome. (b) Percent of collagen content in different groups measured by image J software. Data are expressed as the mean ± SEM

compared with control and exercise. Exercise increased antioxidative markers and lowered MDA levels, as oxidative marker in colitis animals, although there were not comparable to sulfasalazine group [Figure 5].

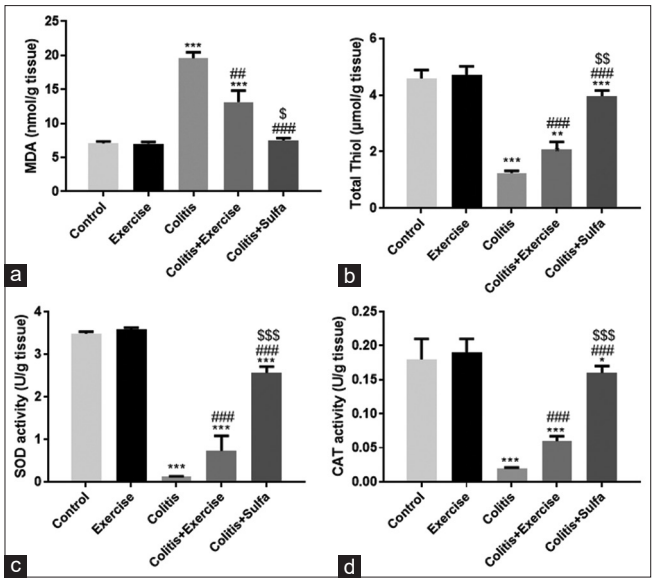

Figure 5: Exercise could balance oxidative stress in colitis mice. Changes of oxidative stress marker (a) Malondialdehyde (MDA) and antioxidative factors including (b) total thiol. (c) Superoxide dismutase (SOD) activity. (d) Catalase activity. Data are presented as the mean ± SEM. *P < 0.05 and ***P < 0.001 vs. control. ##P < 0.01 and ###P < 0.001 vs. colitis. $P < 0.05, $$P < 0.01 and $$$P < 0.001 vs. colitis + exercise group. Data are reported as Mean ± SE. (n = 6 each group)

Discussion

In this study, we aimed to evaluate the effect six weeks exercise on clinical symptoms and histopathological changes in DSS-induced colitis model. We found that exercise training relieved clinical symptoms and colon histological features associated with colitis, showing that exercise training is not only, not detrimental, but also, it may consider as prevention in individuals with acute colitis.

Mice induced to develop UC following DSS are well-established preclinical models and histopathological similar to humans. DSS induced colitis causes diarrhea, stool blood, weight loss, and inflammation by disrupting the epithelium of the colon which is considered as DAI. Exercise appears to be useful in lowering the clinical symptoms of colitis and its accompanying inflammation, which is characterized by spleen enlargement and colon weight to length ratio. As we showed, exercise training in colitis mice significantly improved DAI. Moreover, evaluation of colon weight to length ratio and spleen weight showed that colitis groups had higher levels than control and exercise training reduced both. Chronic inflammatory disorders are thought to be exacerbated by a sedentary lifestyle.[19] IBD has long been associated with a low body weight[20,21] however, several studies showing the significance of visceral adipose tissue and perivascular fat in the etiology of this disease.[22] For example, inflammatory mesenteric fat hypertrophy, which is mediated by an increase in pro-inflammatory adipokines such as TNF-α and IL-1, has been described in individuals with CD.[23] Adipose tissue's pro-inflammatory activity may be a potential risk factor for higher disease activity in IBD patients.[24,25] In contrast to our results, Saxena *et al*. found that exercise had no effect on the clinical signs of acute colitis.[2] It's possible that exercise-trained mice consumed more water than sedentary mice, exposing them to higher levels of DSS and thus masking any therapeutic effects of exercise in colitis animals.[2]

We also observed a significant difference between the colitis group and control group in terms of body weight loss and colon length. Experimental colitis was negatively correlated with the length of the colon, according to previous studies[26,27] and exercise significantly improved body weight and colon length. Colonic inflammation causes the infiltration of inflammatory cells such as inflammatory macrophages and monocytes and thickens the lamina propria due to disruption of the mucosa of the colon and ulceration.[28] Using H/E staining, we found normal-looking colons in the control group with no signs of mucosal thickening, inflammation or ulceration which was clearly obvious in colitis groups. Exercise reduced inflammation- induced dysplasia and improved colonic structure in colitis mice with mild aberrant lesions in colon tissues and reduced inflammation score compared with the colitis group, although, it was not statistically significant with standard drug. In addition, histopathological evaluation of Masson trichrome stained sections revealed that colitis group had higher collagen content and fibrous tissue in colon which can explain the lower colon length in this group. Interestingly, exercise training in colitis groups reduced fibrous tissue and increased colon length which was not significant to sulfasalazine group. Some researchers found that modest forced exercise training helps reduce inflammation in the inflamed colon.[23,24] These findings suggest that the intensity of exercise plays a major role in the end result of either worsening or remission of intestinal alterations associated with voluntary vs. forced exercise performed under controlled conditions.

We also showed that exercise training oxidant/antioxidant balance in the colitis mice compare to sedentary colitis mice. This could be explained by the intestinal mucosa's compensating defensive response to oxidative damage caused by the inflammatory response. As a result, moderate exercise appears to be safe and has been recommended for IBD patients as a means of avoiding illness relapse, maintaining nutritional status, and improving quality of life[29] previous studies indicated that moderate-intensity exercise minimizes oxidative tissue damage[11] while also increasing free radical scavenger activity.[30] However, there have been a few inconsistent results drawn about the effects of exercise on UC[31] and hence the effects of exercise are still unknown.[32] It has been shown swimming for 7 weeks reduced the generation of inflammatory and chemotactic cytokines in male rats.[33] It also indicated that low-intensity exercise training can prevent wild-type rats from oxidative colonic injury caused by DSS treatment.[11]

Conclusions

Physical activity can improve colitis symptoms by reducing the severity of colonic damage, possibly due to improvement in histopathological changes, inflammation and oxidative/antioxidative balance which is comparable to sulfasalazine treatment as standard therapy. More research is needed to determine the optimal intensity of exercise for individuals with chronic or acute colitis.

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Conflicts of interest

There are no conflicts of interest.

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