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The healing effects of moderate exercise on acetic acid-induced gastric ulcer in male rats

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ABSTRACT

Aim: This study aimed to evaluate the effect of moderate exercise on the healing of acetic acid-induced gastric ulcers in male rats.
Background: Gastric ulcers include benign mucosal and submucosal lesions of the gastric wall. Exercise regulates a wide range of physiological processes.
Methods: 48 male Wistar rats were randomly divided into three experimental groups (n=16 per group) as follows: control, which was left untreated after causing stomach ulcers; experimental group 1, the rats were first exercised and then received acetic acid; experimental group 2, the rats received acetic acid, and then exercised. The ulcer was caused by injecting 0.12 ml of a 60% acetic acid solution after 24 hours of not eating. The rats had a period of moderate treadmill activity either before or after the development of ulcers, lasting for a duration of 30 days. On the seventh and fourteenth days after the experiment, the rats were sacrificed, their stomach was removed, and the wound healing parameters, and wound depth were determined.
Results: Exercise before and after inducing gastric ulcers significantly decreased the depth of gastric ulcers in the experimental groups. The average number of PMN in the control group decreased in comparison to the seventh and fourteenth days following the experiment. Conversely, the number of fibroblasts, epithelialization, and new vessels increased. It seems that exercise before the appearance of ulcers has a greater effect on gastric ulcers compared to exercise after inducing gastric ulcers.
Conclusion: Exercise can prepare the gastric mucosa for forthcoming injuries, and heal gastric ulcers. Moderate aerobic exercise has significant restorative effects on gastric ulcers caused by acetic acid and is recommended.

Keywords: Acetic acid, Gastric ulcer, Exercise, Rats, Neutrophils, Fibroblasts, Neovascularization, Epithelialization.

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Introduction

A peptic ulcer is an acid-peptic injury to the digestive tract that induces mucosal and submucosal lesions. Peptic ulcers, most commonly found in the stomach or proximal duodenum, can occur in the esophagus or Meckel's diverticulum. In general, peptic ulcers in the stomach or duodenum are referred to as peptic ulcer disease (1). It has an incidence rate of 8.4%; if left untreated, it can cause mortality (2). Peptic ulcer appears to be linked to both exogenous factors, such as Helicobacter pylori infection, smoking, excessive alcohol consumption, stress, and overuse of non-steroidal anti-inflammatory drugs (NSAIDs), and endogenous factors, such as heredity, excessive gastric acid and pepsin secretion, and impaired mucosal blood flow (3, 4).

Approximately two-thirds of the patients have no symptoms. The most prevalent symptom is epigastric pain, which can be linked to dyspepsia, bloating, fullness in the abdomen, and nausea. Many patients

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may have sporadic symptoms (5). Various therapeutic algorithms are employed to treat peptic ulcers, contingent upon the presence of complications. Anti-ulcer medication is administered to patients who have ulcers caused by NSAIDs, and NSAIDs are discontinued. Proton pump inhibitors (PPIs) are used to treat ulcers when it is not feasible to discontinue the use of NSAIDs. The first-line treatment for H. pylori eradication is vonoprazan (VPZ) plus antibiotics (6).

Most chronic diseases are primarily caused by physical inactivity. Unhealthy behaviors account for more than half of health status; the main causes are diet, inactivity, and smoking. Physical activity primarily refers to any movement of the body that is powered by the skeletal muscles, and requires the use of energy. This movement can be done for active transportation, leisure, occupation, or daily living. Exercise training is a kind of physical activity where one's physical fitness is maintained or increased by performing repetitive, structured, and planned movements of the body. Exercise has been utilized to treat and prevent a variety of chronic conditions, such as diabetes, obesity, pulmonary diseases, and cardiac diseases (7–9). A diverse array of physiological systems is regulated by exercise. These include the brain, respiratory system, heart, gastrointestinal tract, skeletal muscle, immune system, and endocrine system (10, 11).

Regular exercise was found to be even more effective than medication in the rehabilitation of stroke victims and to be on the same level as commonly prescribed medications in the treatment of heart failure, diabetes prevention, and secondary prevention of coronary heart disease (12). Exercise has positive effects on the gastrointestinal tract. For example, it was shown that exercise can help prevent gastric injuries by elevation of antioxidant status (13). Patients suffering from constipation can benefit from exercise, particularly aerobic exercise (14). Exercise can control the energy balance and appetite (15). Physical activity can prevent colorectal cancer (16).

Epidemiological studies have suggested an association between physical inactivity and ulceration (17), however, the mechanisms underlying the ability of exercise to prevent or treat gastric ulcers have not received much attention. As stomach ulcers are very common which have many psychological and economic effects (18), this study aimed to investigate the effect of moderate exercise on the healing of acetic-acid-induced gastric ulcers in male rats by investigating the possible beneficial role of exercise on inflammatory parameters, fibroblasts, neovascularization, epithelialization, and depth of gastric ulcers.

Methods

Subjects

48 Adult male Wistar rats were purchased from Razi Institute, Karaj, Iran. They weighed between 230 and 250 g and were maintained under a 12/12 h light-dark cycle at 22 ± 2 °C and 55–65% humidity. Prior to surgery, rats were accustomed to the laboratory environment and provided with unlimited access to conventional rat pellet meal and tap water. During the adaption phase, the animals were subjected to five minutes of handling every day in order to reduce their stress levels. Furthermore, all guidelines of working with animals were followed during the study. The experimental procedures were approved by the Ethical Committee of Qazvin University of Medical Sciences, Qazvin, Iran (IR.QUMS.REC.1400.040)

Sports training protocol

The training group learned how to work on the treadmill for a week before the main exercises started. Animals from the exercised groups underwent continuous, and periodic exercise protocols following the principle of overload for five days a week in the form of running on a treadmill. Rats were allowed to warm up at 50%–60% of VO2 max for 20 minutes. Then, the treadmill speed was increased by 0.03 m s^{-1} every two minutes. Rats ran five intervals, with 8 minutes of 65%–70% (MOD) of VO2 max and 2 minutes at 50%–60% in groups, after warming up at 50%–60% of VO2 max. The total duration of running reached 60 minutes per day then it was kept constant for 4 weeks until the end of the protocol, which shows the medium intensity of exercise (19).

Experimental design

48 male Wistar rats were randomly divided into three experimental groups (n=16 per group) as follows: control, which was left untreated after causing stomach ulcers by 60% acetic acid; experimental group 1, the rats were first exercised, and then received acetic acid; experimental group 2, the rats received acetic acid and then exercised. Rats were examined on either day 7 or 14 after the experiment.

Induction of gastric ulcer

Gastric ulcers were produced by the luminal application of an acetic acid solution, as reported by Tsukimi and Okabe (20). After 24 h of starvation, animals were anesthetized with ketamine 50 / xylazine 5 mg/kg. After shaving and sterilization, a small incision was made in the abdomen, and the body part of the stomach (greater bending) was slightly extracted. A clamp was used to block the two ends of the stomach, and 0.12 ml of 60% acetic acid solution was injected into the portion of the stomach trunk with no veins using an insulin syringe. The acid was then withdrawn using the same syringe after 45 seconds. The stomach was washed twice with normal saline. Then, the stomach was returned to the first place, first, the peritoneum and then the skin was sutured, and then the mouse was placed on its stomach, and kept in a warm place in a separate cage. After that, the animals were fed a typical diet of lab chow and allowed unlimited access to tap water (21). The degree of wound healing was evaluated by measuring the wound depth and histomorphological parameters. Wound depth was measured on the studied days using a ruler in the microscope with an objective lens (400x).

Histological examination

Half of the rats in the control and experimental groups were anesthetized by intraperitoneal injection of ketamine and xylazine on 7th day and the other half were anesthetized on the 14th day after the experiment. Full-thickness samples were obtained using a large curvature area, and they were then fixed for a week in a 10% formalin solution. After the samples were immersed in paraffin, transverse slices, including the wound bed, were cut to a thickness of five microns using a Leitz microtome. It was stained with hematoxylin and eosin. Neutrophils, fibroblasts, and newly formed vessels were observed and counted. An Iwf-Iox-Holland eye piece was used to count the cells. Slides were descriptively examined and the number of neutrophils and fibroblasts was counted at this stage. The cells were counted using an objective lens (400x) (22). Before counting the number of new vessels, an objective lens (100x) was used to identify the areas with a high density of new vessels. After that, these regions were divided into distinct fields, and the number of vessels produced in each field was counted using an objective lens (400x). Angiogenesis scoring was performed histologically (23) (Table 1). All histomorphological studies were performed by a pathologist blinded to the study groups.

To check the epithelialization, the modified system of histology views of wound tissue, which was previously described by Gal et al. (24) (Table 2).

Statistical analysis

At the end, the data was analyzed using SPSS software, and the statistical method of one-way and multiple ANOVA and supplementary tests (Tukey and LSD post hoc test). Statistical difference values with p value less than 0.05 were considered as significant.

Results

Effect of exercise on PMN, fibroblast, new blood vessels, epithelialization, and wound depth in the studied rats on the seventh day of treatment

Table 1. Histomorphologic classifying of angiogenesis

Classify / Element	0	1	2	3	4
Angiogenesis	No evidence of blood vessels	4-8 vascular channels	12-15 vascular channels	15-20 vascular channels	More than 20 vascular channels

Table 2. Examination of epithelization in examination of tissue slides

Classify / Element	0	1	2	3	4
epithelialization	Absence of organized epithelialization	minimally organized epithelialization	mild organized epithelialization	moderately organized epithelialization	complete organized epithelialization

In both experimental groups 1 and 2 exercise could increase fibroblasts, neovascularization, and epithelialization, and decrease PMN and wound depth. In experimental group 1 these changes were significant in PMN ($p<0.05$), fibroblasts ($p<0.05$), wound depth ($p<0.01$) and epithelialization ($p<0.01$). However, these changes were significant in neovascularization ($p<0.01$), wound depth ($p<0.05$) and epithelialization ($p<0.01$) in the experimental group 2 (Table 3).

Effect of exercise on PMN, fibroblast, new blood vessels, epithelialization and wound depth in the studied rats on the fourteenth day of treatment

On the fourteenth day of the experiment, the number of fibroblasts, neovascularization, and epithelialization rose, while the levels of PMN and wound depth decreased, compared to the data seen on the seventh day. In experimental group 1 these changes were significant in fibroblasts ($p<0.01$), wound depth ($p<0.05$) and epithelialization ($p<0.05$). However, in experimental group 2 these changes were significant in the fibroblasts ($p<0.05$) and wound depth ($p<0.01$) (Table 4).

Discussion

The effect of aerobic exercise on gastric ulcers was evaluated in male Wistar rats. The comparison between control and experimental groups showed that exercise before or after gastric ulceration can have healing effects. Reducing inflammation and producing growth factors may help speed up the healing process of wounds and the exercise process. Additionally, it seems that exercise predisposes one to a higher impact on stomach ulcers than exercise subsequent to the development of ulcers. Exercise promotes tissue regeneration, which includes cardiac, neural, and muscular regeneration, and is well known to support and benefit several biological mechanisms (25). Exercise in mouse models was shown to cause a physiological increase in the size and proliferation rate of adult cardiomyocytes. Meanwhile, it was found that in adult mice, endurance exercise like treadmill training promotes the birth of new cardiomyocytes (26, 27). In rodent models of spinal cord injury, endurance exercise was shown to improve axonal regeneration and sprouting through hormonal and DNA methylation processes (28, 29). Cell renewal brought on by exercise is facilitated by biochemical signals and mechanical stress. Maintaining homeostasis and improving the impaired function of various organs is aided by bioactive substances regulated by exercise, such as exerkines, and mechanical signals like fluid flow, dynamic tension, compression, and hydrostatic pressure (30, 31).

GI tract disorders can benefit from regular, moderate exercise. In general, as a result of exercise, we have an increased metabolism of the tissue which provides delivery of more nutrients to the active tissue and eliminates accumulated metabolic wastes, all of which increase the efficiency of the organs (32).

Improved immune function, less acid secretion, less anxiety, and promotion of a healthy lifestyle by refusing smoking, and excessive alcohol consumption are some of the suggested mechanisms for a putative protective effect of moderate exercise against PU in exercising PUD patients (33). The molecular

Table 3. Effect of exercise on PMN, fibroblast, new blood vessels, epithelialization and wound depth in rats on the 7th day of treatment

Group	PMN	Fibroblasts	Neovascularization	Depth	Epithelialization
Control	43.25 ±2.01	26.75±1.75	14.25±1.29	625±18.45	1.5±0.1
Experimental 1	35.25±1.93*	34.5±1.49*	16.25±1.03	487±14.43**	2±0.2**
Experimental 2	38.5±1.88	32.75±1.93	17.75±1.70**	525±12.5*	2±0.25**

All values are expressed as mean ± SEM, * $P < 0.05$, ** $P < 0.01$, compared with the control group of animals

Table 4. Effect of exercise on PMN, fibroblast, new blood vessels, epithelialization and wound depth in rats on the 14th day of treatment

Groups	PMN	Fibroblasts	Neovascularization	Depth	Epithelialization
Control	1±0.3	45.5±2.59	16±1.29	167.5±24.43	3±0.3
Experimental 1	1±0.28	57.25±2.73**	18±1.70	105.5±9.43*	3.5±0.25*
Experimental 2	0.75±0.29	53±2.78*	16±1.10	86.75±12.24**	3.25±0.28

All values are expressed as mean ± SEM, * $P < 0.05$, ** $P < 0.01$, compared with the control group of animals mechanism might be linked to increased activity of antioxidant enzymes, as well as increased effectiveness of proteasome complexes and enzymes that repair DNA. This adaptation leads to enhanced systemic resistance to oxidative stress and improved physiological performance (34). The results of this investigation align with prior research, reinforcing the positive effect of exercise on wound healing. For instance, Bahadır et al. showed that swimming exercises safeguard gastric tissue from oxidative damage induced by acetic acid. This protection involves mechanisms, such as reduced neutrophil infiltration, decreased reactive oxygen species generation, and maintained antioxidant status. Regular pre-ulcer moderate exercise reduces anxiety, and minimizes additional inflammation on ulcerated gastric mucosa, preparing it for potential injuries (35). Tamer et al. showed endogenous oxytocin as a pivotal mediator in the favorable outcomes of regular physical activity in mitigating gastric injury. In sedentary rats, ulcer induction heightened anxiety, diminished gastric blood flow, and triggered apoptosis and oxidative damage. On the other hand, pre-exercised rats showed reduced lipid peroxidation, limited neutrophil infiltration, and partially restored glutathione content. Exercise reduced corticosterone levels, and reversed behavioral and biochemical changes linked to gastric damage, but it did not stop DNA damage and apoptosis. The findings indicate that in order to alleviate stomach damage via exercise, it is crucial to restore the decreased expression of gastric oxytocin receptors and hypothalamic oxytocinergic neurons (36). In another study, a 30-day moderate treadmill exercise regimen showed significant inhibition of ethanol-induced gastric lesions in rats. Histopathological findings indicated a protective effect of exercise against ethanol-induced damage. Ethanol treatment resulted in a decrease in glutathione peroxidase (GPx) activity, and an increase in thiobarbituric acid reactive substances (TBARS); in contrast, the exercise plus ethanol group showed a decrease in TBARS concentration and an increase in GPx activity when compared to the rats that received ethanol treatment. Rats given ethanol showed a tendency to have lower levels of catalase activity than the control group (13).

Bicycle exercise helped the microcirculation return to normal, particularly where the duodenal ulcers are located. Bicycle exercise could accelerate the healing of ulcer defects, particularly in patients with duodenal ulcers, and hyperkinetic hemodynamics (35). Recent published systematic studies have shown the advantages of fitness training in the management of alcohol use disorder (AUD). Exercise programs have the potential to reduce alcohol intake, enhance fitness, and improve mental health. They can be a useful supplemental treatment for people with alcohol-related disorders, such as AUD (37).

Exercise intensity is significant because research on humans and animals indicates that low to moderate levels of physical activity are beneficial, while intense and prolonged exercise is linked to an increased risk of ulcerogenesis (3). Acute exercise can result in the degradation of mucosal integrity, as well as an increase in cellular metabolism, the requirement for ATP, and the production of more reactive oxygen species. Nonetheless, consistent moderate-intensity exercise lowers tissue levels of pro-inflammatory cytokines and increases anti-inflammatory IL-10 levels. It lowers circulating cortisol levels, which precondition the mucosal barrier and lessen damage to the stomach mucosa (35, 36).

Conclusion

The findings of current study suggest that regular moderate exercise, through its upregulatory effects on fibroblasts, neovascularization and epithelialization, and downregulatory effects on neutrophil-dependent inflammation, prepares the gastric mucosa for a forthcoming injurious event and healing of the gastric ulcer. Exercise has considerable restorative benefits on acetic acid-induced stomach ulcers, and regular aerobic exercise at a moderate intensity is suggested in PU patients. To better understand the gastroprotective benefits of exercise, more studies focusing on how physical activity affects the development and healing of gastric ulcers are required.

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Conflict of interests

The authors declare that they have no competing interests.

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