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Evaluation of Cyclooxygenase-2 and Prostaglandin E2 Expression in Endometrial Tissue Following 8 Weeks of Swimming Exercise and Omega-3 Intake

Fatemeh Rashidpour
(PhD candidate) Department of Exercise Physiology, Sari Branch, Islamic Azad University, Sari, Iran

Parvin Farzanegi
(PhD) Department of Exercise Physiology, Sari Branch, Islamic Azad University, Sari, Iran

Hajar Abbaszadeh
(PhD) Department of Exercise Physiology, Sari Branch, Islamic Azad University, Sari, Iran,

Corresponding author: Parvin Farzanegi
Email: parvin.farzanegi@gmil.com
Tel: +989112230233
Address: Exercise Physiology Department, Faculty of Humanities, Sari Branch, Islamic Azad University, Sari, Iran

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ABSTRACT

Background and objectives: Endometriosis is a chronic disease that affects approximately 10% of women of reproductive age. The purpose of this study was to evaluate the effects of 8 weeks of swimming exercise and omega-3 supplementation on the expression of cyclooxygenase-2 (*COX-2*) and prostaglandin E2 (*PGE2*) genes and serum levels of reproductive hormones in the endometrial tissue of a rat model of endometriosis.

Methods: In this experimental study, 30 adult Wistar rats were randomly divided into 5 groups of healthy-control, patient-control, patient+exercise, patient+omega-3, and patient+omega-3+exercise groups. After the induction of endometriosis, the rats were subjected to 8 weeks of swimming exercise, 5 days a week as well as 2 ml/kg/body weight of omega-3. Data were analyzed using one-way analysis of variance and Tukey post hoc test at the significance level of 0.05.

Results: The expression of COX-2 and PGE2 as well as serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were significantly higher in the patient group compared with the healthy-control group ($p \leq 0.0001$). Exercise and omega-3 supplementation either separately or combined could significantly reduce the expression of both genes and serum levels of LH, FSH, and estradiol ($p < 0.05$). This effect was more profound in the patient+exercise+omega-3 group.

Conclusion: The results of the present study indicate that regulating the expression of *COX-2* and *PGE2* genes as well as serum levels of reproductive hormones through swimming exercise and omega-3 supplementation can improve endometriosis.

Keywords: Cyclooxygenase-2, Prostaglandin E2, Endometriosis, Exercise.

INTRODUCTION

Endometriosis is a chronic disease that affects approximately 10% of women of reproductive age. Endometrial tissue is produced and grows in the ectopic area, especially in the pelvis. The endometrium is most often found in the ovaries, peritoneum, sacral uterine ligaments, Douglas sac, and uterine septum (1). The disease has three distinct forms (peritoneal, ovarian, and rectovaginal endometriosis), and each may have its own set of symptoms, although dysmenorrhea and chronic non-menstrual pelvic pain are the most common. However, a pathogenic mechanism that is shared in all forms of the disease is the effect of estradiol (E2), which has pro-inflammatory and anti-apoptotic effects on endometrial cells, especially in ectopic foci (2). This pathology, in fact, greatly affects women of reproductive age. Although many theories have been proposed about the cause of endometriosis, its pathogenesis remains unclear. Researchers all agree that the growth of endometriotic lesions is supported by an inflammatory environment, increased proliferation, and impaired apoptosis (3).

Prostaglandins are pro-inflammatory mediators that play a key role in the response to inflammation and are derived from arachidonic acid by cyclooxygenase-mediated catalysis in the first stage of their biosynthesis. Cyclooxygenase2 (COX-2) is an induced isoform of cyclooxygenase and a rate-limiting enzyme involved in the synthesis of prostaglandin E2 (PGE2) in response to pro-inflammatory molecules (4). As an eicosanoid with various physiological and pathological functions, PGE2 is considered essential for the development of endometriosis. Researchers have found that PGE2 regulates cell proliferation, angiogenesis, and immune system suppression, which is an important point in the molecular mechanism of endometriosis. It also communicates with its receptors, known as EP1, EP2, EP3, and EP4, thereby acting on specific target cells through alternating or opposite intracellular pathways (5). Research also suggests that PGE2 is involved in the development of endometriosis by the effect of local estrogen and estrogen receptor (6). Estrogens increase the production of prostaglandins by activating nuclear factor-KB (NF-KB) and COX-2. The level of COX-2 is greatly increased in the ectopic endometrial region. On the other hand, PGE2 increases COX-2 levels in the ectopic and uterine endometrium. Both COX-2 and PGE2 promote migration and invasion to endometrial cells (5). In addition, COX-2 is involved in the conversion of arachidonic acid to PGE2, which is a precursor to various molecules, including prostaglandins, thromboxane, and prostacyclin (7). Although various strategies including surgery and medications have been proposed for the treatment of endometriosis (8), traditional treatments are thought to have both physiological and psychological benefits, which can improve the quality of life of the patients (9).

Regular exercise seems to have protective effects against diseases that involve inflammatory processes (10). Recent studies show that exercise may have a therapeutic effect on chronic inflammation and pain perception (8). On the other hand, studies have shown that the use of sports activities is effective in patients with endometriosis and help the patient to improve faster because patients with endometriosis have higher levels of oxidative stress and inflammatory and pro-inflammatory cytokines. Among aerobic exercises, low-intensity swimming aerobic exercise is safe and applicable in various physiological conditions. This exercise type is mostly used in physiological, biochemical, and molecular reaction studies due to its weight intolerance in water compared to non-water sports (9). Exercise significantly inhibits COX-2 activity and leads to the suppression of pro-inflammatory cytokines and changes in oxidation status (11). On the other hand, omega-3 polyunsaturated fatty acids can potentially reduce the painful symptoms associated with endometriosis and the size of the lesion, thereby maintaining the patient's ability to conceive and minimizing side effects (12). It has been proposed that both exercise and omega-3 fatty acid intake can reduce the risk of endometriosis. Lack of mobility and omega-3 supplementation increase the risk of developing inflammatory diseases. This study is the first to evaluate the effects of swimming and omega-3 fatty acids consumption on the expression of *COX-2* and *PGE2* genes in the endometrial tissue of rats with endometriosis.

MATERIALS AND METHODS

Thirty adult Wistar rats aged 6 to 8 weeks (with a mean weight of 202.85±15.62 g were

purchased from the Pasteur Institute of Iran and transferred to the Research Center of Azad Islamic University, Sari Branch. The animals were kept in polycarbonate cages in an environment with a mean temperature of 22±1.4 °C, humidity of 55%, and a 12:12 light–dark cycle. The animals were kept in accordance with the guide for the care and use of laboratory animals. The study protocol was approved by the ethics committee of Islamic Azad University, Sari branch, Iran (IR.IAU.SARI.REC.1398.152). The animals had free access to food and water. The animals were divided into 6 groups: healthy control group, control-patient group, patient+exercise, patient+omega-3, and patient+omega-3+exercise. To induce endometriosis, the rats were first anesthetized with ketamine and xylazine. Then, the abdomen on the right side was cleansed with betadine and an incision was in the skin of the flank in the pelvic area. After opening the abdominal muscle and peritoneal area, the ovarian tissue was removed along with a part of the uterine tube tissue and placed in a sterile container with 1 ml of phosphate buffer saline. Each tissue was then cut into one-by-one-millimeter sections. Tissue sections were grafted to the area of the right pelvic muscle wall, the abdominal peritoneum, the anterior muscle of the abdominal wall, and the fat around the ovary. The operated area was then sutured and the rats were transferred to the appropriate cage (13). Omega-3 was received daily for 2 weeks after induction of the disease in the form of gavage at a dose of 2 ml/kg/body weight of each rat for rats in patient+omega-3 and patient+omega-3+exercise groups. The rats in the patient+exercise and patient+exercise+omega-3 groups were put in a water pool before starting the main protocol for 5 days each time for 20 minutes to get acquainted with water and reduce swimming stress and adapt to training conditions. Then, the rats swam in a water reservoir measuring 50×50×100 cm with a temperature of 30-32°C 5 days a week for 8 weeks (10). The duration of the daily water exercise was 30 minutes. To eliminate the acute effect of exercise, 48 animals were sampled after the last swimming exercise session and supplementation. For this purpose, the animals were first anesthetized by peritoneal injection of ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). Then, blood serum samples were examined for reproductive hormones, and the ovarian tissue was carefully separated and frozen at -80°C. Real-time quantitative PCR (RT-qPCR) was carried out for evaluating the expression of *COX-2* and *PGE2* genes in the ovarian tissues using specific primers and Qiagen kits (Germany). Serum concentrations of estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured using competitive radioimmunoassay. The sensitivity of the kits (Cusabaio, China) for estradiol, FSH, and LH was 40 pg/mL, 0.39 ng/ml, and 0.15 mlU/ml, respectively.

Qualitative data were described using descriptive statistics including mean and standard deviation, while inferential statistics were used to describe quantitative data. Shapiro Wilk test was used to determine the normality of data distribution, and Levene's test was used to determine the homogeneity of variance. Due to the normal distribution of data, parametric tests including one-way analysis of variance and Tukey post hoc test were performed at the significant level of 0.05 to examine the expression changes of *COX-2* and *PGE2* genes. All statistical analyzes were performed using the SPSS 23 software.

RESULTS

The level of FSH, LH, and estradiol was statistically higher in the patient group compared with the healthy-control group (p=0.001, p=0.013, and p=0.006). The level of these hormones was significantly lower in the patient+exercise, patient+omega, and patient+exercise+omega compared with the patient group ($p\leq0.001$) (Figure 1).

Table 1- The mean level of *COX-2* and *PGE2* expression in different groups

Groups	Healthy-control	Patient	Sham	Patient+exercise	Patient +omega-3	Patient +exercise+omega3
COX-2	0.062±0.028	0.749±0.045*	0.807±0.041	0.230±0.065$	0.359±0.177$	0.207±0.067$
PGE2	0.000011±0.000002	0.000295±0.00017*	0.000286±0.00018*	0.000062±0.00001$	0.00083±0.000014$	0.000049$±0.000003

* indicates significant change compared with the control-healthy group. $ indicates significant change compared with the patient group. Data are presented as mean ± SD.

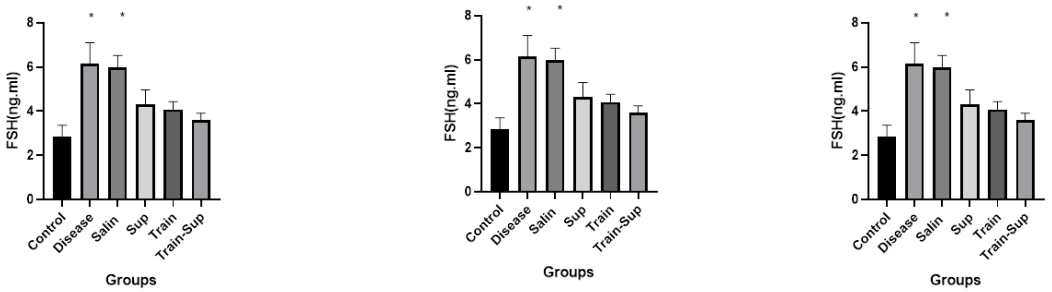

Figure1- Changes in the serum level of hormone levels in different groups. * indicates significant change compared with the healthy-control group.

The expression of *COX-2* and *PGE2* in the patient group was significantly higher than in the healthy-control group ($p \leq 0.0001$ and $p=0.014$, respectively). However, both genes were significantly underexpressed in the patient+exercise, patient+omega, and patient+exercise+omega groups compared with the patient group ($p<0.05$). This underexpression was more profound in the patient+exercise+omega group (Table 1).

DISCUSSION

In the present study, we investigated the effects of a period of regular exercise combined with omega-3 supplementation on *COX-2* and *PGE2* expression as well as the level of reproductive hormones in a rat model for endometriosis. One of the important results of the present study was the overexpression of *COX-2* and *PGE2* in the patient group compared with the healthy-control group. Both genes were underexpressed in the patients+exercise, patient+omega, and patient+exercise+omega groups compared with the patient group. This underexpression was more notable in the patient+exercise+omega group. Similar trends were observed in the study groups for the level of reproductive hormones.

Endometriosis is a disease of the female reproductive system, which is characterized by the presence of glands and stroma outside the uterine cavity. Generally, 6-10% of women of reproductive age have this disease. The main symptoms are infertility and pelvic pain, which affects more than 10% of the cases. Less common symptoms include dysuria, dyspareunia, dysmenorrhea, and irregular uterine bleeding (14). Evidence suggests that inappropriate inflammatory responses and high levels of topical estrogen play a major role in the pathogenesis of endometriosis (15). Increased expression of *COX-2* also plays a major role in the onset and development of endometriosis (16). The product of this gene is a rate-limiting enzyme involved in the synthesis of PGE2, which is induced by mitogens, pro-inflammatory cytokines, growth factors, tumor stimulants, and bacterial toxins (17). The overexpression of *COX-2* helps increase PGE2 in endometriosis and is involved in controlling inappropriate implantation and endometrial growth, angiogenesis, and immune system suppression. Therefore, PGE2 seems to be one of the main controllers of the immune responses in endometriosis. The endometrial gland epithelium is where COX-2 is produced. This production varies according to the menstrual cycle (14). The concentration of PGE2 in the peritoneal fluid is higher in women with endometriosis, which plays an important role in the survival and growth of endometriosis lesions (18). The expression of *COX-2* is low in the early proliferative stages and then gradually increases to a maximum in the secretory stage (14). The NF-KB pathway can directly activate COX-2/PGE2 to increase estrogen production in the endometrium (19). It can also affect the pituitary gland, thereby altering the secretion of FSH and LH and lowering the levels of progesterone and estrogen in the blood (20).

However, there are modifiable factors such as nutrition and physical activity that help prevent and treat the disease. Physical activity can reduce the risk of developing endometriosis in women by reducing oxidative stress, strengthening the immune system, and modulating hormonal factors. Aerobic exercise, such as swimming, increases the quality of life in people with endometriosis due to the improved reduction in the expression of inflammatory genes (21). The response of PGE2 to exercise has been investigated in several studies. Research has

shown that a diet rich in antioxidants can help prevent the growth and metastasis of endometriosis. Trapp et al. reported that a 12-week exercise could increase several components of the COX pathway as well as the PGE2 index (22).

The effect of n-3 polyunsaturated fatty acids on endometriosis-like lesions is being evaluated as a potential anti-inflammatory therapeutic target. Systemic levels of these compounds affect the immune, angiogenic, and proliferative factors involved in the early development of endometriosis and help reduce the size of the lesions as well as the production of topical prostaglandins and cytokines (12,23). Numerous studies have been performed to evaluate the effects of physical activity and omega-3 supplementation on human health problems, such as inflammatory diseases. In a study by Capó et al. on 15 soccer players, 8 weeks of exercise, and fatty acid supplementation, they concluded that docosahexaenoic acid (DHA) omega-3 supplementation increased COX-2 levels by increasing plasma PGE2 (24).

In addition to their effects on prostaglandins, thromboxane, and cleutrin, omega-3 fatty acids reduce the production of interleukin-1 (IL-1B) by suppressing IL-1B mRNA as well as COX-2 mRNA (25). Omega-3 fatty acids are essential for normal growth, development, and prevention/treatment of coronary artery disease, hypertension, inflammatory disorders, autoimmunity, and cancer. Intake of vitamins and dietary supplements, such as omega-3 fatty acids, reduces the production of inflammatory eicosanoids, cytokines, reactive oxygen species, and inflammatory molecules (26). Anderson et al. showed that maximal exercise activity along with omega-3 supplementation could increase plasma levels of inflammatory factors in elite male swimmers (27). Another study also demonstrated that omega-3 supplementation combined with exercise can significantly reduce serum PGE2 levels (28).

CONCLUSION

In general, PGE2 is a major cyclooxygenase product at inflammatory sites where it contributes to local increases in blood flow, edema formation, and pain sensitization. Regular training promotes systemic anti-inflammatory and vasodilator effects by increasing PGE2 levels. Acute exercise and DHA omega-3 supplementation synergistically increase plasma PGE2 and exert anti-inflammatory effects. The results of the present study indicate that regulating the expression of *COX-2* and *PGE2* genes as well as serum levels of reproductive hormones through swimming exercise and omega-3 supplementation can improve endometriosis.

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DECLARATIONS

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Ethics approvals and consent to participate

The animals were kept in accordance with the guide for the care and use of laboratory animals. The study protocol was approved by the ethics committee of Islamic Azad University, Sari branch, Iran (IR.IAU.SARI.REC.1398.152).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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