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Reduction of PARP1 gene expression in lung tissue due to swimming exercise in an animal model of lung cancer with benzopyrene

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ABSTRACT

Introduction: Lung cancer, the second most common cancer in the world, is associated with impaired lung function and physical disorders. Although the role of exercise on the health of cancer patients has been reported, the effect of exercise on the improvement of this type of cancer is not clear. Given the limited information regarding the effect of exercise on oncogenes associated with lung cancer, the present study aimed to investigate the effect of a swimming exercise period on PARP1 gene expression in lung tissue of an animal model of lung cancer with benzopyrene (BZP).

Material & Methods: In this experimental study, 12 BALB/c mice, 8-10 weeks old, weighing 18-22 grams were divided into lung cancer (LC) and lung cancer + swimming exercise (SE) groups. Additionally, 6 mice were considered as healthy control (HC) group. BZP was administered for lung cancer induction at a dose of a dose of 100 mg/kg for two weeks. Mice in the SE group performed swimming exercise with 2% of their body weight for 10 weeks, three sessions per week, each session lasting 5-38 minutes. PARP1 gene expression in lung tissue was measured 48 hours after the last training session using real-time PCR method. Data were analyzed using one-way ANOVA with Tukey's post hoc test in SPSS software version 22 and a significance level of 0.05.

Results: In the LC group, post-test weight and visceral fat weight were significantly lower and PARP1 expression was significantly higher than in the HC group (P=0.001). Study data revealed that in the SE group, post-test weight (P=0.001) and visceral fat weight (P=0.03) were significantly higher and PARP1 expression (P=0.016) were significantly lower than in the LC group.

Conclusion: Generally, it seems that although lung cancer induction increases PARP1 gene expression in lung tissue, regular swimming exercise can lead to a decrease in PARP1 and possibly improve lung cancer. Given the limitations of the data, more studies are needed in this field.

Keywords: Swimming, PARP1, Body Composition, Lung Cancer, Benzopyrene.

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1. Introduction

Lung cancer is a significant public health issue, ranking as the second most frequently diagnosed cancer and the primary cause of cancer-related deaths worldwide. In 2020, there were an estimated 2.2 million new cases and 1.8 million deaths attributed to lung cancer (1). It remains a critical global burden of disease because of its high incidence rate and considerably poor survival rate (2,3). The incidence and mortality of lung cancer varies substantially by geographical regions and sex, with a particularly high burden in Asia and male individuals (4,5). Cigarette smoking is the predominant risk factor for lung cancer globally (5,6). Initiating smoking at a younger age and maintaining an extended duration of smoking significantly elevate the risk of lung cancer (7,8). Environmental exposures, including biomass fuels, radon, arsenic, and air pollution, exhibit notable country-specific variations and contribute to an elevated risk of lung cancer (9,10). Public health strategies to reduce exposure to cigarette as well as environmental factors could alleviate burden of lung cancer (11).

Small cell lung cancer (SCLC) is a type of lung cancer that develops quickly, is aggressive, and has a high fatality rate (12). Although the incidence of SCLC is only 15% of all lung cancer, which is much lower than that of non-small cell lung cancer (NSCLC), SCLC has the notable characteristics of the short tumor doubling times, the high growth fraction, and the early development of extensive metastases. Over the last two decades, frontline therapeutic choices have remained mostly unchanged, and effective treatment options for recurrent disease are also scarce, underscoring the need of novel treatment strategies and the development of validated biomarkers (13). Recently, with the clinical application of next-generation sequencing technologies, as a prominent poly [ADP-ribose] polymerase (PARP) involved in DNA repair, PARP1 has been demonstrated to be aberrant-expressed in SCLC and to participate in DNA damage repair, providing hope for the development of novel therapeutic targets for SCLC patients (14).

Within each cell cycle, DNA damage occurs, and cells have their own regulation repair systems to deal with it (15). Tumor cells suffer more DNA damage than normal cells as a result of chemotherapy and radiation, and the DNA repair mechanism is unusually active (16). When a single strand break occurs, PARP, a sort of irreplaceable polymerases, is engaged in DNA repair. Historically, 17 PARP family proteins have been recognized, only PARP1, PARP2, and PARP3 are involved in DNA repair, particularly PARP1 contributing approximately 90% of the DNA repair role. The majority of the PARP family members, known as mono (ADP-Ribosyl) ases (MARs), can only assemble a single ADPribose unit. The name for this procedure is mono-ADP-ribosyl ribosylation (MARylation). On the other hand, poly ADP-ribosylation refers to the simultaneous synthesis of several ADP-ribosylation units (PARylation). PARP attaches to damaged DNA strands and recruits proteins and repair factors that repair DNA by Poly ADP-ribosylation (PARylation) and Mono ADP-ribosylation (MARylation), which is catalyzed by PARP's nicotinamide adenine dinucleotide (NAD+) (17). As the mechanism of PARP-mediated DNA repair was elucidated, an increasing number of PARP inhibitors are being investigated and employed in clinical trials (18). Since lung cancer often affects the cardiorespiratory system and causes breathing disorders, gas exchange disorders in the lungs, and physical function disorders, this can lead to a decrease in the body's ability to perform daily activities, the occurrence of physiological-psychological diseases, and ultimately a decrease in the quality of life. It seems that regular exercise as a strategy to improve quality of life and cardiorespiratory function in this disease (19). Researchers have stated that regular exercise can lead to reduced length of hospitalization, depression, anxiety, improved blood pressure, increased functional capacity, and increased quality of life in patients with lung cancer (20). In addition, from a physiological perspective, researchers believe that exercise can inhibit the growth and differentiation of cancer cells by inducing apoptosis and hypoxia in tumor-associated tissues and even the tumor itself, by inhibiting Akt, mTOR, p70s6k, and ERK1/2 as the upstream pathway of PARP in human lung-derived cancer cells (21). Although the cellular and molecular mechanisms of exercise training in lung cancer are still not well understood, Mirdar Harijani and Musavi (2020) indicated that regular submaximal aerobic training plays an important role in inhibition of the effects of lung carcinoma induced by NNK via reduction of Ras and Raf-1 activity (22). By our knowledge, the effect of exercise on PARP1 gene expression has not been investigated in lung cancer samples. Therefore, the present study aimed to determine the effect of a swimming training period on PARP1 gene expression in lung tissue of an animal model of lung cancer with benzopyrene (BZP).

2. Methodology

2.1. Materials and methods

This experimental study.

2.2. Participants

This experimental study utilized BALB/c mice, aged 8-10 weeks and weighing 18-22 grams. The animals were obtained from the Pasteur Institute in Karaj and transferred to the Pishtazan animal lab, Shiraz, Iran. Before the experiment, the animals were housed in pathogen-free conditions, maintained a 12 hr:12 hr light/dark cycle

with water and food, with ad libitum access to water and food, and then transferred to the institution's sports physiology laboratory. All ethical guidelines for research were followed, and the Ethics Committee for Research at Islamic Azad University, Shiraz Branch, issued the approval code IR.IAU.SHIRAZ.REC.1403.028 for this study.

2.3. Measurements

Induction of lung cancer and sample grouping: To induce lung cancer, 12 mice were first injected with a single dose of 100 mg/kg of benzopyrene (BZP) obtained from Sigma-Aldrich with the economic code B1760, after fasting for 12 hours. For BZP injection, 24 mg of BZP was dissolved in 1.2 ml of corn oil. Then, 10 international units of the solution were injected intraperitoneally into each animal (23). After 14 days, animals were randomly assigned lung cancer (LC) and lung cancer + swimming exercise (SE) groups. Additionally, 6 mice were considered as healthy control (HC) group.

2.4. Intervention

Exercise training protocol: All the animals in SE groups underwent a one-week swimming pool familiarization period (160 cm diameter, 80 cm height). Initially, rats swam freely for five minutes. After sufficient adaptation, mice in the SE group performed swimming exercise with 2% of their body weight for 10 weeks, three sessions per week, each session lasting 5-38 minutes (22). After each session, rats were dried and returned to their housing.

Tissue collection and real time PCR: Forty-eight hours after the final training session, all samples were anesthetized using an intraperitoneal injection of a ketamine (50 mg/kg) and xylazine (3 mg/kg) combination. Gene expression of PARP1 was measured using Real-time PCR. Total RNA was extracted with the FavorPrep™ Tissue Total RNA Mini Kit (Hong Kong). The quality of the RNA was verified by electrophoresis on an agarose gel and by measuring absorbance at 260 nm using a Sigma PicoDrop spectrophotometer (USA). The RNA was stored at -80°C until use. For cDNA synthesis, 1000 ng of mRNA and random primers were used with a Thermoscientific-Fischer kit. Primers for the target and control genes, as listed in Table 2, were prepared, and the samples were analyzed using a Real-time PCR instrument, which generated amplification plots and CT values. Gene expression was quantified relative to the control using the 2-ΔΔCT method based on the obtained CT values. Further details can be found in Table 1.

Table 1. *Primer Sequences Utilized in the Study*

Genes	Primer Sequences	Sizes (bp)
ACTB	Forward: 5'- CTGTCGAGTCGCGTCCACC -3' Reverse: 5'- ATTCCCACCATCACACCCTGG -3'	219
PARP-1	Forward: 5'- GCACAGTGTCAAAGGTTTGGG -3' Reverse: 5'- TGTCGTTGACACCAGATGGG -3'	110

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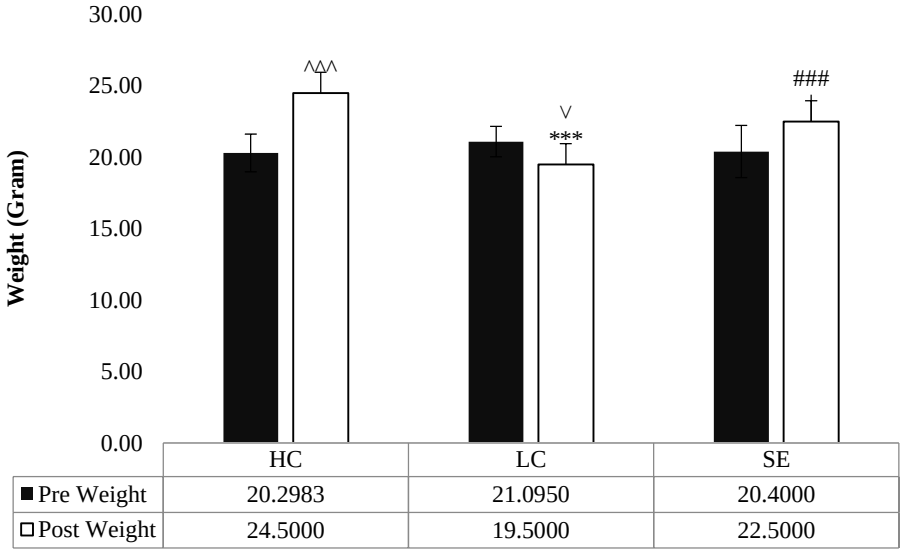
2.5. Statistical Methods

The normal distribution of data was assessed using the Shapiro-Wilk test. To analyze the data, a paired sample t-test, independent sample t-test and one-way analysis of variance (ANOVA) test with Tukey post hoc tests were employed. The statistical analysis was conducted using SPSS 22.0 software (SPSS Statistics/IBM Corp, Chicago, IL, USA). A significance level of $p < 0.05$ was considered for all statistical analyses, indicating the threshold for determining statistically significant results.

3. Results

The results of the paired t-test showed that the weight of the mice in the HC group in the last week was significantly LC group significantly decreased compared to the pre-test ($t = 2.81$ and $p = 0.03$). No significant difference was observed in pre-test and post-test weight values in the SE group ($t = -2.47$ and $p = 0.056$). The results also showed that there were significant differences in post-test weight ($F = 34.5$ and $p = 0.001$), visceral fat weight ($F = 40.56$ and $p = 0.001$), and PARP1 gene expression values in lung tissue ($F = 63.15$and $P = 0.001$) in the research groups. In other words, the post-test weight values in the LC group were significantly lower than in the HC group ($P = 0.001$), but in the SE group they were significantly higher than in the LC group ($P = 0.001$) (Figure 1).



	HC	LC	SE
■ Pre Weight	20.2983	21.0950	20.4000
□ Post Weight	24.5000	19.5000	22.5000

Figure 1. *Weight of animals in pre-test and post-test in the three research groups*
*^^^ (P=0.001) Significant increase in weight in the post-test of the HC group compared to the pre-test of this group; ∨ (P=0.05) Significant decrease in weight in the post-test of the LC group compared to the pre-test of this group; *** (P=0.001) Significant decrease in weight in the post-test of the LC group compared to the post-test weight of the HC group; ### (P=0.001) Increase in weight in the post-test of the SE group compared to the post-test of the LC group*

The weight of visceral fat in the LC group was significantly lower than in the HC group (P = 0.001), but in the SE group it was significantly higher than in the LC group (P = 0.03) (Figure 2).

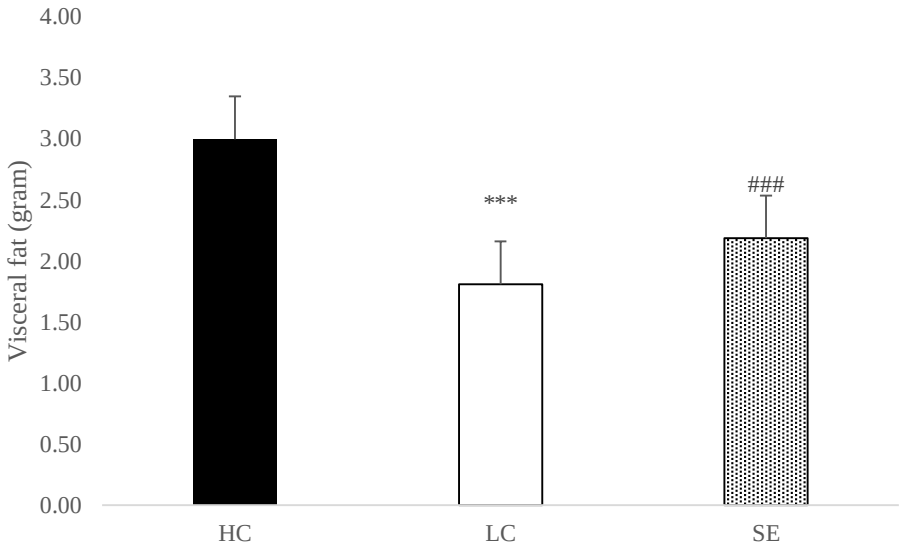


Figure 2. *Visceral fat weight of animals in the three research groups*
**** (P=0.001) Significant decrease compared to HC group; ### (P=0.001) Significant increase compared to LC group*

PARP1 gene expression in the LC group were significantly higher than in the HC group (P = 0.001), but in the SE group it was significantly lower than in the LC group (P = 0.016) (Figure 3).

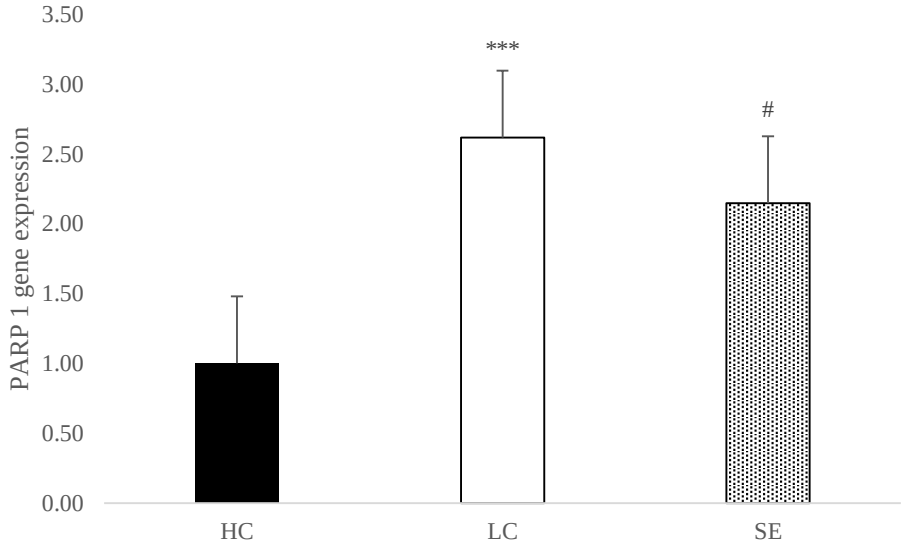


Figure 3. *PARP1 gene expression in animals in the three research groups*
**** (P=0.001) significant increase compared to HC group; # (P=0.05) significant decrease compared to LC group*

4. Discussion

The results of the present study showed that the post-test weight and visceral fat weight in the LC group were significantly lower than the HC group. However, the PARP1 gene expression levels in the lung tissue of the LC group were significantly higher than the HC group. First, due to the limitations of studying the histological and physiological changes of lung cancer, researchers have resorted to using animal models. BZP is used as a lung cancer inducer. In other words, this apoptosis-inducing stimulus can lead to the induction of metastasis and lung cancer by disrupting immunoglobulins, disrupting apoptosis, and disrupting DNA replication (23,24). However, studies have been conducted on the impact of cancer on lung physiological function and body composition. For example, in line with the present study, the results of one study also showed that muscle wasting and reduced body fat mass both play a role in the progression of lung cancer and impaired quality of life in these patients (25). In another study, researchers showed that fat weight loss is directly related to lung cancer progression in patients. With weight loss, atrophy, hypoxia induction, and reduction in muscle mass, the body's metabolism and energy needs decrease, and this is accompanied by an overall decrease in body weight (26). In one study, despite reports of decreased muscle mass in lung cancer patients, no significant changes were reported in the adipose tissue of these patients (27). In another study, researchers showed that despite a decrease in muscle mass in lung cancer patients undergoing chemotherapy, a 5% increase in fat mass was observed (28). Overall, researchers in a review noted that weight changes following lung cancer are dependent on the duration of the disease (29). However, in general, conflicting results have been reported regarding the association of weight and body mass index with lung cancer.

The present study result indicated that PARP1 gene expression in the LC group were significantly higher than in the HC group, but in the SE group it was significantly lower than in the LC group. Despite the studies, no study was found that investigated the effect of exercise on PARP1 gene expression in cancer. Therefore, this issue and the selection of this oncogene gene could be an innovation in the present study. PARPs play a special role in regulating chromatin structure. It seems that disruption of this gene expression and its increase can contribute to the uncontrolled proliferation of cancer cells in lung adenocarcinoma, and as a result, lead to cachexia by weakening muscles such as the diaphragm and skeletal muscles (30). Roggero et al. (2025) have stated that PARP1/2 gene expression increases in lung cancer and their inhibitors, such as CDK4/6, can lead to the cessation of metastasis and physical disorders by regulating and repairing DNA (30). Also, in another study, researchers, in addition to considering PARP1 as an oncogene, believed that pharmacological and non-pharmacological inhibitors of this oncogene could be effective in stopping the metastasis of cancer cells (31). According to evidence, it seems that exercise can lead to the induction of oxidative stress. This oncogene increases in exposure to oxidative stress conditions and repairs DNA, and helps in metabolic pathways, eliminating inefficient cells and abnormal cells (32). n a study that examined the effect of intense exercise training on PARP1, the results showed that three sessions of intense exercise training with both eccentric and concentric contractions led to increased PARP1 expression in skeletal muscle (33). Another study also found that acute exercise can increase PARP1 levels. However, the data showed that trained individuals had higher resistance to DNA damage than untrained

individuals. Trained individuals also had higher levels of PARP1 after exercise (34). This evidence suggests that exposure to exercise-induced oxidative stress leads to increased expression of PARP1, but this factor plays a role in DNA repair and regeneration in damaged cells in healthy individuals. As mentioned, the situation is different in people with cancer, and it seems that although acute and short-term exercise training leads to an increase in reactive oxygen species (ROS) and, as a result, DNA damage factors such as 8-hydroxy-2-deoxyguanosine (8-OHdG). However, long-term training with adaptation induction can be effective first by increasing antioxidant capacity, reducing oxidative stress, and ultimately reducing 8-OHdG, and this factor can lead to faster DNA repair in athletes (35). Due to the limited information regarding the mechanism of the effect of exercise training on PARP1 in cancer, the first limitation of the present study is the inability to compare the results of this study with other studies. Therefore, it is recommended that further studies be conducted in this field. Also, considering the role of PARP1 in DNA function, the lack of investigation of upstream pathways such as 8-OHdG, cyclins, and cell proliferation regulators is another limitation of the present study.

5. Conclusion

Generally, it seems that although cancer induction plays a role in body composition disorder and PARP1 gene expression disorder, regular swimming exercise was able to lead to body composition adjustment and downregulation of PARP1 gene in lung tissue of laboratory mice with lung cancer. However, due to the limited information, more studies are needed in this field.

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Conflict of interests: The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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