The effect of high-intensity interval training on inflammatory markers in male rats undergoing X-ray radiation

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Abstract

Introduction: One of the famous cancer treatments that are associated with an increment in inflammatory factors is X-ray radiation. This study aimed to evaluate the effect of high-intensity interval training on inflammatory markers in male rats undergoing X-ray radiation.
Materials and Methods: In this experimental study, 24 male rats were randomly divided into 4 groups: healthy control (n=6), HIIT (n=6), X-ray radiation (n=6) and X-ray radiation + HIIT (n=6). first, X-ray radiation and HIIT + X-ray radiation groups were anesthetized with ketamine xylazine solution (K, 60-90 kg/mg; Z, 6-10 kg/mg) and then placed on a 1 cm thick Plexiglas plate. The X-ray radiation photon beam was performed using X-ray with 4 Gy linear accelerators (Elekta Compact 6-MV China). The training program included ten weeks of HIIT. Serum levels of Tumor Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL-6) were measured by rat ELISA Kits. One-way ANOVA was used to determine the existence of a significant difference among groups.
Results: The results showed a significant difference between TNF-α and IL-6 in the HIIT, X-ray radiation, and HIIT + X-ray radiation groups with the control group ($P < 0.05$), but there was no significant difference between these three groups ($P > 0.05$).
Conclusion: X-ray radiation can increase TNF-α and IL-6. HIIT, on the other hand, can also enhance these factors. It seems better for people undergoing radiotherapy to use another exercise training instead of HIIT.

Keywords: X-ray radiation, High-intensity interval training, TNF-α, IL-6

Introduction

Cancer is considered the second most dangerous disease that threatens human health. Over the past decades, advances in the prevention, diagnosis, and treatment of various cancers have significantly improved the survival of cancer patients (1). One of the most important methods used to treat cancer is X-ray radiation. This method is used both alone and with other treatments. This treatment damages normal cells despite the removal of cancer cells (2). Nowadays, sophisticated X-ray radiation technologies are used to increase the chance of treatment and reduce the side effects of X-ray radiation. These technologies enhance the accuracy of radiation to the target tumor and reduce the damage to adjacent tissues through intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and Image-guided radiation

therapy (IGRT). Nevertheless, patients continue to suffer from radiation toxicity (3). X-ray radiation ultimately regulates genes involved in inflammation, apoptosis, and angiogenesis by activating complex signal pathways. Inflammation is associated with many types of cancer. Previous studies have shown that the proliferative and metastatic capacity of cancer cells is facilitated with inflammatory factors secreted by the tumor cells themselves and as well as other cells, including T and B lymphocytes, monocytes, fibroblasts, endothelial cells, and astrocytes (5,6). In vitro and in vivo studies have shown that exposure of cells and tissues to X-ray radiation increases the expression of many cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin -1α, interleukin -1β, and interleukin-6 (IL-6). TNF-α is an inflammatory cytokine that plays a key role in proliferation, differentiation, apoptosis, immune regulation, and induction of inflammation (5). A well-controlled study compared serum TNF-α levels in 21 patients before and after X-ray radiation. In that study, after 15 sessions of treatment, a significant increase in TNF-α levels was observed (6). TNF-a mediates the production of matrix metalloproteinase (MMP) in tumor cells, promotes tumor expansion, and plays a pivotal role in tumor metastasis. This cytokine increases the expression of angiogenic factors such as basic fibroblast growth factor (bFGF), IL-8, and vascular endothelial growth factor (VEGF) in tumor endothelial cells (7). IL-6 is a cytokine found in both tumor tissue and serum. IL-6 regulates cancer features such as inhibition of apoptosis, viability, proliferation, angiogenesis, invasiveness, and metastasis. This cytokine is also known to regulate tumor metabolism. In addition, IL-6 protects cancer cells against treatment-induced damage, oxidative stress, and apoptosis (4). It seems that the use of methods that reduce these inflammatory cytokines caused by X-ray radiation can be effective in the better treatment of cancer. Some previous studies have shown that exercise can reduce inflammatory cytokines. It has been reported that aerobic (endurance) physical activity can reduce the expression of the TNF-α gene due to its modulatory effects on the endocrine and nervous systems (8). Pervaiz et al. examined the changes in inflammatory cytokines in response to strenuous exercise in female mice and found that TNF-α levels decreased following strenuous exercise on a treadmill (9). One of the training methods that recently have been considered by athletes and healthcare centers is high-intensity interval training (HIIT). HIIT is one of the effective methods in increasing cardiorespiratory and metabolic function and optimizing physical fitness. The HIIT includes short intervals of intense exercise (above 85 to 90% VO2max) followed by rest or low-intensity recovery. It seems that this training method can reinforce the aerobic and anaerobic systems Simultaneously (10). Gibala and McGee suggested that HIIT is a suitable alternative to traditional endurance training to make similar or even better positive changes in physiological responses (11). Previous studies have shown that this type of training can increase people's health in a much shorter time than traditional long-term continuous training. Zwetsloot et al. reported that four weeks of HIIT reduced inflammatory responses due to strenuous exercise training (12). many people use HIIT, and some studies have shown that exercise training can affect inflammatory factors. However, the effectiveness and safety of these training in people receiving X-ray radiation is not well known. Therefore, the purpose of this study was to evaluate the effect of high-intensity interval training on inflammatory markers in male rats undergoing X-ray radiation.

Materials and Methods

In this experimental study, 24 adult male rats weighing 205 ± 54 g and aged 8 weeks

were selected as the sample. Mice were kept in polycarbonate cages in an environment with a temperature of 22°C and unrestricted access to water and food and a light-dark cycle of 12:12 hours. To observe the ethical issues in the research, the present study was conducted in compliance with all ethical codes of working with laboratory animals approved by the Ministry of Health and Medical Education. For X-ray radiation, first of all, mice were anesthetized with xylazine-ketamine solution (K, 60-90 kg/mg; Z, 6-10 kg/mg) and then placed on a 1 cm thick Plexiglas plate. This plate is finally placed on a plate of the same material with a thickness of 2 cm, which is placed under the device. A plate with a thickness of 1 cm is placed at a distance of 2 cm from the surface of the animal's chest. The distance from the spring to the top Plexiglas plate was considered to be one meter. Based on previous studies in this field, a dose of 4 Gy was selected for X-ray radiation (13). X-ray photon beam radiation with a dose of 4 Gy with a linear accelerator (Elekta Compact 6-MV, China) in the Radiotherapy center was performed at Ayatollah Khansari Hospital in Arak. Subjects in HIIT groups performed a 10-week training program. There were six days of training each week. The training program had 3 phases: familiarization, overload, and intensity stabilization. In the familiarization phase (one week), rats walked on a treadmill daily for 10-15 minutes at a speed of 8 meters per minute. In the overload phase (weeks 2 to 4), rats ran on a treadmill 2-6 3-minute intervals of 40 meters per minute on odd days and 3-20 30-second intervals of 54 meters per minute on even days. Finally, in the stabilization phase, rats performed HIIT for 6-weeks, 30-second intervals at 54 meters per minute. 1-minute active rest done as recovery between intervals. At the beginning of each training session, a 5-minute running with an intensity of 16 meters per minute was done as the warming up. At the end of each training session, a 5-minute light running was done as cooling down (Table 1) (14).

Table 1. The high-intensity interval training (HIIT) program used by the training groups in the current study.

Week	Day	Odd day	Even day
1	1	2 intervals, 40 m/min, 3 min	
	2		3 intervals, 54 m/min, 30 s
	3	2 intervals, 40 m/min, 3 min	
	4		5 intervals, 54 m/min, 30 s
	5	2 intervals, 40 m/min, 3 min	
	6		7 intervals, 54 m/min, 30 s
2	1	3 intervals, 40 m/min, 3 min	
	2		9 intervals, 54 m/min, 30 s
	3	3 intervals, 40 m/min, 3 min	
	4		11 intervals, 54 m/min, 30 s
	5	3 intervals, 40 m/min, 3 min	
	6		13 intervals, 54 m/min, 30 s
3	1	4 intervals, 40 m/min, 3 min	
	2		15 intervals, 54 m/min, 30 s
	3	4 intervals, 40 m/min, 3 min	
	4		17 intervals, 54 m/min, 30 s
	5	5 intervals, 40 m/min, 3 min	
	6		19 intervals, 54 m/min, 30 s
4	1	5 intervals, 40 m/min, 3 min	
	2		19 intervals, 54 m/min, 30 s
	3	6 intervals, 40 m/min, 3 min	
	4		20 intervals, 54 m/min, 30 s
	5	6 intervals, 40 m/min, 3 min	
	6		20 intervals, 54 m/min, 30 s
5-10	1-30	6 intervals, 40 m/min, 3 min	20 intervals, 54 m/min, 30 s

Blood samples were taken 24 hours after the last training session. After blood sampling (5 ml) and clotting, blood samples were centrifuged, then serum was extracted at 3500 rpm for 10 minutes and stored at -70°C for measurement. Serum TNF-α and IL-6 levels were measured by rat ELISA Kit (Eastbiopharm; China) according to the manufacturer's instructions. Analysis of variance and Bonferroni post hoc tests were used for data analysis. All analyses were performed at the $P < 0.05$ level using SPSS software version 27.

Results

The results of the one-way ANOVA test showed that there was a significant difference between groups ($P = 0.004$). Furthermore, the Bonferroni post hoc test showed a significant difference between TNF-α levels in HIIT, X-ray radiation, and HIIT + X-ray radiation groups with the control group ($P < 0.05$), meaning that TNF-α of these groups was significantly higher than the control group. But there was no significant difference between these three groups ($P > 0.05$) (Figure 1).

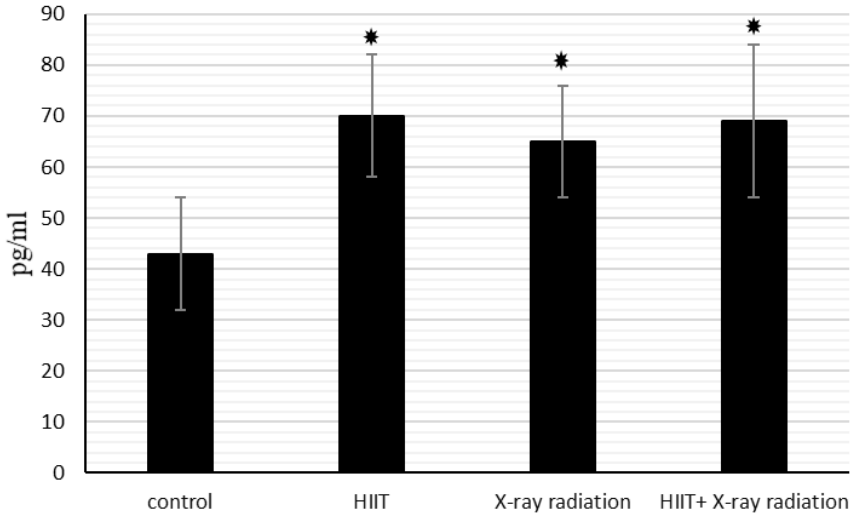

Figure 1. The levels of TNF-α in the different groups of rates under study. HIIT: High-intensity interval training; TNF-α: Tumor necrosis factor alpha. In the HIIT, X-ray radiation, and HIIT + X-ray radiation groups, TNF-α levels were significantly more than the control group. *Significant differences with the control group.

The second part of the data analysis showed a significant difference between the values of IL-6 in different groups ($P = 0.00$). The results of the Bonferroni post hoc test showed a meaningful difference between IL-6 in the HIIT, X-ray radiation, and HIIT + X-ray radiation groups with the control group ($P < 0.05$), in other word, IL-6 in these groups was significantly higher than the control group. It was further identified there was no significant difference between these three groups ($P < 0.05$) (Figure 2).

Discussion

The findings of our study showed a significant difference between the TNF-α in the experimental and the control groups. In other words, the TNF-α of these groups was significantly higher than the control group. We couldn't find any significant difference between the experimental groups. Some studies have shown that serum levels of TNF-α increase significantly after X-ray radiation (6). Similarly, we found that the TNF-α in the X-ray radiation and HIIT + X-ray radiation groups was significantly higher than the control group. Sarkara et al. reported that eight weeks of HIIT increased inflammatory factors such as TNF-α (10). In another study, Zebrowska et al. showed that three weeks of HIIT could increase resting and maximal TNF-α levels in

subjects (15). In their work, Gerosa-Neto et al. concluded that HIIT with an intensity of 90% of maximum heart rate enhances TNF-α by 104% (16).

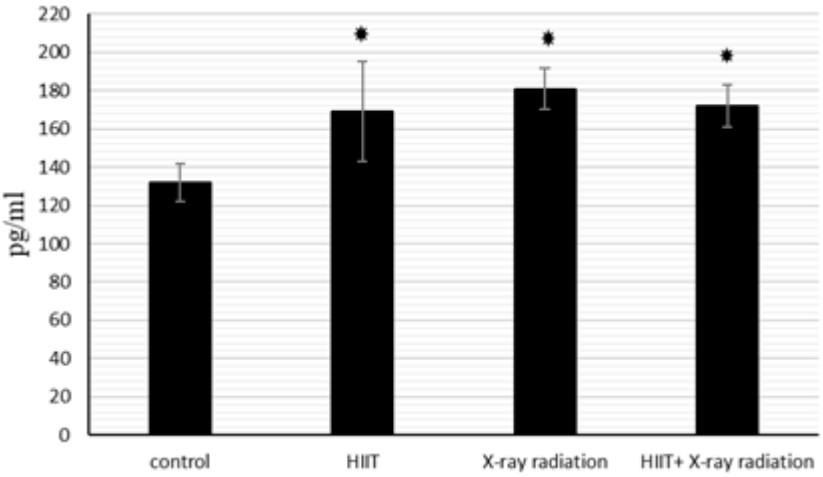

Figure 2. The levels of IL-6 in the different groups of rates under study. HIIT: High-intensity interval training; IL-6: Interleukin 6. In the HIIT, X-ray radiation, and HIIT + X-ray radiation groups, IL-6 levels were significantly more than the control group. *Significant differences with the control group.

On the other hand, Zwetsloot et al. examined the effect of two weeks of HIIT with bicycle on inflammatory factors and concluded that this type of training did not affect TNF-α (17). Also, Bartlett et al. reported that ten weeks of high-intensity interval walking training could not alter the levels of inflammatory factors such as TNF-α (18). the results of these studies are not consistent with the findings of the present study. One of the factors that can lead to such contradictory findings is the type of training used. Zwetsloot et al. and Bartlett et al. used cycling and walking, respectively. But we employed running as a training intervention. Cycling and walking do not seem to provide the stimuli needed to start the inflammation as much as running. Another reason for the inconsistent findings could be the duration of the training schedule. Zwetsloot et al. used only two weeks of training, but we used a 10-week training intervention. In line with our findings, Sprod et al. did not report a significant decrease in TNF-α in the X-ray radiation groups due to exercise training (19). But Monazzami et al. examined the effect of eight weeks of combined training on TNF-α in women with breast cancer who received X-ray radiation. They concluded that combination training could reduce patients' TNF-α levels (20). The discrepancy between Monazzami et al. and our findings can be due to the type of training. They applied combined training, while we used HIIT. besides, they applied cancer patients, but we used healthy rats that received only X-ray radiation. Therefore, the modifications caused by combination training may be different from HIIT. Also, the healthy subjects' and cancer patients' responses to exercise training can be diverse.

By its effects on activating various pathways, X-ray radiation transitorily active major Transcription Factors (TFs) in mammalian cells. These events ultimately lead to the activation of a multidimensional signaling response. This multidimensional signaling response includes nuclear factor kappa B (NF-kB) and signal transducer and activator transcription (STAT). These key transcription factors interact to regulate many of the genes involved in inflammation, apoptosis, and angiogenesis processes and help increase cell resistance to X-ray radiation. NF-κB is a major transcription factor that regulates the expression of more than 200 target genes. For example, the expression of given

genes to suppress apoptosis and cell stimulation, proliferation, metastasis, radioresistance, and inflammation in a wide range of tumors. NF-κB plays a substantial role in immune and inflammatory responses because it can regulate the expression of cytokines and proinflammatory chemokines such as TNF-α, IL-1, and IL-2. X-ray radiation can activate NF-κB via the Ataxia Telangiectasia mutated protein (ATM) or DNA-PK likely via MEK/ERK/p90 pathway (5). Some studies have shown that hypoxia due to HIIT can trigger an inflammatory response that increases cytokines such as TNF-α. This response may be determined by an increase in proinflammatory cytokines (10). Therefore, an increase in TNF-α levels in subjects undergoing X-ray radiation and HIIT is not unexpected.

The other results of our study showed that IL-6 of experimental groups was significantly higher than the control group. But there was no significant difference between them. Previous studies have shown that in vitro and in vivo cells exposure to X-ray radiation increases the expression of cytokines such as IL-6. The findings of the present study also showed a significant increase in IL-6 in X-ray radiation groups. Regarding the effect of HIIT on IL-6, past research has reported that eight weeks of HIIT running workouts significantly increase IL-6 by approximately 16% (10). Sarir et al. also concluded that after performing a 6-week HIIT in rats, IL-6 and TNF-α significantly increased (21). However, some studies conducted inconsistent findings with our findings. For example, Bartlett et al. reported that ten weeks of HIIT (walking training) did not affect IL-6 levels (18). A study by Gerosa-Neto et al. also found that sixteen weeks of HIIT reduced serum levels of IL-6 in obese women (16). As mentioned earlier, these inconsistencies could be arising from the difference between types of training (running vs. walking) and the subjects (rats vs. obese women).

The immune system plays a pivotal role in tumors control. Immune agents can stop the tumor by killing the cancer cells or inhibiting their growth. On the other hand, immune cells can create a microenvironment that suppresses the immune system, which helps the tumor to progress (22). IL-6 is a pleiotropic cytokine. It holds proinflammatory and anti-inflammatory properties and causes acute phase reactions. Therefore, we cannot rule out other effects of IL-6, including control of treatment-related inflammation. However, despite the pleiotropic properties of IL-6, cancer patients with high circulating IL-6 levels are generally associated with a poor prognosis and shorter survival rates, whenever low IL-6 levels are associated with a better response to treatment (23).

One of the reasons for the increase in IL-6 in the present study could be the activation of fast-twitch muscle fibers during HIIT, as previous studies have shown that increasing the speed of contraction can expand the expression of IL-6 (24). recalling of These muscle fiber types increases the concentration of cytosolic calcium and decreases their glycogen stores (25). These conditions can increase IL-6 expression. In addition, some previous studies have reported that increased HIIT-induced free radicals can affect IL-6 and TNF-α levels (26). Exercise training induces many changes in cellular energy states and the immune system. Increased production of IL-6 by skeletal muscle during training sessions plays a pivotal role in providing cellular energy. In the condition of high adenosine monophosphate/adenosine triphosphate ratio and low glycogen stores, IL-6stimulates lipolysis (27). It also promotes the production of IL-10, which in turn inhibits the activity of the NF-κB, as a result, may counteract the effects of proinflammatory cytokines (28). One of the limitations of the present study is the

lack of control over the nutrition of the rats. Nutritional status has a significant effect on cytokines. It seems that it is necessary to control the nutritional status of the subjects in future studies. Further, since HIIT didn't compare with other exercise training models in our work, it is suggested that HIIT compare with different training types, especially moderate-intensity training, to diagnose the effects of exercise training on inflammatory factors.

Conclusion

In conclusion, our findings showed that IL-6 and TNF-α in rats undergoing X-ray radiation, HIIT, or HIIT + X-ray radiation increased significantly compared to the control group. Therefore, it seems that people undergoing X-ray radiation should not use high-intensity interval training. However, further studies are warranted to confirm these findings.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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