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Research Paper

The Effect of Six Weeks of Aerobic Exercise on Malondialdhyde and Superoxide Dismutase of Heart Tissue in Rats Poisoned With Steroid Dianabol

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ABSTRACT

Background and Aim: Anabolic steroids cause damage to various tissues, including the heart. This study aimed to evaluate the effect of aerobic exercise on Malondialdehyde (MDA) and superoxide dismutase (SOD) of heart tissues in rats poisoned with the anabolic steroid Dianabol.

Materials and Methods: In this experimental-fundamental study, 18 rats were selected and divided into three 6-series groups, including normal saline intake (Sh), Dianabol (D), and steroid intake with aerobic exercises (D+RT). For six weeks, the steroid and aerobic exercise groups received 5 mg/kg of Dianabol per day peritoneally, and the steroid aerobic exercise group performed aerobic exercise five sessions per week. Measurement of MDA and SOD gene expression in heart tissue was measured by ELISA. Kolmogorov-Smirnov statistical tests, a 1-way analysis of variance with Tukey post hoc test were used to analyze the results ($P \leq 0.05$).

Results: Steroid Dianabol had a significant effect on increasing MDA (P=0.001) and decreasing SOD (P=0.001) in heart tissue. However, aerobic exercise decreased MDA (P=0.001) and increased the SOD antioxidant index (P=0.000) in the heart tissue of rats exposed to Dianabol.

Conclusion: Anabolic steroids appear to increase oxidative stress indices and decrease antioxidants in heart tissue, while aerobic exercise can improve elevated levels of oxidative stress and decreased levels of antioxidants.

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Journal of Vessels and Circulation
Qom University of Medical Sciences

1. Introduction

Anabolic androgenic steroids (AAS) are synthetic derivatives related to the male sex hormone (testosterone) that play a vital role in body growth. These compounds are used in some clinical applications, such as muscle atrophy, growth retardation, anemia, hypogonadism, and reducing bone minerals [1]. According to the anabolic properties of AAS, it is one of the most common drugs with a special position among athletes. Consumption of AAS can lead to better physical performance, lean mass, strength, and muscle size [2]. Also, the combination of AAS with aerobic exercise leads to better physical performance, lean mass, muscle size, strength, protein metabolism, bone metabolism, and collagen synthesis [3]. Dianabol is one of the crucial AAS that is widely used by humans and racehorses. Dianabol increases muscle size by stimulating protein synthesis and reducing its degradation [4]. The oxidation of anabolic steroids, especially Dianabol in the body leads to the production of reactive oxygen species (ROS) and the peroxidation of fats and provides the basis for cell damage [5]. Many chronic diseases, such as cardiovascular diseases and some cancers are caused by free radicals and subsequent oxidation of fats, nucleic acids, and proteins [6].

Oxidative stress occurs as a result of an imbalance between the production of free radicals and ROS on the one hand and antioxidant defense on the other hand, as a result of which many macromolecules are damaged [7]. Oxidative stress is a condition in which the amount of ROS in the body increases and overcomes the antioxidant capacity and causes damage to cellular components, including deoxyribonucleic acid (DNA), protein, and lipid structures, which ultimately lead to pathophysiological disorders [8]. Malondialdehyde (MDA) is one of the major products of the degradation of unsaturated fatty acids by free radicals, and it is formed by a group of free radicals called hydroxyl radicals, which causes the peroxidation of fats. MDA is known as an index of oxidative stress [9]. To deal with the produced oxidative stress, the body is equipped with an antioxidant defense system [8].

The body's antioxidant system includes enzymatic and non-enzymatic antioxidants affected by exercise and nutrition. Enzymatic antioxidants include superoxide dismutase (SOD) and catalase, and non-enzymatic antioxidants include vitamin A, vitamin C, vitamin E, glutathione peroxidase, etc. which minimize the production and formation of free radicals and prevent their destructive effects [10]. SOD is an antioxidant enzyme that has three isozymes. SOD is the first line of the body's enzymatic defense against free radicals, which converts superoxide into hydrogen peroxide. By maintaining the body's antioxidant defense, SOD moderates the oxidative stress caused by the increase of free radicals [11].

On the other hand, performing regular sports exercises by reducing the level of free radicals in the body and strengthening the antioxidant system increases the resistance against oxidative stress and controls the number of cell damage [10]. Many studies have been conducted concerning the effect of sports activity on oxidative stress markers, many of which have shown that sports activity leads to reduced oxidative stress and improved antioxidant status; for example, Quan et al. noted the reduction of MDA after aerobic exercises with average intensity [12]. Karabulut et al. observed a significant decrease in MDA and an increase in some antioxidant enzymes after regular exercises [13]. In contrast, Rinaldi et al. in their study entitled "The effect of eight weeks of aerobic exercises on a treadmill on rat cardiac SOD," observed an increase in this index following aerobic exercises, however, no significant changes were observed in the levels [14]. According to the widespread use of anabolic-androgenic steroids by athletes and its side effects on heart tissue and the wide and unsupervised prescription of these drugs to athletes and young people by unqualified people [2], as well as the contradictory results of studies related to oxidative stress and aerobic exercise, and lack of observing a study that investigates the effect of aerobic exercise on MAD and heart antioxidant indices in people who consume the steroid Dianabol, the present study aims to investigate the effect of aerobic exercise on MAD and SOD indices in heart tissue of rats exposed to the anabolic steroid Dianabol.

2. Materials and Method

The current research is an experimental-fundamental type. In this study, 18 Sprague-Dawley rats with a weight range of 150 to 200 grams and an average age of 8 weeks were purchased and kept in a laboratory environment in standard conditions for one week to adapt to the new environment. Then, rats were divided into three 6-series groups, including normal saline intake (Sh), Dianabol (D), and aerobic exercise and Dianabol (D+RT). The aerobic exercise group with steroids performed aerobic exercise for six weeks [15]. Also, groups (D) and (D+RT) received 5 mg/kg of Dianabol peritoneally daily [16]. The temperature of the animal-

keeping room was 22±1.4°C with 65%-75% humidity. Rats were kept according to the cycle of 12 hours of sleep, wakefulness, and availability of water and food.

Aerobic exercise protocol

In the first stage, rats ran on a treadmill at a speed of 10-5 m per minute for 10 minutes to familiarize themselves and reduce stress. To warm up and cool down before starting and after finishing the exercises, aerobic exercises were performed on a treadmill for 2 minutes at a speed of 10 m per minute. The training protocol for 8 weeks and 5 sessions per week with an intensity of 10 m per minute and a duration of 15 m with a slope of 5% started in the first week and gradually increased to an intensity of 25 m per minute with a duration of 30 minutes with a slope of 5% in the last week. It was performed in the first 2 weeks with a speed of 10 m per minute and a duration of 15 minutes with a slope of 5% and gradually in the second 2 weeks, it was carried out with the intensity of 15 m per minute and a duration of 20 minutes with a slope of 5%. In the third 2 weeks, the exercise protocol was performed with an intensity of 20 m per minute, a duration of 25 minutes, and a slope of 5%. In the fourth 2 weeks, the protocol was performed with an intensity of 25 m per minute and a duration of 30 minutes with a slope of 5% [17].

Heart tissue sampling steps

Rats were anesthetized 48 h after the last training session and injection of Dianabol with ketamine at a dose of 95 mg/kg and xylazine at a dose of 5 mg/kg intraperitoneally with an insulin syringe, and the heart tissue of rats was separated by laboratory experts and immediately frozen in liquid nitrogen and stored at 70°C. For molecular investigations at the level of gene expression, RNA was extracted from the heart tissue according to the manufacturer's protocol (Sinagen, Iran). Then, using the property of absorbing light at a wavelength of 260 nm with the help of the following equation, the concentration and purity of the sample RNA were quantitatively obtained (Equation 1).

1. C (µg/µl)=A260×ε×d/1000

After extracting RNA with high purity and concentration from all studied samples, cDNA synthesis steps were performed according to the manufacturer's protocol, and then the synthesized cDNA was used to perform the reverse transcription reaction. First, the designed primers related to the genes were examined, and then the gene expression was quantitatively examined using the q-RT PCR. The gene expression of the desired factors from the heart tissue was measured by the ELISA method and real-time PCR technique and all primers were designed by Allele ID v. 7.8 software while using the β²m (beta 2 microglobulin) gene as an internal control. Gene expression values were analyzed using the $2^{-\Delta\Delta Ct}$ formula.

Statistical analysis

To examine the normality of the distribution of the findings, the Kolmogorov Smirnov test was used, and to analyze the findings, the one-way analysis of variance with Tukey's post hoc test was used in SPSS software (P≥0.05).

3. Results

Figures 1 and 2 show MDA and SOD gene expression levels, respectively. The results of one-way analysis of variance showed a significant difference in the levels of MDA (P=0.001, F=49.82), and SOD (P=0.001, F=16.52) in the heart tissue of rats in three groups. Tukey's post hoc test results showed that MDA levels (P=0.001) in the steroid Dianabol group were significantly higher than in the control group. However,

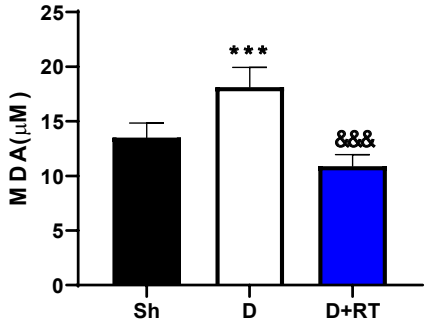

Figure 1. Malondialdehyde (MDA) levels in three research groups

Journal of Vessels and Circulation
Qom University of Medical Sciences

&&& P<0.001 significant derease compared to Sh groups and S consumption. *** P>0.001 significant increase compared to the Sh group.

Journal of Vessels and Circulation
Qom University of Medical Sciences

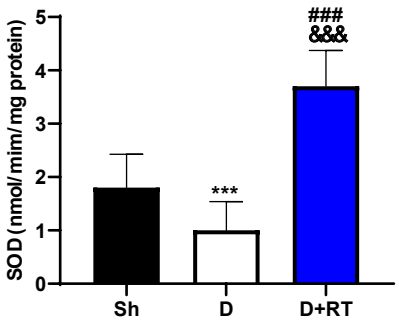

Figure 2. Superoxide Dismutase (SOD) levels in three research groups

Journal of Vessels and Circulation
Qom University of Medical Sciences

*** P=0.001 significant decrease compared to Sh group. &&& P=0.000 significant increase compared to S group. ### P=0.002 significant increase compared to Sh group.

MDA levels in the training group with Dianabol use were significantly lower than in the control and Dianabol use groups (P=0.001) (Figure 1). SOD levels in the steroid Dianabol group were significantly lower than in the control group (P=0.001); however, the training group with Dianabol was significantly higher than the control group (P=0.002) and Dianabol (P=0.000) (Figure 2).

4. Discussion

The results of the present study showed that consumption of the anabolic steroid Dianabol decreases SOD levels in the heart tissue of rats. On the other hand, aerobic exercise has a significant effect on the increase of SOD in the heart tissue of rats poisoned with Dianabol. AAS misuse by increasing the release of apoptotic factors, such as apoptosis-inducing factor, caspase 3, and cytochrome C [18] decreases cell survival and increases the occurrence of cell death process [1]. This issue is consistent with the results of previous studies and indicates that after consuming anabolic steroids, the amount of oxidants increases, and antioxidant reserves, such as SOD, glutathione peroxidase, and catalase decrease [1]. Two hypotheses confirm that AAS increases the production of free radicals. The first hypothesis is the dysfunction of the mitochondrial electron transport chain. Continued excessive and long-term use of AAS reduces the activity of the mitochondrial respiratory chain [19].

The electron transport chain can be the consequence of the excessive production of ROS against the antioxidant system. Cytochrome oxidase P450 is another hypothesis that explains the increase of free radicals [20]. In this regard, Rozbehi et al. (2019) concluded that the use of anabolic steroid stanozolol via reducing antioxidant reserves decreases SOD and glutathione peroxidase at the same time [21]. Also, Dornels et al. (2017) investigated the effect of different amounts of anabolic steroids on the oxidant and antioxidant status of liver and kidney tissue and showed that reduced hepatic glutathione was reduced in the steroid group [22].

Contrary to the findings of the present study, it was reported in a study that resistance training for 12 weeks with an intensity of 70% of one repetition maximum does not have a significant effect on the changes of catalase and glutathione peroxidase in rats [23]. Also, Katoli et al. (2017) showed that eight weeks of training, five sessions per week, and each session of running at a speed of 25-30 m per minute do not have a significant effect on the levels of catalase and glutathione peroxidase in rats poisoned with nandrolone [24].

The present study shows that the activity of SOD enzymes in the heart tissue of exercised rats receiving Dianabol has increased compared to the Dianabol and control groups, therefore, it is clear that the oxidative stress increases after receiving Dianabol. Continuous or short-term reception of Dianabol through the messenger pathway produced by free radicals increases the expression of antioxidant enzymes [25]. Also, the results of the present study showed that cardiac SOD enzyme activity in training groups increases along with consumption of Dianabol. This observation is consistent with the results of past studies [21, 26]. However, some studies have reported contradictory results that have shown the reduction and absence of antioxidant changes [27, 28].

These contradictions are rooted in the different intensities or duration of the exercises used by the studies. Short-term training (one intense training session) has been associated with an increase in free radicals, although long-term training (4 weeks, 8 weeks, and

long-term) is associated with cellular adaptations that increase antioxidant enzymes [21]. Another reason for the contradictory findings can be the examination of the studied tissue. The present study was conducted on the heart tissue of rats; however, Oganovski et al. (2017) studied liver tissue, Yahyai et al. studied cerebellum tissue (2019), Levenberg et al. (2018) studied skeletal muscles, and Giomera et al. (2016) studied kidney tissue, indicating inconsistent results with the present study [22, 28, 30].

Other results of the present study showed that the consumption of Dianabol had a significant effect on the increase of MDA. This issue is consistent with the results of the previous studies and indicates that after using Dianabol, the amount of produced oxidants increases. This hypothesis exists and confirms that AAS increases the production of free radicals during the dysfunction of the mitochondrial electron transport chain. Continued excessive and long-term use of AAS reduces the activity of the mitochondrial respiratory chain complex [22]. Dysfunction of the electron transport chain can be the result of excessive production of ROS against the antioxidant system [31]. Also, studies have shown that AAS, such as Dianabol, by creating catabolic products, which are considered potential catalysts for damage caused by free radicals, along with the oxidant metabolites of anabolic steroids, cause oxidative damage in body tissues [32]. In this regard, Kara et al. studied the effect of stanozolol on the mechanisms of apoptosis and oxidative stress in the heart tissue of rats and concluded that the consumption of stanozolol increases the parameters of MDA and PC [33]. Also, Tosun et al. studied the effect of AAS consumption on oxidative stress indices in the liver of rats and concluded that AAS consumption can increase oxidative stress indices as well as MDA and PC [34]. Dorlis compared the effect of steroid stanozolol and boldenone on oxidative stress parameters of rats' liver and kidney and concluded that in the stanozolol consumption group, ROS indicators such as MDA were highly increased [35] that are consistent with the results of the present study. It has been reported that AAS misuse by increasing the release of apoptogenic factors, such as the apoptosis-inducing factor, caspase 9, and cytochrome C [36], leads to decreased cell survival and increased process of cell death [1]. In this regard, the consumption of Dianabol increases lipid peroxidation through the increase of serum lipids. On the other hand, the increase in lipid peroxidation caused by the consumption of Dianabol causes increased free radicals and decreased antioxidant reserves.

Also, the present study showed that 8 weeks of aerobic exercises in rats exposed to Dianabol caused a significant decrease in MDA concentration. However, regarding the lack of studies in the field of investigating exercise activity on the MDA index of heart tissue under poisoning with anabolic steroids, the present study had limitations. However, some studies have examined the effect of sports training or the simultaneous effect of sports training and the misuse of anabolic steroids on oxidative stress indicators. For example, in a study, Kamiletti, Moyran, et al. showed that very intense exercise could reduce the effects of brain redox caused by the consumption of stanozolol in Wistar rats [37]. Rodrigues et al. showed that 6 weeks of a swimming exercise program reduced fat and protein oxidation in diabetic rats so that plasma MDA levels in rats in the exercise group were significantly reduced compared to the control group [38]. Badkobeh et al. also showed that 8 weeks of aerobic training significantly reduces MDA levels in the heart tissue of rats [39], which is consistent with the results of the current research. According to the results of this research, it seems that aerobic exercise has been able to control the oxidant effects of Dianabol in rats. Dianabol also induces an effect similar to exercise on antioxidant enzymes, although the mechanisms of the effects of exercise and anabolic steroids are different. The stimulation of exercise to induce antioxidant enzymes is rooted in the increase in ROS production caused by muscle contraction and activity [40].

It seems that a series of factors are effective in reducing the concentration of MDA following the training period, and the improvement of the oxidative stress conditions cannot be considered as the result of the improvement of the antioxidant status. It has been reported that the resistance of the cell membrane, especially the red cells, which increases against ROS after exercise may contribute to this result [41]. In any case, it seems that the activation of cellular signaling pathways increases the expression of enzymatic antioxidants and ultimately reduces fat peroxidation and MAD [42]. In fact, in the present study, MDA in the training group with Dianabol had a significant decrease compared to the Dianabol group. However, regarding the lack of studies in the field of aerobic exercise on the MDA index of heart tissue under Dianabol intoxication, the present study had limitations. However, some studies have investigated the simultaneous effect of sports training and misuse of anabolic steroids on oxidative stress indicators; for example, in a study by Erazi et al. on the interaction of resistance training and misuse of Sustanon on liver antioxidant activity in rats showing that the activity of

Journal of Vessels and Circulation
Qom University of Medical Sciences

SOD, glutathione peroxidase, and glutathione reductase in the resistance training and Sustanon group had a slight decrease compared to the Sustanon group [43]. Kamiletti-Moyran et al. showed that very intense exercise could reduce the effects of brain redox caused by stanozolol consumption in Wistar rats [37]. The results of past studies show the effect of sports activity on reducing the amount of ROS in subjects exposed to AAS which is consistent with the results of the present study. Despite this, some studies have reported contradictory results showing a decrease and no change in antioxidants or an increase in ROS [44-46].

One of the reasons for the contradictory results is the studied tissues. Dianabol is a strong activator of androgen receptors that can increase antioxidants. Another reason for the difference in the obtained results is rooted in the androgen receptors of the tissues. For example, fast-twitch fibers have fewer receptors compared to slow-twitch fibers [47]. It seems that the androgen receptors of the heart are aligned with the slow-twitch fibers, which increase antioxidant activity. However, confirmation of this issue requires more research and it is suggested that future researchers investigate and compare the interactive effect of combined exercise, intense interval exercise, continuous exercise, and stanozolol on SOD and ROS indicators of slow and fast-twitch fibers and heart.

5. Conclusion

According to the results obtained from the present research, it seems that the consumption of the anabolic steroid Dianabol leads to increased MDA and decreased SOD in the heart tissue, while aerobic exercise can improve the increased levels of oxidative stress and decreased antioxidants.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Biomedical Research Ethics Committee at the Islamic Azad University (IR.IAU.M.REC.1399.004) under the suport of the Miyaneh Branch, Islamic Azad University.

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Authors' contributions

Methodology, Data collection, and Data analysis: Sajjad Ramezani, Mohsen Yagoubi; Conceptualization, Research and review: Sajjad Ramezani, Mohsen Yagoubi, Bahman Valinejad. Draft writing: Sajjad Ramezani, Bahman Valinejad. Editing and finalization: All authors.

Conflict of interest

The authors declared no conflict of interest..

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