Original Article:

The Effect of Resistance Training on Malondialdehyde and Protein Carbonyl Concentration in the Heart Tissue of Rats Exposed to Stanozolol

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Article info:
Received: 14 Apr 2020
Accepted: 15 Jun 2020

Keywords:
Malondialdehyde, Protein carbonyl, Resistance training, Stanazolol, Heart

ABSTRACT

Background: Consumption of anabolic steroids causes damage to various tissues, including the heart.

Objectives: This study aimed to investigate the effect of Resistance Training (RT) on Malondialdehyde (MDA) and Protein Carbonyl (PC) in the heart tissue of rats exposed to stanozolol (S).

Methods: In this experimental study, 18 rats with the mean age of 8 weeks and weight range of 150 to 200 g were selected and divided into three groups of 6 rats: 1. Sham (normal saline consumption) (Sh), 2. S, and 3. S+RT. For 8 weeks, the S and S+RT groups received 5 mg/kg/d S, and the S+RT group performed 5 RT sessions per week. Measurement of MDA and PC in the heart tissue was performed with the enzyme-linked immunosorbent assay.

Results: Stanozolol had a significant effect on increasing MAD (P=0.001) and PC (P=0.03) in the heart tissue. However, RT led to a decrease in MDA and PC in the heart tissue of rats exposed to S (P=0.001).

Conclusion: It appears that S consumption leads to an increase in MDA and PC levels in the heart tissue, while RT can improve the elevated levels of MDA and PC.

Introduction

Anabolic-androgenic Steroids (AAS) are artificial derivatives of the male sex hormone (testosterone) that play a key role in body growth [1]. Their biological activities include anabolic effects and increased muscle growth, behavioral effects, aggression creation, and hematopoietic effects. AAS can lead to improved physical function, lean mass, strength, and muscle mass [2]. Although in some pathological conditions it seems that using AAS can help improve one's condition, most competitive athletes use AAS to increase muscle mass and improve athletic performance [3].

Citation Arjmand A, Abedi B, Hosseini SA. The Effect of Resistance Training on Malondialdehyde and Protein Carbonyl Concentration in the Heart Tissue of Rats Exposed to Stanozolol. Pharmaceutical and Biomedical Research. 2020; 6(4):261-268. http://dx.doi.org/10.18502/pbr.v6i4.5112

doi: http://dx.doi.org/10.18502/pbr.v6i4.5112

Stanozolol (S) is an androgenic steroid that increases muscle size by stimulating protein synthesis and reducing its degradation [4]. Oxidation of anabolic steroids, especially S, in the body leads to the production of Reactive Oxygen Species (ROS), and peroxidation of fats and provides the ground for cellular damage [5]. Many chronic diseases, such as cardiovascular disease and some cancers, are caused by free radicals following oxidation of fats, nucleic acids, and proteins [6]. Oxidative stress is caused by an imbalance between the production of free radicals and ROS on the one hand and antioxidant defenses on the other hand, due to which many macromolecules are damaged [7].

Oxidative stress is a condition in which the amount of ROS in the body increases and overcomes antioxidant capacity, causing damage to cellular components such as Deoxyribonucleic Acid (DNA), protein, and lipid structures, which ultimately leads to pathophysiological disorders [8]. Malondialdehyde (MDA) is one of the major products of the breakdown of unsaturated fatty acids by free radicals and is formed by a group of free radicals called radical hydroxyl that causes the peroxidation of fats. MDA is known as an oxidative stress marker [9]. On the other hand, Protein Carbonyl (PC) is the most common type of carbonylated protein oxidation. Carbonylation is an irreversible deformation caused by oxidative stress, which often leads to loss of function and altered biological activity of proteins. PC is made up of different types of oxidative mechanisms [10]. To counteract the oxidative stress produced, the body is equipped with an antioxidant defense system. The body's antioxidant system includes enzymatic and non-enzymatic antioxidants that can be affected by exercise and nutrition.

Enzymatic antioxidants include Superoxide Dismutase (SOD) and catalase, and non-enzymatic antioxidants include vitamin A, vitamin C, vitamin E, and glutathione [11]. SOD is an antioxidant enzyme that has three isoenzymes. SOD is the body's first enzymatic line of defense against free radicals, which converts superoxide to hydrogen peroxide and by preserving the body's antioxidant defenses, modulates oxidative stress caused by increased free radicals [12]. On the other hand, the regular exercise by reducing the level of free radicals in the body and strengthening the antioxidant system increases resistance to oxidative stress and controls the rate of cell damage [13].

There have been many studies on the effect of exercise on oxidative stress markers, many of which have shown that exercise reduces oxidative stress [13-15]. On the one hand, AAS are widely used by athletes despite side effects on the heart tissue. On the other hand, disqualified individuals administer these drugs uncontrollably to athletes and young people [2]. In the meantime, there are contradictory results of studies on oxidative stress and Resistance Training (RT) and there is no investigation on the effect of RT on MDA and PC in the heart tissue in the presence of S, this study aimed to investigate the effect of RT on MDA and PC in the heart tissue of rats exposed to S.

Materials and Methods

In this experimental study, 18 Sprague Dawley rats with a weight range of 150 to 200 g and an average age of 8 weeks were purchased from the animal lab of Islamic Azad University, Marvdasht Branch, Marvdasht City, Iran, and kept in the laboratory for one week to adapt to the new environment under standard conditions (humidity of 45% to 55%, a dark-light cycle of 12-12 h and temperature of 23±2°C) and free access to food (standard food pellets, including crude protein 23%, crude fat 3.5%-4.5%, crude fiber 4%-4.5%, ash maximum 10%, calcium 0.95%- 1%, phosphorus 0.65%-0.75%, salt 5%-5.5%, humidity maximum 10%, lysine 1.15%, methionine 0.33%, methionine+cysteine 0.63%, threonine 0.72%, and tryptophan 0.25%) and water. Then, they were divided into three groups of 6 rats: 1. Sham (normal saline consumption) (Sh), 2. S, and 3. S+RT. The S+RT group performed RT for 8 weeks [16] and the S and S+RT groups received 5 mg/kg/d S intraperitoneally [17].

The Stanozolol was purchased from WEBER Company (Germany) in injection form. Forty-eight hours after the last training session and injection of S, the rats after having 12 h fasting were anesthetized with ketamine 10% (50 mg/kg) and xylazine 2% (10 mg/kg), and the heart tissue of rats was removed by laboratory experts and then immediately frozen in liquid nitrogen and kept at -70˚C. The measurement of MDA (CAT No.: ZB-MDA-96A; ZellBio GmbH, Germany) and protein carbonyl (CAT No. KCAR-96; KiaZist, Iran) was performed by the enzyme-linked immunosorbent assay.

RT protocol

The rats performed RT for 8 weeks and 5 sessions per week using a 1-m high ladder, with a distance of 4 cm between the stairs, and a slope of 85˚. RT started at 30% of body weight in the first week and ended with 100% body weight of rats in the eighth week. It is noteworthy that to warm up at the beginning of the training, the rats climbed the training ladder four times without weights. Also, the training in each session included performing 4 sets (the first set was 50%, the second set 75%, the third

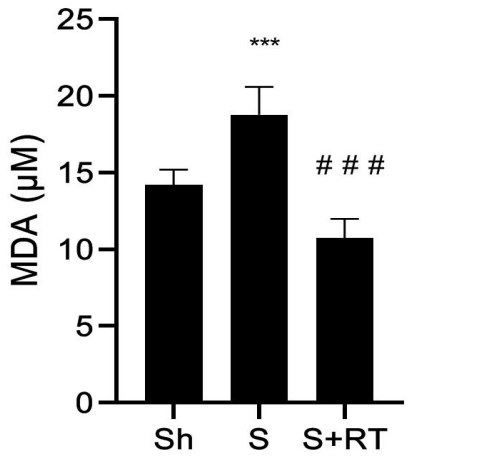

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Figure 1. MDA levels in the three study groups

*** P<0.001: A significant increase compared to the control group. ###P<0.001: A significant decrease compared to the control and stanozolol consumption groups. Sh: Sham; S: Stanozolol; RT: Resistance Training.

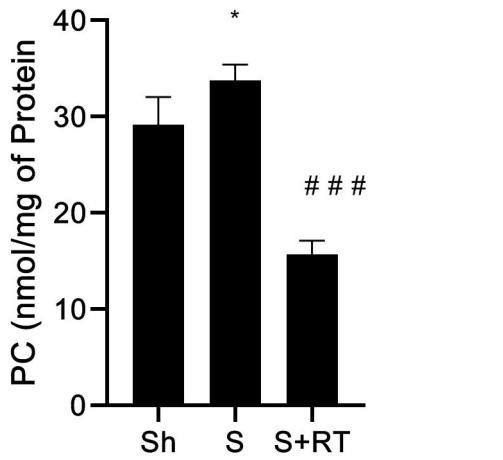

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Figure 2. PC levels in the three study groups

*P<0.001: A significant increase compared to the control group. ###P<0.001: A significant decrease compared to the control and stanozolol consumption groups. Sh: Sham; S: Stanozolol; RT: Resistance Training.

set 90%, and the fourth set 100% of the weight set for that week) and two repetitions (twice climbing the stairs). The interval between each set was 2 to 3 minutes and the interval between each repetition was 40 to 60 seconds [18]. This study was approved by the Animal Experiment Ethics Committee of Marvdasht Branch of Islamic Azad University (Code: IR.IAU.M.REC.1399.004).

Data analysis procedure

The Shapiro-Wilk test was used to examine the normal distribution of the variables, and 1-way ANOVA along with Tukey's post hoc tests was used to analyze the findings in SPSS V. 22. ($P \leq 0.05$).

Results

Levels of MDA and PC in the heart tissue of rats are shown in (Figures 1 and 2), respectively. The result of the Shapiro-Wilk test showed that the distribution of MDA (P=0.87) and PC (P=0.43) were normal. The results of 1-way ANOVA showed a significant difference in the levels of MDA (P=0.001, F=49.82) and PC (P=0.001, F=79.96) in the heart tissue of rats in the three research groups.

The results of Tukey's post hoc test showed that the levels of MDA (P=0.001) and PC (P=0.03) in the S group were significantly higher than the Sh group; however, MDA and PC levels in the S+RT group were significantly lower than the S and Sh groups (P=0.001) (Figures 1 and 2).

Discussion

The present study showed that stanozolol consumption had a significant effect on increasing MDA and CP. This result is consistent with the results of previous studies and suggests that after using S, the amount of oxidants production increases. This hypothesis confirms that the AAS increases the production of free radicals during mitochondrial electron transport chain dysfunction. Continuous excessive and long-term use of AAS reduces mitochondrial respiratory chain complex activity [19]. Electron transport chain dysfunction can be the result of the over-production of ROS against the antioxidant system [20]. Studies have also shown that AAS, like S, causes oxidative damage to the body's tissues by creating catabolic products, which are potential catalysts for free radical-induced damage, along with the oxidative metabolites of anabolic steroids [21].

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 Stanozolol consumption increases the parameters of MDA and PC [22]. Also, Tusson et al. studied the effect of Stanozolol consumption on oxidative stress markers in the liver tissue of rats and concluded that Stanozolol consumption can increase oxidative stress as well as MDA and PC markers [23]. In his study, Dornelles compared the effects of Stanozolol and boldenone steroids on the oxidative stress parameters of the liver and kidneys of rats and

concluded that the Stanozolol consumption group had a further increase in ROS markers such as MDA [24], the results of which are consistent with the present study. It has been reported that AAS abuse leads to decreased cell survival and increased cell death by increasing the release of apoptogenic factors such as apoptotic inducers, caspase 9, and cytochrome C [25, 26].

In this regard, it has been shown that Stanozolol consumption by increasing serum lipids leads to increased lipid peroxidation. On the other hand, increasing lipid peroxidation due to Stanozolol consumption increases free radicals and decreases antioxidant reserves [26]. The results of this study also showed that 8 weeks of RT in S-exposed rats significantly reduced the concentration of MDA and PC. In this regard, in a study by Rodriguez et al., 6 weeks of swimming training program reduced fat and protein oxidation in diabetic rats, so that plasma MDA and PC levels in the training group were significantly reduced compared to the control group [27]. Also, Karabulut et al. reported a significant reduction in MDA as a result of exercise [14].

In a study by Karskova et al., 10 weeks of aerobic training on the treadmill reduced PC levels [28]; the results of which are consistent with the present study. On the other hand, several studies have shown that one session of high-intensity physical activity can increase lipid peroxidation index [29, 30]. Another study found that performing one session of endurance training increased the rate of lipid peroxidation in the heart muscle of trained rats [31]. The results of the mentioned studies are inconsistent with the present study. This inconsistency seems to be due to the intensity or duration of the training used in the studies. Short-term training (one session of strenuous training) has been associated with increased free radicals, although long-term training (4 weeks, 8 weeks, and long-term) is associated with cellular adaptation, which increases antioxidants [32].

According to the results of this study, it seems that RT has been able to control the oxidative effects of Stanozolol in rats. Similar to the exercise, Stanozolol induces effects similar to antioxidant enzymes, although the mechanisms of the effects of exercise and Stanozolol differ. Stimulating exercise to induce antioxidant enzymes is rooted in increased ROS production due to muscle contraction and activity [14]. ROS as a secondary peak activates redox transcription factors activator such as (Ap-1-Activator protein 1) and nuclear factor kappa B (NF-KB). These factors are at the forefront of the ZN-SOD, CU, MN-SOD, catalase, and GPX encoding genes [33]. It seems that a set of factors are effective to reduce the concentration of MDA and PC following the training period, and the improvement in oxidative stress conditions cannot be attributed solely to the improvement of antioxidant status.

The resistance of cell membranes, especially red blood cells, to ROS has been reported to increase the following exercise and may contribute to this effect [34]. However, activation of cellular signaling pathways appears to increase the expression of enzymatic antioxidants and ultimately reduce fat peroxidation and MAD [34]. In the present study, MDA and PC in the RT+S group were significantly reduced compared to the Stanozolol group. However, due to the lack of studies on the effect of RT on MDA and PC in the heart tissue exposed to S, the present study had limitations. However, studies have examined the simultaneous effect of RT and anabolic steroid abuse on oxidative stress markers. For example, Camiletti-Moiron et al. showed that high-intensity exercise was able to reduce the effects of S-induced brain redox in Wistar rats [35].

In another study, Subordio et al. examined the effect of consuming 2 mg Stanozolol (5 days a week for 8 weeks) along with a period of exhausting exercise in oxidative damage to skeletal muscle in male rats and showed that SOD levels decreased slightly in the exercise with Stanozolol groups compared to the Stanozolol [36]. Arazi et al. in a study examined the interaction of RT and sustanon abuse on the antioxidant activity of the liver in male rats and their results showed that the activity of SOD, liver glutathione peroxidase, and glutathione reductase in the RT group and sustanon has been slightly reduced compared to the sustanon group [37].

The results of the studies show the effect of exercise on reducing the amount of ROS in AAS-exposed subjects which is consistent with the results of the present study. However, some studies have reported contradictory results, showing a decrease or non-alteration of antioxidants or an increase in ROS [38-40]. It seems that one of the reasons for the contradictory results is the tissues studied [41-43].

Stanozolol is a potent activator of androgen receptors that can increase antioxidants. Another reason for the difference in results is related to the androgen receptors in tissues. For example, fast-twitch fibers have fewer receptors than slow-twitch fibers [44]. The androgen receptors in the heart appear to be in direct contraction with slow-twitch fibers, resulting in increased antioxidant activity. However, further research is needed to confirm this, and prospective researchers are encouraged to study and compare the interactive effect of endurance training and Stanozolol consumption on the SOD and ROS markers of slow and fast-twitch fibers and heart. Unable to

measure the MDA, SOD, catalase, and GPX protein and gene expression levels by Western blotting and real-time PCR methods were the research limitations of the present study. So it is recommended that the effects of RT with different intensities on protein and gene expression levels of antioxidant markers be investigated in future studies.

Consumption of Stanozolol seems to increase the levels of MDA and PC in the heart tissue, while RT can improve the levels of MDA and PC.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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