



## Effects of Regular and Continuous Exercise on Oxidative Stress and Apoptosis

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### Keywords

Exercise,  
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BAX / BCL-2

**Abstract:** This study, it was aimed to investigate the effects of intense acute exercise and regular and continuous exercise on oxidative stress parameters and apoptosis-related Bax and Bcl-2 protein levels in rats. In the study, 1 control and 4 experimental groups were formed from 35 male Wistar-Albino rats, 7 in each group. The control group was not exercised, the other four groups exercised at a speed of 1.5 km/h for 1 hour on a 20-degree incline treadmill every day. Control and 1st, 2nd, 3rd, and 4th groups at the end of the 1st, 7th, 15th, and 30th day, respectively, were sacrificed. Malondialdehyde (MDA) as an indicator of lipid peroxidation, and Glutathione (GSH), Catalase (CAT), Glutathione Peroxidase (GSH-Px) activity as an antioxidant indicators in muscle and plasma were measured. BAX and BCL-2 protein expression levels were also checked for apoptosis in skeletal muscle. According to the results obtained, skeletal muscle and plasma MDA values increased after acute exercise ( $P<0.05$ ), while skeletal muscle and plasma GSH-Px and CAT values increased significantly after regular and continuous exercise ( $P<0.01$ ). It was observed that BAX protein expression level increased, BCL-2 protein expression level decreased and BAX/BCL-2 ratio increased in acute exercise ( $p<0.05$ ). As a result, it was concluded that regular and continuous exercise has a protective effect against oxidative stress and, apoptosis triggered by acute exercise can be suppressed by regular and continuous exercise.

## Düzenli ve Sürekli Egzersizin Oksidatif Stres ve Apoptozise Etkisi

### Anahtar Kelimeler

Egzersiz,  
Oksidatif  
stres,  
Apoptozis,  
BAX/BCL-2

**Özt:** Bu çalışmada, ratlarda zorlayıcı veya yoğun bir şekilde yapılan akut egzersiz ile düzenli ve sürekli olarak yapılan egzersizin oksidatif stres parametreleri ve apoptozis ile ilişkili Bax ve Bcl-2 protein düzeyleri üzerine etkisinin araştırılması amaçlandı. Çalışmada 35 adet Wistar-Albino ırkı erkek sıçanlardan, her grupta 7 adet olacak şekilde 1 kontrol ve 4 deney grubu oluşturuldu. Kontrol grubuna egzersiz yaptırılmadı, diğer dört gruba her gün 20 derece eğimli koşu bandında 1 saat boyunca 1,5 km/h hızında egzersiz yaptırıldı. 1., 7., 15. ve 30. gün sonunda sırasıyla kontrol ve 1., 2., 3. ve 4. gruplar kurban edildi. Kas ve plazmada, lipid peroksidasyonunun göstergesi olarak Malondialdehit(MDA) seviyelerine, antioksidan göstergesi olarak Glutasyon(GSH), Katalaz(CAT), Glutasyon Peroksidaz(GPx) aktivitelerine bakıldı. İskelet kasındaki apoptozis için de BAX ve BCL-2 protein ekspresyon düzeylerine bakıldı. Elde edilen sonuçlara göre, akut egzersiz sonrası iskelet kası ve plazma MDA değerleri yükselirken ( $P<0,05$ ), düzenli egzersize devam ettikten sonra, iskelet kası ve plazma GPx, CAT değerlerinde anlamlı artış olduğu belirlendi ( $P<0,01$ ). Akut egzersizde BAX protein ekspresyon düzeyinin arttığı, BCL-2 protein ekspresyon düzeyinin azaldığı ve BAX/BCL-2 oranının arttığı ( $p<0,05$ ) görüldü. Sonuç olarak, düzenli ve sürekli egzersizin oksidatif strese karşı koruyucu etkisinin olduğu ve akut egzersizle tetiklenen apoptozisin düzenli ve sürekli egzersizle baskılanabileceği kanısına varıldı.

## 1. INTRODUCTION

Physical activities carried out within a certain plan and program to develop or protect one or more structures of the body are called exercise [1]. A healthy and productive life depends on individuals exercising regularly [2], but the type, and intensity of exercise have different effects on human metabolism. It has been determined that acute, intense exercise triggers the formation of free radicals, affects the antioxidant defense system in different ways, and causes programmed cell death by activating apoptotic mechanisms in the cell, thus causing cellular damage. In cases where exercise is applied regularly for a long time, it has been determined that the level of oxidative damage is reduced, antioxidant enzyme activity is increased and apoptotic mechanisms are not significantly affected [3,4].

Both at rest and during contraction, skeletal muscles produce reactive oxygen (ROS) and nitrogen species (RNS). Physiologically, low levels of ROS are produced in the muscles to regulate muscle tone and maintain their contractility, but excessive ROS formation occurs as a result of intense and long-term exercises, which causes muscle damage, limitations in muscle function, and dysfunction in muscle contractions [5]. This is the result of intense and prolonged exercise inflicting oxidative damage to both proteins and lipids in contracted muscle fibers [6]. Regular exercise causes changes in both enzymatic and non-enzymatic antioxidants in skeletal muscle. Numerous studies in both animals and humans have shown that after aerobic exercise, antioxidant enzyme activity increases in blood and tissues [7,8].

In addition to acute resistance exercise, endurance exercises cause an increase in apoptosis [4,9,10], while moderate exercise does not significantly affect apoptosis. The intensity of potential mediators of apoptosis increases with exercise intensity and, after exceeding a certain level, they trigger apoptosis [11].

This study, it was aimed how acute exercise affects oxidative stress in skeletal muscle and plasma and how it shapes some protein expressions related to apoptosis. At the same time, it is aimed to investigate how these two mechanisms will be affected when exercise is continued regularly and continuously.

## 2. MATERIAL AND METHOD

This study was conducted with the permission of Firat University Animal Experiments Local Ethics Committee (Meeting: 2019/06, Decision No: 58). In the study, 35 Wistar Albino breed male rats, 3-6 months old and weighing 250-300 grams, were used. Experimental applications were carried out in accordance with the conditions of care and use of laboratory animals (12 hours light: 12 hours dark and  $24 \pm 3^\circ\text{C}$ ). During the experimental applications, standard commercial rat food (pellet food) and tap water were given to the rats. After a one-week adaptation period, the rats were divided into 5 groups, 7 in each group, as indicated below. The application of exercise on the groups is as the following:

Control Group: No exercise was applied. 1. Experimental Group: One day, acute exercise was done at a speed of 1.5 km h<sup>-1</sup> for 1 hour on a 20-degree incline treadmill. 2. Experimental Group: Acute exercise was done for 1 hour at a speed of 1.5 km h<sup>-1</sup> on a 20-degree incline treadmill every day for a week. 3. Experimental Group: Acute exercise was done at a speed of 1.5 km h<sup>-1</sup> for 1 hour on a 20-degree incline treadmill every day for 15 days. 4. Experimental Group: Acute exercise was done at a speed of 1.5 km h<sup>-1</sup> for 1 hour on a 20-degree incline treadmill every day for a month. After intraperitoneal administration of the xylazine (10 mg kg<sup>-1</sup>)/ketamine (60 mg kg<sup>-1</sup>) combination, the rats were sacrificed under anesthesia and tissue samples were taken from the biceps femoris muscle and blood samples from the vena cava caudalis. The samples were stored in deep freeze at  $-20^\circ\text{C}$  until analysis. MDA and GSH levels, CAT and GSH-Px enzyme activity in biceps femoris muscle and plasma were measured spectrophotometrically. BAX and BCL-2 protein expression levels, which are markers of apoptosis in skeletal muscle, were measured by western blot technique [12,13].

The spectrophotometric method of Placer et al.[14] was used for the determination of lipid peroxidation. The level of GSH-Px activity in tissue and plasma was measured as stated by Lawrence et al.[15] GSH level in tissue and plasma was measured as stated by Sedlak and Lindsay [16]. Working principle, all non-protein sulfhydryl groups in the samples were found in the form of GSH. Tissue and plasma CAT activity was determined by the method described by Goth [17]. The Lowry [18] method was used for protein determination. A purple-blue color was formed by treating the phenol reagent with copper and adding it to the mixture. Protein determination was made by reading the resulting mixture in a spectrophotometer at 650 nm.

Whether the values obtained as a result of the study were normally distributed or not was determined by Shapiro-Wilk normality analysis. To compare the group means, it was determined by ONE WAY ANOVA test whether there was a significant difference in the arithmetic means of more than two independent groups. Differences between groups were determined by the DUNCAN test. The significance level was accepted as  $p < 0.05$ . IBM SPSS Statistics 22 package program was used to perform statistical analyzes and data are given as  $X \pm \text{SD}$ . **2.1.**

## 3. RESULTS

### 3.1. Oxidative Stress Parameters

Plasma MDA levels of the 1st group increased compared to the control group, 3rd and 4th groups ( $p < 0.05$ ). Skeletal muscle MDA levels of the 1st and 2nd groups were higher than the control group ( $p < 0.05$ ). The plasma CAT activity of the 4th group was higher than the 1st and 2nd groups and control group ( $p < 0.01$ ). The skeletal muscle CAT activity of the 3rd and 4th groups were found to be significantly higher in the control group and 1st group ( $p < 0.01$ ). An increase was observed in the

plasma GSH-Px activity of the 4th group compared to the control and 1st and 2nd groups ( $p<0.05$ ). The skeletal muscle GSH-Px activity of the 4th group was found to

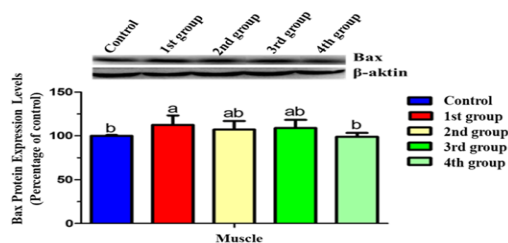
be significantly higher than the control and 1st group ( $p<0.05$ ). (Table 1)

**Table 1.** Oxidative Stress Parameters (a,b: The statistical difference between different letters in the same column is important).

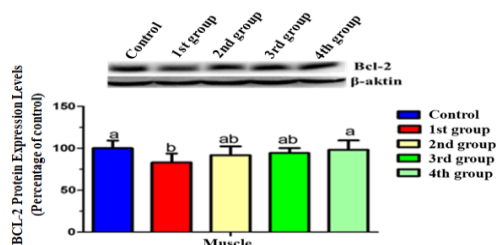
| Groups             | MDA (nmol/g)             |                          | GSH (nmol/g) |           | GSH-Px (IU/g protein)    |                           | Catalaz (kU/g protein)   |                          |
|--------------------|--------------------------|--------------------------|--------------|-----------|--------------------------|---------------------------|--------------------------|--------------------------|
|                    | Muscle                   | Plasma                   | Muscle       | Plasma    | Muscle                   | Plasma                    | Muscle                   | Plasma                   |
| Control            | 14.69±1.98 <sup>b</sup>  | 21.95±4.08 <sup>b</sup>  | 3.42±0.11    | 2.35±0.22 | 18.94±5.39 <sup>b</sup>  | 22.64±4.30 <sup>b</sup>   | 21.43±2.91 <sup>c</sup>  | 10.93±2.16 <sup>b</sup>  |
| 1st group          | 16.84±1.18 <sup>a</sup>  | 29.69±5.72 <sup>a</sup>  | 3.88±0.35    | 2.41±0.13 | 18.88±4.89 <sup>b</sup>  | 21.32±5.94 <sup>b</sup>   | 24.22±3.48 <sup>bc</sup> | 11.33±2.91 <sup>b</sup>  |
| 2nd group          | 16.76±0.67 <sup>a</sup>  | 26.45±2.01 <sup>ab</sup> | 3.82±0.45    | 2.48±0.32 | 22.78±6.95 <sup>ab</sup> | 21.31±9.59 <sup>b</sup>   | 27.32±1.53 <sup>ab</sup> | 11.34±4.80 <sup>b</sup>  |
| 3rd group          | 16.15±1.60 <sup>ab</sup> | 24.78±1.13 <sup>b</sup>  | 3.72±0.54    | 2.63±0.51 | 23.90±5.08 <sup>ab</sup> | 28.02±10.55 <sup>ab</sup> | 30.00±5.04 <sup>a</sup>  | 12.57±3.05 <sup>ab</sup> |
| 4th group          | 15.85±1.13 <sup>ab</sup> | 24.51±4.48 <sup>b</sup>  | 3.74±0.28    | 2.73±0.64 | 26.88±4.51 <sup>a</sup>  | 33.41±8.76 <sup>a</sup>   | 30.62±3.06 <sup>a</sup>  | 16.66±1.85 <sup>a</sup>  |
| Significance Level | P<0.05                   | P<0.05                   | P>0.05       | P>0.05    | P<0.05                   | P<0.05                    | P<0.001                  | P<0.05                   |

### 3.2. BAX-BCL-2 Protein Expression Levels

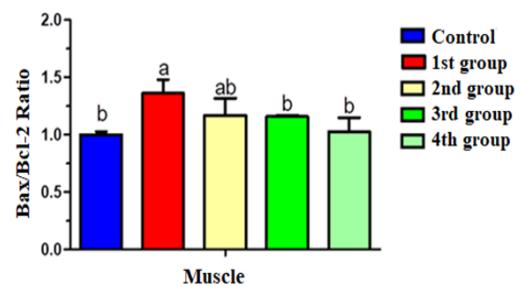
Skeletal muscle BAX protein expression levels of the 1st group were higher than the control group and 4th group ( $p<0.05$ ). (Figure 1). It was observed that the skeletal muscle BCL-2 protein expression levels of the first group was lower than the control group and 4th group ( $p<0.05$ ). (Figure2). It was determined that the skeletal muscle BAX/BCL-2 ratio of the 1st group was higher than the control group ( $p<0.05$ ). When the experimental groups were compared among themselves: The skeletal muscle BAX/BCL-2 ratio of the 1st group was found to be significantly higher than that of the 3rd and 4th groups ( $p<0.05$ ). (Figure3).



**Figure 1.** Muscle BAX Protein Expression Levels, Mean, SD,  $p<0.05$ . (a,b: The statistical difference between different letters in the same column is significant).



**Figure 2.** Muscle BCL-2 Protein Expression Levels, Mean, SD,  $p<0.05$ . (a,b: The statistical difference between different letters in the same column is significant).



**Figure 3.** Muscle BAX/BCL-2 Ratio Mean, SD,  $p<0.05$ . (a,b: The statistical difference between different letters in the same column is significant).

### 4. DISCUSSION

Our study demonstrates that acute intense exercise increases lipid peroxidation in muscle and plasma, while regular and continuous exercise decreases lipid peroxidation. While it was seen that acute exercise did not make a significant contribution to the antioxidant defense system, it was found that regular and continuous exercise contributed significantly to the antioxidant defense mechanism. At the same time, it was determined that apoptosis triggered by acute exercise was suppressed after regular and continuous exercise.

It has been observed that muscle and plasma MDA levels, which increase with acute intense exercise, decrease when exercise is continued regularly [19,20,21,22,23]. Although these results are in parallel with many studies, there are studies indicating that resistance exercise significantly increases ROS production [24,25,26]. We can think that the reason for this difference in studies is related to the type, intensity and duration of the exercise. Although muscle and plasma GSH activity were found to be higher in the exercise groups compared to the control group, this increase was not statistically significant. Muscle and plasma GP-X and CAT activities in all exercise groups were higher than the control group ( $p<0.05$ ). Specific studies on the type, intensity and intensity of exercise in shaping the antioxidant mechanism are not sufficient [24]. The high GP-X and CAT activities in all groups in our study indicate that both acute and regular exercise

positively affect the antioxidant mechanism. In their study, Chadorneshin et al.[23] showed that intense exercise increases CAT and GP-X activities. Lambertucci et al.[27] reported that aerobic exercise increased antioxidant enzyme activity in both old and young rats.

The formation of exercise-induced free radicals varies with the type, intensity and duration of physical exercise [28]: therefore, oxidative stress has been associated with decreased physical performance, muscle fatigue, muscle damage and overtraining [29]. It has been hypothesized that the body's physiological amount of antioxidants is not sufficient to prevent exercise-induced oxidative stress and that additional antioxidants are needed to reduce oxidative stress and muscle damage [30]. In many studies, the effects of exercise duration on this situation have been revealed [31]. The intensity, duration and type of exercise determine the direction in which the balance of oxidant and antioxidant defense mechanisms will shift [32]. While the balance is deteriorated towards oxidative stress in acute strenuous exercises [33,34], regular, short-term and non-vigorous exercises shift the balance towards antioxidant defense systems.

When the findings were evaluated, skeletal muscle and plasma BAX protein expression values were increased in the 1st group and decreased in the 2nd, 3rd and 4th groups, respectively. On the other hand, BCL-2 values decreased in the 1st group and increased in the 2nd, 3rd and 4th groups. The ratio of BAX/BCL-2 decreased, respectively. These results show that acute exercise-induced apoptosis is suppressed with regular exercise [35,36,37].

As a result, it shows that while acute exercise does not significantly contribute to the antioxidant defense system in plasma and muscle tissue, regular exercise provides a significant contribution to the antioxidant defense mechanism by increasing the GSH-Px and CAT activities. The gradual decrease of MDA level, which increases significantly in muscle and plasma during acute exercise, shows that regular exercise strengthens the antioxidant defense system, on the contrary, it reduces free radicals and lipid peroxidation. It can be said that the critical balance between exercise-induced apoptosis signal, prosurvival and proapoptotic factors and intracellular protection systems that contribute to apoptosis resistance depends on the intensity and duration of exercise. At the same time, after regular exercise, the apoptotic process in muscle tissue can be inactivated. Both ROS production and apoptosis increased in the acute period after exercise. During periods of regular exercise, the decrease in ROS level and the decrease in apoptosis show parallelism. This shows that there is a strong relationship between apoptosis and oxidative stress.

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