Jordan Medical Journal

ORIGINAL ARTICLE

Prior Exercise Training Improves Hepatotoxicity and Liver Damage Induced by Different Doses of Doxorubicin

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Received: June 5, 2024

Accepted: August 28, 2024

DOI:
https://doi.org/10.35516/jmj.v59i1.2749

Abstract

Background and Aims: Doxorubicin (DOX) is known as a powerful drug in the fight against various cancers. However, clinical use of DOX is restricted by its specific cytotoxic side effects such as hepatoxicity and liver cirrhosis. The purpose of this study is to investigate the effects of aerobic exercise in rats prior to receiving various dosages of DOX.

Materials and Methods: Forty-eight Wistar male rats were divided randomly into training (T) and control (C) groups. After 3 weeks, rats in each group were randomly assigned to 6 subgroups: C+saline, C+$DOX_{10\ mg/kg}$, C+$DOX_{20\ mg/kg}$, T+saline, T+$DOX_{10\ mg/kg}$, and T+$DOX_{20\ mg/kg}$. The training program included treadmill running between 25-39 min/day and 15-17 m/min, 5 days/week. Dox was administered in two different dosages (10 and 20 $_{mg/kg}$) while the saline groups received saline of a comparable volume. Histopathological analysis of the liver tissues and values of nitric oxide (NO), serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were determined.

Results: Although $DOX_{10\ mg/kg}$ and, especially, $DOX_{20\ mg/kg}$ caused liver cirrhosis and imbalance in MDA, NO, SOD, GPx, AST and ALT levels ($p<0.05$), the oxidative stress induced by DOX was remarkably reduced by aerobic exercise before administering Dox, as compared to the control group. Moreover, significant differences were detected in MDA, AST, and ALT levels between the T+$DOX_{10\ mg/kg}$ and T+$DOX_{20\ mg/kg}$.

Conclusions: The findings demonstrated that aerobic exercise can mitigate DOX-induced hepatotoxicity, which could be attributed to modulating the balance in oxidant/antioxidant capacity during aerobic exercise.

Keywords: Aerobic Exercise, Liver Cirrhosis, Doxorubicin, Oxidative Stress.

BACKGROUND & OBJECTIVES

Doxorubicin is a powerful, well-established, and highly effective drug against many kinds of cancers, but its clinical usefulness is still restricted due to its specific toxicities on cardiac and liver tissues [1,2]. The mechanism of the organ toxicity is unknown [3]. However, oxidative damage to the lipids of membrane and other cellular components seems to be the major factor of toxicity. It is believed that oxidative stress and the formation of free radicals play a crucial role in the mechanism of DOX toxicity [4,5]. Several studies have shown that the combination of the inflammatory process, free radical oxidative stress, and lipid peroxidation are frequently associated with liver damage and fibrosis, induced by toxic agents such as DOX [4]. Free radical production (Reactive Oxygen Species, ROS) has some roles in normal cell signaling and homeostasis. Cells have a variety of defense mechanisms that intercept free radicals to prevent or limit intracellular damage and ameliorate the harmful effects of ROS, which include low molecular weight antioxidants and antioxidant enzymes. Normal functional cells can sustain and tolerate background-level damage, but if an imbalance occurs, then cellular damage will increase [6]. On the other hand, emerging evidence demonstrates that exercise is a non-drug therapeutic protective strategy in patients undergoing DOX treatment through several adaptations that promote liver health, including improvement in the antioxidant defense system and the reduction of ROS and oxidative stress [1,2,6]. Furthermore, there is a growing interest in the usage of aerobic regular training as a protective therapy against DOX-induced problems such as cardiotoxicity [4-7], skeletal muscle toxicity [2,7], hepatotoxicity, and liver cirrhosis [1,7]. It was hypothesized that pretreatment with short-term exercise, as a non-drug therapeutic, could prevent DOX hepatotoxicity and liver cirrhosis via eliciting oxidative stress adaptations. To test this hypothesis, sedentary (saline group) and aerobic exercise-trained animals acutely administered against various dosages of DOX ($DOX_{10\ mg/kg}$ and $DOX_{20\ mg/kg}$), were examined.

MATERIALS AND METHODS

Experimental Design

The experimental protocol of the current study was approved by the Ethics Committee of University of Mazandaran and was performed according to guiding procedures in the care and use of animals, prepared by the Council of the American Physiological Society. The experiments were carried out with forty-eight Wistar male rats, (8 weeks old, initially weighing 269±4 g), which were obtained from the laboratory of animal bearing and multiplying at the Pasture Institute of Iran. Rats were housed in standard cages of polycarbonate (20×15×15 cm), in a large, air-conditioned room with a controlled temperature of 22±2°C, light-dark cycles of 12:12 h, and humidity of 50±5%. Rats were fed with a standard rat chow provided by the Pasture Institute for Animals and Poultry with a daily regimen of 10 g per 100 g body weight for each rat. Water was available *ad libitum.*

Pretreatment of exercise training and subject's classification

Animals were habituated to treadmill running for 5 days (10 min exercise/day at 10 m/min, 0% grade). Following this familiarization period, they were randomly assigned into sedentary and trained groups. Exercise training protocol was performed on treadmill with zero slopes between 25 to 39

min/session and 15 to 20 meter/min, 5 days/week for 3 weeks [8].

DOX administration

DOX was obtained from EBEWE Pharma Ges.m.b.H.Nfg.KG (A-4866, Unterach, Austria) as a vial. In order to bring the drug concentration of 10 and 20 mg/kg, it was dissolved in 0.9% saline for administration. The dose of 20 $mg.kg^{-1}$ of DOX is the human clinical dose that was pharmacologically scaled for use in rats [9]. Saline was used as the vehicle and the placebo treatment and was used to form saline solution (0.9% NaCl).

Tissue collection

All groups were anesthetized with ketamine and xylazine and decapitated after 10 to 12 hours of overnight fasting. Liver tissues were weighed and placed into Petri dishes containing cold isolation medium (0.1 mol/L KH2PO4, 0.15 mol/L NaCl, pH 7.4) to remove the blood and were frozen immediately in liquid nitrogen and stored at -80ºC for subsequent analysis.

Biochemical Analyses

Liver tissue was squashed in liquid nitrogen, homogenized in a lysis buffer (5 ml/g of tissue) with a protease inhibitor cocktail for mammalian cell and tissue extracts 100 *ul*/1 ml, and 10 ml of x M Tri-base (Sigma-Aldrich, St. Louis, USA), pH 7.4 and centrifuged at 1500 g at 4ºC for 15 min. The homogenates were diluted with cold 20 mM Tris-HCl and centrifuged (10 min at 58C, 3000 g). Biochemical measurements on activity of the GPx enzyme were conducted using GPx-340kit (OXIS, Portland, OR, USA). In the supernatants, the activity of GPx was estimated by spectrophotometry. SOD activity was determined spectrophotometrically [10]. In brief, for total SOD (tSOD) activity, the adequate amount of protein (2 mg tissue wet weight) was incubated at 258ºC with 1 mM N, N bis (2-(bis(carboxymethyl) amino)-ethyl) glycine (DTPA) in 50 mM Tris-HCl, *pH* 8.2, in 1 ml final volume. Furthermore, the NO concentration was determined by first reducing the nitrate to nitrite using nitrate reductase. Lipid peroxidation levels in the homogenate tissue were measured with the thiobarbituric acid reaction [11]. The thiobarbituric acid-reactive substances (TBARS), were quantified at 532 nm by comparing the absorption to a standard curve of Malondialdehyde (MDA) equivalents generated by acid catalysed hydrolysis of 1,1,3,3 tetramethoxypropane. Liver damage was evaluated by assessing for serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels using commercially available kits (Zellbio Chemical, Germany) according to the manufacturer's instructions.

Histopathological Analyses

Liver biopsies were done at the end of the experiment. Masson's Trichrome was performed to detect fibrotic scars of the liver. The biopsies were fixed in 4% formaldehyde for 48 hours. Subsequently, the biopsies were embedded in paraffin, cut into 5µm sections, and then stained with Hematoxylin-Eosin (HE) and Mallory Trichrome according to the standard protocol [1]. A light microscope and a micro camera system were used to assess the degree of liver cirrhosis.

After obtaining the images, the quantification of the percentage of the fibrosis was made with the help of software and a pathologist who was not aware of the treatment.

Data Analyses

All data have been expressed as mean±SD. Statistical analysis was performed using SPSS version 23.0 for Windows. A one-way analysis of variance was used to detect statistical differences between groups.

A post-hoc test (Tukey test) was performed to determine differences in the various biomarkers between groups. Differences were considered statistically significant at *p*-value<0.05.

RESULTS

Mean Values from MDA, NO, SOD, GPx, AST, and ALT in rats that were acutely exposed to DOX-induced hepatotoxicity with various dosages ($DOX_{10\ mg/kg}$ and $DOX_{20\ mg/kg}$), are shown in Table 1. After $DOX_{10\ mg/kg}$ administration, there was a significant increase (33.8% and 29.17%, respectively) in MDA (p=0.01) and AST (p=0.009) levels, insignificant increase (20% and 12.56%, respectively) in NO and ALT levels and insignificant decrease in SOD and GPx levels (7.39% and 9.21%, respectively) as compared to the control+saline (C+S) group. However, $DOX_{20\ mg/kg}$ treatment groups showed a significant increase in MDA, NO, AST and ALT levels (70.99%, 35%, 70.63 and 53.61% respectively) (p=0.001, 0.008, 0.001, 0.004 respectively) and a significant decrease (24.85%) in SOD levels (p=0.01) and insignificant decrease (23.56%) in GPx levels, in comparison with control+saline (C+S) group.

Table 1. Changes in oxidative stress biomarkers, liver fibrosis and liver enzymes after three weeks of aerobic training and DOX treatment

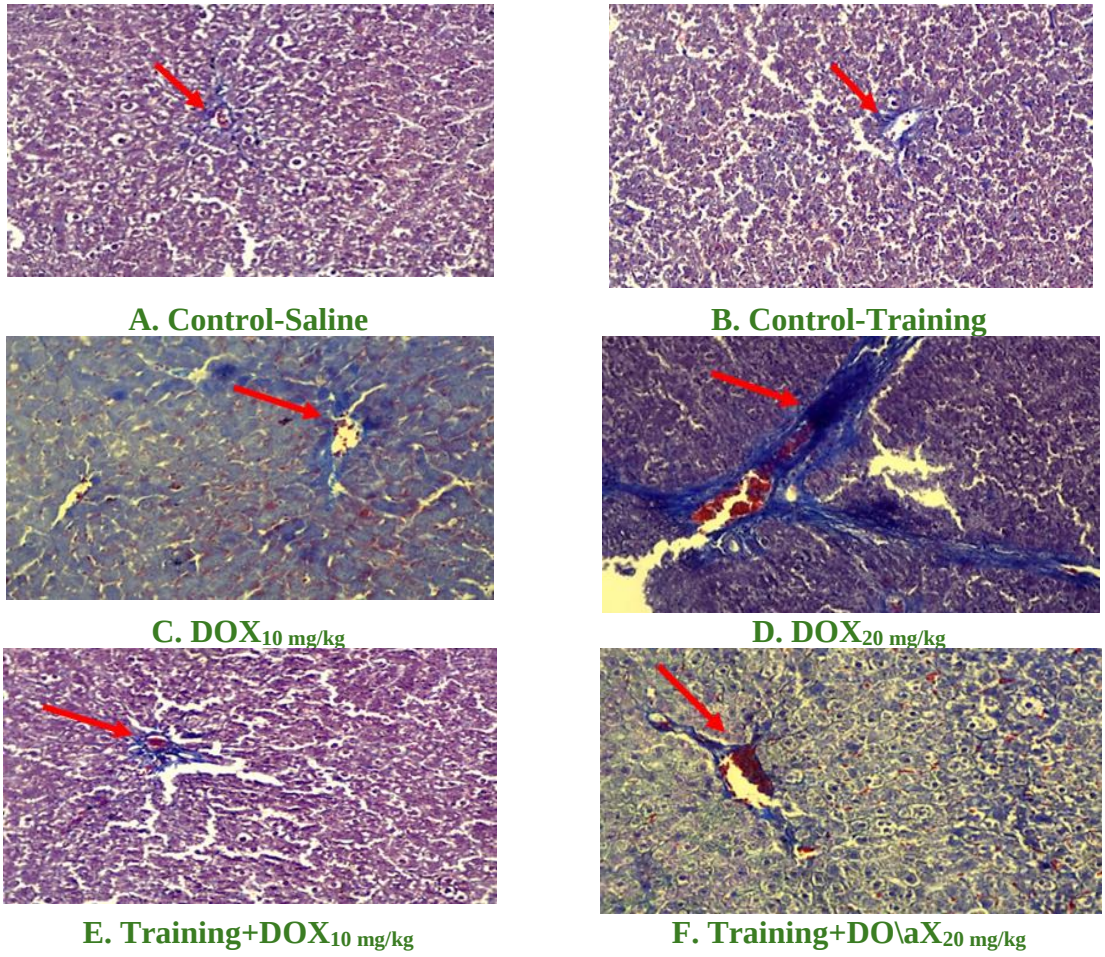
Biochemical biomarkers and groups	Saline		$DOX_{10\ mg/kg}$		$DOX_{20\ mg/kg}$	
	Control	Training	Control	Training	Control	Training
MDA (nm/mg protein)	22.13±3.7	23.52±2.8	29.45±3.5 €ϕ	27.79±3.6 €	37.84±4.6 ϕ	34.98±4
NO (nm/mg protein)	0.2±0.02	0.21±0.03	0.24±0.034	0.25±0.018	0.27±0.033 ϕ	0.27±0.018
SOD (µ/mg protein)	104±9	112.96±7	96.93±6.5	107.21±4.2 #	78.66±8 ϕ	99.93±8 #
GPx (µm.mg protein)	11.84±3	14.34±2.4	10.75±2	11.76±2.5	9.05±2.7	10.22±2.8
AST (U/L)	30.17±3.5	28.15±3.6	38.97±5 €ϕ	31.47±3.8 €#	51.48±5.3 ϕ	43.71±5.2 #
ALT (U/L)	36.6±3.4	39.1±2	41.2±5.4 €	42.22±5.2 €	56.22±4.8 ϕ	51.9±5.8
Liver fibrosis (%)	0.0042±0.0003	0.0047±0.0007	0.009±0.0003 ϕ	0.005±0.0004 #	0.01±0.0001 ϕ	0.007±0.003 €#

Abbreviations: Malondialdehyde (MDA), Nitric oxide (NO), Superoxide dismutase (SOD), Glutathione peroxidase (GPX), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT).
ϕ Significantly different to control+saline group (P<0.05), # significantly different to similar control group (P<0.05), € significantly different between $DOX_{10\ mg/kg}$ and $DOX_{20\ mg/kg}$ treatment groups (P<0.05).

Three weeks of aerobic training led to an insignificant decrease in MDA levels (5.64%, 7.56%) and an insignificant increase in NO (4.17%,0.022%) and GPx (9.39%,12.93%) in $T+DOX_{10\ mg/kg}$ and $T+DOX_{20\ mg/kg}$ as compared to similar control groups. Also, after three weeks of treadmill running a significant increase in SOD (p=0.04, 0.02) levels (10.61%, 27.40%) and a significant decrease in AST (p=0.04) levels (19.25%, 15.1%) were detected in $T+DOX_{10\ mg/kg}$ and $T+DOX_{20\ mg/kg}$, compared to similar control groups. Furthermore, after 3 weeks of training, there was no significant difference between the

T+DOX$_{10\ mg/kg}$ and T+DOX$_{20\ mg/kg}$ groups in GPx, SOD and NO levels, significant differences were detected in MDA, ALT and AST levels between the T+DOX$_{10\ mg/kg}$ and T+DOX$_{20\ mg/kg}$ groups (p<0.05).

The administration of DOX$_{10mg/kg}$ and DOX$_{20mg/kg}$ in rats in the present study showed histopathological changes such as liver cirrhosis. Microscopic findings showed the highest percentage of fibrosis was related to the DOX $_{20\ mg/kg}$ group (0.008736%) and the lowest value was related to the control groups (saline, 0.004149% and training 0.00471%,). Liver cirrhosis induced by DOX was remarkably prevented by training (Fig. 1D). The histopathological grade values of the fibrosis into the liver were lower by training (Fig. 1D) and saline (Fig. 1A).



A. Control-Saline **B. Control-Training**

C. DOX$_{10\ mg/kg}$ **D. DOX$_{20\ mg/kg}$**

E. Training+DOX$_{10\ mg/kg}$ **F. Training+DO\aX$_{20\ mg/kg}$**

Fig 1. Effects of DOX$_{10\ mg/kg}$ and DOX$_{20\ mg/kg}$ administration on Liver cirrhosis. Rats' liver tissues were sectioned at 5 µm. These slides were processed and stained by Hematoxylin-Eosin (HE) and Mallory Trichrome staining (final magnification 100×). Blue colored areas are a sign of fibrosis of liver tissue vessels in the various groups. (A) Saline, (B) Control-none saline (C) DOX$_{10\ mg/kg}$. (D) DOX$_{20\ mg/kg}$. (E) Training+DOX$_{10\ mg/kg}$. (F) Training+DOX$_{20\ mg/kg}$.

DISCUSSION

In the present study, $DOX_{10\ mg/kg}$ and $DOX_{20\ mg/kg}$ treatment induced increase in MDA and NO and a decrease in SOD, GPX and AST activity in liver tissue. After three weeks of aerobic training a significant increase was detected in the SOD levels in both dosages of DOX administration. In agreement with clinical trials on doxorubicin-induced hepatotoxicity, the present data showed that DOX causes important changes in histopathology of the liver containing fibrosis in liver tissue in the DOX group, as compared to saline group [12]. ROS/RNS are known to play a dual role in biological systems since they can be either harmful or beneficial to living systems. In contrast, at high concentrations, ROS can be important mediators of damage to cell structures, including lipids and membranes, proteins and nucleic acids (termed oxidative stress) [13,14]. Doxorubicin is known to produce hydroxyl radicals, hydrogen peroxide and superoxide anions. Doxorubicin is converted to a semi-quinone free radical by NADPH-cytochrome P-450 which leads to the generation of superoxide anion and hydroxyl radicals causing membrane lipid peroxidation [3]. In consequence, glutathione peroxidase may be stimulated in response to the accumulated peroxides which can subsequently lead to the formation of hydroxyl radicals in the presence of metal ion catalysts [15]. On the other hand, MDA is a major oxidation product of peroxidase poly-unsaturated fatty acids and increased MDA content is an important indicator of lipid peroxidation [15]. In our study, MDA levels increased in DOX-treated groups. It may be suggested that an increase in MDA levels can be an indicator of DOX injury [15-17].

It was previously reported that the increase in levels of liver enzymes such as ALT and AST was indicative of hepatic injury and a marker of liver damage [18]. Our findings demonstrated that 10 and 20 $_{mg/kg}$ of DOX treatment induced an increase in the concentration of AST and ALT which was attributed to liver damage and decreased liver function [18, 19]. In addition, our findings showed that the induction of $DOX_{20\ mg/kg}$, compared to $DOX_{10\ mg/kg}$ led to greater and more significant increase in AST and ALT levels. Doxorubicin has the ability to produce superoxide radicals and peroxy-nitrite radicals during its metabolism in the liver. Thus, the level of these enzymes serves as biomarkers for hepatotoxicity [18, 20].

In our study, three weeks' treadmill training used in combination with DOX treatment has led to insignificant decrease in MDA levels, an insignificant increase in NO and GPx and a significant increase in SOD levels. Several studies have reported the protective effects of exercise against DOX-induced cardiotoxicity [21-26]. Exercise training has been reported to produce adaptive responses to oxidative stress [27]. The significant reduction in the levels of the enzymes AST after three weeks' treadmill training in comparison to similar control groups could account for the improvement of the DOX-induced liver damage. The reduction in the ALT levels was observed only in the $T+DOX_{20\ mg/kg}$ group which might be explained by more severe changes of this enzyme due to the higher dose of DOX. These reports are in agreement with the results of other studies [28, 29]. Regular exercise causes adaptations in the antioxidant capacity, protecting cells against the harmful effects of oxidative stress, thus preventing cellular damage. Mild oxidative stress produced by regular exercise appears to be able to reduce oxidative damage [30]. Because of the major role of the liver in

aerobic energy production through glucose release to the bloodstream and expected gluconeogenesis during exercise [29], it is possible that exercise-induced hepato-protection against DOX-hepatotoxicity may be related to antioxidative effects of endurance training [27-31].

CONCLUSION

In summary, this experimental work provides essential information with respect to the protective effects of the three weeks' aerobic exercise on doxorubicin-induced hepatotoxicity. Findings from this investigation demonstrate that DOX treatment induces an imbalance in the biomarkers of oxidative stress and damages to the hepatic tissue. Nevertheless, aerobic exercise training prevents liver tissue oxidative damage induced by DOX. Our data suggests that increases in the liver tissue antioxidants (SOD, GPx and NO) could contribute to the exercise training-induced hepatoprotection following DOX administration.

However, more research on the involvement of physical activity and training in Doxorubicin-induced Hepatotoxicity is merited. The age and body weight of animals can affect drug metabolism, gene expression, metabolic parameters, and other dependent variables measured in animal studies [32-34]. Rats are much more resilient to doxorubicin than humans, meaning that higher dosages of doxorubicin have to be administered [34]. It is known that different concentrations of doxorubicin may activate different mechanisms of Doxorubicin-induced Hepatotoxicity. Besides that, there are many differences between the human liver and the liver of animals. So, this should be taken into account when designing new experiments.

ACKNOWLEDGEMENTS

Authors are thankful to the Department of Sports Physiology, University of Mazandran, Iran for providing facilities to conduct this experiment. Furthermore, we are thankful to professor Mehdi Hedayati (Cellular and Molecular Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran) due to the excellent technical assistance.

Funding statement

No funding was provided for this work

Conflict of Interest

The authors declare no conflict of interest

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التدريب الرياضي المسبق يؤدي إلى تحسين سمية الكبد وتلف الكبد الناجم عن جرعات مختلفة من الدوكسوروبيسين

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Received: June 5, 2024

Accepted: August 28, 2024

DOI: https://doi.org/10.35516/jmj.v59i1.2749

الملخص

الخلفية والأهداف: يُعرف عقار دوكسوروبيسين (DOX) بأنه عقار قوي في مكافحة أنواع مختلفة من السرطان. ومع ذلك، فإن الاستخدام السريري لعقار دوكسوروبيسين مقيد بآثاره الجانبية السامة المحددة مثل سمية الكبد وتليف الكبد. والغرض من هذه الدراسة هو التحقيق في تأثيرات ما قبل العلاج للتمارين الهوائية في الفئران التي تتلقى جرعات مختلفة من عقار دوكسوروبيسين.

منهجية الدراسة: تم تقسيم ثمانية وأربعين من ذكور جرذان ويستار عشوائيًا إلى مجموعتين، تتضمن المجموعة التدريبية (T) والمجموعة الضابطة (C). بعد 3 أسابيع، تم تعيين الفئران في كل مجموعة عشوائيًا في 6 مجموعات فرعية: محلول ملحي +C، C+DOX10 مجم/كجم، C+DOX20 مجم/كجم، T+محلول ملحي، T+DOX10 مجم/كجم، وT+DOX20 مجم/كجم. تضمن برنامج التدريب الجري على جهاز المشي بين 25−39 دقيقة/يوم و15−17 متر/دقيقة، 5 أيام/أسبوع. تم إعطاء الدوكسوروبيسين بجرعتين مختلفتين (10 و20 مجم/كجم) بينما تلقت مجموعات المحلول الملحي محلول ملحي بحجم مماثل. تم تحديد التحليل النسيجي المرضي وقيم أكسيد النيتريك (NO) وأسبارتات أمينوترانسفيراز المصل (AST) وألانين أمينوترانسفيراز (ALT) في أنسجة الكبد.

النتائج: على الرغم من أن DOX10 مجم/كجم وخاصة DOX20 مجم/كجم تسبب في تليف الكبد واختلال التوازن في مستويات MDA وNO وSOD وGPx وAST وALT ($p<0.05$)، إلا أن الإجهاد التأكسدي الناتج عن DOX تم منعه بشكل ملحوظ من خلال المعالجة المسبقة بالتمارين الهوائية، مقارنة بالمجموعة الملحية. وعلاوة على ذلك، تم الكشف عن اختلافات كبيرة في مستويات MDA وAST وALT بين DOX10 +T مجم/كجم وDOX20 +T مجم/كجم.

الاستنتاجات: أظهرت النتائج أن المعالجة المسبقة للتمارين الهوائية يمكن أن تؤدي إلى تفاقم السمية الكبدية الناجمة عن DOX، والتي تعزى إلى التوازن في قدرة الأكسدة / مضادات الأكسدة أثناء التمارين الهوائية.

الكلمات الدالة: التمارين الهوائية، تليف الكبد، الدوكسوروبيسين، الإجهاد التأكسدي.