**Doxorubicin-dependent skeletal muscle atrophy: exercise and mitochondrial dysfunction**

**Doksorubisin bağlı iskelet kası atrofisi: egzersiz ve mitokondrial disfonksiyon**

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**ABSTRACT**

Doxorubicin (DOX) is a type of chemotherapy with harmful side effects due to its accumulation in various tissues. DOX is widely known for having a significant effect on skeletal muscle atrophy. The most significant of these side effects is DOX-induced mitochondrial dysfunction in skeletal muscle atrophy. Exercise is a treatment approach that serves to maintain muscle homeostasis by decreasing or eliminating these effects. The goal of this review article is to give current knowledge on the causes of DOX-induced skeletal muscle atrophy, the basic processes involved in mitochondrial dysfunction caused by DOX, and the effects of exercise on DOX-induced skeletal muscle atrophy.

**Keywords:** Doxorubicin, skeletal muscle atrophy, mitochondria, exercise

**ÖZ**

Birçok dokuda birikmesi nedeniyle, Doksorubisin (DOX) sitotoksik yan etkilere neden olan bir kemoterapötiktir. DOX’un iskelet kası atrofisi üzerinde önemli bir etkiye sahip olduğu yaygın olarak bilinmektedir. Bu etkilerden en dikkat çekeni DOX’un neden olduğu mitokondriyal fonksiyon bozukluğunun neden olduğu iskelet kası atrofisi nedeniyle, egzersiz bu etkileri azaltarak ve her iki kas ve mitokondriyal disfonksiyondaki temel mekanizmaları ve DOX’un neden olduğu kas atrofisinde egzersizin etkileri hakkında güncel bilgiler sağlayacaktır.

**Anahtar Sözcükler:** Doksorubisin, iskelet kası atrofisi, mitokondri, egzersiz

**INTRODUCTION**

A cytotoxic drug known as doxorubicin (DOX) serves for the treatment of specific types of cancer (1). DOX is an extremely effective treatment, but it has several side effects, including skeletal muscle atrophy (2, 3). The DOX affects the quality of life for cancer patients because it promotes skeletal muscle atrophy and fatigue (4).

It has been demonstrated that DOX treatment induces mitochondria to produce more reactive oxygen species (ROS) (5, 6). Oxidative damage to skeletal muscle serves as a stimulus that accelerates the degradation of muscle by activating key proteolytic systems (7, 8). Skeletal muscle atrophy is triggered by these negative molecular mechanisms. DOX appears to affect muscular function by reducing athletic performance and causing muscle fatigue (9).

Skeletal muscle dysfunction following DOX treatment is a challenging issue to manage, exercise may be beneficial in reducing the negative effects of DOX on the skeletal muscles (10). This review article will discuss the adverse effects of DOX on skeletal muscle as well as explain how mitochondrial dysfunction generates these effects and the evidence that exercise can counteract these effects.

**Doxorubicin, chemical structure, and mechanism**

Doxorubicin HCl, the first anticancer drug, has been clinically demonstrated to be effective against some malignancies, including solid cancers, leukemias, and lymphomas (11). The molecular formula for DOX is C27H29NO11HCl, with a molecular weight of 579.98 g/mol. The drug is an aglyconic and sugar-containing class I nonselective anthracycline. The aglycone is formed up of a tetracyclic ring with adjacent quinone-hydroquinone groups, a short side chain containing a methoxy substituent, and a carbonyl group. One of the rings has a glycosidic link binding the sugar component to it (12, 13).

Certain mechanisms, including topoisomerase II (TOP2B) inhibition, cytochrome C release from mitochondria, and...
the formation of ROS leading to oxidative stress, have been associated with cytotoxic effects of DOX (14, 15).

DOX intercalates with the DNA, preventing the macromolecular production process (16). TOP2B poisoning induces DNA damage because cancer cells are more susceptible to DNA breaks than healthy ones (17, 18).

Following the splitting of the DNA chain for replication by TOP2B, DOX stabilizes the structure by inhibiting the DNA double helix and stopping replication activity (19). Another way that DOX acts is to produce free radicals, which may damage DNA and cell membrane lipids and proteins (11, 20). This can give rise to oxidative stress, which may eliminate tumor cells through the process of apoptosis (17, 21).

**Doxorubicin-induced skeletal muscle atrophy**

Skeletal muscles, which account for over 40% of a healthy person’s body weight, are highly dynamic and flexible tissues that can change at the cellular and molecular levels in response to various stressors (22). Skeletal muscle protein turnover is a metabolic process that balances protein synthesis/degradation and maintains skeletal muscle function and mass (23). Skeletal muscle atrophy is characterized by a decrease in protein content, fiber diameter, strength production, and resistance to fatigue. Skeletal muscle atrophy is the loss of skeletal muscle mass as a result of increased myofibrillar protein degradation and decreased protein synthesis (24). Skeletal muscle atrophy is an outcome of multiple diseases, including cancer, neuromuscular disorders, myopathy, and inflammatory diseases (25). DOX, a cancer treatment drug, promotes skeletal muscle atrophy, which acts a crucial role in the adverse effects of a variety of diseases or disorders.

Different cancers have been treated with DOX (1, 26). DOX is a highly successful chemotherapy, but it has several adverse effects, including skeletal muscle atrophy, and tiredness (2, 3, 27, 28). DOX treatment impairs the quality of life for cancer patients by causing skeletal muscle weakness and exhaustion (4). Because of its cytotoxic activity, it has been proven in several human and animal studies to initiate skeletal muscle atrophy. Mitochondrial and contractile dysfunction are triggered by cellular and molecular processes in skeletal muscle damage related to the activation of proteolytic and apoptotic signaling pathways by DOX-induced oxidative stress (29, 30).

DOX and paclitaxel, two drugs frequently administered to breast cancer patients, decreased myosin expression and promoted mitochondrial degradation via ROS (3). Muscle dysfunction and atrophy have also been associated with DOX treatment, which is used to treat limb sarcoma tumors (31).

Skeletal muscle functionality gradually deteriorated in five days following DOX administration and all muscle tissues were dysfunctional, vascular activity quickly reduced, and DOX concentration was highest in the heart (32).

DOX dramatically decreased muscular tissue weights and cross-sectional area (CSA) of muscle. (33). A recent study found that prolonged DOX treatment significantly diminished body weight and gastrocnemius mass (34). 10, 12.5, or 15 mg/kg DOX applications reduced maximal contraction force in the soleus muscle by 45%, 60%, and 74%, respectively (35). Skeletal muscle and cardiac wasting were nearly equal 4 weeks after the treatment with a 24 mg/kg dose of DOX (36). The fiber CSA of the soleus, plantaris, and diaphragm muscles significantly was decreased after receiving a single dose of DOX (20 mg/kg) (2). DOX diminished soleus weight by around 15% and cancer chemotherapy’s combined effects led to a similar decline in muscle mass and CSA (6). DOX treatment significantly lowered muscle fiber CSA by 17% according to a meta-analysis (37). 15 mg/kg DOX injection was administered intraperitoneally, and the CSA of EDL muscle was reduced (38).

TOP2B overexpression contributes to DOX-induced myotoxicity. DOX significantly deteriorated the muscle weight of the gastrocnemius and specific clinical characteristics (35). Additionally, this study found that DOX reduced BECN1 (autophagy marker) expression but did not affect myogenic regulatory factor (MRF) activity (39).

In in vitro and in vivo studies, DOX decreased soluble guanylate cyclase (sGC) action, and there was a correlation between sGC function and CSA of skeletal muscle activating the ubiquitin-proteasome system (UPS) and impairing protein synthesis (40). Additionally, cells exposed to DOX showed immunostained responses, which were indicating oxidative stress. The essential differentiation was attributed to the intracellular density of the identified mitochondrial reactivity, increased MAFbx expression, and atrophic changes due to Forkhead box O3 (FoxO3) (41). DOX significantly decreased muscular function in mice, and upregulated pro-inflammatory cytokines and inflammatory M1 macrophages (42).

**Doxorubicin and mitochondrial dysfunction**

DOX-induced mitochondrial damage induces cellular malfunction (43, 44). According to studies, DOX treatment has been shown to increase the generation of mitochondrial ROS (5, 6). Cardiolipin, an inner mitochondrial membrane phospholipid, has been associated with the generation of ROS after mitochondrial failure (45). DOX produces cardiolipin dysfunction, resulting in increased ROS generation (46). When DOX is localized to the inner mitochondrial
membrane, it is reduced by nicotinamide adenine dinucleotide (NADH)-dehydrogenase, leading to the generation of superoxide radicals, which in turn increases ROS production and mitochondrial dysfunction. ROS generation triggers oxidative damage in skeletal muscle.

When ROS levels increase, the mitochondrial structure is seriously damaged and resulted in apoptosis and reduced contraction, which compromises cardiac and respiratory performance. ROS increases protein breakdown in skeletal muscle by activating caspase-3 and the UPS. UPS is a different mechanism related to DOX-induced atrophy. Furthermore, autophagy has been hypothesized as a potential mechanism for DOX-induced protein breakdown. Min et al. reported that a single dose of DOX lowered mitochondrial respiration while enhancing mitochondrial uncoupling. DOX administration resulted in substantially increases in mitochondrial ROS, 4-hydroxy-2-nonenal (4-HNE) modified proteins, calpain activation, and caspase-3 activity in skeletal and cardiac muscles.

DOX affects complex I and II and mitochondrial respiration in skeletal muscle. DOX improved skeletal muscle mitochondrial H2O2-emitting potential and oxidative variations of myofibrillar proteins. Following DOX treatment, the function of the whole muscle is negatively affected by both elevated reactive protein carbonyl levels and post-translational modifications of proteins induced by increased cellular oxidants.

DOX administration (15 mg/kg) significantly enhanced the TUNEL apoptotic index, the protein abundance of Beclin1/Bax, and the ratio of LC3 II to LC3 I in skeletal muscle. DOX injection promoted autophagy marker expression in type I soleus muscle, and the autophasosome initiation protein, Beclin1, significantly lowered in gastrocnemius muscle under atrophic conditions, and increased expression of PGC 1 induced by genetic manipulation was found to suppress FoxO3, reducing type II fiber atrophy in the tibialis anterior muscle.

Exercise diminishes mitochondrial dysfunction, oxidative stress, and protease stimulation, which in turn inhibits diaphragm fiber atrophy.

Exercise capacity can be affected by changes in musculoskeletal function, and patients exposed to DOX showed greater exercise intolerance and decreased aerobic capacity. Through activation of AMP-activated protein kinase (AMPK), aerobic exercise in DOX treatment enhanced maximum aerobic capacity without affecting muscle mass or fiber CSA. In DOX-treated rats, exercise diminished MuRF1 signaling but not Atrogin-1/MAFbx signaling via preserving mitochondrial respiratory function and redox balance. Exercise enhanced regeneration and preserved mitochondrial function. The a-actinin (ACTN) protein was noticeably affected by DOX, but exercise training appeared to restore it. FOXO3a protein expression was elevated by DOX-induced myotoxicity and was precisely regulated by exercise. In addition to protecting muscle against oxidative stress induced by DOX and reducing the expression of autophagy genes, endurance exercise enhances antioxidant levels. Kwon et al. reported that exercise increased citrate synthase levels, autophagy markers (LC3-I/II, LAMP, etc.), and improved muscle regeneration (MYOD) in chronic conditions, type 2 diabetes, sarcopenia, and some forms of cancer, can benefit significantly from regular exercise.

Combs and colleagues demonstrated that exercise training offers therapeutic advantages that reduce DOX toxicity. It has been shown that endurance training decreased DOX-induced oxidative damage and the induction of proteolytic mechanisms in skeletal muscle atrophy. Exercise has been associated with slow-twitch oxidative muscles compared to fast-twitch glycolytic, but DOX-induced skeletal muscle atrophy emerges independently of skeletal muscles with different fiber types (type I or type II muscles). One study demonstrated that the chronic DOX usage in combination with interval training was also sufficient to prevent soleus muscle atrophy. Therefore, exercise training before or at the beginning of DOX treatment may prevent skeletal muscle atrophy and weakening. Exercise increases the activity of endogenous antioxidant enzymes, oxidant buffering capacity and prevents DOX damage. One study demonstrated that the chronc DOX usage in combination with interval training was also sufficient to prevent soleus muscle atrophy. Therefore, exercise training before or at the beginning of DOX treatment may prevent skeletal muscle atrophy and weakening. Exercise increases the activity of endogenous antioxidant enzymes, oxidant buffering capacity and prevents DOX damage. In one study, the combination of exercise and DOX treatment enhanced antioxidant levels in heart and liver tissues. PGC 1 significantly lowered in gastrocnemius muscle under atrophic conditions, and increased expression of PGC 1 induced by genetic manipulation was found to suppress FoxO3, reducing type II fiber atrophy in the tibialis anterior muscle.
DOX-induced skeletal muscle atrophy (39). However, the interesting finding of this study was that both DOX treatment and exercise were not associated with the AMPK or AKT/mTOR signaling pathways (39). Exercise reduced levels of both carbonyl and the 4-HNE, demonstrating protection against skeletal muscle atrophy caused by DOX (50). Exercise prevents skeletal muscle atrophy when initiated before or at the beginning of DOX administration.

CONCLUSION

Since it has been proposed that the medication produces DOX-induced skeletal muscle atrophy, it is critical to determine a preventive approach. One of these protective benefits is exercise, which lowers the side effects of chemotherapy in the setting of muscle physiology. Future research should investigate the combination of multiple treatments and exercise.

Conflict of Interest / Çıkar(6,266),(998,301) Çatışmalar

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