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Therapeutic Modulation of Glucocorticoid-Induced Sarcopenia by Boron: A Multimodal Preclinical Assessment

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Abstract

Boron is a bioactive trace element with emerging roles in musculoskeletal homeostasis and reported antioxidant, anti-inflammatory, and cytoprotective properties. These biological activities make boron a potential candidate for targeting the multifactorial processes underlying skeletal muscle deterioration. Sarcopenia, characterized by progressive loss of muscle mass and function, remains a major therapeutic challenge, with no pharmacological treatment currently established specifically for restoring sarcopenia-related muscle loss and functional impairment. This unmet therapeutic need is particularly relevant to glucocorticoid-induced muscle wasting, a clinically important adverse consequence of prolonged glucocorticoid exposure. Despite its biological properties, the therapeutic potential of boron in glucocorticoid-induced sarcopenia remains largely unexplored. Therefore, this study investigated whether boron supplementation could promote functional and structural muscle recovery in a dexamethasone (DEX)-induced sarcopenia model in female Sprague–Dawley rats for the first time. After administering DEX (1 mg/kg/day, intraperitoneally) for 14 days, boron was given via drinking water at concentrations of 50 or 100 mg/L for 28 days. Muscle function was assessed through forelimb grip strength and hanging grid tests. The preservation of skeletal muscle was further evaluated with MRI, histopathological analysis, and muscle weight measurements. We also analyzed organ weights, serum biochemical parameters, and blood indices to assess systemic safety. Boron supplementation promoted functional and structural recovery following DEX-induced skeletal muscle wasting. By Day 42, forelimb grip strength was approximately 84-94% higher in boron-treated animals than in the untreated sarcopenia model (~6.5–6.8 vs. ~3.5 kgf), accompanied by greater preservation of skeletal muscle volume on MRI. Consistent with these functional and imaging findings, histopathological assessment demonstrated a dose-dependent attenuation of muscle atrophy, with atrophy scores reduced by approximately 50% and 80% following treatment with 50 and 100 mg/L boron, respectively ($p = 0.014$ and $p < 0.001$ vs. the sarcopenia model). Importantly, boron treatment was not associated with overt adverse changes in major organ weights or the evaluated biochemical and hematological parameters, indicating favorable systemic tolerability under the experimental conditions. Collectively, these findings provide preclinical

evidence that boron supplementation may promote functional and structural recovery following DEX-induced skeletal muscle wasting and support further mechanistic and translational investigation.

Keywords: Sarcopenia; Boron; Dexamethasone; Glucocorticoid-induced muscle atrophy; Muscle function; Muscle recovery

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1. Introduction

Sarcopenia is characterized by a progressive decline in skeletal muscle mass and function, resulting in impaired mobility, reduced physical performance, and diminished quality of life, particularly in older adults [1]. This condition may also begin in mid-life and is particularly common in specific groups, including individuals with cancer, kidney issues, liver cirrhosis, and metabolic disorders [2–6]. Sarcopenia affects an estimated 10–16% of older adults worldwide and represents a growing public health concern. It is associated with an increased risk of falls, fractures, metabolic and cognitive complications, prolonged hospitalization, and poorer clinical outcomes, ultimately contributing to increased morbidity and mortality [7, 8]. Sarcopenia has a multifactorial pathophysiology involving complex interactions between age-related, intrinsic, and extrinsic factors. Within skeletal muscle, dysregulation of inflammation, apoptosis, autophagy, mitochondrial function, neuromuscular junction integrity, and calcium homeostasis can impair myogenesis and promote progressive muscle wasting. These alterations may be further exacerbated by physical inactivity, hormonal imbalance, inadequate nutrition, immobilization, and systemic inflammation [9–11].

Glucocorticoids, widely prescribed for their anti-inflammatory and immunosuppressive effects, can contribute to skeletal muscle wasting when used chronically or at supraphysiological doses. Similar effects may occur under conditions of excessive endogenous glucocorticoid production. Synthetic glucocorticoids such as dexamethasone (DEX) are well established to induce skeletal muscle atrophy [12–14]. Mechanistically, glucocorticoid-induced muscle atrophy is driven, at least in part, by disruption of muscle protein homeostasis, including suppression of protein synthesis and activation of the ubiquitin-proteasome system. This catabolic response involves FoxO3 α -regulated induction of the muscle-specific E3 ubiquitin ligases MAFbx/atrogen-1 and MuRF1, thereby promoting

muscle protein degradation and progressive loss of skeletal muscle mass [15]. Accordingly, experimental assessment of glucocorticoid-induced muscle wasting requires complementary evaluation of both muscle mass and function. Relevant clinical assessments have been utilized in animal studies, incorporating non-invasive structural imaging techniques like high-resolution magnetic resonance imaging (MRI) [16], grip strength tests in rodents [17], and hanging grid tests [18]. Glucocorticoid-induced rodent models reproduce key catabolic features of muscle wasting and therefore provide a relevant experimental platform for evaluating novel therapeutic strategies. Importantly, despite increasing understanding of the molecular mechanisms underlying sarcopenia and the investigation of several therapeutic candidates, no pharmacological treatment has yet been established specifically for sarcopenia [12, 19, 20].

Boron is a naturally occurring trace element that exhibits a wide range of biological effects in both humans and animals. It influences various organ systems by promoting bone formation, reducing cardiac fibrosis, supporting liver and brain functions, and modulating immune responses. The mechanisms through which boron operates include the regulation of key enzymes such as vitamin D-metabolizing hydroxylases, stabilization of mitochondrial membranes, and modulation of cell proliferation pathways [21, 22]. Boron is crucial for osteogenesis, and its deficiency has been linked to negative impacts on bone development and regeneration. Furthermore, boron affects the production and activity of steroid hormones, through which this trace mineral contributes to the prevention of calcium loss and bone demineralization. Supplementation with boron has been shown to stimulate bone growth in animals deficient in vitamin D and to mitigate dysfunctions in mineral metabolism associated with vitamin D deficiency [23–25]. Numerous studies indicate that boron supplementation can enhance muscle growth or increase muscle mass in both animals and humans. These effects are attributed to the indirect influence of increased steroidal hormones in the plasma [26]. In addition, boron exhibits antimicrobial properties against various pathogens and promotes wound healing through its anti-inflammatory and antioxidant activities. These diverse functions are consistently dose-dependent, with beneficial effects observed at optimal levels, while excessive intake can lead to toxicity in different tissues [22].

Beyond its established roles in mineral and endocrine homeostasis, experimental evidence reveals that boron-containing compounds may exert strong cytoprotective effects. In fact, borax and ulexite have been shown to attenuate chemically induced hematotoxicity, oxidative DNA damage, and apoptosis while supporting endogenous antioxidant defense mechanisms

[27, 28]. Similarly, boric acid has demonstrated protective effects against chemically induced neurotoxicity, while boron nitride nanoparticles have shown anti-apoptotic and neuroprotective activity in experimental models [29, 30]. Collectively, these findings suggest that the biological effects associated with boron-containing compounds extend beyond mineral metabolism and may involve cellular stress-response and survival pathways relevant to tissue preservation. These findings also underscore the importance of comprehensive evaluation when investigating the biological effects of bioactive compounds. Studies involving natural and other bioactive agents have shown that their effects may encompass modulation of oxidative stress, genotoxicity, cytotoxicity, and cellular defense responses. Experimental evidence indicates that some compounds can mitigate chemically induced DNA damage and oxidative injury, whereas others may exert concentration-dependent cytotoxic, cytogenetic, or oxidative effects [31–37]. Taken together, these observations highlight the importance of evaluating potential protective effects alongside relevant cellular and toxicological endpoints when characterizing the biological activity of candidate therapeutic agents. Previous preclinical studies of structurally diverse bioactive compounds have demonstrated the value of integrating efficacy-related outcomes with complementary cellular and toxicological assessments [38–40]. Such a multidimensional approach may provide a more comprehensive characterization of the therapeutic potential and tolerability of candidate interventions.

The complex and multifactorial nature of sarcopenia has prompted the development of diverse therapeutic strategies, including exercise, nutritional interventions, and emerging pharmacological and biological approaches. However, treatment responses remain variable, and no definitive pharmacological therapy has yet been established [10, 41, 42]. This unmet therapeutic need is particularly relevant to glucocorticoid-induced muscle wasting, in which sustained catabolic signaling compromises skeletal muscle mass and function. Despite growing evidence for the biological and cytoprotective activities of boron, its therapeutic potential in glucocorticoid-induced skeletal muscle wasting remains largely unexplored. In particular, whether boron can promote muscle recovery after glucocorticoid-induced injury has not been adequately investigated. Based on its reported effects on musculoskeletal homeostasis and cellular stress responses, we hypothesized that boron supplementation initiated after DEX exposure would promote the recovery of skeletal muscle structure and function. Hence, the present study evaluated the therapeutic effects of two concentrations of boron following DEX-induced muscle wasting in female Sprague–Dawley rats using a

multimodal preclinical approach integrating longitudinal functional assessments, MRI-based muscle volume analysis, muscle histopathology, and weight measurements, together with organ weights and biochemical and hematological profiling to assess systemic tolerability.

2. Material and Method

2.1 Animals and Ethical Approval

A total of 16 female Sprague-Dawley rats (10–12 weeks old; initial body weight: 226–268 g), obtained from the Atatürk University Medical Experimental Application and Research Center (ATADEM, Erzurum, Türkiye), were included in the study. Prior to the commencement of experimental procedures, the animals were acclimatized to the laboratory environment for 10 days. During this acclimatization phase, they were kept in standard polycarbonate cages under carefully controlled environmental conditions, which included a temperature of 22 ± 2 °C, a relative humidity of 50–60%, and a regulated 12-h light/dark cycle. Throughout the duration of the study, the animals had *ad libitum* access to a standard laboratory chow diet and fresh drinking water. All animal handling and experimental procedures were carried out in strict adherence to the ARRIVE 2.0 (Animal Research: Reporting of *In Vivo* Experiments) guidelines [43] and were approved by the Atatürk University Animal Experiments Local Ethics Committee (Approval No.: 2200366213). Following the acclimatization period, the initial body weights of all animals were recorded, and the rats were randomly allocated into four experimental groups to ensure a homogeneous distribution of body weights. Baseline anthropometric measurements confirmed that there were no statistically significant differences in body weight among the experimental groups ($p > 0.05$).

2.2 Experimental Design and Induction of Dexamethasone-Induced Sarcopenia

To create the experimental sarcopenia model, dexamethasone (DEX; MedChemExpress, USA; Cat. No. HY-14648) was prepared following a previously established protocol [43]. In summary, the powdered substance was dissolved in sterile physiological saline with 5% dimethyl sulfoxide (DMSO). The resulting DEX solution was administered intraperitoneally (i.p.) at a daily dosage of 1 mg/kg for 14 consecutive days to the specified experimental groups [44–47]. To ensure accurate dosing, injection volumes were calculated and adjusted individually based on daily body weight measurements, maintaining a standard volume of approximately 1 mL per 250 g of body weight. Animals in the healthy control group did not receive any pharmacological treatment. To reduce animal stress and eliminate inter-operator

variability, all injections were conducted under highly standardized conditions by a single investigator.

2.3 Boron Treatment Protocol

After completion of the 14-day DEX administration period, boron treatment was initiated on Day 15 and continued for 28 consecutive days. Boron was administered *ad libitum* via drinking water at concentrations of 50 or 100 mg/L. These concentrations were selected based on previous experimental evidence demonstrating the biological activity and tolerability of boric acid and related boron compounds across *in vitro* and *in vivo* models [48–50] while providing two exposure levels to explore a potential concentration-dependent therapeutic response. During the same period, the healthy control and untreated sarcopenia model groups received standard drinking water without boron supplementation. The overall experimental period was 42 days.

2.4 Monitoring of Body Weight, Food Intake and Water Consumption

Throughout the experiment, body weight, food intake, and water consumption were recorded daily. Body weight measurements obtained on Days 1, 14, and 42 were used for statistical analyses.

2.5 Behavioral Tests

To quantitatively assess changes in skeletal muscle function, grip strength and hanging wire grid tests were performed weekly over the 42-day experimental duration. These functional assessments yielded objective, longitudinal data regarding forelimb muscle strength, physical endurance, motor coordination, and overall neuromuscular performance. The quantitative results were meticulously incorporated into the following statistical analyses to assess recovery induced by the treatment [45].

2.5.1 Forelimb Grip Strength Test

Forelimb grip strength was measured using an AMF-20 digital force gauge. In summary, each rat was permitted to grasp the wire grid of the apparatus with its forepaws and was then gently pulled backward by the base of the tail along a horizontal plane until its grip was released. To reduce fatigue and ensure the reliability of the data, each animal participated in three consecutive trials, with sufficient inter-trial rest intervals in between. To decrease

measurement variability, the maximum and minimum recorded values were excluded, and the median of the remaining values was used for further analysis. To address systemic differences in animal size, grip strength was normalized to the individual body weight and expressed as relative grip strength (%) according to the following formula [52, 53]:

$$\text{Relative grip strength (\%)} = \frac{\text{Grip strength (kgf)}}{\text{Body weight (g)}} \times 100$$

2.5.2 Hanging Grid Test

Skeletal muscle endurance and coordination were assessed through the hanging wire grid test, which is a well-established method for evaluating physical endurance and neuromuscular strength in experimental models of muscle dysfunction. This assay utilized a specially designed wire grid apparatus measuring 45 × 45 cm. Each rat was positioned at the center of the grid, allowing it to securely grasp the mesh with all four limbs (both forelimbs and hindlimbs). The grid was then carefully inverted to a horizontal orientation, suspending the animal upside down above a padded surface until it released its hold. The time taken to fall was recorded in seconds with the help of a digital stopwatch. To reduce muscle fatigue while ensuring consistency, each animal underwent two consecutive trials with a 15-minute recovery period between them, and the average hanging time from the two trials was computed for further statistical analysis [51].

2.6 Magnetic Resonance Imaging (MRI)

On the concluding day of the study (Day 42), magnetic resonance imaging (MRI) was conducted before euthanasia to non-invasively assess skeletal muscle morphology and muscle volume [55]. The MRI scans were performed using a 3 T clinical scanner (Magnetom Skyra; Siemens Healthineers, Erlangen, Germany) with the rats placed in a prone position. To minimize assessment bias, the acquired images were analyzed by investigators blinded to the experimental group assignments.

2.7 Blood Collection, Euthanasia and Tissue Sampling

After the MRI acquisition, surgical anesthesia was initiated through the intraperitoneal injection of a ketamine/xylazine mixture. The depth of anesthesia was clinically verified by the total absence of pedal withdrawal and corneal reflexes, along with a significant decrease in spontaneous respiration. While under deep surgical anesthesia, blood samples were

obtained through intracardiac puncture for later biochemical and hematological analysis. Plasma was promptly separated from whole blood using centrifugation, quickly frozen in liquid nitrogen, and preserved at -80 °C for additional molecular investigations. Following the blood collection, euthanasia was performed through cervical dislocation, in strict compliance with the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals: 2020 Edition [52]. Subsequently, the heart, brain, liver, kidneys, longissimus dorsi and gastrocnemius muscles, femurs, and adipose tissues were meticulously dissected. Tissue samples intended for molecular analysis were immediately snap-frozen in liquid nitrogen and stored at -80 °C until further examination.

2.8 Histopathological Examination

For histopathological assessment, specimens of the longissimus dorsi and gastrocnemius muscles were carefully washed with physiological saline to remove any residual blood and fixed in 10% neutral buffered formalin for 48 h. Following complete fixation, the tissues were routinely processed through dehydration and clearing, embedded in paraffin, and sectioned at a thickness of 4 µm according to established histological protocols. The sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope (Olympus BX51, Japan).

The degree of muscle fiber atrophy was evaluated using a semi-quantitative scoring system ranging from 0 to 3, based on the overall extent and severity of the observed histomorphological alterations. Score 0 (no atrophy) was assigned to muscle tissue showing predominantly uniform and regularly arranged myofibers, with no evident fiber shrinkage or appreciable degenerative changes. Score 1 (mild atrophy) was assigned when most myofibers were preserved, but occasional fibers exhibited a mild reduction in size and/or focal mild hyalinization. Score 2 (moderate atrophy) was assigned when clear variation in myofiber size, moderate fiber shrinkage, and/or multifocal hyalinization and degenerative changes were observed. Score 3 (severe atrophy) was assigned when marked and widespread myofiber atrophy was accompanied by extensive hyalinization, fragmentation, and/or degenerative changes. The final score for each specimen was determined according to the overall extent and severity of the observed histomorphological alterations.

To minimize observer bias, the histopathological evaluations were performed under blinded conditions, with the evaluator unaware of the experimental group assignments. The previously described MRI image analyses were also performed under blinded conditions.

2.9 Statistical Analysis

Statistical analyses were performed using SPSS (version 25; IBM Corp., Armonk, NY, USA). Quantitative data are presented as mean $\pm$ standard deviation (SD). Normality and homogeneity of variance were assessed using appropriate diagnostic tests. Differences among experimental groups were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for post hoc comparisons. A two-sided P value <0.05 was considered statistically significant.

3. Results

3.1 Body Weight Analysis

At baseline (Day 1), the mean body weights of all experimental groups (Control, Sarcopenia Model, Boron 50 mg/L, and Boron 100 mg/L) were comparable, with no statistically significant differences observed among the groups ($p > 0.05$). These findings confirmed the homogeneous distribution of the experimental animals across the study groups.

The induction of the experimental sarcopenia model through repeated administration of DEX from Day 1 to Day 14 led to a significant and severe reduction in total body mass within the Sarcopenia Model and boron-treatment groups when compared to the healthy Control group. While the Control cohort exhibited a steady increase in weight, indicative of normal growth, a notable decline in body weight was observed in all DEX-treated animals by Day 14 (**Figure 1**).

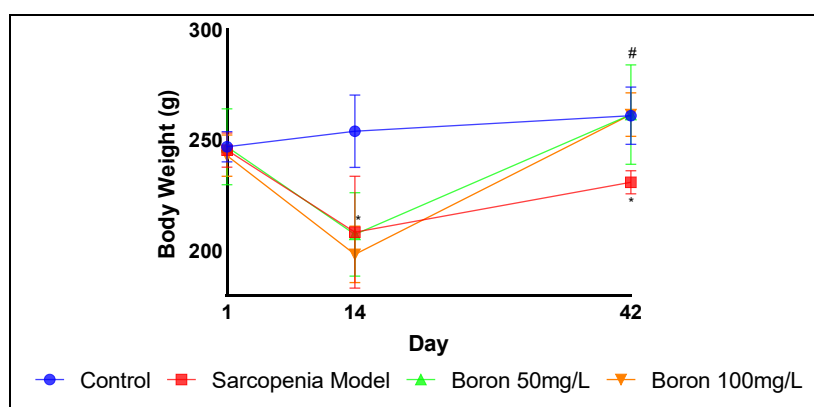


Figure 1. Comparison of rat body weights among control, dexamethasone-induced Sarcopenia Model, and boron-treated groups (50 mg/L and 100 mg/L) at Days 1, 14, and 42 of the experiment. Data are expressed as mean $\pm$ SD. * $p < 0.05$ indicates a statistically significant difference compared to the Control group; # $p < 0.05$ indicates a statistically significant difference compared to the Sarcopenia Model group.

At the beginning of the study (Day 1), there were no significant differences in body weights among the experimental groups. Following DEX administration, a significant weight reduction was observed in all experimental groups compared to the Control group on Day 14 ($p < 0.05$). However, a distinct recovery in body mass was noted in the boron-supplemented groups throughout the remainder of the study (Days 15–42). By the end of the experiment (Day 42), the body weights of both the 50 mg/L and 100 mg/L boron treatment groups had completely recovered to Control levels, showing no significant difference from the Control group ($p = 1.000$). In contrast, the Sarcopenia Model group remained significantly lower than the Control group ($p = 0.038$). Furthermore, both the 50 mg/L and 100 mg/L boron-treated groups demonstrated significantly higher body weights compared to the untreated Sarcopenia Model group ($p = 0.035$ for both). These findings indicate that boron supplementation plays a crucial role in mitigating dexamethasone-induced wasting and promoting body weight normalization.

3.2 Behavioral Tests

3.2.1 Hanging Grid Test Analysis

To evaluate time-dependent alterations in muscle strength and motor endurance, the hanging grid test was performed weekly throughout the 42-day experimental period, and mean falling latencies (in seconds) were recorded (**Figure 2**).

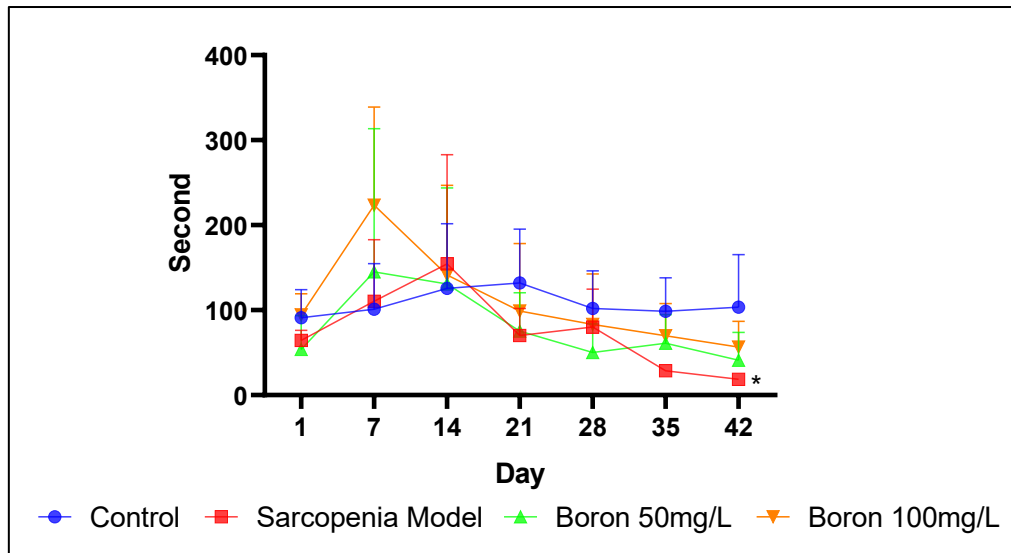


Figure 2. Effects of Boron treatments (50 and 100 mg/L) on hanging grid test performance in the DEX-induced Sarcopenia Model over 42 days (Mean $\pm$ SD). * $p < 0.05$ indicates a statistically significant difference in the Sarcopenia Model group compared to the Control group.

Throughout the study, the Control group exhibited a stable progression, consistently demonstrating the longest hanging duration across all time points. During the sarcopenia induction phase, the experimental animals displayed a temporary increase in hanging latencies on the grid system. However, upon the cessation of DEX administration, a marked downward trend in hanging times was initiated in these groups. Evaluating the overall treatment trajectory and final neuromotor performance, the Boron 100 mg/L group maintained the highest muscle endurance following the Control group. This was followed by the Boron 50 mg/L group, whereas the Sarcopenia Model group recorded the shortest hanging latencies, reflecting the most severe loss of muscle strength. These findings indicate that, particularly, the 100 mg/L boron treatment exerted a protective effect on muscle endurance against the neuromotor fatigue and muscular weakening that commenced after dexamethasone withdrawal.

3.2.2 Forelimb Grip Strength Measurement Analysis

Evaluation of the weekly forelimb grip strength measurements revealed significant time-dependent variations across the experimental groups (**Figure 3**). During the initial 14-day sarcopenia induction phase, animals exposed to DEX experienced a rapid and substantial

decline in muscle force, whereas the control group maintained a steady trajectory over the course of the experiment.

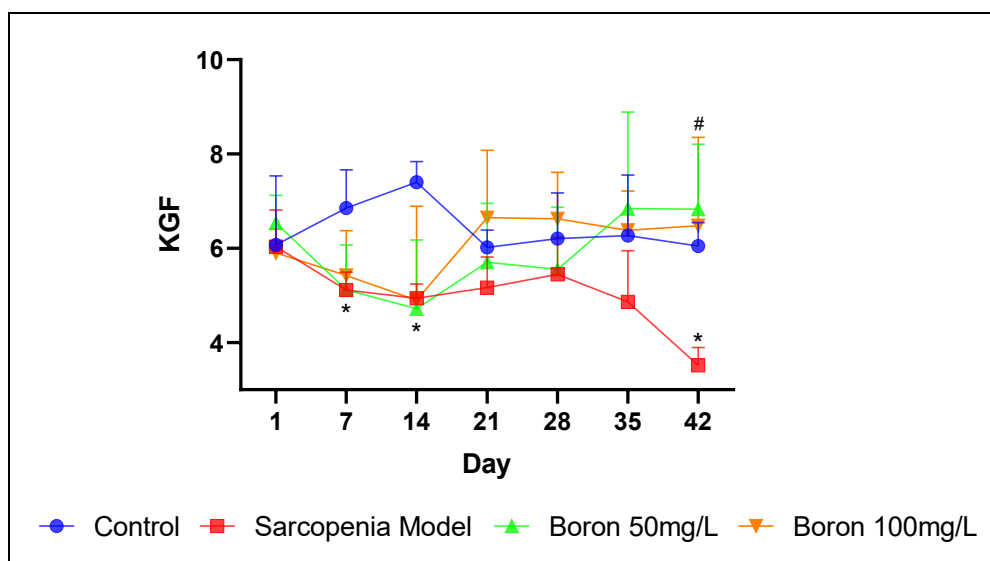


Figure 3. Effects of boron treatments (50 and 100 mg/L) on forelimb grip strength performance in the DEX-induced Sarcopenia Model over 42 days (Mean $\pm$ SD). * $p < 0.05$ indicates a statistically significant difference compared to the Control group; # $p < 0.05$ indicates a statistically significant difference compared to the Sarcopenia Model group.

At the baseline (Day 1), no significant differences in forelimb grip strength were observed among the groups. Following the induction phase, on Days 7 and 14, all experimental groups exhibited a significant reduction in grip strength compared to the Control group ($p < 0.05$). Following the introduction of boron supplementation via drinking water from week two onward (Days 15–42), the treated groups exhibited a marked recovery trend and progressive functional restoration in forelimb motor performance. By the conclusion of the 42-day protocol, the untreated Sarcopenia Model group consistently displayed the lowest grip force values, remaining significantly lower than the Control group ($p = 0.049$). In contrast, a pronounced functional enhancement in grip strength was achieved in both boron-treated groups, which recovered to levels statistically comparable to the Control group. Furthermore, the Boron 50 mg/L and Boron 100 mg/L groups demonstrated significantly higher grip strength compared to the untreated Sarcopenia Model group ($p = 0.010$ and $p = 0.020$, respectively). Overall, these findings indicate that oral boron administration exerts a potent protective and restorative effect on muscle strength in the DEX-induced Sarcopenia Model.

3.3 MRI Analysis

In order to quantitatively assess morphological changes in skeletal muscle mass, *in vivo* MRI was conducted on three randomly chosen animals from each experimental group ($n = 3$). The volumetric analysis included the combined paraspinal and iliopsoas, quadriceps femoris, and gluteal muscle groups, with the total skeletal muscle volume determined from the obtained serial cross-sectional images.

The quantitative MRI analysis indicated that the untreated Sarcopenia Model group displayed the lowest total muscle volume among all experimental groups (**Figure 4**). This significant decrease in muscle volume following chronic administration of DEX aligns closely with the pronounced skeletal muscle atrophy typical of this experimental model.

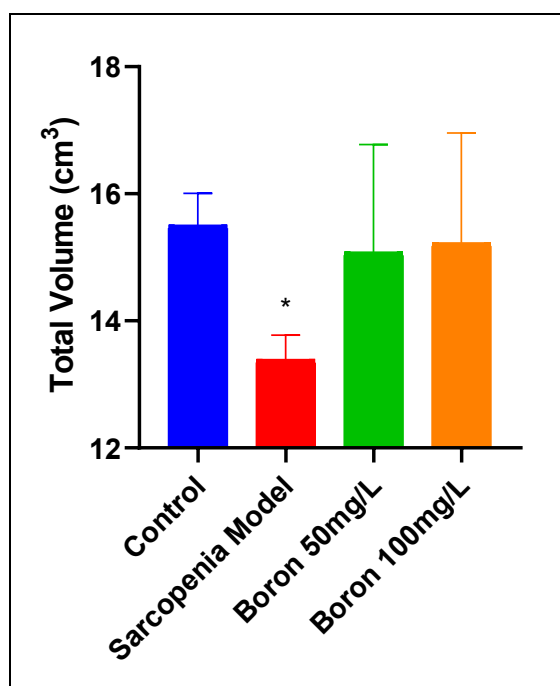


Figure 4. MRI analysis of total skeletal muscle volume. Quantitative comparison shows a marked reduction in total muscle volume in the DEX-induced Sarcopenia Model and its subsequent preservation following boron treatment (50 mg/L and 100 mg/L). Data are expressed as mean $\pm$ SD. * $p < 0.05$ indicates a statistically significant difference compared to the Control group.

MRI analysis of total skeletal muscle volume revealed a significant reduction in the untreated Sarcopenia Model group compared to the healthy Control group ($p = 0.039$). In contrast, both boron-supplemented groups (Boron 50 mg/L and Boron 100 mg/L) exhibited preserved total

muscle volumes that were statistically indistinguishable from the Control group ($p = 0.937$ and $p = 0.980$, respectively). The observation that boron-treated animals maintained muscle volumes nearly matching those of the healthy controls strongly implies that boron supplementation effectively mitigates dexamethasone-induced muscle wasting and serves a protective function in maintaining skeletal muscle mass.

3.4 Organ Weight Analysis

At the end of the 42-day experimental period, the absolute weights of key visceral organs (heart, brain, kidneys, and liver) were measured to evaluate the systemic effects of DEX-induced sarcopenia and the subsequent administration of boron supplementation (**Table 1**). A one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post hoc test indicated that there were no statistically significant differences in the wet weights of the heart, kidneys, or liver among the Control, Sarcopenia Model, Boron 50 mg/L, and Boron 100 mg/L groups ($p > 0.05$). In terms of brain weight, while the more lenient Fisher's least significant difference (LSD) post hoc test suggested possible differences between the boron-treated groups and the untreated Sarcopenia Model group ($p < 0.05$), these differences did not maintain statistical significance when analyzed with the more stringent Type I error control of Tukey's HSD test ($p > 0.05$). Overall, these results indicate that neither chronic exposure to DEX nor boron supplementation at the tested dosages caused any significant morphological or gravimetric changes in essential organs, suggesting a lack of overt systemic or target-organ toxicity under the conditions of this experiment.

Table 1. Effect of boron administration on major organ weights in a DEX-induced sarcopenia model.

Groups	Heart	Brain	Kidney	Liver
Control	0.41 ± 0.05	0.77 ± 0.06	0.76 ± 0.09	3.80 ± 0.42
Sarcopenia Model	0.46 ± 0.04	0.87 ± 0.07	0.79 ± 0.07	3.34 ± 0.58
Boron (50 mg/L)	0.41 ± 0.05	0.75 ± 0.11	0.75 ± 0.07	3.73 ± 0.57
Boron (100 mg/L)	0.40 ± 0.04	0.74 ± 0.03	0.71 ± 0.02	3.52 ± 0.21

Data are presented as mean ± standard deviation (SD). No statistically significant differences were observed among the experimental groups for the evaluated major organ weights ($p > 0.05$).

3.5 Pathology Analysis

The assessment of muscle atrophy encompassed four distinct grades, each determined by the extent of histopathological alterations observed. When no atrophy was present (**Figure 5A**), muscle fibers demonstrated an orderly configuration, with myofibrils displaying uniform diameter measurements and typical structural characteristics. Mild atrophy (**Figure 5B**) was distinguished by a modest decrease in myofibril diameter accompanied by limited hyalinization in select myofibrils, whereas the fundamental structural organization of the muscular tissue remained substantially intact. Moderate atrophy (**Figure 5C**) was defined by considerable heterogeneity in myofibril diameter, generalized reduction in diameter dimensions, and intermediate-level hyalinization. Severe atrophy (**Figure 5D**) was characterized by extensive myofibril degeneration coupled with substantial hyalinization, fragmented and necrotic myofibrils, and sporadic instances of multinucleated degenerative muscle fibers.

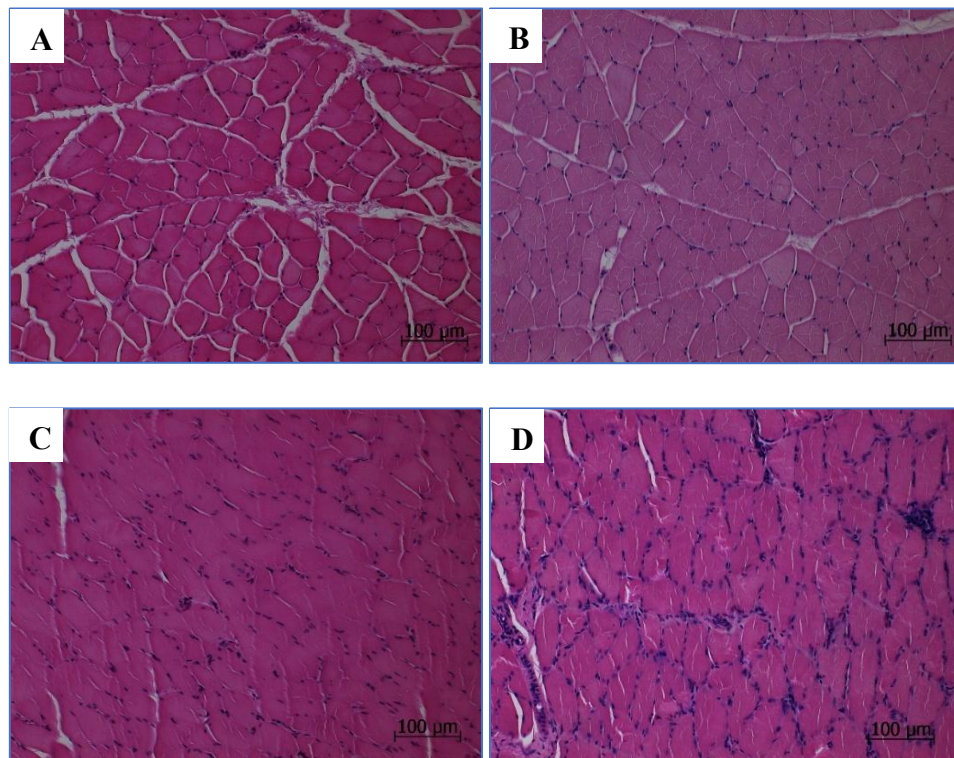


Figure 5. Representative H&E-stained histopathological grading of skeletal muscle atrophy showing (A) regular morphology, (B) mild fiber diameter reduction and hyalinization, (C) distinct variations in myofibril diameter, and (D) severe muscle fiber atrophy with necrotic degeneration (scale bars = 100 µm).

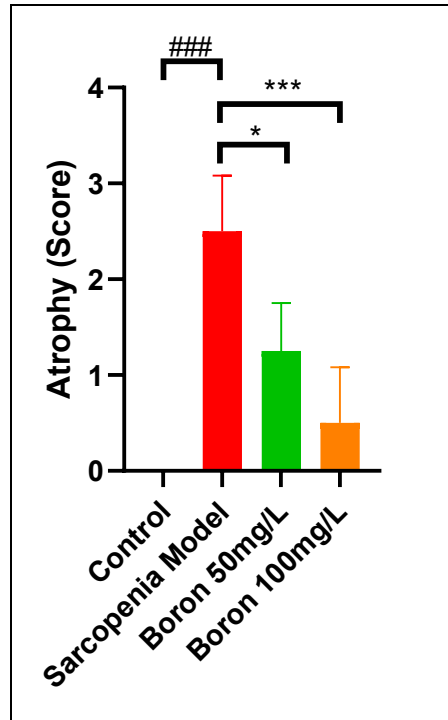


Figure 6. Quantitative analysis results of histopathological atrophy scores among the experimental groups, demonstrating the dose-dependent ameliorative effect of Boron treatment (50 and 100 mg/L) against DEX-induced pathological tissue damage (### $p < 0.001$ vs. Control; * $p < 0.05$, *** $p < 0.001$ vs. DEX Model).

Histopathological evaluation of skeletal muscle tissues revealed statistically significant differences in atrophy scores among the experimental groups (one-way ANOVA, $p < 0.001$). No atrophic changes were observed in the healthy Control group (score = 0), whereas the Sarcopenia Model group subjected to chronic DEX administration exhibited marked degenerative alterations in muscle fibers accompanied by a significant increase in atrophy scores ($p < 0.001$; **Figure 6**). These findings confirm the successful establishment of the experimental sarcopenia model.

Evaluation of the histopathological effects of boron treatment demonstrated a dose-dependent improvement in muscle morphology. Compared with the Sarcopenia Model group, animals treated with Boron 50 mg/L showed a significant reduction in atrophy scores ($p = 0.014$; **Figure 6**). Increasing the boron concentration to 100 mg/L resulted in a more pronounced reduction in atrophy scores, with this group differing significantly from the untreated Sarcopenia Model group ($p < 0.001$; **Figure 6**). Furthermore, no statistically significant difference in atrophy scores was observed between the Boron 100 mg/L and healthy Control

groups ($p = 0.480$). Collectively, these findings suggest that boron supplementation, particularly at 100 mg/L, may substantially attenuate dexamethasone-induced skeletal muscle atrophy and contribute to the preservation of normal muscle histological architecture.

3.6 Biochemical and Hematological Analysis

Table 2. Effect of boron administration on serum biochemical parameters and cellular blood indices in a sarcopenia model.

Parameter	Control	Sarcopenia model	Boron (50 mg/L)	Boron (100 mg/L)
Renal & metabolic function				
Urea (mg/dL)	47.79 ± 5.32	44.59 ± 1.75	45.74 ± 8.76	44.54 ± 2.69
Glucose (mg/dL)	290.75 ± 103.26	218.25 ± 21.88	257.50 ± 19.94	290.50 ± 68.87
BUN (mg/dL)	22.33 ± 2.49	20.84 ± 0.84	21.38 ± 4.09	20.82 ± 1.28
Creatinine (mg/dL)	0.34 ± 0.08	0.28 ± 0.08	0.31 ± 0.04	0.29 ± 0.08
Hepatic function & enzymes				
AST (U/L)	188.18 ± 47.46	205.35 ± 39.93	144.13 ± 21.68	215.50 ± 54.83
ALT (U/L)	51.53 ± 3.49	57.38 ± 13.52	54.47 ± 17.39	68.35 ± 10.94
Total bilirubin (mg/dL)	0.11 ± 0.03	0.11 ± 0.03	0.09 ± 0.03	0.06 ± 0.05
Direct bilirubin (mg/dL)	0.06 ± 0.03	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.02
Lipid profile				
Triglyceride (mg/dL)	123.33 ± 43.47	55.75 ± 9.91*	74.00 ± 9.54	63.33 ± 2.52*
Cholesterol (mg/dL)	49.75 ± 6.80	46.25 ± 5.44	35.50 ± 6.88*	41.75 ± 5.56
HDL (mg/dL)	58.67 ± 6.43	64.25 ± 10.14	45.25 ± 3.77#	50.75 ± 11.35
LDL (mg/dL)	27.00 ± 7.00	24.25 ± 2.87	16.25 ± 2.06	20.75 ± 4.92
Electrolytes & minerals				
Ca (mg/dL)	10.38 ± 0.35	9.68 ± 0.37	10.38 ± 0.27	10.39 ± 0.50
P (mg/dL)	6.57 ± 1.28	7.15 ± 1.49	8.51 ± 1.23	8.92 ± 1.46
Mg (mg/dL)	2.19 ± 0.38	2.21 ± 0.15	2.59 ± 0.32	2.56 ± 0.33
Cl (mmol/L)	99.76 ± 2.72	105.68 ± 1.97	102.11 ± 2.29	102.12 ± 2.07
Na (mmol/L)	138.50 ± 3.11	135.00 ± 1.41	134.75 ± 1.28	135.50 ± 0.58
K (mmol/L)	5.11 ± 0.96	5.51 ± 0.62	5.84 ± 0.68	5.59 ± 0.35
Iron (ug/dL)	428.27 ± 23.57	285.88 ± 19.94**	299.52 ± 57.59*	283.47 ± 48.07**

Proteins				
Total protein (g/dL)	7.15 ± 0.37	6.30 ± 0.18	6.45 ± 0.26	6.38 ± 0.22
Albumin (g/dL)	3.28 ± 0.30	2.90 ± 0.29	2.85 ± 0.10	2.90 ± 0.08
Hematology indices				
PLT	748.50 ± 21.79	630.33 ± 79.03	597.00 ± 76.79	649.50 ± 107.01
Serum quality indices				
ICT	Normal	Normal	Normal	Normal
LIP	Normal	Normal	Normal	Normal
HEM	Normal	Normal	Normal	Normal
Inflammatory markers				
CRP (mg/L)	0.74 ± 0.18	0.73 ± 0.21	0.78 ± 0.12	0.96 ± 0.22

Blood biochemical and hematological analyses were performed to evaluate the effects of the experimental treatments (**Table 2**). No statistically significant differences were observed among the groups for urea, glucose, BUN, creatinine, AST, ALT, total bilirubin, direct bilirubin, LDL, calcium, phosphorus, magnesium, chloride, sodium, potassium, total protein, albumin, PLT, ICT, LIP, HEM, or CRP levels ($p > 0.05$).

In contrast, significant differences were detected in several lipid and iron-related parameters (**Table 2**). Tukey's HSD post-hoc analysis showed that triglyceride levels differed significantly between the Control group and both the Sarcopenia Model ($p = 0.012$) and Boron 100 mg/L ($p = 0.034$) groups. However, triglyceride levels did not differ significantly between the Sarcopenia Model and either boron treatment group ($p > 0.05$). For cholesterol, a significant difference was observed only between the Control and Boron 50 mg/L groups ($p = 0.031$), whereas no significant differences were detected between the Control and Sarcopenia Model groups ($p = 0.854$) or between the Sarcopenia Model and boron treatment groups ($p > 0.05$).

Iron levels also differed significantly among the groups. Compared with the Control group, significantly different iron levels were observed in the Sarcopenia Model ($p = 0.005$), Boron 50 mg/L ($p = 0.011$), and Boron 100 mg/L ($p = 0.008$) groups. However, neither boron treatment resulted in a significant difference in iron levels compared with the Sarcopenia Model group ($p > 0.05$).

Regarding HDL levels, neither boron treatment nor the Sarcopenia Model differed significantly from the Control group ($p > 0.05$). Nevertheless, HDL levels were significantly

different between the Boron 50 mg/L and Sarcopenia Model groups ($p = 0.042$), whereas no significant difference was observed between the Boron 100 mg/L and Sarcopenia Model groups ($p = 0.180$).

4. Discussion

The present study provides evidence that post-DEX boron supplementation is associated with functional and structural recovery of skeletal muscle following DEX-induced muscle wasting. The functional findings were supported by complementary structural and histopathological outcomes. By Day 42, forelimb grip strength reached approximately 6.5–6.8 kgh in the 50 and 100 mg/L boron groups, respectively, compared with approximately 3.5 kgf in the untreated sarcopenia model, corresponding to an approximately 84–94% higher grip force. MRI assessment at Day 42 similarly demonstrated greater total skeletal muscle volume in both boron-treated groups than in the untreated model, with mean volumes approaching those observed in healthy controls. Histopathological findings provided further evidence of a concentration-dependent response: compared with the untreated sarcopenia model, atrophy scores were significantly reduced following treatment with 50 mg/L boron ($p = 0.014$) and showed a more pronounced reduction at 100 mg/L ($p < 0.001$). Atrophy scores in the 100 mg/L group were not significantly different from those of healthy controls ($p = 0.480$). Taken together, the convergence of functional, MRI-based, and histopathological findings suggests that boron supplementation may facilitate skeletal muscle recovery following DEX-induced injury rather than merely influencing a single experimental endpoint.

DEX-induced skeletal muscle atrophy is a multifactorial process involving interconnected disturbances in redox homeostasis, inflammatory signaling, mitochondrial function, proteostasis, and regenerative capacity. Among these mechanisms, oxidative stress and redox imbalance appear to constitute an important component of muscle deterioration. DEX-associated disruption of mitochondrial homeostasis can further amplify cellular oxidative stress and compromise metabolic function, while disturbances in mitochondrial function and calcium homeostasis may additionally impair muscle integrity [53, 54]. Redox regulation is also closely linked to muscle proteostasis, as loss of SELENOW, a muscle-enriched redox-related selenoprotein, aggravates muscle loss through disruption of protein synthesis and ubiquitin–proteasome-mediated degradation [55]. Importantly, oxidative stress is accompanied by alterations in inflammatory responses in DEX-treated muscle, suggesting that redox and inflammatory dysregulation may act as interconnected contributors to the development and persistence of muscle damage [54]. These processes converge with

suppression of anabolic AKT/mTOR signaling and activation of FOXO/E3 ubiquitin ligase-dependent proteolysis, thereby shifting muscle protein homeostasis toward net protein loss [56, 57]. The involvement of MAFbx in DEX-induced atrophy further supports the importance of ubiquitin-dependent proteolysis in this process [58]. In addition, alterations in peroxisomal ACOX1-related metabolism, intracellular metabolic signaling, and myogenic regeneration may further contribute to the structural and functional deterioration of skeletal muscle [54, 59, 60]. Thus, DEX-induced muscle atrophy appears to arise from a network in which oxidative and inflammatory stress, mitochondrial dysfunction, accelerated protein degradation, and impaired regenerative responses collectively disrupt skeletal muscle homeostasis.

Boron compounds have previously demonstrated cytoprotective activity against oxidative cellular injury. In fact, boric acid and borax protected human lymphocytes against oxidative stress and associated genotoxic damage [61] while boric acid improved functional and histopathological outcomes in an *in vivo* model of chemically induced peripheral tissue injury [62]. Evidence that a boron-containing compound (2-aminoethoxydiphenyl borate) can modulate skeletal muscle mitochondrial function further suggests a potential link between boron-related signaling and mitochondrial homeostasis [63]. In this context, the simultaneous improvement in muscle function, muscle volume, and myofiber histology observed in the present study is compatible with the hypothesis that boron may facilitate post-DEX muscle recovery by limiting oxidative and inflammatory cellular stress and thereby creating a more favorable environment for preservation or restoration of muscle-cell homeostasis. The functional and histological improvements observed following boron supplementation may also warrant investigation of cellular pathways involved in tissue preservation. Oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis are interconnected processes that contribute to cellular injury and have been identified as relevant therapeutic targets in experimental studies of bioactive compounds and degenerative disorders [31, 64]. Although these pathways were not directly evaluated in the present study, their potential involvement provides a mechanistic basis for future investigations into the muscle-protective effects of boron.

The coordinated functional and structural recovery observed in the present study provides a phenotypic basis for proposing a cytoprotective mechanism of boron against DEX-induced muscle injury. At Day 42, 50 and 100 mg/L boron-treated animals exhibited (84% and 94%, respectively) higher forelimb grip strength than the untreated sarcopenia model, together with

greater MRI-derived skeletal muscle volume and a marked reduction in histopathological atrophy. Notably, atrophy scores were significantly reduced at both 50 mg/L ($p = 0.014$) and 100 mg/L ($p < 0.001$), and the 100 mg/L group was no longer significantly different from the healthy control ($p = 0.480$). The concordance between recovery of myofiber architecture, muscle volume, and contractile performance suggests that boron may act at cellular processes governing myofiber integrity and recovery rather than merely producing an isolated functional effect. A plausible mechanism involves attenuation of the redox–inflammatory–apoptotic cascade that contributes to DEX-induced cellular injury. Boric acid has been shown to regulate oxidative stress and inflammatory responses while suppressing CASP3 and CYCS and restoring anti-apoptotic Bcl-2 expression *in vivo* [65], whereas boric acid and borax protect against oxidative stress-associated cellular and genotoxic injury [61]. Such effects could reduce oxidative and inflammatory stress and limit apoptosis in damaged muscle, thereby preserving viable myofibers and providing a cellular environment conducive to the restoration of muscle mass and function, consistent with the histological, MRI, and grip-strength improvements observed here. Proteostasis may constitute an additional downstream component of this response because DEX-induced atrophy involves FOXO-dependent activation of MAFbx and MuRF1 and accelerated ubiquitin–proteasome-mediated protein degradation. The ability of boron-containing pharmacophores to engage components of protein quality-control machinery, including the proteasome [66] and VCP/p97 [67], provides a rationale for investigating this pathway, although these compounds are pharmacologically distinct from the boron supplementation used in the present study and do not demonstrate direct target engagement by boron in skeletal muscle. Thus, our findings support a working model in which boron facilitates post-DEX muscle recovery primarily by limiting oxidative, inflammatory, and apoptotic cellular stress, with possible downstream restoration of proteostasis through the AKT/mTOR–FOXO–MAFbx/MuRF1 and VCP/p97–ubiquitin–proteasome networks.

The convergence of functional, MRI-based, and histopathological recovery also provides a rationale for systems-level investigation of the molecular response to boron. Future studies integrating targeted assessment of redox status, inflammatory mediators, mitochondrial function, apoptotic signaling, and proteostasis with transcriptomic and multi-omics approaches could determine whether the observed phenotypic recovery reflects coordinated remodeling of these interconnected pathways. Such approaches have proven useful for resolving molecular networks and metabolic crosstalk underlying complex biological

phenotypes [68, 69] and may help identify molecular signatures and biomarkers associated with boron-responsive muscle recovery.

5. Conclusions

The present study demonstrates that post-DEX boron supplementation promotes functional and structural recovery of skeletal muscle following DEX-induced muscle wasting. The concordant improvements in grip strength, MRI-derived muscle volume, and histopathological architecture indicate that the response extends beyond functional recovery and is accompanied by restoration of muscle integrity. The more pronounced histopathological improvement observed at 100 mg/L further supports a concentration-related biological response. Although the underlying molecular mechanisms remain to be established, the present findings, together with existing evidence on the redox-modulatory, anti-inflammatory, and cytoprotective properties of boron compounds, support a potential role for restoration of cellular homeostasis and proteostasis in boron-mediated muscle recovery. These findings provide a preclinical basis for further mechanistic studies targeting redox–inflammatory signaling, mitochondrial function, apoptosis, and the AKT/mTOR–FOXO–ubiquitin–proteasome axis, as well as for subsequent validation in larger and sex-balanced experimental models.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Sayer AA, Cooper R, Arai H, et al (2024) Sarcopenia. *Nat Rev Dis Primers* 10:68. <https://doi.org/10.1038/s41572-024-00550-w>

2. Shu X, Lin T, Wang H, et al (2022) Diagnosis, prevalence, and mortality of sarcopenia in dialysis patients: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 13:145–158. <https://doi.org/10.1002/jcsm.12890>
3. Tantai X, Liu Y, Yeo YH, et al (2022) Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. *J Hepatol* 76:588–599. <https://doi.org/10.1016/j.jhep.2021.11.006>
4. Feng L, Gao Q, Hu K, et al (2022) Prevalence and Risk Factors of Sarcopenia in Patients With Diabetes: A Meta-analysis. *J Clin Endocrinol Metab* 107:1470–1483. <https://doi.org/10.1210/clinem/dgab884>
5. Yuan S, Larsson SC (2023) Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. *Metabolism* 144:155533. <https://doi.org/10.1016/j.metabol.2023.155533>
6. Ceyhan AB, Altay O, Zhang C, et al (2025) Unravelling the Complexity of Sarcopenia Through a Systems Biology Approach. *Int J Mol Sci* 26:8527. <https://doi.org/10.3390/ijms26178527>
7. Yuan S, Larsson SC (2023) Epidemiology of sarcopenia: Prevalence, risk factors, and consequences. *Metabolism* 144:155533. <https://doi.org/10.1016/j.metabol.2023.155533>
8. Zhang X, Huang P, Dou Q, et al (2020) Falls among older adults with sarcopenia dwelling in nursing home or community: A meta-analysis. *Clinical Nutrition* 39:33–39. <https://doi.org/10.1016/j.clnu.2019.01.002>
9. Cai Z, Liu D, Yang Y, et al (2022) The role and therapeutic potential of stem cells in skeletal muscle in sarcopenia. *Stem Cell Res Ther* 13:28. <https://doi.org/10.1186/s13287-022-02706-5>
10. Najm A, Niculescu A-G, Grumezescu AM, Beuran M (2024) Emerging Therapeutic Strategies in Sarcopenia: An Updated Review on Pathogenesis and Treatment Advances. *Int J Mol Sci* 25:4300. <https://doi.org/10.3390/ijms25084300>
11. Moin MdR, Pal S, Das S, et al (2026) Selective Small-Molecule AdipoR1 Agonist 3-Hydroxy Pterocarpan Salt (CDRI-1709S) Ameliorates Skeletal Muscle Atrophy. *J Cachexia Sarcopenia Muscle* 17:. <https://doi.org/10.1002/jcsm.70328>
12. Shi H, Sun W, Cao X, et al (2025) Irisin Increases Sirtuin 1 to Improve Glucocorticoid-Induced Sarcopenia and Mitochondrial Dysfunction. *Cells* 14:1675. <https://doi.org/10.3390/cells14211675>
13. Lee M-K, Jeong HH, Kim M-J, et al (2022) Nutrients against Glucocorticoid-Induced Muscle Atrophy. *Foods* 11:687. <https://doi.org/10.3390/foods11050687>
14. Permpoon U, Moon J, Kim CY, Nam T (2025) Glucocorticoid-Mediated Skeletal Muscle Atrophy: Molecular Mechanisms and Potential Therapeutic Targets. *Int J Mol Sci* 26:7616. <https://doi.org/10.3390/ijms26157616>

15. Moon J, Lee J-H, Jeong E, et al (2025) Protective Efficacy of *Lactobacillus plantarum* Postbiotic beLP-K in a Dexamethasone-Induced Sarcopenia Model. *Int J Mol Sci* 26:7504. <https://doi.org/10.3390/ijms26157504>
16. Hooijmans MT, Schlaffke L, Bolsterlee B, et al (2024) Compositional and functional MRI of skeletal muscle: A review. *Journal of Magnetic Resonance Imaging* 60:860–877. <https://doi.org/10.1002/jmri.29091>
17. Bigossi G, Marcozzi S, Giuliani ME, et al (2025) A Comparative Analysis of Grip Strength Evaluation Methods in a Large Cohort of Aged Mice. *J Cachexia Sarcopenia Muscle* 16:. <https://doi.org/10.1002/jcsm.70050>
18. Ueno H, Takahashi Y, Murakami S, et al (2022) The prevention of home-cage grid climbing affects muscle strength in mice. *Sci Rep* 12:15263. <https://doi.org/10.1038/s41598-022-19713-4>
19. Prabakaran AD, McFarland K, Miz K, et al (2024) Intermittent glucocorticoid treatment improves muscle metabolism via the PGC1 α /Lipin1 axis in an aging-related sarcopenia model. *Journal of Clinical Investigation* 134:. <https://doi.org/10.1172/JCI177427>
20. Wang BY-H, Hsiao AW-T, Wong N, et al (2023) Is dexamethasone-induced muscle atrophy an alternative model for naturally aged sarcopenia model? *J Orthop Translat* 39:12–20. <https://doi.org/10.1016/j.jot.2022.11.005>
21. Biță A, Scorei IR, Bălșeanu TA, et al (2022) New Insights into Boron Essentiality in Humans and Animals. *Int J Mol Sci* 23:9147. <https://doi.org/10.3390/ijms23169147>
22. Hong C, Chen X, Tang J, et al (2026) The Biological Effects of Boron in Animals and Humans. *Biol Trace Elem Res* 204:5698–5713. <https://doi.org/10.1007/s12011-026-05062-0>
23. Rondanelli M, Faliva MA, Peroni G, et al (2020) Pivotal role of boron supplementation on bone health: A narrative review. *Journal of Trace Elements in Medicine and Biology* 62:126577. <https://doi.org/10.1016/j.jtemb.2020.126577>
24. Estevez-Fregoso E, Kilic A, Rodríguez-Vera D, et al (2023) Effects of Boron-Containing Compounds on Liposoluble Hormone Functions. *Inorganics (Basel)* 11:84. <https://doi.org/10.3390/inorganics11020084>
25. Al Khalif O, Sezer G (2025) Concentration-Dependent Effects of Boric Acid on Osteogenic Differentiation of Vascular Smooth Muscle Cells. *Biol Trace Elem Res* 203:953–962. <https://doi.org/10.1007/s12011-024-04204-6>
26. RI C-C, MF C-R, D R-V, et al (2023) Boron-Containing Compounds for Prevention, Diagnosis, and Treatment of Human Metabolic Disorders. *Biol Trace Elem Res* 201:2222–2239. <https://doi.org/10.1007/s12011-022-03346-9>

27. Alak G, Parlak V, Aslan ME, et al (2019) Borax Supplementation Alleviates Hematotoxicity and DNA Damage in Rainbow Trout (*Oncorhynchus mykiss*) Exposed to Copper. *Biol Trace Elem Res* 187:536–542. <https://doi.org/10.1007/s12011-018-1399-6>
28. Alak G, Ucar A, Parlak V, et al (2021) Antioxidant Potential of Ulexite in Zebrafish Brain: Assessment of Oxidative DNA Damage, Apoptosis, and Response of Antioxidant Defense System. *Biol Trace Elem Res* 199:1092–1099. <https://doi.org/10.1007/s12011-020-02231-7>
29. Çolak S, Geyikoğlu F, Keles ON, et al (2011) The neuroprotective role of boric acid on aluminum chloride-induced neurotoxicity. *Toxicol Ind Health* 27:700–710. <https://doi.org/10.1177/0748233710395349>
30. Küçükdoğru R, Türkez H, Arslan ME, et al (2020) Neuroprotective effects of boron nitride nanoparticles in the experimental Parkinson's disease model against MPP+ induced apoptosis. *Metab Brain Dis* 35:947–957. <https://doi.org/10.1007/s11011-020-00559-6>
31. Turkez H, Sozio P, Geyikoglu F, et al (2014) Neuroprotective Effects of Farnesene Against Hydrogen Peroxide-Induced Neurotoxicity In vitro. *Cell Mol Neurobiol* 34:101–111. <https://doi.org/10.1007/s10571-013-9991-y>
32. Türkez H, Geyikoğlu F (2007) An in vitro blood culture for evaluating the genotoxicity of titanium dioxide: the responses of antioxidant enzymes. *Toxicol Ind Health* 23:19–23. <https://doi.org/10.1177/0748233707076764>
33. Türkez H, Aydın E (2016) *In vitro* assessment of cytogenetic and oxidative effects of α -pinene. *Toxicol Ind Health* 32:168–176. <https://doi.org/10.1177/0748233713498456>
34. Çelik K, Toğar B, Türkez H, Taşpınar N (2014) In vitro cytotoxic, genotoxic, and oxidative effects of acyclic sesquiterpene farnesene. *TURKISH JOURNAL OF BIOLOGY* 38:253–259. <https://doi.org/10.3906/biy-1309-55>
35. Türkez H, Geyikoglu F, Aslan A, et al (2010) Antimutagenic effects of lichen *Pseudovernia furfuracea* (L.) Zoph. extracts against the mutagenicity of aflatoxin B1 in vitro. *Toxicol Ind Health* 26:625–631. <https://doi.org/10.1177/0748233710377779>
36. Turkez H, Aydın E, Aslan A (2012) *Xanthoria elegans* (Link) (lichen) extract counteracts DNA damage and oxidative stress of mitomycin C in human lymphocytes. *Cytotechnology* 64:679–686. <https://doi.org/10.1007/s10616-012-9447-0>
37. Geyikoglu F, Turkez H, Aslan A (2007) The protective roles of some lichen species on colloidal bismuth subcitrate genotoxicity. *Toxicol Ind Health* 23:487–492. <https://doi.org/10.1177/0748233708089044>
38. Sozio P, Fiorito J, Di Giacomo V, et al (2015) Haloperidol metabolite II prodrug: Asymmetric synthesis and biological evaluation on rat C6 glioma cells. *Eur J Med Chem* 90:1–9. <https://doi.org/10.1016/j.ejmech.2014.11.012>

39. Cacciatore I, Fornasari E, Marinelli L, et al (2017) Memantine-derived drugs as potential antitumor agents for the treatment of glioblastoma. *European Journal of Pharmaceutical Sciences* 109:402–411. <https://doi.org/10.1016/j.ejps.2017.08.030>
40. Emsen B, Aslan A, Turkez H, et al (2018) The anti-cancer efficacies of diffractaic, lobaric, and usnic acid: In vitro inhibition of glioma. *J Cancer Res Ther* 14:941–951. <https://doi.org/10.4103/0973-1482.177218>
41. Kirk B, Cawthon PM, Arai H, et al (2024) The Conceptual Definition of Sarcopenia: Delphi Consensus from the Global Leadership Initiative in Sarcopenia (GLIS). *Age Ageing* 53:. <https://doi.org/10.1093/ageing/afae052>
42. Liu X, Chen X, Cui J (2025) Therapeutic advances in sarcopenia management: From traditional interventions to personalized medicine. *Clinical Nutrition* 51:187–197. <https://doi.org/10.1016/j.clnu.2025.06.007>
43. Bae S, Mai V, Mun S, et al (2025) Lonafarnib Protects Against Muscle Atrophy Induced by Dexamethasone. *J Cachexia Sarcopenia Muscle* 16:. <https://doi.org/10.1002/jcsm.13665>
44. CHEN D, YANG M-R, HUANG L-N, et al (2014) Dexamethasone-induced hyposensitivity to rocuronium in rat diaphragm associated with muscle-fiber transformation. *Mol Med Rep* 9:527–534. <https://doi.org/10.3892/mmr.2013.1819>
45. Kim S, Kim K, Park J, Jun W (2021) Curcuma longa L. Water Extract Improves Dexamethasone-Induced Sarcopenia by Modulating the Muscle-Related Gene and Oxidative Stress in Mice. *Antioxidants* 10:1000. <https://doi.org/10.3390/antiox10071000>
46. Kawano F, Tanihata J, Sato S, et al (2009) Effects of dexamethasone on the expression of β 1-, β 2- and β 3-adrenoceptor mRNAs in skeletal and left ventricle muscles in rats. *The Journal of Physiological Sciences* 59:383–390. <https://doi.org/10.1007/s12576-009-0046-6>
47. Flis DJ, Bialobrodzka EG, Rodziewicz-Flis EA, et al (2022) The Effect of Long-Lasting Swimming on Rats Skeletal Muscles Energy Metabolism after Nine Days of Dexamethasone Treatment. *Int J Mol Sci* 23:748. <https://doi.org/10.3390/ijms23020748>
48. Saeb SQ, Deniz GY, Arslan M, et al (2026) Boric acid attenuates sepsis-induced cardiac injury through TLR4/mTOR modulation. *Journal of Trace Elements in Medicine and Biology* 94:127846. <https://doi.org/10.1016/j.jtemb.2026.127846>
49. Turkez H, Alper F, Bayram C, et al (2025) Boric acid impedes glioblastoma growth in a rat model: insights from multi-approach analysis. *Medical Oncology* 42:47. <https://doi.org/10.1007/s12032-025-02600-z>
50. Tırkez H, Geyikoğlu F, Tatar A, et al (2007) Effects of Some Boron Compounds on Peripheral Human Blood. *Zeitschrift für Naturforschung C* 62:889–896. <https://doi.org/10.1515/znc-2007-11-1218>

51. Wu W, Guo X, Qu T, et al (2024) The Combination of Lactoferrin and Creatine Ameliorates Muscle Decay in a Sarcopenia Murine Model. *Nutrients* 16:1958. <https://doi.org/10.3390/nu16121958>
52. Underwood W, Anthony R (2020) AVMA guidelines for the euthanasia of animals: 2020 edition
53. Gao X, Feng X, Feng G, et al (2026) 3,3'-Diindolylmethane ameliorates muscle atrophy by modulating mitochondrial function and calcium homeostasis. *Phytomedicine* 159:158409. <https://doi.org/10.1016/j.phymed.2026.158409>
54. Ma D, Liu Y, Zhao J, Li Q (2026) Ameliorative Effects of Pumpkin Seed Protein Peptides on Dexamethasone-Treated Sarcopenia and Their Effects When Combined with Vitamin D. *Foods* 15:1162. <https://doi.org/10.3390/foods15071162>
55. Yang J-C, Liu M, Huang R-H, et al (2024) Loss of SELENOW aggravates muscle loss with regulation of protein synthesis and the ubiquitin-proteasome system. *Sci Adv* 10:. <https://doi.org/10.1126/sciadv.adj4122>
56. Park E, Kim H, Lee S, et al (2025) Gymnemantoside A Ameliorates Steroid-Induced Skeletal Muscle Atrophy via Bridging Glucocorticoid and Insulin Receptor Signalling. *J Cachexia Sarcopenia Muscle* 16:. <https://doi.org/10.1002/jcsm.70118>
57. Choi D-I, Lee H, Heo S, et al (2026) Cryptotaenia japonica extract attenuates glucocorticoid-induced muscle atrophy via regulation of the AKT/mTOR–FOXO/E3 ubiquitin ligase axis. *Front Physiol* 17:. <https://doi.org/10.3389/fphys.2026.1860064>
58. Chae J, Woo SM, Seo SU, et al (2026) Deubiquitinase YOD1 Inhibition Suppresses DEX- and Denervation-Induced Muscle Atrophy Through MAFbx Destabilization. *J Cachexia Sarcopenia Muscle* 17:. <https://doi.org/10.1002/jcsm.70300>
59. He Y, Tan Y, Song Z, Chen Y (2025) Ferulic acid attenuates Sarcopenia progression by inhibiting peroxisomal ACOX1. *Free Radic Biol Med* 240:183–196. <https://doi.org/10.1016/j.freeradbiomed.2025.08.025>
60. Wang C, Chen H, Shen L, et al (2026) Sema4A Protects Against Muscle Atrophy and Promotes Repair by Regulating Intracellular Metabolic Signalling. *J Cachexia Sarcopenia Muscle* 17:. <https://doi.org/10.1002/jcsm.70315>
61. Turkez H, Tozlu OO, Arslan ME, et al (2024) Boric Acid and Borax Protect Human Lymphocytes from Oxidative Stress and Genotoxicity Induced by 3-Monochloropropane-1,2-diol. *Biol Trace Elem Res* 202:5006–5016. <https://doi.org/10.1007/s12011-024-04060-4>
62. Yildirim C, Cevik S, Yamaner H, et al (2022) Boric acid improves the behavioral, electrophysiological and histological parameters of cisplatin-induced peripheral neuropathy in rats. *Journal of Trace Elements in Medicine and Biology* 70:126917. <https://doi.org/10.1016/j.jtemb.2021.126917>

63. Dubinin M V., Chulkov A V., Igoshkina AD, et al (2024) Effect of 2-aminoethoxydiphenyl borate on the functions of mouse skeletal muscle mitochondria. *Biochem Biophys Res Commun* 712–713:149944.
<https://doi.org/10.1016/j.bbrc.2024.149944>
64. Turkez H, Arslan ME, Barboza JN, et al (2022) Therapeutic Potential of Ferulic Acid in Alzheimer's Disease. *Curr Drug Deliv* 19:860–873.
<https://doi.org/10.2174/1567201819666211228153801>
65. Kar E, Kar F, Koçak FE, et al (2026) Multifactorial protective effects of boric acid against postoperative intra-abdominal adhesions in a rat model. *Tissue Cell* 99:103244.
<https://doi.org/10.1016/j.tice.2025.103244>
66. Vuong B, Sanghai N, Afridi MSK, Tranmer GK (2026) Boron-Containing Drug Candidates in Clinical Trials
67. Zhang Y, Xie X, Wang X, et al (2021) Discovery of novel pyrimidine molecules containing boronic acid as VCP/p97 Inhibitors. *Bioorg Med Chem* 38:116114.
<https://doi.org/10.1016/j.bmc.2021.116114>
68. Meng L, Jin H, Yulug B, et al (2024) Multi-omics analysis reveals the key factors involved in the severity of the Alzheimer's disease. *Alzheimers Res Ther* 16:213.
<https://doi.org/10.1186/s13195-024-01578-6>
69. Arif M, Klevstig M, Benfeitas R, et al (2021) Integrative transcriptomic analysis of tissue-specific metabolic crosstalk after myocardial infarction. *Elife* 10:.
<https://doi.org/10.7554/eLife.66921>