Evaluation of The Effects of Dexmedetomidine against Carbontetracloride-Induced Nephrotoxicity via Oxidative Stress and Apoptosis

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ABSTRACT

Objective: The objective of this work is to investigate the histological and biochemical consequences of administering Dexmedetomidine (DEX), an alpha-2 adrenergic receptor agonist with notable sedative qualities as well as antioxidant and anti-inflammatory characteristics, in the context of Carbon tetrachloride (CCl4)-induced kidney injury.

Materials and Methods: The experimental design involved the random allocation of 30 Sprague-Dawley rats into three distinct groups. The experimental group designated as Group 1 received a single intraperitoneal administration of 1ml of saline solution containing 0.09% NaCl. Group 2 received an intraperitoneal injection of carbon tetrachloride (CCl4) at a dosage of 2 milliliters per kilogram. Group 3, referred to as the CCl4+Dexmedetomidine group, received a solitary intraperitoneal (i.p.) dosage of 100 µg/kg dexmedetomidine one hour before the intraperitoneal administration of 2mL/kg CCl4.

Results: Extensive necrosis and debris accumulation were observed in the tubules, particularly in the proximal tubules, within the CCl4-applied group. An elevation in malondialdehyde (MDA) concentrations and terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) positivity, along with a reduction in glutathione (GSH) levels, was found in the renal tissues of the CCl4 experimental group as compared to the control group. In contrast, the CCl4+DEX group exhibited a reduction in the quantity of necrotic tubular cells, levels of MDA, and TUNEL positive. Additionally, there was an elevation in GSH levels compared to the group treated with CCl4 alone.

Conclusions: The administration of dexmedetomidine has been observed to potentially provide a protective effect against renal damage induced by CCl4. This phenomenon could potentially be linked to the modulation of tissue oxidative stress markers and the attenuation of apoptotic rate. The findings of our investigation provide evidence in favour of the utilization of dexmedetomidine as a promising therapeutic drug for mitigating renal injury.

Keywords: Apoptosis, Dexmedetomidine, Kidney, Nephrotoxicity, Oxidative stress

INTRODUCTION

Carbon tetrachloride (CCl4) is a solvent of hydrocarbon structure that is frequently used in industrial applications (1). CCl4 is also a widely used solvent in food and water analysis. It is reported that respiratory and skin exposure to this substance may have carcinogenic effects in laboratory personnel (2). Long-term respiratory exposure is described to cause hepatocarcinogenesis (3). CCl4 is used to induce cirrhosis models in rat studies (4). It is converted into trichloromethyl (CCl3), which is a toxic substance, by the CYP2E1 (Cytochrome P450 Family 2 Subfamily E Member 1) enzyme, leading to necrosis and fibrosis in the liver tissue (4). It was shown to result in histopathological findings such as vascular congestion, infiltration, and vacuolar degeneration in cells in the liver (1). Moreover, it induces oxidative damage by increasing the amounts of malondialdehyde (MDA), which is an oxidative stress marker, in the intestine and the lung, as well as increasing the number of cells marked by the TUNEL method, which indicates necrotic cells (5,6).
The kidney is an organ where the numerous toxic substances and medications that enter the body are metabolized and detoxified (7). Accordingly, it is the organ that is most exposed to toxic substances and medications (7). Animal model studies in the literature have shown that CCl4 exposure causes nephrotoxicity (8). Proximal tubular epithelial cells of the kidney are especially sensitive to CCI4 toxicity due to high cytochrome P450 content (9). Cytochrome P450 enzyme systems metabolize CCI4 into trichloromethyl and trichloromethyl peroxyl free radicals, resulting in cell damage (10). Histopathological evaluations showed CCI4 exposure to cause injury in the kidney tissue via reactive oxygen species (ROS) (7). Although not yet in clinical use, antioxidants that may be employed to prevent CCI4-related nephrotoxicity have been studied in the literature (11,12).

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist that is used for anesthesia and sedation, especially in children, due to not causing respiratory depression and providing cardiovascular stability (13). The numerous studies in the literature conducted on dexmedetomidine in recent years suggest that it possesses organ protective effects that probably derive from its α-2 agonistic effect mechanisms (14). Rat models of sepsis demonstrated that it had protective effects on kidney tissue via anti-inflammatory, anti-apoptotic, and antioxidant properties (15,16).

Our review of the literature did not identify any studies that have investigated the effects of dexmedetomidine in CCI4-induced nephrotoxicity. Based on the anti-inflammatory, anti-apoptotic, and antioxidant properties of dexmedetomidine, we designed an exploratory study to examine the possible protective effects of dexmedetomidine against CCI4-induced renal toxicity. In particular, we aim to understand the role of oxidative stress and apoptosis in kidney tissue and how these processes are modulated by dexmedetomidine. This study may provide an important basis for evaluating the use of dexmedetomidine as a potential treatment strategy against renal toxicity.

**MATERIAL and METHODS**

This study was performed with approval from Recep Tayyip Erdoğan University Local Ethics Committee for Animal Research dated 02-05.2022 with the approval number 2022-23. All rats were obtained from the Animal Research Unit of Recep Tayyip Erdoğan University. The rats were housed under a 12-hour lightness and 12-hour darkness cycle at 55-60% humidity and a temperature of 22±2 °C. They had ad libitum access to standard pellet chow and water.

**Experimental Animal Study**

A total of thirty male Sprague-Dawley rats weighing 292±38 gr were randomly assigned to groups of 10 rats, each using a computer-compatible number generator. The control group (Group 1) was given only 1ml of physiological serum intraperitoneally (i.p.). The CCI4 group (Group 2) was given of 2mL/kg i.p. CCI4. The CCI4+Dexmedetomidine group (Group 3) was treated with a single i.p dose of 100 µg/kg dexmedetomidine (Precedex, USA) one hour before the administration of 2mL/kg i.p. CCI4. Two days after the administration of CCI4, all rats were sacrificed under anesthesia with 50 mg/kg ketamine hydrochloride and 30 mg/kg xylazine HCL, and kidney tissues were excised to collect specimens for biochemical, histopathological and immunohistochemical analyses.

**Biochemical Analysis**

**Preparation of Tissue Homogenate**

Kidney tissue specimens were added with phosphate buffer at a ratio of ½. All specimens were homogenized (30 hertz/1 min) and subsequently centrifuged at 3000 g for 15 minutes. The resulting supernatants were used for biochemical assays.

**Determination of Tissue Glutathione (GSH) Levels**

A 50 µL kidney tissue specimen was added with 200 µL 3M disodium hydrogen phosphate and 50 µL Ellman’s reagent (17). The resulting, yellow-colored complex was measured spectrophotometrically at 412 nm. The results were expressed in units of nmol/mg tissue.

**Determination of Tissue Malondialdehyde (MDA) Levels**

MDA, which is the final product of lipid peroxidation, was measured as described by Ohkawa et al. (18). In brief, 50 µL 8.1% sodium dodecyl sulfate (SDS), 200 µL kidney tissue supernatant was added with 375 µL 20% acetic acid (v/v) pH 3.5 and 375 µL 0.8% thiobarbituric acid (TBA). Following incubation in a water bath for 1 hour, it was cooled and then centrifuged at 750 rpm for 10 minutes. It was measured spectrophotometrically at 532 nm. The results were expressed in units of nmol/mg tissue.

**Histopathological Analysis**

Kidney tissue specimens excised from the rats were trimmed to a volume of 1.5 cm3 and placed into tissue processing cassettes. In line with routine histological tissue processing, tissue processing cassettes were subjected to fixation by being kept in a 10% formalin solution (Merck KGaA, Darmstadt, Germany) for 24-36 hours. After the fixation procedure, kidney tissue specimens were dehydrated by being passed through ascending series of ethanol (Merck KGaA, Darmstadt, Germany) using a tissue processor (Shandon Citadel 2000, Thermo Scientific Inc., Germany) and mordanted by being kept in two series of xylol (Merck KGaA, Darmstadt, Germany). In the next stage, kidney tissue specimens were embedded in paraffin blocks using soft and hard paraffin (Merck KGaA, Darmstadt, Germany). Sections of 4-5 µm were obtained from the resulting kidney tissue specimens using a rotary microtome (Leica RM2525, Leica Biosystems, Germany). The sections were stained with Masson Goldner trichrome (Merck, Darmstadt, Germany) using a histological stainer (Leica Biosystems, 5020ST, Germany).

**Immunohistochemical Analysis**

Sections of 2-3µm obtained from paraffin blocks of kidney tissue were incubated with Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) primary antibody (ab18487, Abcam, UK) and secondary antibody (Goat Anti-Rabbit IgG H&L HRP, ab205718, Abcam, UK). Kidney tissue sections and primary and secondary antibodies were incubated for 60 minutes using the Bond MAX IHC/ISH (Leica Biosystems, Australia) device. After incubation, sections of kidney tissue were stained with diaminobenzidine chromogen solution (Ultra Viem, Abcam,
United Kingdom) for visualization under a light microscope. In the last stage, the tissues were counterstained with Harris Hematoxylin (Merck KGaA, Darmstadt, Germany) and mounted with an appropriate mounting solution.

**Semi-quantitative analysis**

In histopathological evaluation, a renal pathological damage score (RPDS) was calculated for kidney tissue sections in consideration of findings of tubular necrosis, tubular debris accumulation, and vascular congestion according to studies of nephrotoxicity based on experimental animals (Table 1) (19,20). Twenty different regions per section were evaluated by two histopathologists blinded to the study groups.

### Table 1. Renal Pathological Damage Score (RPDS).

<table>
<thead>
<tr>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular Necrosis Score (Acording to Necrotic Tubular Epithelial Cells)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>≤5%</td>
</tr>
<tr>
<td>1</td>
<td>≤25%</td>
</tr>
<tr>
<td>2</td>
<td>≤50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;51%</td>
</tr>
<tr>
<td>Tubular Debris</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>≤5%</td>
</tr>
<tr>
<td>1</td>
<td>≤25%</td>
</tr>
<tr>
<td>2</td>
<td>≤50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;51%</td>
</tr>
<tr>
<td>Vascular Congestion</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>≤5%</td>
</tr>
<tr>
<td>1</td>
<td>≤25%</td>
</tr>
<tr>
<td>2</td>
<td>≤50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;51%</td>
</tr>
</tbody>
</table>

Cells showing TUNEL positivity were scored using immunohistochemical methods as shown in Table 2. Twenty different regions per section were evaluated by two histopathologists blinded to the study groups.

### Table 2. Immun-Positivity Score.

<table>
<thead>
<tr>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤5%</td>
</tr>
<tr>
<td>1</td>
<td>≤25%</td>
</tr>
<tr>
<td>2</td>
<td>≤50%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;51%</td>
</tr>
</tbody>
</table>

**Statistical Analysis** All data obtained from biochemical analyses, histopathological damage scoring, and the scoring of immunopositive cells were analyzed using the SPSS 20.0 (IBM Corp., Armonk, NJ, USA) statistics software. Data were analyzed with the Shapiro-Wilk test, Q-Q plot, Skewness-Kurtosis, and Levene’s tests.

### Table 4. Renal Pathological Damage Score (RPDS, median-25%-75% interquartile range)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Tubular Necrosis</th>
<th>Tubular Debris Accumulation</th>
<th>Vascular Congestion</th>
<th>RPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
<td>0(0-0)</td>
</tr>
<tr>
<td>CCL4</td>
<td>2(2-2)*</td>
<td>2(2-2)*</td>
<td>2(2-2)*</td>
<td>6(6-7)*</td>
</tr>
<tr>
<td>CCL4+Dex</td>
<td>1(1-1)abc</td>
<td>1(0-1)abc</td>
<td>0(0-1)abc</td>
<td>2(1-3)ab</td>
</tr>
</tbody>
</table>

* p<0.001; versus Control group,  
  ** p<0.001; versus CCL4 group,  
  *** p<0.001; versus CCL4 group,  
  **** p<0.001; versus Control group,  
  Kruskal Wallis/Mann Whitney U test with Bonferroni corrections

CCL4, Carbon tetrachloride.

Parametric biochemical data obtained from the analyses were calculated as mean + standard deviation. Parametric data were analyzed with One-way ANOVA and post-hoc Bonferroni test. Non-parametric histopathological and semi-quantitative data were calculated as median, 25%, and 75% interquartile values. Differences between the groups were analyzed with the non-parametric Kruskal Wallis test and the post hoc Mann Whitney U test with Bonferroni correction. (p<0.05 was considered significant).

**RESULTS**

**Biochemical Analysis**

Kidney tissue sections of the CCI4 group showed higher MDA levels compared to the control group (Table 3, p=0.001). In contrast, in the CCI4+DEX group, we observed a reduction in MDA levels compared to the CCI4 group (Table 3, p=0.001).

### Table 3. Biochemical Analysis Results (mean±standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>MDA (nmol/mg tissue)</th>
<th>GSH (nmol/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.65±0.22</td>
<td>48.30±1.46</td>
</tr>
<tr>
<td>CCL4</td>
<td>1.23±0.25*</td>
<td>34.16±2.84*</td>
</tr>
<tr>
<td>CCL4+Dex</td>
<td>0.82±0.77b</td>
<td>46.53±1.43b</td>
</tr>
</tbody>
</table>

* p<0.001; versus Control group,  
  b p<0.001; versus CCL4 group,  
  Kruskal Wallis/ Bonferroni test

Cells showing TUNEL positivity were scored using immunohistochemical methods as shown in Table 2. Twenty different regions per section were evaluated by two histopathologists blinded to the study groups.

**Statistical Analysis** All data obtained from biochemical analyses, histopathological damage scoring, and the scoring of immunopositive cells were analyzed using the SPSS 20.0 (IBM Corp., Armonk, NJ, USA) statistics software. Data were analyzed with the Shapiro-Wilk test, Q-Q plot, Skewness-Kurtosis, and Levene’s tests.

**Histopathological Analysis** Masson Goldner-stained kidney tissues of the control group showed normal glomeruli and proximal and distal tubules in the cortical region. We also observed normal epithelial cells in Henle's tubules in the medullary region (Table 4, Figure 1a-b, RPDS: 0(0-1)). In contrast, in the CCI4 group, there were widespread necrotic epithelial cells and debris accumulation in renal tubules in the cortical region, especially in proximal tubules. Similarly, we observed widespread debris accumulation in Henle's tubules in the medullary region. There was also extensive vascular congestion (Table 4, Figures 1c-d, RPDS: 6(6-7)). Meanwhile, in the CCI4 +DEX group, we determined fewer necrotic epithelial cells and less vascular congestion in renal tubules in the cortical and medullary regions (Table 4, Figures 1e-f, RPDS: 2(1-3)).
Figure 1. Representative light microscopic image of Masson Goldner-stained kidney tissue.
(Proximal tubule p), Distal Tubule (d), Glomerulus (G) A(x20)-B(x40) Control Group: Kidney tissue sections showing glomeruli and renal tubules of normal structure. Especially in proximal tubules, marked brush-border structure (tailed arrow) in epithelial cells (arrow) can be seen (RPDS: 0(0-1)). C(x20)-D(x40) CCL₄ Group: Kidney tissue sections showing tubular necrosis (spiral arrow), tubular debris accumulation (asterisk) and vascular congestion (c). Debris accumulation is observed especially in Henle's tubules in the medullary region (RPDS: 6(6-7)). E(x20)-F(x40) CCL₄+Dex Group: Sections of kidney tissue showing reduced tubular necrosis and tubular debris accumulation as well as a decrease in vascular congestion (RPDS: 2(1-3))
Immunohistochemical Analysis

Cortical glomerular, proximal, and distal tubular epithelial cells in kidney tissue sections of the control group were found to be TUNEL-immunonegative. We also determined the epithelial cells in Henle’s tubules in the medullary region to be TUNEL-immunonegative (Table 5, p=0.001, Figure 2, TUNEL positivity score: 0(0-1)). In kidney tissue sections of the CCl4 group, an increase was observed in necrotic cells showing extensive immunopositivity in renal tubules in the cortical region and epithelial cells in Henle’s tubules in the medullary region (Table 5, p=0.001, Figure 2, TUNEL positivity score: 2(1-2)). In contrast, in the CCl4 +DEX group, we observed a decrease in necrotic cells showing TUNEL positivity compared to the CCl4 group (Table 5, p=0.001, Figure 2, TUNEL positivity score: 1(0-1)).

Table 5. Immuno-Histochemical Analysis Score (RPDS, median-25%-75% interquartile range)).

<table>
<thead>
<tr>
<th>Group</th>
<th>TUNEL Positivity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0(0-1)</td>
</tr>
<tr>
<td>CCl4</td>
<td>2(1-2)</td>
</tr>
<tr>
<td>CCl4+Dex</td>
<td>1(0-1)</td>
</tr>
</tbody>
</table>

*p<0.001; versus Control group,
*p<0.026; versus Control group,
*p<0.001; versus CCl4 group,
Kruskal Wallis/Mann Whitney U test with Bonferroni corrections

CCl4, Carbon tetrachloride.

Figure 2. Representative light microscopic image of apoptotic cells in kidney tissue sections marked with the TUNEL method.

A(x20)-B(x40) Control Group: Kidney tissue sections showing immunonegative epithelial cells (arrow) in proximal, distal, and Henle’s tubules of normal structure (TUNEL positivity score: 0(0-1)). C(x20)-D(x40) CCl4 Group: Extensive immunopositivity in proximal and distal tubular epithelial cells in the cortical region in kidney tissue sections. Also, extensive immunopositivity in epithelial cells of Henle’s tubules in the medullary region. (TUNEL positivity score: 2(1-2)). E(x20)-F(x40) CCl4+Dex Group: A decrease in immunopositivity can be seen in tubular epithelial cells in the cortical and medullary regions in kidney tissue (TUNEL positivity score: 1(0-1)).
DISCUSSION

The presented study shows that CCl4 causes histopathological and biochemical damage to tubules, particularly to proximal tubules, in kidney tissue; while dexmedetomidine pretreatment reverses this damage, restoring glomerular and tubular architecture, as well as reducing the number of necrotic cells and shifting the oxidant/antioxidant status in favor of antioxidants. In the literature, various studies have shown the toxicities induced by CCl4 in the kidneys. Data from the literature support the damage caused to kidney tissue by CCl4 in the present study. Studies in the literature report that the primary change caused by CCl4 in the kidney tissue is observed in the mitochondria, followed by cell swelling and smooth endoplasmic reticulum proliferation (11). Following the administration of CCl4, the cell exhibits changes in calcium homeostasis and signs of early damage such as impairment of protein synthesis via ribosomal RNA hypomethylation (21). In its radical form, CCl4 can bind to cellular lipids and proteins (22). Adewole et al. reported that CCl4 caused kidney changes such as necrosis and brush-border loss in epithelial structure, infiltration, edema, and glomerular hypercellularity, which may lead to renal dysfunction (23). In addition to these, interstitial fibrosis and infiltration, glomerular and tubular degenerations (vacularization in tubular cells, atrophy) in the kidney have also been demonstrated (10). The fibrosis induced in the kidneys was also found in perivascular areas (24). CCl4 was also observed to generate renal vein congestion and degeneration in the renal tubules (25). The literature also presents CCl4-related damage in renal glomeruli and Bowman’s capsule (12). Similarly, in the present study, we observed tubular necrosis, debris accumulation in renal tubules, and vascular congestions. Differently from Adewole et al., the finding of fibrosis was not determined in this study. This may be attributed to the fact that our study investigates acute kidney injury and does not encompass a three-month period that is necessary for fibrosis due to not focusing on chronic effects.

Although the damage mechanism underlying the nephrotoxicity caused by CCl4 is not completely known, current studies suggest that oxidative stress and apoptosis are involved (7–10,12). Accordingly, a study by Hismiogullari et al. reported an increase in the number of kidney cells showing TUNEL-positive staining, which is a marker of apoptosis, in the CCl4 group compared to the control group (26). Similarly, in the present study, findings of apoptosis in epithelial cells as determined by TUNEL positivity were present primarily in proximal tubules as well as in distal tubules and Henle’s tubules.

CCl4 is described to not only elevate oxidative damage markers but also cause DNA fragmentation, and subcellular damage via lipid peroxidation, and result in an increase in the protein content of kidney tissue (8). In urine, high levels of protein, elevated albumin levels, and proteinuria associated with a decrease in serum levels of these parameters were shown (27). Makni et al. determined high levels of protein oxidation in addition to oxidative damage and histopathological findings (9), CCl4 also extensively increases inflammatory cytokines such as IL-1β, IL-2, and TNF-α (12). In a study conducted by Habashy et al., CCl4 was described as causing morphological changes in kidney tissue by inducing the production of necroinflammatory mediators such as NF-κB, iNOS, COX-2, and TNF-α (25).

Dexmedetomidine (DEX), a highly selective alpha-2 receptor agonist, is preferred due to its minimal effect on respiration and safety (14). DEX counters ischemia/reperfusion by reducing the levels of creatinine and TNF-α while increasing the levels of SOD in kidney tissue; it is described to exert a protective effect by reducing the histopathological damage score and tubular damage (28). It was shown to exert an antiapoptotic effect by ameliorating stress-induced apoptosis and to reduce MDA levels in response to acute stress-induced injury in the kidneys (29). Moreover, DEX was reported to exert a protective effect against stress-induced damage by preventing oxidative damage, elevating SOD, GSH, and CAT levels, and stabilizing prooxidative and antioxidant enzymes in lipopolysaccharide-induced acute kidney injury (30). In another study on lipopolysaccharide-induced kidney injury, DEX was demonstrated to reverse the histopathological damage in the renal cortex and medulla, reduce oxidative stress, improve renal function, and alleviate acute kidney injury by inhibiting the AP-1 and NF-κB signaling pathways (31). Similarly, in the present study, we observed that MDA levels decreased and GSH levels increased, suppressing oxidative stress, as well as a decrease in tubular necrosis and tubular debris accumulation in kidney tissue.

This study has certain limitations. Firstly, this is a pilot animal model study focused on the determination of the oxidative stress status and the presence of necrosis based on TUNEL positivity in acute kidney injury induced by CCl4 toxicity and the effects of dexmedetomidine. Thus, it cannot be applied to clinical use. Accordingly, it needs to be supported by clinical studies. Since evidence from the literature indicates that DEX treatment exerts a greater organ-protective effect when it is administered as a pretreatment, in the present study, we administered DEX before CCl4 exposure. However, CCl4 exposure may not always be a condition that can be predicted. In addition, in the present study, we did not measure albumin and protein excretion in urine or glomerular filtration rates. Future studies that will determine these parameters will provide further information. Our study examined the acute effects of CCl4 and DEX. Long-term studies should be performed to identify the effects that will develop in the chronic period. Our study needs to be supported by other molecular studies that will involve mitochondrial and intracellular calcium levels.

CONCLUSION

The present study shows that CCl4 administration causes biochemical and histopathological damage to kidney tissues in a rat model, leading to necrosis and reducing the levels of antioxidants. However, the administration of dexmedetomidine before CCl4 protected the renal glomerular and tubular architecture and restored the antioxidant status. Dexmedetomidine yielded an antiapoptotic, antioxidant effect by ameliorating stress-induced apoptosis and reducing the levels of necrosis and inflammation in the kidneys. Oxidative stress, improvement in renal function, and alleviation of acute kidney injury were observed in the DEX group compared to the control group. Future studies should focus on the effects of DEX treatment on the acute phase and long-term studies should be performed to identify the effects that will develop in the chronic period. Our study needs to be supported by other molecular studies that will involve mitochondrial and intracellular calcium levels.

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Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Author Contributions: ED, TM, LT: Designed and directed the study. ED, TM, ZST, KA, AY: Data collection, analysis, and interpretation of results. ED, TM: Wrote the final draft of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study. This study was approved by the Experimental Animal Research Ethics Committee of recep Tayyip Erdogan University, Rize, Turkey (Decision: 02-05.2022 with the approval number 2022-23). The relevant rules and regulations carried out all methods applied.

REFERENCES


