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RESEARCH

Investigation of the protective effect of selenium supplementation on renal function in cisplatin-administered rats

Sisplatin uygulanan sıçanlarda selenyum takviyesinin böbrek fonksiyonu üzerindeki koruyucu etkisinin araştırılması

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Abstract

Purpose: Selenium is an important antioxidant and anticarcinogen with the ability to protect cells from oxidative stress, a significant marker of cisplatin-induced toxicity. This study aimed to reveal the effect of selenium on free radicals in cisplatin-induced nephrotoxicity by examining changes in creatinine, neutrophil gelatinase-associated lipocalin (NGAL), and galectin-3, which are associated with kidney damage.

Materials and Methods: Twenty-four Wistar albino rats, aged 60 days, were equally divided into four groups: control, cisplatin, selenium, and cisplatin+selenium. The experiment started on the 39th day after the rats were born. Controls were intraperitoneally administered a single dose of physiological saline. Rats in the selenium and cisplatin+selenium groups were administered 1 mg/kg of selenium by gastric gavage per day for 21 days. The rats in the cisplatin and cisplatin+selenium groups were intraperitoneally administered 7.5 mg/kg of cisplatin on the 57th day. The experiment was terminated 3 days after single-dose administration. Tissue samples were analyzed using the ICP-MS method for selenium, the biochemical method for plasma creatinine, and the ELISA method for NGAL and galectin-3.

Results: Kidney tissue selenium levels were significantly higher in the selenium-supplemented groups (control;146.8 ± 10.8 ng/dl, selenium;520.2 ± 31.2 ng/dl, cisplatin;140 ± 6.4 ng/dl; cisplatin + selenium; 363.4 ± 33.6 ng/dl). Plasma creatinine levels were statistically significantly higher in the cisplatin-administered groups (control; 0.32 ± 0.01 mg/dl, selenium; 0.32 ± 0.01 mg/dl, cisplatin; 0.47 ± 0.02 mg/dl; cisplatin + selenium; 0.45 ± 0.04). There was no difference in kidney tissue NGAL levels; however, galectin-3 levels were significantly increased in the cisplatin group compared with the other groups. This increase was lower in the cisplatin+selenium

Öz

Amaç: Selenyum, hücreleri cisplatin kaynaklı toksisitenin önemli bir belirteci olan oksidatif stresten koruma yeteneğine sahip önemli bir antioksidan ve antikarsinojendir. Bu çalışma, böbrek hasarı ile ilişkili kreatinin, nötrofil jelatinaz ile ilişkili lipokalin (NGAL) ve galektin-3'teki değişiklikleri inceleyerek, cisplatin kaynaklı nefrotoksisitede selenyumun serbest radikaller üzerindeki etkisini ortaya çıkarmayı amaçlamıştır.

Gereç ve Yöntem: 60 günlük 24 Wistar albino sıçan eşit olarak dört gruba ayrıldı: kontrol, cisplatin, selenyum ve cisplatin+selenyum. Deney, sıçanların doğumundan sonraki 39. günde başladı. Kontrollere intraperitoneal olarak tek doz fizyolojik salin uygulandı. Selenyum ve cisplatin+selenyum gruplarındaki sıçanlara 21 gün boyunca günde 1 mg/kg selenyum gastrik gavaj yoluyla verildi. Cisplatin ve cisplatin+selenyum gruplarındaki sıçanlara 57. günde 7,5 mg/kg cisplatin intraperitoneal olarak uygulandı. Deney, cisplatin uygulamasından üç gün sonra sonlandırıldı. Doku örnekleri selenyum için ICP-MS yöntemi, plazma kreatinin için biyokimyasal yöntem, NGAL ve galektin-3 için ELISA yöntemi kullanılarak analiz edildi.

Bulgular: Böbrek dokusu selenyum düzeyleri selenyum takviyesi verilen gruplarda anlamlı derecede yüksekti (kontrol;146.8 ± 10.8 ng/dl, selenyum;520.2 ± 31.2 ng/dl, cisplatin;140 ± 6.4 ng/dl, cisplatin + selenyum; 363.4 ± 33.6 ng/dl ()). Plazma kreatinin seviyeleri cisplatin uygulanan gruplarda istatistiksel olarak anlamlı derecede yüksekti (kontrol; 0.33 ± 0.01 mg/dl, selenyum; 0.30 ± 0.01 mg/dl, cisplatin; 0.47 ± 0.02 mg/dl, cisplatin + selenyum; 0.45 ± 0.04). Böbrek dokusunda gruplar arasında NGAL düzeyinde fark bulunmazken, Galectin-3 düzeyinde diğer gruplara göre cisplatin grubunda artış görüldü. Bu artış cisplatin+selenyum grubunda cisplatin

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group than in the cisplatin group. Heart tissue NGAL and galectin-3 levels were higher in the cisplatin group.
Conclusion: Selenium supplementation may have a healing effect on the nephrotoxicity and cardiotoxicity caused by cisplatin, as indicated by changes in creatinine, NGAL, and galectin-3 levels.
Keywords:. Kidney, heart, cisplatin, selenium, NGAL, galectin-3

grubuna göre daha düşüktü. Kalp dokusu NGAL ve galektin-3 düzeyleri cisplatin grubunda daha yüksekti.
Sonuç: Selenyum takviyesinin, kreatinin, NGAL ve galektin-3 seviyelerindeki değişikliklerden de anlaşılacağı üzere cisplatinin neden olduğu nefrotoksisite ve kardiyotoksisite üzerinde iyileştirici bir etkisi olabilir.
Anahtar kelimeler: Böbrek, kalp, cisplatin, selenyum, NGAL, galektin-3

INTRODUCTION

Because of the crucial function of the kidneys in the elimination process of medications within the human body, certain drugs might be nephrotoxic to this organ. This group encompasses chemotherapy medications primarily used for the treatment of cancer. Cisplatin, a chemotherapeutic agent used in cancer treatment, induces nephrotoxicity by impairing both tubular secretion and glomerular filtration, primarily affecting the proximal and distal tubules of the kidneys[1,2]. Cisplatin reduces the activity of antioxidant enzymes and ROS in kidney tissue[3]. Cisplatin-induced toxicity is closely linked to oxidative stress, a condition arising from an imbalance between ROS generation and their elimination by antioxidant defense mechanisms[4].

In addition to selenium being an essential element for the human body[5], it has recently been identified as an anticarcinogen[6]. However, there are only a limited number of studies on the protective effect of selenium on the nephrotoxicity caused by cisplatin. Two randomized controlled studies showed that the effect of nephrotoxicity and bone marrow suppression in cisplatin-containing chemotherapy was reduced by selenium treatment and that selenium had protective properties[7,8]. Another recent study reported that selenium partially reduced the side effects of cisplatin by selectively protecting normal cells from the DNA-damaging effects of chemotherapeutic agents[9]. Various studies investigating cisplatin-induced toxicity have analyzed the levels of routinely examined and well-known indicators of oxidative stress, such as catalase, superoxide dismutase, malondialdehyde, and glutathione peroxidase, in an attempt to reveal the status of oxidative damage.

Galectin-3 is localized in the cytoplasm and nucleus[10]. Galectins play an important and complex role in intracellular pathways and disease mechanisms[11]. Galectin-3, a versatile protein with various biological functions, plays a pivotal role in acute and chronic inflammation, outshining its other roles in processes like fibrosis, angiogenesis, and apoptosis[12]. Animal studies have shown an increase in galectin-3 levels after myocardial infarction[13] in the atherosclerotic process[14] and after kidney damage[15]. NGAL is a protein from the lipocalin family. It has been found to activate nephron formation in the embryonic kidney, is rapidly and largely induced in renal failure, and has renal protective activity[16,17]. Recently, NGAL has been proven to be one of the earliest markers of ischemic or nephrotoxic damage in the kidney[18,19]. In addition, studies have shown that NGAL can be detected in the blood and urine of people immediately after acute heart failure[18]. Although NGAL and galectin-3 are proteins frequently studied as biomarkers in kidney damage and failure and heart diseases, the number of studies using NGAL and galectin-3 as biomarkers in cisplatin-induced nephrotoxicity and cardiotoxicity is limited[20]. In addition, the antioxidant effect of selenium has never been studied with NGAL and galectin-3 biomarkers in the nephrotoxicity and cardiotoxicity caused by cisplatin. Therefore, considering the information given above, the hypothesis of the study is that selenium may have a protective effect on the nephrotoxicity and cardiotoxicity caused by cisplatin and that this effect may change the levels of NGAL and galectin-3. This study will contribute to the literature by investigating the therapeutic role of selenium in cisplatin-induced toxicity by examining changes in NGAL and galectin-3 levels.

MATERIALS AND METHODS

Experimental animals

In this study, 24 60-day-old male Wistar albino rats produced at Selçuk University Experimental Medicine Application and Research Center were used. The rats were housed in individual solid-bottom plastic cages on sawdust bedding at a constant temperature of 21 °C and humidity of 55% with 12-h periods of light–dark exposure. The animals were allowed access to standard rat chow and

water ad libitum. A 7-day period of acclimatization was used. Healthy rats weighing 180-200 g were randomly selected and divided into four groups: control group, cisplatin group, cisplatin+selenium group, and selenium group.

Procedure

This study adhered to the guidelines outlined in the Guide for the Care and Use of Laboratory Animals to ensure the protection of animal rights. Approval was obtained from the Animal Experiments Ethics Committee of Selcuk University Experimental Medicine Application and Research Center with the decision number 2023-23, dated April 28, 2023. The use of unnecessary experimental animals was avoided, and ethical principles were followed to prevent the infliction of pain on the experimental subjects. The researchers who performed the experimental procedure have a PhD degree in Physiology or Biochemistry and a Laboratory Animal Use Certificate.

Administration of cisplatin and selenium

Control group (n = 6): Only a single dose of 2 ml of serum physiological was intraperitoneally administered to the rats in the control group on the same day as cisplatin administration in two of the experimental groups.

Selenium group (n = 6): Selenium was administered at a dose of 1 mg/kg by gastric gavage (dissolved in 1 ml physiological saline) every day for 21 days[21-22]. Selenium (sodium selenite) (CAS;10102-18-8) was obtained from Thermo Scientific Chemicals.

Cisplatin group (n = 6): A single dose of 7.5 mg/kg of cisplatin was intraperitoneally administered to the rats in this group only on the 57th day[23] (Koçak Farma Co. İstanbul, Turkey, 50 mg/100 mL, intravenous).

Cisplatin+selenium group (n = 6): A single dose of cisplatin was intraperitoneally administered at 7.5 mg/kg on the 57th day, and selenium was administered at 1 mg/kg by gastric gavage (dissolved in 1 ml physiological saline) every day for 21 days[21-23]

Analysis of kidney tissue selenium levels

Kidney tissue samples were analyzed for selenium levels at the Advanced Technology Research and Application Center of Selçuk University using the inductively coupled plasma–mass spectrometry method. After the samples were weighed, 2 ml of hydrogen peroxide and 5 ml of nitric acid were added to them. Microwave heating was performed at 1600 Watts at 100°C for 120 min. Then, the resulting liquid was reduced to 50 mL with ultrapure water.

Analysis of plasma creatinine levels

Blood samples collected intracardially from the anesthetized rats were centrifuged at 3,500 g for 10 min. Serum samples obtained after centrifugation were transferred to Eppendorf tubes and stored at 80°C until analysis. The concentration of creatinine in blood plasma was measured using Roche Cobas kits and a Roche 8000 Cobas C 702 analyzer. The analyzer was calibrated and verified using its own calibration solution.

Analysis of NGAL and Galectin-3 levels

Following the homogenization of the tissues that were stored at 80°C, the samples were treated with 0.01 M phosphate-buffered saline and placed in 96-well plates prepared for each parameter kit. The biotin antibody and horseradish peroxidase conjugate were added, and the samples were incubated at 37 °C. After adding the substrate reagent, each well was analyzed spectrophotometrically for both galectin-3 and NGAL at a wavelength of 450 nm using an enzyme-linked immunosorbent assay device (Clariostar Microplate Reader, United Kingdom).

Statistical analysis

One-way ANOVA was used to analyze galectin3, selenium, and creatinine levels in blood, which showed normal distribution for both kidney and heart tissue, and student Newman-Keuls multiple comparison test was used to compare between groups. Kruskal-Wallis test was used to analyze non-normally distributed NGAL levels for both kidney and heart tissue, and Dunn's multiple comparison test was used to compare between groups. In this study, using Gpower 3.1.9.2, the sample size was determined to be 24, with a 95% confidence interval (1-α), 90% test power (1-β), effect size d = 0.80, and anova-test in multiple groups. All statistical analysis performed on Sigma Stat 3.5 software and Origin Pro 9.1 software was used to draw graphs. The significance level was set as $p < 0.05$.

RESULTS

In the ICP-MS analysis of kidney tissue selenium, the mean value was determined to be 146.8 ± 10.8 ng/dl in the control group, 520.2 ± 31.2 ng/dl in the

selenium group, 140 ± 6.4 ng/dl in the cisplatin group, and 363.4 ± 33.6 ng/dl in the cisplatin+selenium group, indicating statistically significant differences between the groups ($p < 0.001$). In addition, the selenium level was lower in the cisplatin+selenium group than in the selenium group, despite the same amount of selenium supplementation ($p < 0.002$) (Fig. 1).

In the biochemical analysis of plasma creatinine, the mean value was determined to be 0.33 ± 0.01 mg/dl in the control group, 0.30 ± 0.01 mg/dl in the selenium group, 0.47 ± 0.02 mg/dl in the cisplatin group, and 0.45 ± 0.04 mg/dl in the cisplatin+selenium group, indicating statistically significant differences between the groups ($p < 0.001$). Creatinine levels were higher in the cisplatin and cisplatin+selenium groups than in the control and selenium groups ($p < 0.003$) (Fig. 2).

While there was no statistically significant difference in the NGAL levels of kidney tissue between the control and cisplatin-treated rats, the NGAL level tended to be higher in the cisplatin group, although this increase was not statistically significant ($p > 0.05$). The concentration of galectin-3 in kidney tissue was significantly higher in the cisplatin group than in the control and selenium groups ($p < 0.001$). Interestingly, the galectin-3 level was also significantly lower in the cisplatin+selenium group than in the cisplatin group ($p < 0.001$) (Fig. 3).

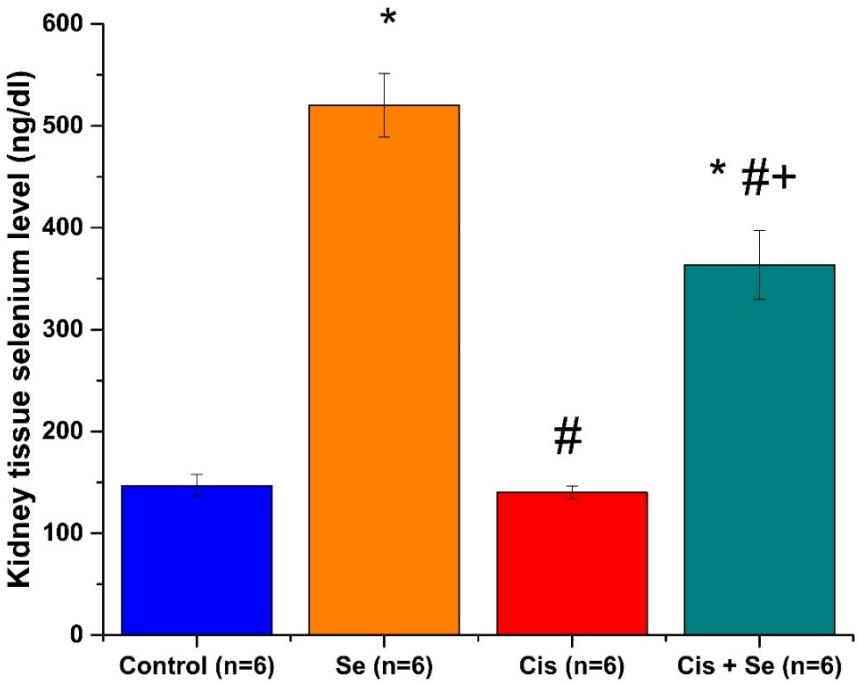

Figure 1. Kidney tissue selenium levels of the rats in the control and experimental groups.

Values are given as mean ± standard error (n = 6). * indicates a significant difference compared to the control group. # indicates a significant difference compared to the selenium group. + indicates a significant difference compared to the cisplatin group. Selenium group (se), Cis group (cis), Cisplatin+selenium group (cis+se).

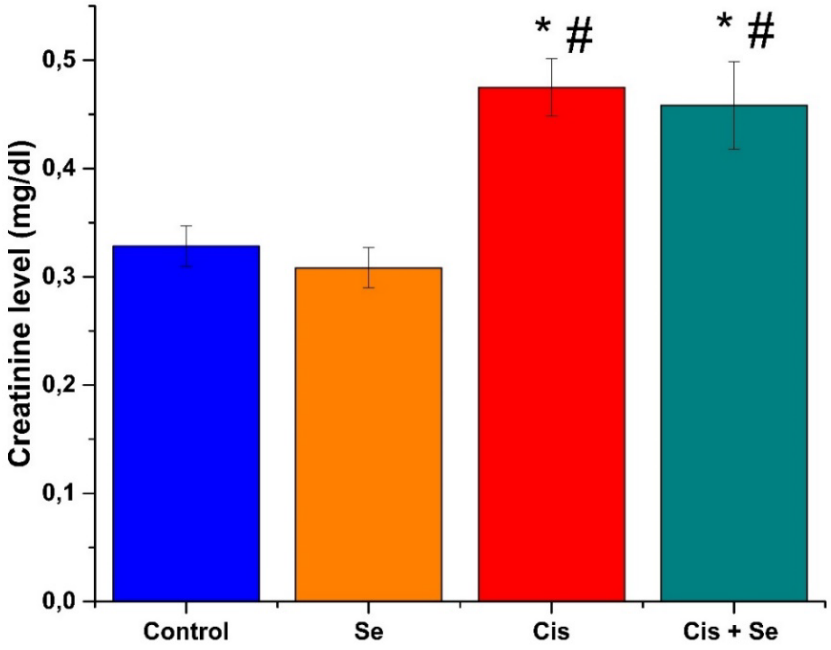

Figure 2. Kidney plasma creatinine levels of the rats in the control and experimental groups.

Values are given as mean ± standard error (n = 6). * indicates a significant difference compared to the control group. # indicates a significant difference compared to the selenium group. Selenium group (se), Cis group (cis), Cisplatin+selenium group (cis +se).

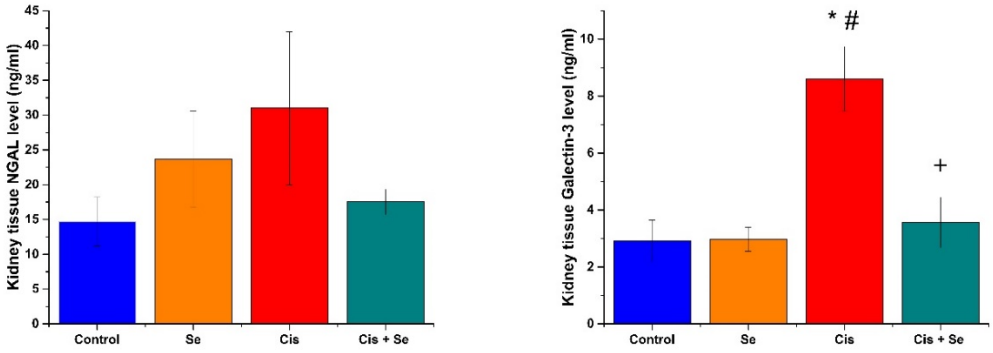

Figure 3. Kidney tissue neutrophil gelatinase-associated lipocalin (NGAL) and galectin-3 levels of the rats in the control and experimental groups.

Values are given as mean ± standard error (n = 6). * indicates a significant difference compared to the control group. # indicates a significant difference compared to the selenium group. Selenium group (se), Cis group (cis), Cisplatin+selenium group (cis+se).

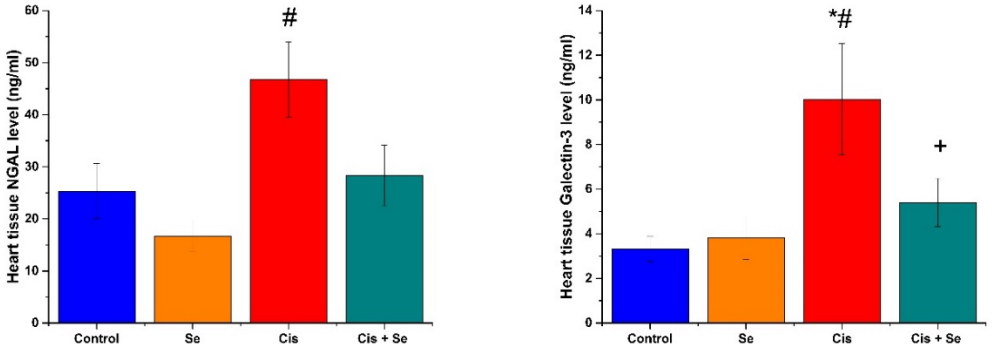

Figure 4. Neutrophil gelatinase-associated lipocalin (NGAL) and galectin-3 levels of the rats in the control and experimental groups.

Values are given as mean ± standard error (n = 6). * indicates a significant difference compared to the control group. # indicates a significant difference compared to the selenium group. + indicates a significant difference compared to the cisplatin group. Selenium group (se), Cis group (cis), Cisplatin+selenium group (cis+se).

Although the NGAL level in heart tissue did not differ significantly between the cisplatin-treated and control groups, the NGAL level was higher in the cisplatin group than in the selenium group ($p<0.016$). The amount of galectin-3 was higher in the cisplatin group than in the control and selenium groups ($p < 0.034$). Notably, the galectin-3 level was lower in the cisplatin+selenium group compared to the cisplatin group ($p < 0.043$) (Fig. 4).

DISCUSSION

In this study, we aimed to determine the effects of selenium on toxicity and changes in renal biomarkers, namely creatinine, NGAL, and galectin-3, after a single dose of 7.5 mg/kg of intraperitoneal cisplatin administration in rats. Although the mechanisms underlying the nephrotoxic and cardiotoxic effects of cisplatin have not yet been fully elucidated, there are studies showing that oxidative stress plays an important role by increasing free radical production[24-26]. For this reason, many substances with known antioxidant effects (N acetyl cysteine, curcumin, betaine, E vitamin.) has been used to reduce this toxicity[27-29]. Selenium was preferred in our study because it contributes to the regulation of enzymatic antioxidant defense. It is known that selenium deficiency can increase free oxygen radicals in body tissues, and there are limited studies on kidney and heart damage[30,31]. For this reason, the findings of this study are important.

Because cisplatin is predominantly excreted by the kidneys, it is considered the primary target organ for cisplatin toxicity[32]. Nephrotoxic damage caused by cisplatin is indicated by elevated creatinine levels. The dose we used to induce nephrotoxicity was 7.5 mg/kg, which resulted in an increase in the creatinine levels of the cisplatin group, consistent with studies in the literature using the same dose[33-35] our study, supporting the literature, creatinine values were observed to increase in the cisplatin and cisplatin+selenium groups compared with the control and selenium groups. Creatinine results also demonstrated the nephrotoxic effect of cisplatin.

NGAL expression in several human tissues, such as the kidney, liver, lung, and heart, significantly increases in response to acute injury to these organs[36]. NGAL production is significantly stimulated by both ischemic and toxic effects[37-39]. Animal studies have shown that NGAL is one of the genes highly upregulated in renal dysfunction[40]. In a study evaluating patients receiving cisplatin treatment, Gaspari et al. found that the level of NGAL in the urine samples of patients increased on the second day after cisplatin administration[41]. In other studies, plasma and urine NGAL levels have been reported to

be elevated following acute kidney injury and chronic kidney disease in humans[20,42,43]. Urine and plasma NGAL levels have also been investigated in animal models[30]. We conducted our study directly on kidney tissue samples, not urine samples, and found that NGAL levels measured in kidney tissue increased in the cisplatin-administered group and decreased in the cisplatin+selenium group, whereas no significant distinctions emerged between the groups. The heart is a organ most affected by renal dysfunction[18,44]. Research has demonstrated that NGAL not only serves as an indicator of kidney damage but also as a potent predictor of various heart-related complications[44]. An earlier study revealed elevated serum NGAL levels in patients with acute and chronic heart failure following myocardial infarction[45]. In a study by Güntürk et al., the development of cardiotoxicity was shown by creatine kinase (CK) and CK-MB levels increasing approximately two to three times in rats administered a single dose of 10 mg/kg of cisplatin compared with the control group[25]. In another study using the same dose as in our investigation, cisplatin administration similarly caused a significant increase in low-density lipoprotein and CK-MB levels, as well as a concomitant deterioration in the histological architecture, i.e., the structure and function, of the heart[46]. All these findings explain the possible development of cardiotoxicity as a result of cisplatin administration in our study, which was indicated by the high NGAL level in the cisplatin group. In our study, although cisplatin increased the NGAL level in heart tissue, the NGAL level in the cisplatin+selenium group did not exhibit a significant difference from that in the control group. This decrease observed in the group receiving selenium supplementation along with cisplatin suggests that selenium supplementation may be effective in reducing cisplatin toxicity, and future studies are needed to better explain this.

Galectin-3 is a 30-kDa lectin that plays a role in many pathophysiological events, including kidney injury and fibrosis[47]. Galectin-3 is primarily expressed intracellularly by inflammatory cells and neutrophils, including macrophages, mast cells, and fibroblasts[11,15]. It has been reported that there is an increase in the expression of galectin-3, mRNA, and protein following injury in renal ischemia/reperfusion[47,48]. In a cisplatin-induced acute renal failure model, Li et al. reported increased renal galectin-3 expression on day 3, associated with the overexpression of protein kinase C-α, cell apoptosis, and collagen type I synthesis[49]. Recent research has implicated galectin-3 in the pathogenesis of heart failure, with animal models demonstrating its upregulation specifically in decompensated heart failure compared with compensated heart failure[14,50]. In our study, consistent with the literature, galectin-3 levels were found to be higher in the cisplatin group in both kidney and heart tissue samples. However, in the cisplatin+selenium group, galectin-3 levels decreased significantly in both examinations.

Although the effects of selenium on cisplatin-induced nephrotoxicity have been widely studied, the results are still conflicting. In some studies, it has been found that selenium does not have protective effects in adult Wistar rats[22]. However, in the study conducted by Nazıroğlu et al., Se and vitamin E were found to protect GSH levels, increase the synthesis of glutathione peroxidase (GPx), prevent the increase in malondialdehyde (MDA) levels, and prevent the increase in malondialdehyde (MDA) levels in rats administered cisplatin. Therefore, they have been shown to be effective in reducing nephrotoxicity[51]. Our study supports the notion that selenium can reduce nephrotoxicity by reducing the level of galectin-3 in kidney tissue.

This study has three main limitations. First, the inclusion of only male rats in the sample limited our ability to evaluate the potential sex-dependent effects of cisplatin and selenium. Our second limitation is that because a single dose of selenium was used in our study, we did not elucidate the effects of different doses of selenium. Third, the study results were not confirmed at the molecular and histopathological levels. It has been proven in some studies that gender differences may lead to differences in cisplatin nephrotoxicity[52,53] and that men have a higher susceptibility to cisplatin-induced kidney damage than women[54]. The possible mechanism underlying the gender difference is thought to result from gender-specific regulation of renal blood flow by the renin-angiotensin system[55,56]. Because of this difference between genders, we could not confirm the role of gender difference in the effect of selenium on cisplatin nephrotoxicity and cardiotoxicity. Our first recommendation for future studies is to study both male and female rats simultaneously in experimental groups to eliminate the limitations arising from gender differences. Selenium has been applied at different doses and frequencies in the literature[6,7]

However, in these studies, the healing effect of different levels of selenium use on nephrotoxicity and cardiotoxicity was not measured using NGAL and galectin-3 biomarkers. Therefore, our second recommendation for future studies is to create experimental groups with different doses to determine the effective selenium dose. Our final recommendation for future studies is to perform molecular and histopathological analyses.

In conclusion, it is thought that selenium supplementation may have a healing effect on the nephrotoxicity and cardiotoxicity caused by cisplatin, with changes in creatinine, NGAL, and galectin-3 levels. Therefore, above suggested further studies are needed to fully explain the antioxidant effect of selenium on cisplatin toxicity.

Author Contributions: Concept/Design : MA, GA; Data acquisition: MA, GA; Data analysis and interpretation: MA, BÖ; Drafting manuscript: MA; Critical revision of manuscript: MA, GA, BÖ; Final approval and accountability: MA, GA, BÖ; Technical or material support: -; Supervision: MA, BÖ; Securing funding (if available): n/a.
Ethical Approval: This study was approved by the Animal Experiments Ethics Committee of the XXX University Experimental Medicine Application and Research Center with decision number 2023-23, dated April 28, 2023.
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Conflict of Interest: Authors declared no conflict of interest.
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