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RESEARCH

Beneficial Effects of Selenium on Kidney Injury via Nf-Kb and Aquaporin-1 Levels

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Abstract

Systemic inflammation is a serious condition that can affect various tissues and organs, such as the kidneys, and can be life-threatening. Selenium (Se) is an antioxidant and anti-inflammatory trace element. In this study, we aimed to examine the effects of Se, which has antioxidant and anti-inflammatory properties, on lipopolysaccharide (LPS)-induced kidney damage to maintain aquaporin-1 (AQP-1) levels. Four experimental rat groups ($n=8$) consisting of the control, LPS alone, LPS + Se, and Se alone were so applied for 7 consecutive days. Upon sacrifice, histopathological results, diagnostic markers of kidney functions, oxidative stress, and inflammation were analyzed. Our results showed that LPS induced mononuclear cell infiltration, cellular residue, and protein deposition in the kidney proximal tubules, and also decreased total antioxidant status levels and increased total antioxidant status and oxidative stress index values. LPS increased the level of creatinine, increased the level of Nuclear Factor kappa B, which has an important role in the inflammation process, and decreased the levels of AQP-1 due to the damage it caused. Se has shown its effect by reversing all these situations. This data suggests that Se can be used as an additive to mitigate LPS-induced toxicity in the kidney.

Keywords Aquaporin-1 · Inflammation · Kidney · Lipopolysaccharide · Selenium

Introduction

Kidney damage secondary to systemic inflammatory diseases is a dangerous and progressive scene. As a result of this damage, there is a problem in the excretion of toxic metabolites that need to be eliminated from the body, and different additional diseases may develop due to the accumulation of these toxic agents in various organs [1]. Many cellular damage mechanisms such as oxidative stress, inflammation, and apoptosis are involved in damage formation. It has been proven that antioxidant, anti-inflammatory, and antiapoptotic molecules used in recent studies can prevent this developing scene [2]. In animal experimental models, some agents, such as lipopolysaccharide (LPS), are used to mimic systemic inflammation.

LPS, composed of lipid A, core oligosaccharide, and O antigen, is a glycolipid found in the outer membrane of gram-negative bacteria [3, 4]. The interaction of LPS with cell surface receptor Toll-like receptor-4 (TLR-4) activates some intracellular mechanisms as the nuclear factor-kB (NF-kB) pathway which triggers the release of various proinflammatory cytokines such as interleukin-1beta and caspase-3 [5, 6].

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As known, inflammation causes oxidative stress results in the formation of reactive oxygen species (ROS) as superoxide anion ($O_2^{-\cdot}$), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2). These increments of ROS are tried to be balanced by intracellular and extracellular antioxidant mechanisms [7]. Many cell components such as lipid, protein, and DNA are damaged as a result of the inability to balance high amounts of ROS with antioxidant mechanisms [8]. Parameters such as total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) are also used to indicate oxidative stress status [9].

These damages to cells can be reversible to some extent, but if it is more severe, irreversible death mechanisms occur such as cell necrosis and apoptosis. Apoptosis is a complex form of programmed cell death in which energy-dependent biochemical mechanisms play a role and mostly caspases (caspase-3, caspase-9 etc.) are involved [10].

Aquaporins (AQPs) are water channels and structures that provide fluid translocation in various parts of the body such as the lungs and kidneys. Although AQP-1 is a protein seen in urinary exosomes, it is known to play an important role in the processing of renal water handling. Recent studies have revealed that AQP-1 plays an important role in tubule water permeability and countercurrent exchange mechanisms in the kidney [11]. It can be observed in pathological conditions such as edema, and it also has an important role in kidney functions that require filtration [12]. AQP levels, which decrease in number due to damage to the kidney tissue for various reasons, may cause decreases in the filtration function of the kidney [13].

Selenium (Se) is an antioxidant and anti-inflammatory trace element [14]. Selenoproteins such as glutathione peroxidase, thioredoxin reductase, iodothyronine deiodinase, selenoprotein P, selenoprotein W, and selenophosphate synthetase contain Se to contribute to antioxidant mechanisms, but also to the regulation of apoptosis, regulation of thyroid hormones, immunomodulation, and many other cellular events [10].

This study aims to examine the effects of Se, which has antioxidant and anti-inflammatory properties, on kidney damage caused by LPS to protect the AQP levels.

Methods

Ethical Approval

In this study, all experiments were performed under the guidelines for animal research from the National Institutes of Health and were approved by the Committee on Animal Research of Suleyman Demirel University, Isparta (Ethic No: 06.01.2022–01-05).

Study Animals and Experiment Design

A total of 32 male Wistar Albino rats weighing 250–350 g were placed in room-controlled temperature (21–22 °C) and humidity (60% ± 5%) conditions. 12:12-h light/dark cycle was maintained. All rats were fed a standard commercial chow diet (Korkuteli Yem Gida San. A.S., Antalya, Turkey).

The experimental design of this study is shown in Fig. 1. All rats were distributed into four groups, each containing eight rats. Groups as:

1. **Control Group ($n = 8$)**; 1 ml of saline was given to the rats by oral gavage for 7 days and intraperitoneally (ip) from the right inguinal region of the rats between 2 and 7 days.
2. **LPS Group ($n = 8$)**; 1 ml of saline was given to the rats by oral gavage for 7 days. LPS (048K4126, Sigma-Aldrich, USA) (0.1 mg/kg, 0.5–1 ml, ip) [15] was applied to the right inguinal region of the rats between 2 and 7 days.
3. **LPS + Se Group ($n = 8$)**; Se (sodium selenate, NS412130207, Alfa Aesar, USA) was given to the rats by oral gavage at a dose of 4 mg/kg/day [16] for 7 days. LPS (0.1 mg/kg, 0.5–1 ml, ip) was applied to the right inguinal region of the rats between 2 and 7 days.
4. **Se Group ($n = 8$)**; Se was given to the rats by oral gavage at a dose of 4 mg/kg/day for 7 days. Saline (1 ml) was applied to the right inguinal region of the rats between 2 and 7 days.

Experimental animals were sacrificed under anesthesia of 50–80 mg/kg ketamine and 8–10 mg/kg xylazine 6 h after the last LPS administration. After the abdominal incision, the maximum amount of blood was collected for surgical exsanguination performed for euthanasia in rats and approximately 4–5 ml was transferred to tubes for biochemical analysis. Kidney samples were taken for biochemical, histopathological, and immunohistochemically analyses.

Histopathological Analysis

At the end of the experiment, kidney tissues from rats were placed in buffered 10% formaldehyde solution for histopathological examinations and left for 24 h to fix. After the fixation of the kidney tissues was completed, they were washed overnight in tap water. Tissues were then kept in 70%, 80%, 90%, and 100% alcohol series for 1 h for dehydration, respectively. Kidney tissues were kept in alcohol-xylol mixture for 5 min and only in xylol for 5 min at the next stage. After the follow-up phase

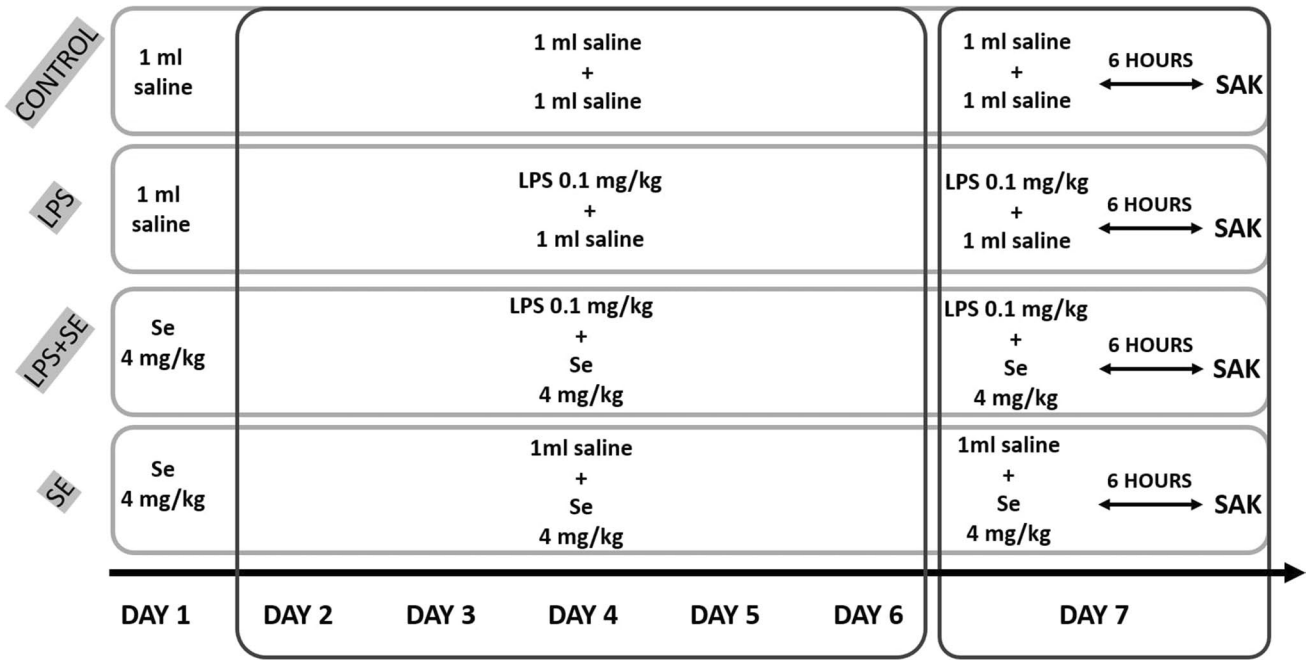

Fig. 1 Experimental design of this study. LPS, lipopolysaccaride; LPS + Se, lipopolysaccaride + selenium; Se, selenium; SAK, sacrification

of the tissues was completed, embedding in paraffin blocks was performed. Five-micrometer thick sections were taken from the kidney tissues in the paraffin blocks with a microtome (Leica RM2155, Leica Microsystems, Wetzlar, Germany). Finally, kidney tissue sections were subjected to hematoxylin–eosin (H-E) staining. Finally, kidney preparations stained with H-E were examined under a ZEISS AX10 Lab.A1 light microscope and their images were photographed.

Immunohistochemical Analysis

Kidney tissues taken from rats were fixed with 10% formol. After the histological follow-up methods were applied, they were blocked in paraffin. Sections of 5-µm thickness were taken from the obtained blocks. Immunohistochemical staining methods were applied to AQP-1 (Catalog no: bs-1506R, Bioss), Caspase-3 (Catalog no: FNab01289, Fine Test), and NFkB p65 (Catalog no: bs-20159R, Bioss) and were examined and evaluated in a ZEISS AX10 Lab.A1 photomicroscope. Structural changes in the kidney tissue sections of the experimental and control groups were evaluated according to the scoring made by Abdel-Wahhab et al. [17] (Table 1).

Biochemical Analysis

Oxidative stress was analyzed in kidney tissue. Kidney tissues were diluted with 5 × (w/v) phosphate buffered saline (10 mM pH 7.4) and homogenized using Janke&Kunkel IKA Ultra Turrax T25 (Germany) tissue homogenizator. After the homogenization process, the samples were centrifuged at + 4 °C at 2000 rpm for 20 min (Nuve NF 1200 R, Turkey). From the supernatanants, tissue TAS and TOS levels were measured on Beckman Coulter AU 5800 biochemistry autoanalyzer (USA), and also the OSI levels of the samples were also calculated [18]. TAS was measured using an automated colorimetric measurement method developed by Erel [9]. Antioxidants in the sample reduce the dark blue-green colored 2,2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical to a colorless reduced ABTS. The change in absorbance at 660 nm is related to the total antioxidant level of the sample. In this way, the antioxidative effect of the sample against the free radical reactions

Table 1 Scoring table of histopathological and immunohistochemical evaluations

(−) score	Negative score	It means the absence of any structural changes
(+) score	1 positive score	It refers to a slight structural change
(++) score	2 positive scores	It represents moderate structural change
(+++) score	3 positive scores	It represents a serious structural change

initiated by hydroxyl radicals can be measured. The tissue TAS levels were expressed as μmol trolox equiv/l.

TOS of kidney tissue was measured using an automated colorimetric method [19]. Oxidants in the sample oxidize the ferrous ion-dianisidine complex to the ferric ion. The oxidation reactions are enhanced by glycerol, which is abundant in the reaction medium. In an acidic medium, the ferric ion forms a colored complex with xylenol orange. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules already present in the sample. The assay was calibrated using H_2O_2 and the results were expressed as μmol H_2O_2 equiv/l. OSI was calculated using the formula: OSI = TOS/TAS [20].

The blood of the rats was taken into gel-containing tubes, and the serum was separated by centrifugation at 3000 rpm for 10 min. Samples were stored at − 80 °C until they were analyzed. Serum creatinine (Cre) and blood urine nitrogen (BUN) levels were measured by the spectrophotometric method with Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter, USA) using the kit compatible with the instrument.

Statistical Analysis

For statistical analysis, the biochemical and immunohistochemical scores of each group were compared between each other groups, and for this purpose, the SPSS-18.0 package program and one-way ANOVA LSD tests were used. The significance level was accepted as $p < 0.05$.

Results

At the end of the exposure, male rats were kept in a standard temperature and humidity environment (21–22 °C temperature and 55% humidity) in a room controlled to 12 h of light and 12 h of darkness. The survival rate is 100%.

Histopathological Results

As a result of the examination of the kidney tissues of the control group, no histopathological findings were found. When the preparations of the Se group were examined under the light microscope, no histopathological change was observed, similar to the control group. As a result of the examination of the kidney tissues of the LPS applied group, shrinkage and narrowing of the glomeruli, degeneration in the proximal and distal tubules, hemorrhage and congestion in the vessels, and mononuclear cell infiltration were detected compared to the control and Se groups. According to the examination and comparison of the images of the LPS + Se group and the LPS group, it was observed that there was a decrease in hemorrhage and congestion in the vessels, mononuclear cell infiltration, a decrease in the degeneration of the proximal and distal tubules, and a recovery in the glomeruli.

As a result of the examinations, histopathological findings were found in the kidney tissues of the LPS group compared to the control and Se groups ($p < 0.005$). When the kidney tissues of the LPS + Se group were compared with the LPS group, significant improvements were observed in histopathological findings ($p < 0.005$). Histopathological appearances are shown in Fig. 2 and histopathological examination scores have shown in Table 2.

Immunohistochemical Results

AQP1 secretion of the kidney tissues of the control group was found to be at a normal level. Similar to the control group, AQP1 synthesis was observed to be normal in the Se group. However, when the kidney tissues of the LPS group were examined, it was determined that AQP1 synthesis was decreased. In the group given LPS + Se, an increase in AQP1 synthesis was observed again in the LPS group ($p < 0.005$).

As a result of the examination of caspase-3 staining of kidney tissues of the LPS group, it was determined that it increased considerably compared to the control and Se groups. In the group given LPS + Se, it was observed that caspase-3 staining was statistically significantly decreased compared to the LPS group ($p < 0.005$).

NFkB/p65 immunostaining reaction was not found as a result of the examination of kidney tissues of Se and control groups. In the LPS group, as a result of immunohistochemical staining, NFkB/p65 synthesis was found to be very severe. As a result of the examinations, it was determined that there was a decrease in NFkB/p65 synthesis in the kidney tissue preparations of the LPS + Se applied group compared to the LPS group ($p < 0.005$).

Immunohistochemical appearances are shown in Fig. 3 and immunohistochemical examination scores are shown in Table 3.

Biochemical Results

TAS levels were significantly decreased in the LPS group compared to the control group ($p = 0.001$). However, a significant increase was detected in the LPS + Se group compared to the LPS group ($p = 0.003$). TAS levels were significantly increased in the Se group compared to the LPS group ($p = 0.001$). TOS and OSI levels increased significantly in the LPS group compared to the control group ($p < 0.001$ for both). TOS and OSI levels were significantly decreased in the LPS + Se group compared to the LPS group ($p = 0.012$ and $p = 0.016$, respectively). TOS and OSI levels decreased significantly in the Se group compared to the LPS group ($p < 0.001$ and $p = 0.001$, respectively) (Fig. 4).

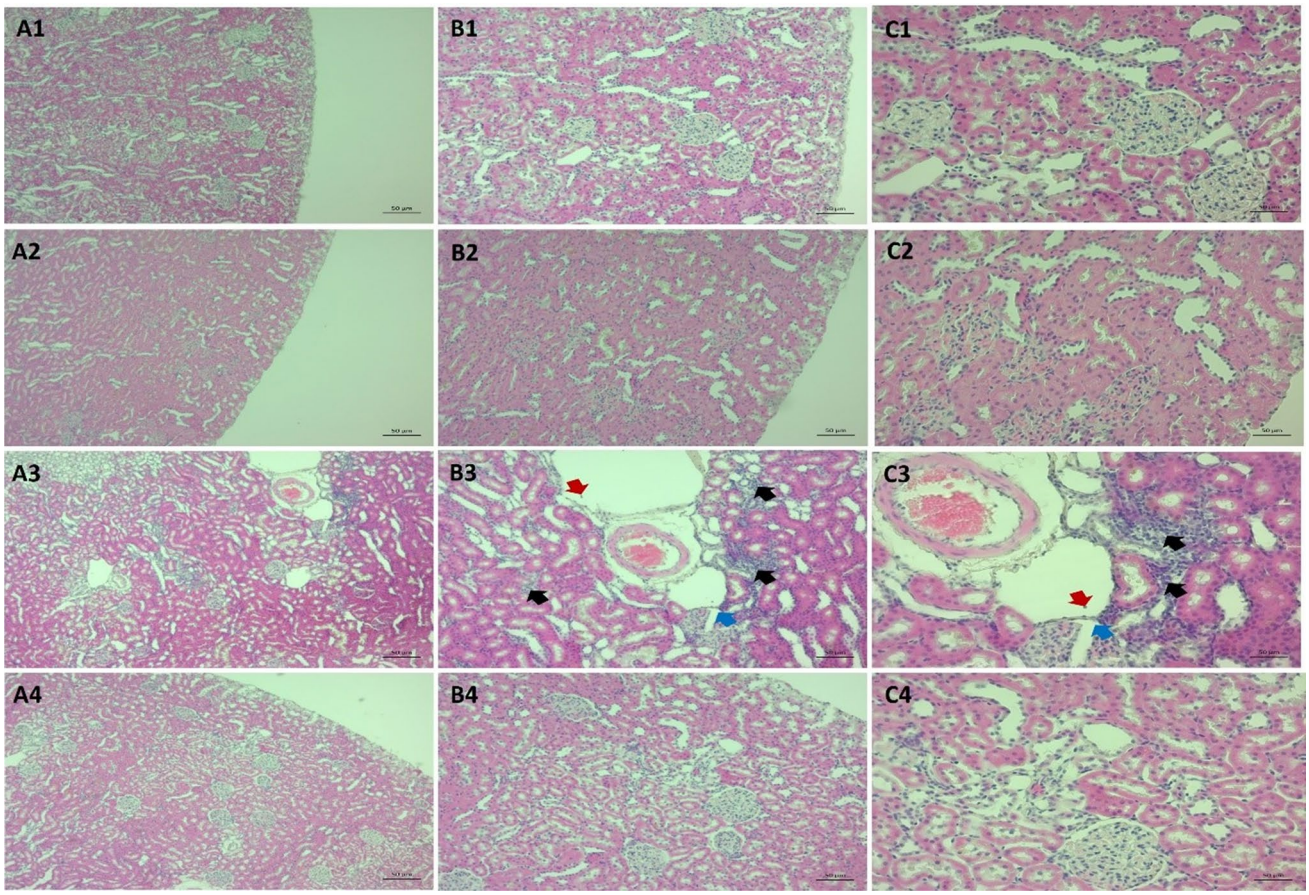

Fig. 2 Histopathological findings. Groups: Control (A1, B1, and C1), selenium (A2, B2, and C2), LPS (A3, B3, and C3), and LPS + selenium (A4, B4, and C4). Histopathological findings were not found in the control group. In the LPS group, glomerular degeneration and retraction (blue arrow), distal tubular degeneration (red arrow), mononuclear cell infiltration (black arrow), and cellular debris (red arrow) were observed (A: × 5, B: × 10, and C: × 20 magnification). These deformations were not observed in the selenium-containing groups (scale bar = 50 µm)

Table 2 Scores of kidney tissue histopathologic analysis

	CONTROL	LPS						LPS + SE					SE		
Parameters/scores	−	+	−	+	++	+++	*p*	−	+	++	+++	*p*	−	+	*p*
Shrinkage/retraction of the glomeruli	7	1	2	4	2	0	a	4	3	1	0		7	1	b
Tubuler dilation	7	1	2	6	0	0	a	5	3	0	0		7	1	b
Brush border reduction in proximal tubule	7	1	2	4	2	0	a	6	2	0	0	b	7	1	b
Mononuclear cell infiltration	7	1	1	5	0	2	a	4	4	0	0	b	7	1	b
Cellular debris	7	1	0	6	2	0	a	3	5	0	0	a,b	8	0	b,c
Proteinous deposition in tubules	7	1	0	4	4	0	a	5	2	1	0	b	7	1	b

Histological changes: (−) score (negative score), no structural damage; (+) score (one positive score), minimal damage; (++) score (two positive scores), middle damage; (+++) score (three positive scores): severe damage. The relationships between groups and the results of immunohistochemical scores are assessed by one-way ANOVA test (post hoc LSD test). *LPS*, lipopolysaccharide; *Se*, selenium. a, $p \leq 0.05$, compared with the control group. b, $p \leq 0.05$, compared with the LPS group. c, $p \leq 0.05$, compared with the LPS + Se group

Mean CRE levels are increased in the LPS group compared to the control group ($p < 0.001$). A significant decrease was found in the mean CRE level in the LPS + Se group compared to the LPS group ($p < 0.01$) (Fig. 5). There was no significant difference between the groups in the mean BUN levels.

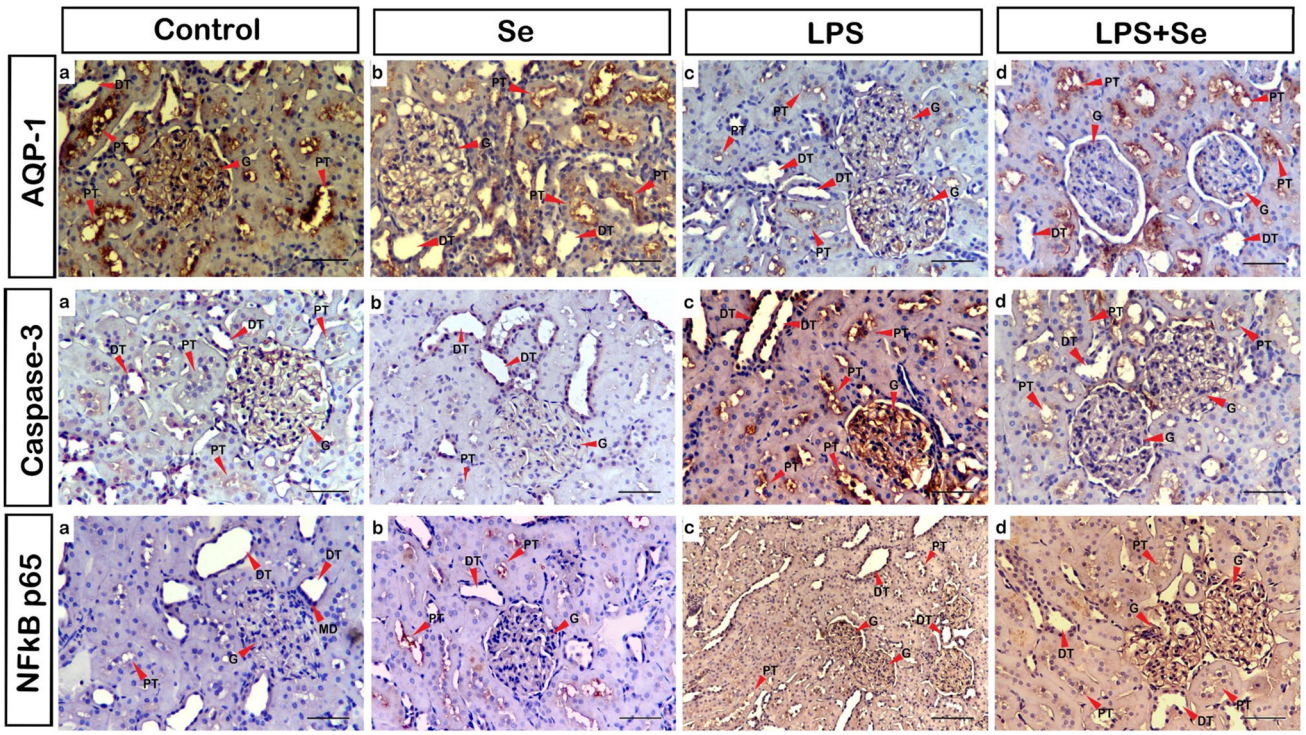

Fig. 3 Immunohistochemical staining results. Groups: Control (**A**), selenium (**B**), LPS (**C**), and LPS + selenium (**D**). AQP-1, Caspase-3, and NFkB/p65 immunoreactivity in the proximal tubule (PT), glomerule (G), and distal tubule (DT) of the medulla and cortex. LPS, lipopolysaccaride; LPS + Se, lipopolysaccaride + selenium; Se, selenium; AQP-1, aquaporine-1; NFkB p65, nuclear factor kB p65. (DABx20, scale bar = 100 µm)

Table 3 Immunoreactivity scores of AQP-1, caspase-3, and NF-kB of kidney tissues

	CONTROL				LPS					LPS + SE					SE				
Parameters/scores	−	+	++	+++	−	+	++	+++	*p*	−	+	++	+++	*p*	−	+	++	+++	*p*
AQP-1	0	1	2	5	2	4	2	0	a	0	3	2	3	b	0	1	3	4	b
Caspase-3	7	1	0	0	0	1	2	5	a	2	3	3	0	a,b	7	1	0	0	b,c
Nf-kB/p65	6	2	0	0	0	1	3	4	a	2	5	1	0	a,b	1	7	0	0	b

Immunohistochemical changes: (−) score (negative score), no structural damage; (+) score (one positive score), minimal damage; (++) score (two positive scores), middle damage; (+++) score (three positive scores): severe damage. The relationships between groups and the results of immunohistochemical scores are assessed by one-way ANOVA test (post hoc LSD test); *LPS*, lipopolysaccharide; *Se*, selenium; *AQP-1*, aquaporin-1; *NF-kB*, nuclear factor-kappa beta. a, $p \leq 0.05$, compared with the control group. b, $p \leq 0.05$, compared with the LPS group. c, $p \leq 0.05$, compared with the LPS + Se group

Discussion

Systemic inflammation can be triggered by some pathological processes such as sepsis. In this pathological process, oxidative stress may occur together with the inflammatory condition that occurs in the blood. Inflammatory cytokines and oxidant substances circulating freely in the blood can trigger intracellular mechanisms by binding to their receptors on the cell surface in many organs. This spontaneous damage that can occur in some vital organs such as the kidney can accelerate the progression in a short time due to the positive feedback mechanism caused by the stimulation of other cells by cytokines synthesized by the affected cell.

In this study, the relationship between NF-kB, which has a central role in inflammation, and AQP-1, which mediates fluid transport in kidney tissue, was investigated. There is no study yet on the effects of the trace element selenium on this connection. Clarifying the mechanism of this element, which plays a very important role in the synthesis of antioxidant enzymes and is easy to obtain, and prevents damage to the kidney tissue due to inflammation, will make a very important contribution to the literature.

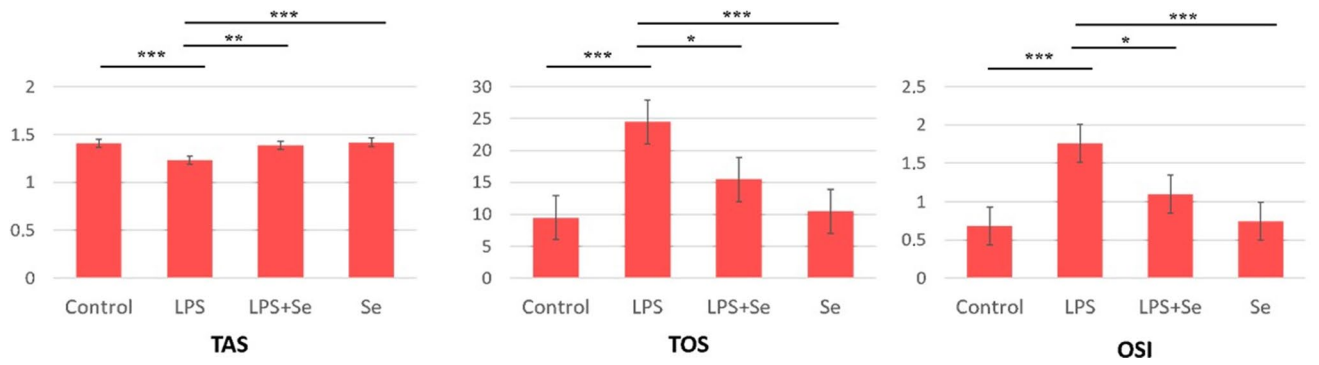

Fig. 4 TAS, TOS, and OSI levels in kidney tissue. Values were presented as mean ± SD. LPS, lipopolysaccaride; LPS + Se, lipopolysaccaride + selenium; Se, selenium; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

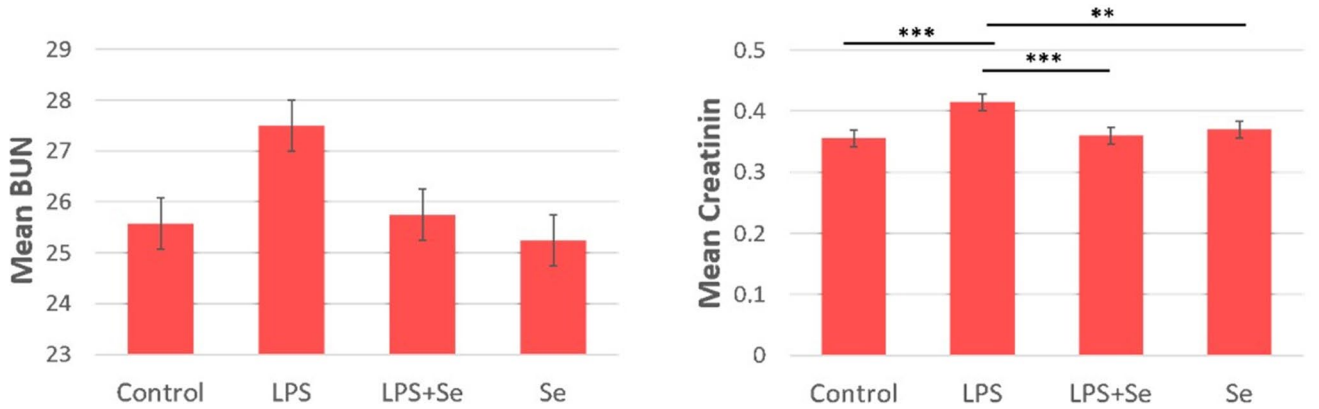

Fig. 5 Mean BUN and creatinin levels of kidney tissues in rats. BUN, blood urea nitrogen; LPS, lipopolysaccharide; Se, selenium. "**" represents $p < 0.01$. "***" represents $p < 0.001$

Kidney tissue can be affected by many systemic events in a short time and in large amounts due to its being both an elimination organ very bloody.

This study's experimental method also fits the model of kidney injury secondary to systemic inflammation, and neutrophil cell infiltration in kidney tissue also supports the stated situation [21, 22]. The fact that Se, observed in histopathological results, has a reducing effect on this neutrophilic infiltration can be interpreted that it can be used in cases where kidney damage develops for various reasons. In addition, depending on the degree of glomerular and tubular damage, some kidney-specific pathological events such as protein loss or deterioration in ultrafiltration occur [23]. It is vital that the glomeruli are intact and urination takes place in systemic diseases such as hypertension where the intravascular volume should be reduced. The effectiveness of drugs that act on the tubules and provide urine output, such as diuretics, also requires the tubules to be intact [24]. In the case of tubular damage detected in this study, the remnants of epithelial cells appear as cellular debris and may cause a decrease in the effect of such drugs. In addition, loss of functionality may occur in kidney functions such as water retention and urine filtering ability secondary to tubular dilatation observed in the proximal tubules in this study.

It is known that AQPs are more concentrated in some organs of the body, such as the eyes, lungs, and kidneys [25]. Decreases in these AQP levels, secondary to damage mechanisms, trigger problems in fluid distribution and clinical situations that develop accordingly. In this study, reversing the glomerular and tubular changes seen in damage with Se treatment can be interpreted as preserving AQP-1 levels because Se reduces inflammation and oxidative stress. The observation of AQP-1 levels close to control in the group administered Se alone, without creating a damage model, supports this situation.

Many publications show that Se causes an increase in antioxidant enzyme levels [26, 27]. The preference of parameters such as TAS and TOS, which are used to show antioxidant activity, in current approaches also provides support for the innovative side of this study. The increase

in oxidant substances that occur in pathological events can cause an increase in antioxidant enzymes produced by the body. Antioxidant activity, which is insufficient against the production of oxidant substances from the subscription, can be replaced by exogenous molecules. The decreased TAS and increased TOS, OSI levels detected in this study prove this situation. The significant increase in TAS levels with Se treatment reversed the increase in other oxidant substances.

According to studies, oxidative stress can also cause inflammation and apoptosis [28]. It has been proven that oxidant and inflammatory substances that bind to cell surface receptors cause progressive damage by triggering various intracellular mechanisms such as the NF-kB pathway [29]. The increase in the levels of NF-kB and its activated form, NF-kB/p65, are the main causes of the intense inflammatory picture created by the body and apoptosis. In this study, increased NF-kB/p65 levels detected in the proximal tubule apical membrane, glomeruli, and distal tubule may be the reason for the development of inflammation and apoptosis, which is also shown by histopathological staining. Because the increased caspase-3 levels detected in the injury group are also parallel to the increased NF-kB/p65 levels, which proves this situation.

Apoptosis of cells was also prevented, thanks to the protective activity created by the antioxidant and anti-inflammatory effect obtained with Se treatment.

The normalization of increased CRE levels in the blood, which is an indicator of the damage at the glomerular level in the kidney tissue and used in routine follow-up, by Se shows that clinical chase of the effects of Se can also be done.

Conclusion

As a result, the decrease in AQP-1 levels and the increase in caspase-3 and NF-kB levels indicate inflammatory and apoptotic processes, which have been proven in this study. It is possible to reverse all these negative effects with Se treatment. In future studies, detailed studies on this subject and investigating different intracellular mechanisms are needed.

Author Contribution All authors participated in the design, interpretation of the studies and analysis of the data, and review of the manuscript. BC, NFK, and KG conducted the experiments. KG, ES, and DUK performed histopathological and immunohistochemical analyses. BC and NFK wrote the manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Data Availability All data generated or analyzed during this study are included in this published article.

Declarations

Competing Interests The authors declare no competing interests.

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