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Original investigation

Effect of Different Doses of Vitamin E with Selenium on Renal Damage Caused by Unilateral Ureteral Obstruction Model?

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ABSTRACT

Objective: Chronic kidney disease (CKD) is still common worldwide. We investigated the effect of two different doses of vitamin E with selenium (Se) administration to prevent CKD leads to renal damage via unilateral ureteral obstruction (UUO).

Material and Methods: Thirty-two female Wistar Albino rats were divided into four groups; a sham group (left UUO+no medication); left UUO with no treatment, left UUO treated with 100 mg/kg dose Vitamin E+Se (RPVE+Se) and left UUO treated with 1000 mg/kg Vitamin E+Se (HDVE+Se) mixture. All rats subjected during 14 days and killed humanely. Malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), levels were determined in kidney tissue, whereas total antioxidant status (TAS), total oxidant status (TOS) and DNA damage marker 8-hydroxy-2-deoxyguanosine (8-OHdG) in serum. Histologic examination were also done.

Results: The unilateral ureteral obstruction model increased MDA ($p<0.05$), TOS ($p<0.001$) and 8-OHdG levels ($p<0.001$) via oxidative mechanisms. In the treatment groups increased TAS, SOD ($p< 0.001$), and GSH ($p<0.001$) levels were determined, but in RPVE+Se group, TAS levels were slightly higher than the HDVE+Se group ($p=0,039$). In terms of histological findings, tubular necrosis ($p=0.003$) and lymphocyte infiltration ($p=0.002$) were observed renal tissue images. RPVE+Se group findings were similar to the sham group, while in HDVE group these images similar to the UUO group.

Conclusions: It was observed that UUO caused oxidative stress resulting in renal damage, and controlled vitamin E application with Selenium administration, which is considered to be an effective antioxidant couple, inhibited oxidative stress.

Key words: Vitamin E [supply & distribution], renal insufficiency, Selenium [supply & distribution], ureter

INTRODUCTION

Kidney failure is a worldwide public health problem, with many clinical outcomes such as chronic kidney disease (CKD), cardiovascular disease, and premature death. In CKD, irreversible abnormalities in kidney structure are due to ischemic, toxic or obstructive damage (1).

Obstructive damage etiology includes inflammatory situations, urinary tract infections, urolithiasis, tumors, and vesicoureteral reflux. Persisting obstructive damage results in renal fibrosis through the oxidative stress. Oxidative stress affects several cellular parts and consists of reactive oxygen specimens (ROS) which cause renal function loss. Increased ROS production causes lipid peroxidation, as well as protein and DNA damage (2).

Malondialdehyde (MDA) is the final product of lipid peroxidation occurs in oxidative processes. Oxidative processes had increased levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), which is a damage indicator to DNA, and pivotal biomarker of generalized and cellular damage (2, 3). The literature indicates that serum level of 8-OHdG is a valuable indicator of the severity of oxidative tissue damage (3). In addition, increased renal levels of ROS have been detected in damaged kidneys, together with decreased activities of the major protective antioxidant systems superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px) (4, 5).

There are also non-enzymatic antioxidant mechanisms, involved in the defense system against ROS mediated tissue or cellular damage. One of these, Vitamin E, is a lipid-soluble, chain-breaking antioxidant that prevents the propagation of free radicals. It also conducts antioxidant activity during the peroxidation of unsaturated lipids. Chronic kidney diseases patients had an impaired antioxidant defence system because of the uremic state (5, 6). It is also well-known Vitamin E therapy can influence in vivo DNA damage in a positive protective way (3).

Many studies revealed, Vitamin E therapy has renoprotective effects in animal UUO models and this vitamin could have some therapeutic significance to prevent the progression of renal fibrosis in human (5–8).

Vitamin E and Selenium (Se) have a synergistic effect on lipid peroxidation mechanisms. Antioxidant trace element has an important role in GSH-Px-dependent mechanisms that protects cellular components from oxidative stress and damage (7). Selenium atoms are covalently bound to cysteine residues in GSH-Px have strong antioxidant properties, acts synergistically with vitamin E (7, 9).

Many experimental studies have shown that selenium supplementation has an ability to prevent oxidant damage by reducing ROS activities. In renal damage, selenium intake has proven to be effective in improving selenium status and immune function (7, 9).

Some studies suggest, Vitamin E can be used in high doses for preventing oxidative damage (7, 9). Contrary, high doses of Vitamin E can occur with hemorrhagic stroke, ecchymosis and prolonged prothrombin time and may increase all-cause mortality. Because of this risk, the recommended daily dose is 30 mg per day, and side-effects are usually experienced at doses above 1 g/kg. (7, 8, 10)

We aimed to reveal what is the beneficial dose of Vitamin E and selenium in preventing renal damage. We planned to investigate the role of two different doses of Vitamin E with selenium in preventing renal damage due to unilateral ureteral obstruction (UUO). For this purpose, we analyzed oxidative damage markers in kidney tissue and serum.

MATERIALS AND METHODS

Study group

Thirty-five female Wistar albino rats bred in our laboratory were used. At the start of the experiment, the rats aged 16 weeks weighed 185–220 g. All animal experimental protocols were reviewed and approved by the Ethics Committee of Pamukkale University's Medical Faculty Experimental Animals. In our study, 35 female albino rats randomly divided to four group.

Sham group: Under the anesthesia [10 milligrams per kilogram (mg/kg) xylazine, 90 mg/kg ketamine], five rats were sham-operated (abdominal incision with no ureteric ligation and receiving no treatment).

Unilateral ureteral obstruction model: Thirty rats' abdominal cavity was exposed via midline incisions, and the left ureters were ligated at one point with 4–0 silk. The rats were put under general anesthesia by intraperitoneal injection of 10 mg/kg xylazine and 90 mg/kg ketamine. Group Unilateral ureteral obstruction (UUO) with no treatment (UUO): Nine rats in the UUO group had no treatment during ten day period.

Group Reno protective (RP) dose vitamin E and selenium (RPVE+Se): Nine rats in RP dose, received vitamin E (100 mg/kg BW) and selenium (1.5 mg/kg BW) daily with flexible plastic feeding tubes during ten day period.

Group high dose (HD) vitamin E and selenium (HDVE+Se): Nine rats in HD Vitamin E group received vitamin E (1000 mg/kg BW) and selenium (1.5 mg/kg BW) daily with flexible plastic feeding tubes during ten day period.

One death was occurred during the study in each experiment group (totally three deaths).

Samples and biochemical analysis

All the rats were anesthetized via intraperitoneal injections of ketamine and sacrificed the left kidneys, on the 11th day. Kidney tissues were separated into two parts for biochemical and histological examination. Kidney tissue was frozen in the liquid nitrogen and stored at -80°C. On the analysis day, tissues were thawed and homogenized. Homogenization was done in 10 ml of cold 20 mM HEPES buffer and centrifuged at 1500 g for five minutes at 4°C. GSH, MDA and SOD analyzed from the supernatant.

GSH was analyzed using the method that was defined by Moron et al. (11). Samples' absorbance was recorded at 412 nm. MDA levels were obtained via using the procedure of Ohkawa et al. (12). All sample absorbance was recorded at 532 nm. Superoxide dismutase levels were analyzed with superoxide dismutase commercial kit (Cayman Chemical, Ann Arbor, MI, USA) in supernatants.

All results compared to each analyte standard results and calculated.

Tissue glutathione, MDA and SOD levels were standardized by total protein level and glutathione, MDA expressed in nmol/g tissue while SOD in U/g tissue.

Blood samples were also taken via cardiac puncture and allowed to coagulate at the temperature of 4°C for 30 minute. After centrifugation, serum samples were stored at -80°C until the assessment was made of the serum levels of 8-OHdG, as well as the total antioxidant status (TAS) and total oxidant status (TOS) concentrations. The TAS and TOS levels were determined using a new automated measurement technique (μmol H2O2 equiv/L) (13).

Serum creatinine, urea, uric acid, total protein and albumin levels analyzed with ElectroChemiLuminescence method on Roche Cobas 701 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

Oxidative DNA damage was measured using serum 8-hydroxy-2′-deoxy-guanosine levels with competitive inhibition, enzyme immunoassay method using commercial ELISA kit (USCN Life Science Inc., Wuhan, China).

Histological analysis

The rats were anesthetized with 30 mg/kg ketamine HCl and 6 mg/kg xylazine HCl injected intraperitoneal, and sacrificed by decapitation. Kidney tissues were fixed in 10% formaldehyde overnight (070312510; Tekkim Chemistry Bursa, Turkey). The tissues were washed for 1 hour with tap water then dehydrated with 50.60.70.80.90 and 100% concentrated ethanol for 1 hour, cleared in xylene and embedded in paraffin. Kidney weights' varied between 0.828–1.234 g. Transverse sections of left kidney were cut at 5 µm using microtome (Leica, Wetzlar, Germany) and mounted on lysine-coated glass slides (23573; Marienfeld Laboratory Glassware Histobond, Marienfeld, Germany). Sections stained with hematoxylin and eosin (H & E) (Merck, Germany). A minimum of 50 proximal tubules associated with 50 glomeruli were examined for each slide and an average score was calculated. Severity of lesion was graded from 0 to 3 according to the percentage of tubular damage. Slides were assigned for severity of changes using scores on scale in which Grade 0 no change; Grade 1 mild, changes affecting <25% tubular damage; Grade 2 moderate, changes affecting 25–50% of tubules, Grade 3 severe, changes affecting >% 50 of tubules. The Banff classification of kidney pathology was used for scoring the degree of mononuclear cell infiltration. Focal leukocyte infiltration was assessed in randomly five sections prepared from each kidney sample. The score was graded from 0 to 3, depending on the severity of histological characteristics by the Banff classification.

Statistical analysis

SPSS software, version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for statistical analyses. The distribution of continuous variables was analyzed using the Shapiro Wilk test, in order to assess significant departures from normality. For samples with normal distribution statistical analysis for the differences expressed as mean ± SD with 95% confidence intervals. Whenever the parameters presented normal distribution multiple comparisons between groups were performed by one-way ANOVA. Tukey test was used for the analysis of differences. For all statistical analyses, significance was accepted at p less than 0.05.

RESULTS

Biochemistry and histological analyses of oxidative stress parameters in kidney tissue homogenates and serum of all groups are presented in Table 1 and 2, and Figure 1 and 2.

Biochemistry analytes

There was no significant differences for serum creatinine, urea, uric acid, total protein and albumin levels between groups (Table 1).

DNA damage

Significant increased serum 8-OHdG levels (217.55±16.4 pg/mL) in Group UUO were observed and there was statistical difference when compared this group to others (p<0.001) (Table 1).

Decreased levels of 8-OHdG in Group RPVE+Se (178.97±7.12 pg/mL) and Group HDVE+Se (173.84±11.97 pg/mL) were determined but there was no statistical differences compared to sham group (180.79±13.26 pg/mL) (Figure 1 A).

Oxidative markers

In both treatment groups, MDA levels showed difference compared to Group sham and Group UUO (p<0.001). Lipid peroxidation product; MDA levels were higher in Group RPVE+Se

Table 1. Effects of UOO and two treatment modalities on five serum biochemistry parameters, and oxidant/antioxidant parameters in each rat groups.

	Sham group (n=5)	UUO group (n=9)	RPVE+ Se group (n=9)	HDVE+ Se group (n=9)
Creatinine (mg/dl)	0.54±0.20	0.55±0.10	0.53±0.20	0.55±0.10
Urea (mg/dl)	69±9.00	71.1±7.70	70±8.00	71±8.90
Uric acid (mg/dl)	0.60±0.10	0.65±0.50	0.62±0.30	0.65±0.40
Total protein (g/L)	79±5.10	78±7.40	76±8.20	75±7.30
Albumin(g/L)	44±3.30	42±5.10	40±4.30	43±2.10
MDA (nmol/g tissue)	28.15 ± 0.72* (27.57 - 28.81)	39.02 ± 1.76$^{\lambda}$ (37.85 - 40.32)	34.14 ± 1.04$^{\&,\perp}$ (33.44 - 34.78)	30.76 ± 0.63$^{\varepsilon,\Psi}$ (30.34 - 31.2)
Glutathione (nmol/g tissue)	2.73 ± 0.25+ (2.52 - 2.94)	3.24 ± 0.1 (3.17 - 3.31)	3.5 ± 0.15 (3.41 - 3.6)	5.47 ± 1.79$^{\Psi}$ (4.39 - 6.77)
SOD (U/g tissue)	190.07 ± 2.28 (188.16-191.95)	165.58 ± 21.89Δ (149.18-178.88)	197.62 ± 1.7$^{\Psi}$ (196.58 - 198.73)	206.67 ± 3.58$^{\perp}$ (204.05 - 208.93)
8-OHdG (pg/ml)	180.79 ± 13.26 (170 - 191.9)	217.55 ± 16.4 λ (206.17-229.18)	178.97 ± 7.12⊥ (173.88 - 183.56)	173.84 ± 11.97$^{\Psi}$ (166.27 - 181.54)
TAS (µmol H2 O2 equiv/L)	1.09 ± 0.15 (0.98 - 1.23)	1 ± 0.08 (0.94 - 1.06)	1.16 ± 0.11$^{\omega}$ (1.08 - 1.23)	1.1 ± 0.12 (1.02 - 1.17)
TOS (µmol H2 O2 equiv/L)	7.58 ± 1.18 (6.49 - 8.36)	32.01 ± 11.62 λ (24.15-40.16)	12.52 ± 7.62Ψ (7.99 - 18.03)	7.26 ± 2.11⊥ (5.76 - 8.57)

Notes: Values are expressed as mean±SD (95%bootstrap confidence interval).
Difference between Sham and HDVE+ Se groups *p= 0,002, $^{+}$p< 0.001
Difference between Sham and RP VE+ Se groups $^{\&}$p< 0.001
Difference between Sham and UUO groups $^{\lambda}$p< 0.001, $^{\Delta}$p=0.004
Difference between HDVE+ Se and RPVE+ Se groups $^{\varepsilon}$p<0.001
Difference between HDVE+ Se and UUO groups $^{\Psi}$p<0.001
Difference between RPVE+ Se and UUO groups $^{\perp}$p<0.001, $^{\omega}$p=0,039

(34.14±1.04 nmol/g tissue) when compared to Group HDVE+Se (30.76±0.63 nmol/g tissue) (Figure 1 B).

RPVE+ Se consumption increases glutathione levels (5.47±1.79 nmol/g tissue) compared to Group UUO (3.24±0.1 nmol/g tissue) and Group HDVE+Se (3.5±0.15 nmol/g tissue) (Figure 1 C).

Increase SOD levels determined in Group HDVE+Se (206.67±3.58 U/g tissue) and Group RPVE+Se (197.62±1.7 U/g tissue) when compared to Group UUO levels (165.58±21.89 U/g tissue) (p<0.001).

There was no statistical differences between Group sham (190.07±2.28 U/g tissue) and treatment groups in terms of SOD levels (Figure 1 D).

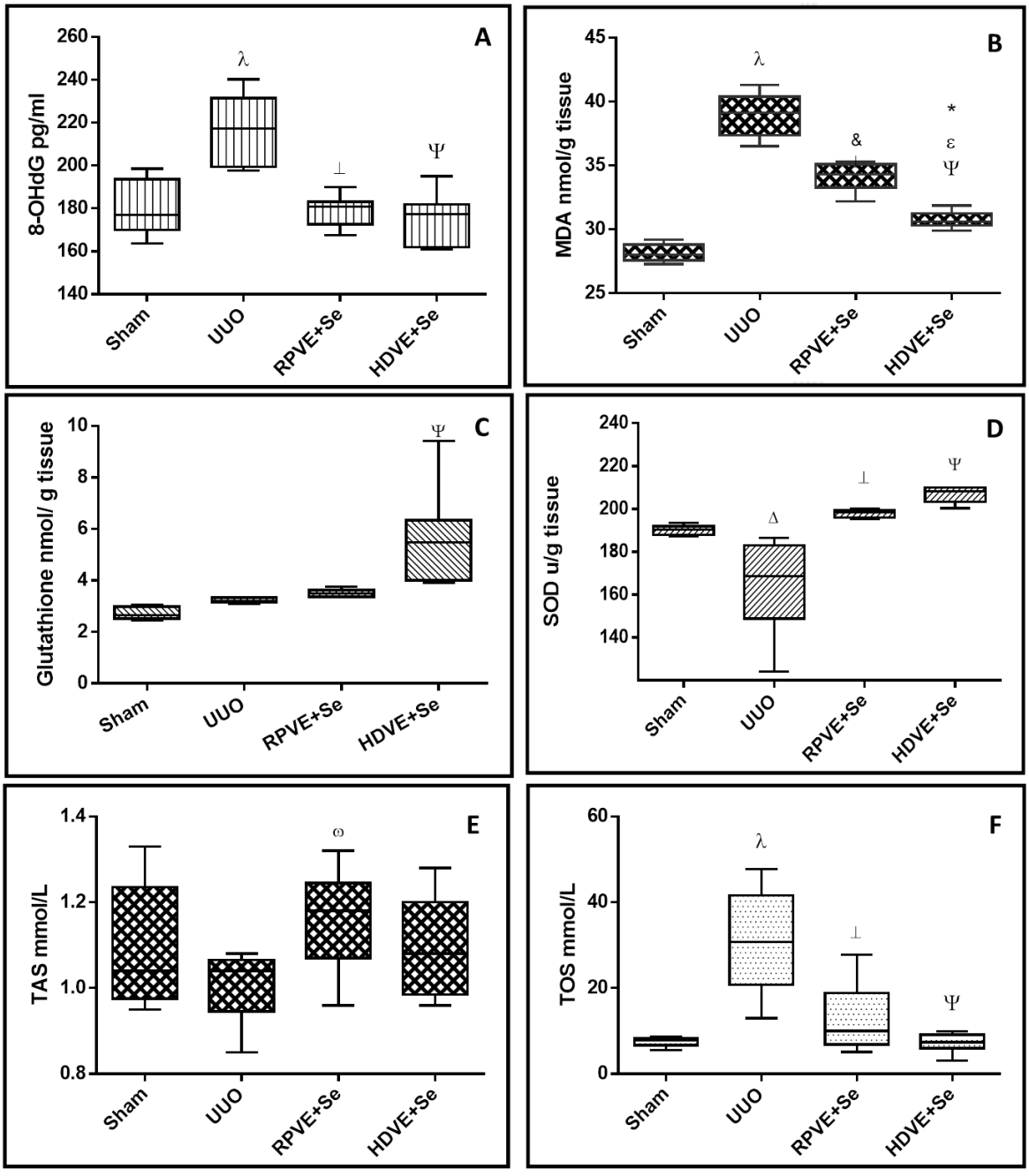

Figure 1. 8-Oxo-2'-deoxyguanosine, Malondialdehyde, Glutathione, Superoxide Dismutase levels and Total Antioxidant Status, Total Oxidant Status in renal tissues of Vitamin E and Selenium treated rats. **A:** Effect of high and renoprotective dose with selenium on 8-OHdG levels in serum specimens. Significance between HDVE+ Se and UUO $^{\Psi}$p= 0.0001, significance between RPVE+ Se and UUO $^{\perp}$p= 0.0001, significance between Sham and UUO $^{\lambda}$p= 0.0001**. B:** Malondialdehyde levels in renal tissues in treatment, UUO and sham groups. Significance between HDVE+ Se and sham *****p= 0,002, significance between HDVE+ Se and RPVE+ Se $^{\varepsilon}$p= 0.0001, significance between HDVE+ Se and UUO $^{\Psi}$p= 0.0001, significance between sham and RP VE+ Se $^{\&}$p= 0.0001 and significance between sham and UUO $^{\lambda}$p= 0.0001. **C:** Glutathione levels in renal tissue tissues in treatment, UUO and sham groups. Significance between HDVE+ Se and UUO $^{\Psi}$p= 0.0001. **D:** Superoxide dismutase levels in renal tissue tissues in treatment, UUO and sham groups. Significance between HDVE+ Se and UUO $^{\Psi}$p= 0.0001, significance between RPVE+ Se and UUO groups $^{\perp}$p= 0.0001, significance between sham and UUO groups. **E:** Effect of high and renoprotective dose with selenium on total antioxidant status levels in serum specimens. Significance between RPVE+ Se and UUO $^{\omega}$p=0,039. F: Effect of high and renoprotective dose with selenium on total oxidant status levels in serum specimens. Significance between HDVE+ Se and UUO, $^{\Psi}$p= 0.0001, significance between RPVE+ Se and UUO, $^{\perp}$p= 0.0001, significance between sham and UUO $^{\lambda}$p= 0.0001.

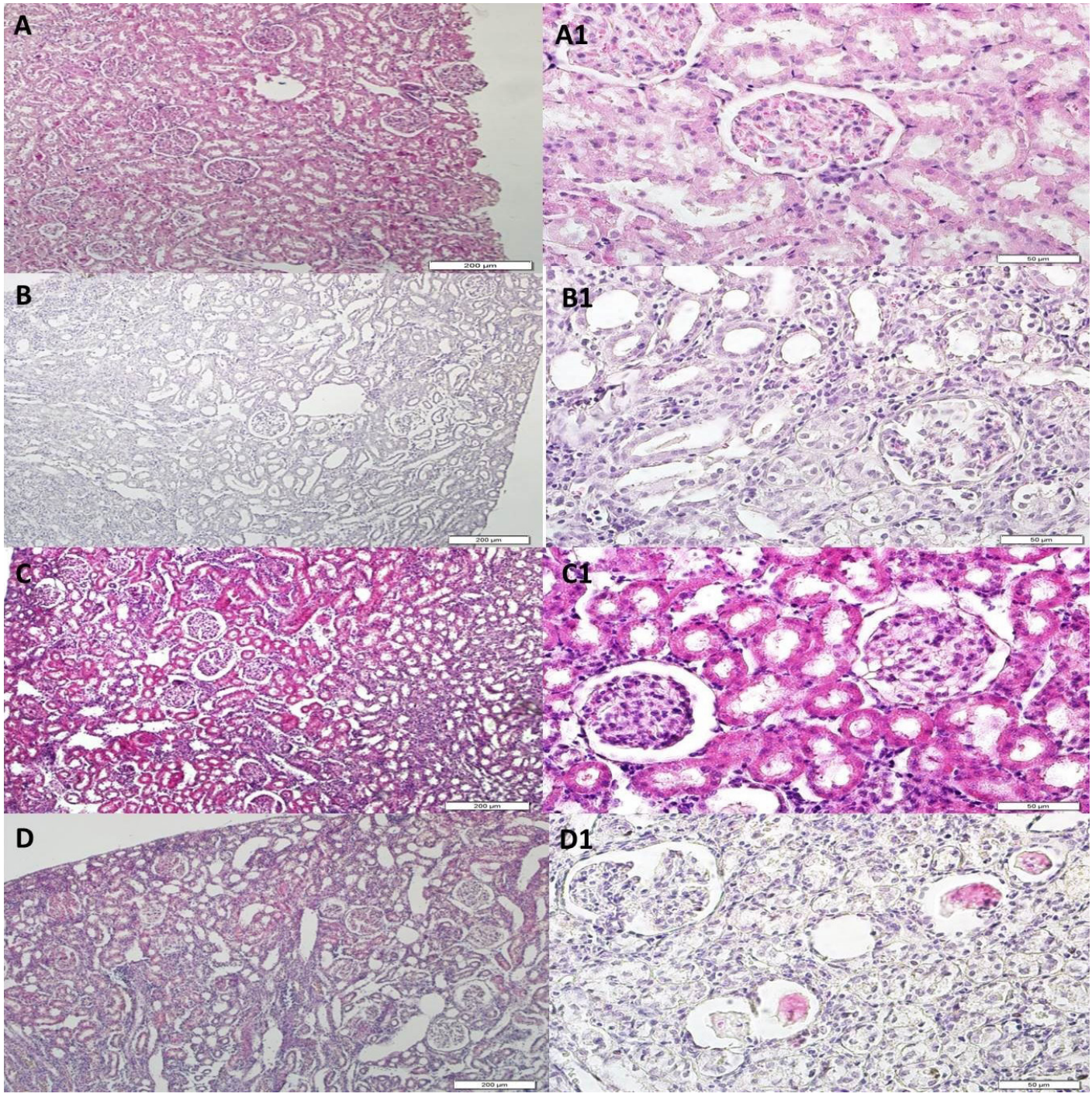

Figure 2. Histological images of renal cortex glomerulus and tubules in all groups; A, **A1:** Sham, B, B1: UUO, C, **C1:** RPVE+Se, D, **D1:** HDVE+Se, Tissue sections were stained with hematoxylin and eosin. A, B, C, D 10X; A1, B1, C1, D1 40X.

TAS levels only showed difference between Group RPVE+Se and Group UUO (p=0.039). The highest level of TAS was in Group RPVE+Se (1.16±0.11 µmol H2O2 equiv/L). In Group UUO, increased TOS levels (32.01±11.62 µmol H2O2 equiv/L) were determined, when compared the other groups (p<0.001) (Figure 1 E, F).

Histological findings

In the Group Sham, the cortex of renal corpuscles and proximal and distal tubules structures were histologically normal (Figure 2 A, A1). No mononuclear cell infiltration and tubular necrosis were observed. In the Group UUO, flattening of epithelium in some tubules and lumen dilatation was observed (Figure 2 B, B1). Cell swelling, necrotic cell nucleus and basal lamina degeneration were also seen in some areas of tubules (Figure 2 B, B1). There was mild and severe tubular necrosis in UUO group when it was compared RPVE+Se and sham groups (p=0.003). Tubular necrosis and macrophage infiltration were similar in HDVE+Se and UUO groups (p=0.003). In the Group RPVE+Se, histological images were similar to sham group. Ameliorating effects of Group RPVE+Se combination was remarkable in tubules and glomerulus

Table 2. Semi-quantitative analysis of tubular necrosis and lymphocyte infiltration in sham, UUO, RPVE+ Se and HDVE+ Se groups

	Grade	Groups				Total	
		Sham	UUO	RPVE+Se	HDVE+Se		p
Tubular necrosis	0	4 (%80)	0 (%0)	0 (%0)	0 (%0)	4 (%12.9)	0.003
	1	1 (%20)	0 (%0)	3 (%33.3)	0 (%0)	4 (%12.9)	
	2	0 (%0)	2 (%22.2)	3 (%33.3)	3 (%37.5)	8 (%25.8)	
	3	0 (%0)	7 (%77.8)	3 (%33.3)	5 (%62.5)	15 (%48.4)	
Lymphocyte infiltration	0	3 (%60)	0 (%0)	0 (%0)	0 (%0)	3 (%9.7)	0.002
	1	2 (%40)	0 (%0)	0 (%0)	0 (%0)	2 (%6.5)	
	2	0 (%0)	1 (%11.1)	5 (%55.6)	3 (%37.5)	9 (%29)	
	3	0 (%0)	8 (%88.9)	4 (%44.4)	5 (%62.5)	17 (%54.8)	

Notes: Grade 0= No degeneration, 1=mild degeneration, 2=moderate degeneration, 3=severe degeneration,

structures. In some tubules, damaged tubule epithelium could be seen rarely (Figure 2 C, C1). In the Group HDVE+Se, when regeneration of tubules epithelium were present partly, in some tubule cells, swellings were observed likely UUO Group (Figure 2 D, D1). Quantitative analysis showed that RPVE+Se group leukocyte infiltration reduced in interstitial areas (p=0.002) (Table 2).

DISCUSSION

Our study proposed high dose of Vitamin E with selenium treatment might be harmful and if necessary renoprotective doses of Vitamin E with selenium could be used. The present study confirmed antioxidant treatment has protective role on renal damage after UUO in rats. Our results showed that both renoprotective and high dose Vitamin E treatment with selenium had decreased MDA, TOS and 8-OHdG levels and increased GSH, SOD and TAS levels in UUO groups. In terms of histological findings, RPVE+Se treatment modality is more effective than the HDVE+Se approach.

All parts of cell (lipid membrane, DNA etc.) were influenced by ROS damage the present study revealed. Similar to our study, in the literature, UUO model had increased MDA, TOS and 8-OHdG levels, and decreased SOD, TAS and GSH levels expectedly (1–9, 14).

Obstructive uropathy is a common in many clinic practice and can occur anywhere along the urinary tract. Unilateral ureteral obstruction causes subacute renal injury characterized by tubular cell injury, interstitial inflammation and fibrosis. If this condition was not treated in acute period, chronic kidney disease may occur in weeks. There are a lot of study suggesting antioxidant therapy is one of preventing way, when it was applied properly (8, 15, 16, 17).

Literature indicated that antioxidant therapy; vitamins, drugs etc. ameliorate tissue damage in UUO models (1–10). One of them, Vitamin E provides a hydroxyl group for suppressing ROS formation and reduces radical development via chelating metal ions (2, 4–6). Vitamin E also has ability to suppress fibrotic gene and decelerate chronic kidney disease progression. Lunec et al revealed day supplementation of vitamin E (400 i. u. /day) has ability to decrease 8-OHdG levels that strongly expressed after UUO induced by ROS (3). These were well-known effects of Vitamin E; preventing lipid peroxidation and DNA damage, studied in many times and published.

Tasanarong et al studied Vitamin E treatment on mice UUO model in two studies and revealed this therapy is negative consequence on analytes those were effective on interstitial fibrosis process (4, 5).

We added Selenium into treatment to reveal not only to show antioxidant properties but also synergistic effect could improve the immunity and provide adequate immunity response. Using the two different doses of Vitamin E with Selenium administration employed in this study, we have described protective effects of this combined treatment.

Both of two doses increased all antioxidant response, but HDVE+Se approach had increased GSH, SOD more than RPVE+Se, whereas RPVE+Se treatment more effective on TAS levels. Otherwise, histologic examination revealed HDVE+Se treatment modality findings were similar to UUO, while RPVE+Se more likely with sham group.

Although biochemistry findings revealed HDVE+Se approach more effective than the RPVE+Se, histological findings showed RPVE+Se group examination more likely with sham group and the HDVE+Se was similarly to UUO. The discordance between histological and biochemistry findings is confusing, but TAS levels were more correlated with this condition. There might be another mechanism apart from the antioxidant mechanisms occurred in preventing renal damage. Moosavi suggested α-tocopherol administration could prevent oxidative damage in the obstructive kidney of Male Sprague-Dawley rats. However they did not reveal this improvement in acute ureteral obstruction (7). Another mechanisms such as metabolic pathways might be contribute this process, still unlighted.

Vitamin E treatment dosage is a controversial topic in literature. Naziroglu and his friends proposed high dose vitamin E with selenium combination may prevent nephropathy that was induced by cisplatin in forty female rats (16). In an another study conducted by Gonca and her colleagues, Vitamin E and Selenium recruitment ameliorates glomerular fibrosis, cellular and mesangial proliferation in Sprague-Dawley rats fed with cholesterol + Vitamin E + Se (8). Selenium has a key activity on glutathione peroxidase and reduces the activity of peroxidases. It shows antioxidant properties by stopping free radical and peroxide formation (7). In this study, antioxidant therapy using was recommended in renoprotective dose. We might propose Vitamin E dose controlling is important in treatment models. High dose might be harmful and had toxic damages to tubules and glomerulus.

This finding also supported Miller and his colleagues results that usage of high dose Vitamin E (>400 IU/d) may increase the mortality in long term period and so authors suggested high dose Vitamin E treatment should be avoided (18). Viana et al. demonstrated high dose Vitamin E (500 mg) have a negative effect in pregnant diabetic rats resulted with malformations in fetus. They revealed maximal benefit in normal fetus maturation was found with doses of 100 or 150 mg (19). High dose Vitamin E might have toxic effects on fetus. Kuemmerle revealed that sufficient plasma levels of vitamin E, reduce levels of free oxygen radicals in kidney tissue and blocks fibrogenic processes by suppressing TGFβ-1 levels (6).

In contrast, Aksoy et al. proposed high dose Vitamin E with selenium combination could play a pivotal role in the prevention of nephrotoxicity that prompted by cisplatin (17). Atasayar revealed the same results; administration high dose Vitamin E in nephrotoxic rat created by cisplatin, suppressed oxidant activity (14). Cisplatin is a directly cytotoxic agent, which can be used in cancer treatments. Cisplatin might have used a different path of damage or molecular mechanisms, and high dose Vitamin E ameliorated its toxic results.

There are some limitations in this study. We created UUO model on female rats because in experimental laboratory there were only female rats were ready for the study. Literature indicated that there is a clear sexual dimorphism in the prevalence of end stage CKD. Females are resistant to development of CKD. Another limitation is occurring three deaths in experimental group. Because of one death in each group, our experiment was not affected of these deaths.

Finally, we proposed Vitamin E and selenium treatment is an effective approach to prevent renal damage caused by ROS occurred via UUO. Dosage management is an important issue and needs further studies to support the use.

CONCLUSIONS

The present study suggested Vitamin E in protective doses with Selenium consumption may be a potential agent for the treatment of obstructive nephropathy in future. Antioxidant therapy is a debated and needed further examinations in renal damage issues. Dose management is not the unique problem but antioxidant therapy necessity also should be criticized.

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