TURKISH JOURNAL OF UROLOGY
Turk J Urol 2019; 45(Supp. 1): S70-S77 • DOI: 10.5152/tud.2018.22556
GENERAL UROLOGY
Original Article

The effect of coenzyme Q and selenium on kidney in rats with partial unilateral ureteral obstruction

Mustafa Koray Kırdağ[1], Devrim Tuğlu[1], Ercan Yuvanç[1], Üçler Kısa[2], Mahi Balcı[3], Ertan Batislam[1], Erdal Yılmaz[1]

Cite this article as: Kırdağ MK, Tuğlu D, Yuvanç E, Kısa Ü, Balcı M, Batislam E, et al. The effect of coenzyme Q and selenium on kidney in rats with partial unilateral ureteral obstruction. Turk J Urol 2019; 45(Supp. 1): S70-S77.

ABSTRACT

Objective: In this study, we aimed to investigate the antioxidant effects of selenium and coenzyme Q on renal damage in a partial unilateral ureteral obstruction (PUUO) in a rat model.

Material and methods: A total of 24 Sprague-Dawley rats were divided into four groups as Group 1 Control Group, Group 2, PUUO Group, Group 3 PUUO + coenzyme Q group, Group 4 PUUO + selenium group. Paraoxonase (PON), total antioxidant capacity (TAC), and total oxidant levels (TOS) were analyzed biochemically from tissue and blood samples. Tissue samples were examined histopathologically.

Results: The TAC in the tissues was found to be statistically significantly increased in Groups 3 and 4, compared to Group 2. Tissue TOS was found to be significantly reduced in Groups 3 and 4, compared to Group 2. Serum PON levels were significantly increased in Group 3 and 4, compared to Group 1 and 2. Histopathological examination showed that interstitial inflammation and congestion were lesser in the coenzyme Q and selenium groups than in the PUUO group. A more significant decrease was found in the selenium group than in the coenzyme Q group.

Conclusion: Our study results showed that coenzyme Q and selenium reduced the oxidation and the damage in tissue in PUUO in rats.

Keywords: Coenzyme Q; kidney; oxidative stress index; paraoxonase; partial unilateral ureteral obstruction; selenium; total antioxidant capacity; total oxidant status.

[1]Department of Urology, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[2]Department of Biochemistry, Kırıkkale University School of Medicine, Kırıkkale, Turkey
[3]Department of Pathology, Kırıkkale University School of Medicine, Kırıkkale, Turkey

Submitted: 03.04.2018
Accepted: 26.06.2018
Available Online Date: 19.11.2018

Corresponding Author: Mustafa Koray Kırdağ
E-mail: koraykirdag@gmail.com

Available online at www.turkishjournalofurology.com

Introduction

Dilatation may occur in kidneys in the early periods of obstruction, and necrosis, cellular inflammation, atrophy and apoptosis may occur in the following periods. In ureters, stasis may occur due to congenital, iatrogenic factors or secondary to other pathologies.[1] Oxidative stress may induce tissue damage and loss of function. This type of damage mechanism may also take place in the kidneys. In several studies and clinical trials, it has been shown that changes occur in tubular, endothelial and tubulointerstitial structures of the kidney tissue due to oxidative stress. Some renal diseases also develop secondary to this destructive mechanism including acute renal failure, glomerular damage and chronic renal failure.[1,2]

Coenzyme Q10 (CoQ10, ubiquinol-10 or ubiquinone-10) is a fat-soluble vitamin-like structure which can be found in every cell and it function as a coenzyme in the key enzymatic steps during cellular energy production.[3] It shows antioxidant properties by interfering with oxygen-derived radicals and singlet oxygen to prevent lipid peroxidation and damage of biomolecules.[4]

Selenium reduces the activity of hydroperoxidase and lipoperoxidase via its glutathione peroxidase-like activity. It shows antioxidant properties by stopping free radical and peroxide formation.[5]

To the best of our knowledge, there is no study showing the effect of coenzyme Q and sele-

nium against the oxidation in the kidney tissue during partial unilateral ureteral obstruction (PUUO) in the literature. Therefore, in the present study, we aimed to investigate the effect of antioxidant properties of coenzyme Q and selenium on oxidative stress, histopathological changes, and apoptosis in PUUO in rats.

Material and methods

In our study, a total of 24, 3-to 4-month-old female Sprague-Dawley rats weighing between 150 and 250 g (mean: 200 g) were used. The study design was accepted by Ankara Training and Research Hospital Local Ethics Commitee (Protocol Number: 276/06.03.2014). All procedures were carried out under veterinary control in accordance with the requirements of the 1986 International Strasbourg Universal Declaration of Animal Rights, with the approval of Ethical Board from Ankara Training and Research Hospital, Medical Sciences Experimental Research and Application Center (MSERAC). The subjects were housed in standard rat cages (n=6 in each cage) in a MSERAC-controlled setting. The rats were fed with pellet special for rodents and water. The removal of animal wastes, the supply of water and feed, the cleaning and control of the cages were carried out by the veterinarian and experienced staff of the center.

Meperidine hydrochloride (HCl) 5-10 mg/kg intraperitoneal (i.p.) was administered to provide postoperative analgesia to the rats, and the rat chows and water were given after the effect of the anesthetic agent had passed. At the end of 15 days postoperatively, the abdomen of the rats was opened through the abdominal incisions in the same manner and the ligated ureter was found and excised including the kidney pelvis. Some specimens were taken into vials containing formaldehyde and stored at +4°C for histopathological examination. Some specimens were taken into vials without formaldehyde and prepared for immunohistochemical and antioxidant examination.

Experiment groups

In our study, the subjects were divided into four groups.

Group 1 (Control Group): General anesthesia was provided by intramuscular (i.m.) injection of 5-10 mg/kg xylazine (Rompun, Bayer-Istanbul) and 50-70 mg/kg ketamine hydrochloride (Ketalar, Pfizer-İstanbul) to subjects before surgery. The midline of the abdominal wall was cleaned with 10% povidone iodine solution. A 2 cm-long midline abdominal skin and subcutaneous incisions were performed. After reaching the right ureter in the abdominal cavity, the layers were closed properly and the incision was closed with warm and wet compresses. At the end of 15 days, right nephrectomy was performed after these surgical procedures.

Group 2 (PUUO Group): The midline of the abdominal wall was cleaned with 10% povidone iodine solution. A 2-cm long midline abdominal skin and subcutaneous incisions were performed. After reaching the right ureter in the abdominal cavity, the ureter was ligated into the psoas muscle with 2.0 silk sutures to obtain partial obstruction. To produce a unilateral partial obstruction the psoas-implanting technique described in 1962 by Ulm and Miller was adapted.[6] The layers were, then, closed anatomically and no active substance was administered to the rats. At the end of 15 days, the abdomen was opened through an abdominal incision by the same method and right nephrectomy was performed.

Group 3 (PUUO + Coenzyme Q Group): Surgery was performed in Group 2. In addition oral coenzyme Q 10 mg/kg/day (median lethal dose: 5.2-8.2 g/kg of coenzyme Q) (MicroTherapeutics Inc., Irvine, CA, USA) was administered for 15 days. At the end of 15 days, the abdomen was opened through an abdominal incision by the same method and right nephrectomy was performed. The dose of coenzyme Q was chosen on the basis of previous study.[7]

Group 4 (PUUO + Selenium Group): Surgery was performed in Group 2. In addition selenium 0.25 mg/kg/day i.p. was administered for 15 days. At the end of 15 days, the abdomen was opened through an abdominal incision by the same method and right nephrectomy was performed. The dose of selenium was chosen on the basis of previous study.[8]

Histopathological, immunohistochemical and biochemical investigations

Histopathological analyzes were performed by the same pathologist at Kirikkale University Medical Faculty Pathology Department.

Hematoxylin & eosin staining

Paraffin sections in 5-μm thickness which were obtained via rotary microtome (RM 2135, Leica) were incubated at 60°C for one night for deparaffinization. They were subjected to xylene twice, each for 30 min. Tissue sections were passed through the alcohol series in the descending dilutions from 95% to 60% for the re-hydration process and, then, washed under running water for 5 min. After staining with hematoxylin (01562E, Surgipath, Bretton, Peterborough, CBE, UK) for 30 min, it was washed under running water for 5 min to remove excess stain from the tissue. The sections were, then, stained with eosin (01602E, Surgipath, Bretton, Peterborough, CBE, UK) for 2 min. In the same way, after washing under running water for 5 min, they were passed through 80% and 95% alcohol series, respectively. The air-dried sections were held in xylene twice each for 30 min to make them transparent. They were, then, closed with Entellan bonding material (UN 1866, Merck, Darmstadt, Germany). A

Turk J Urol 2019; 45(Supp. 1): S70–S77
DOI:10.5152/tud.2018.22556

Table 1. Biochemical results

	Group 1 (n=6) (Control)	Group 2 (n=6) (PUUO)	Group 3 (n=6) (PUUO+CQ)	Group 4 (n=6) (PUUO+SE)	p (ANOVA)
TAC (nmoLTrolox Equiv. per mg protein)	0.71±0.24	1.01±0.05	1.17±0.04	1.31±0.10	<0.001
TOS (nmoL H_2O_2 Equiv.per mg protein)	22.71±1.75	29.02±2.90	17.04±1.21	14.53±5.10	<0.001
OSI (arbitrary unit)	26.80±3.88	28.71±2.54	14.84±1.52	11.22±4.20	0.003
PON (mUI/mL)	45.6±2.4	36.2±3.5	51.6±1.3	62.3±2.4	<0.001

TAC: total antioxidant capacity; TOS: total oxidative status; PUUO: partial unilateral uretaral obstruction; CQ: coenzym Q; SE: selenium; OSI: oxidative stress index

Table 2. Histopathological results (histopathological examination scoring)

	Control	PUUO	PUUO+Coenzyme Q	PUUO+Selenium
Interstitial inflammation	-	+++	++	+
Tubular and glomerular degeneration	-	++	+	+
Tubular dilatation	-	++	+	+

PUUO: partial unilateral uretaral obstruction; CQ: coenzym Q; SE: selenium

semi quantitative evaluation of renal tissues was accomplished by scoring the degree of severity according to previously published criteria. All sections of kidney samples were examined for tubular necrosis. Briefly, minimum of 50 proximal tubules associated with 50 glomeruli were examined for each slide and an average score was obtained. Severity of lesion was graded from 0 to 3 according to the percentage of the tubular involvement. Slides were examined and severity of changes was evaluated using scores on a scale in which (0) denotes no change; grade 1-changes affecting <25% tubular damage (mild); grade 2-changes affecting 25-50% of tubules (moderate); Grade 3 – changes affecting >50% of tubules (severe).[9]

Immunohistochemical staining

For immunohistochemistry, the antibody M30 CytoDEATH (12140322001, Roche Diagnostics Gmbh, Germany) was used as the primary antibody. In the preliminary studies, the optimal dilution rate was found to be 1/10 and primary antibodies were applied in this dilution. The following procedures were applied for immunohistochemical examination, respectively. The sections with a thickness of 5 μm were taken from the study blocks and the preparations were incubated at 60°C for one night. Then, the preparations were placed in a Bench Mark GX (Ventana, Roche) staining device. During the staining procedure, 150 μL primary antibody prepared with a 1/10 dilution was added to each preparation. At the end of the staining process, the preparations were washed with alcohol and left to dry at 60°C. All preparations taken from the oven were waited in xylene for 5 min and closed with slide after dropping Entellan material. In the immunohistochemical study with M-30, the staining differences between the groups were evaluated semi-quantitatively, and scored accordingly.

0: no immunoreaction
1: slight staining
2: medium staining
3: marked immunoreaction.

Biochemical examinations

Total antioxidant capacity

The TAC kit was used for the measurement of total antioxidant status. The principle of the method is based on the reduction of dark blue-green colored ABTS radical to the colorless ABTS form by the antioxidants in the sample. For TAC measurement, after adjusting the spectrophotometer (Shimadzu UV 1700A) to 25°C, 500 mL of reagent 1 (measurement buffer) and 30 mL of serum were mixed, and the absorbance was measured at 660 nm, as indicated in the kit procedure. Seventy-five millilitre of reagent 2 (colored ABTS solution) was added to the mixture and incubated for 10 min, and the absorbance was re-measured at 660 nm. Standards were studied using standard solutions of the kit, 0 (standard 1) and 1 (standard 2) rather than serum in concentrations of millimolar Trolox equivalent/liter (mmol Trolox Eq/L). The change in absorbance (ΔAbs) was calculated from the difference between the second and first measurements. TAC levels in the serum (mmol Trolox Eq/L) were calculated according to the kit formula: TAC=[(ΔAbs standard 1)-(ΔAbs sample)] / [(ΔAbs standard 1)-(ΔAbs standard 2)]. The TAC was measured using the total antioxidant activity method. The measurement results were expressed in μmol Trolox equivalent/L.[10]

Total oxidant status

The TOS kit was used for the measurement of total oxidant status. The principle of the method is based on the fact that the oxi-

Table 3. Immunohistochemical results

	0	1	2	3
S1	+			
S2	+			
S3	+			
S4	+			
S5	+			
S6	+			
C1				+
C2				+
C3				+
C4			+	
C5			+	
C6				+
CQ enzyme			+	
CQ2		+		
CQ3				+
CQ4		+		
CQ5	+			
CQ6	+			
SE1	+			
SE2		+		
SE3		+		
SE4		+		
SE5	+			
SE6	+			

S: sham; C: control; CQ: coenzym Q; SE: selenium

dants in the sample oxidize the ferrous ion-chelator complex to the ferric ions and that the color of resulting ferric ions changes with the chromogenic material in the acidic environment. For the measurement of TOS, as indicated in the kit procedure, after adjusting the spectrophotometer (Shimadzu UV 1700A) to 25°C, 500 mL of reagent 1 (measurement buffer) and 75 mL of serum were mixed, and the absorbance was measured at 530 nm. Then, 25 mL reagent 2 (pro-chromogenic solution) was added to the mixture and incubated for 10 min and, the absorbance was measured again at 530 nm. For the quality assessment of the kit, as indicated in the kit procedure, the absorbance of the reactive blind examined with deionized water rather than sample was less than 0.500. The standard was studied by using a diluted standard solution containing 20 micromolar hydrogen peroxide (H_2O_2) equivalent/liter (mmol H_2O_2Eq/L) rather than serum. The change in absorbance (ΔAbs) was calculated from the difference between the second and first measurements. TOS of the serum (mmol H_2O_2Eq/L) was calculated according to the kit formula: TOS= [(ΔAbs serum) / (ΔAbs standard)] x 20. The results of the measurements were expressed in mmol H_2O_2Eq/L.[11]

Oxidative stress index

The Oxidative Stress Index (OSI) value was accepted as the percentage rate of TAC and TOS values. Initially, the TAC values were converted to mmol/L. Then, the OSI value was calculated according to the formula: OSI (Arbitrary Unit)=TOS (mmol H_2O_2Eq/L)/TAC (mmol Trolox Eq/L).[11]

Paraoxonase

The PON-1 activity was determined by using commercial experimental kits (Relassay®, Gaziantep, Turkey). The PON-1 experiment can be performed in the presence or absence of sodium chloride (NaCl), and molar absorptivity coefficient of 18290 was used to calculate M-1 cm-1 enzyme activity.[12]

Statistical analysis

All statistical analyzes were carried out using Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA). Student t and One way ANOVA test with Bonferroni correction were used for comparing normally distributed data. Subsequently, the relation between these parameters was evaluated using linear regression analysis (Backward). These distinctions were accepted significant when possibility was less than 0.05.

Results

Biochemical findings

When the tissue TAC levels were evaluated ipsilaterally, the levels were found to be statistically significantly increased ($p<0.001$) in Groups 3 and 4, compared to Group 1. There was also a statistically significant increase in Group 3, compared to Group 2, and also in Group 4, compared to Group 2 ($p<0.001$) (Table 1). There was also a statistically significant increase between Group 3 and Group 4 ($p<0.001$) (Table 1).

When the tissue TOS values were examined, there was a statistically significant decrease in Group 4, compared to Group 1 ($p<0.001$), a statistically significant decrease in Group 3 and 4, compared to Group 2 ($p<0.001$), indicating a statistically significant difference between Groups 3 and 4 ($p<0.001$).

In terms of the OSI parameters, there was a statistically significant decrease in Groups 3 and 4, compared to Group 1 (Table 1). In addition, there was a statistically significant decrease in Group 3 and 4, compared to Group 2, and there was a statistically significant decrease between Groups 3 and 4 ($p<0.025$) (Table 1).

Turk J Urol 2019; 45(Supp. 1): S70-S77
DOI:10.5152/tud.2018.22556

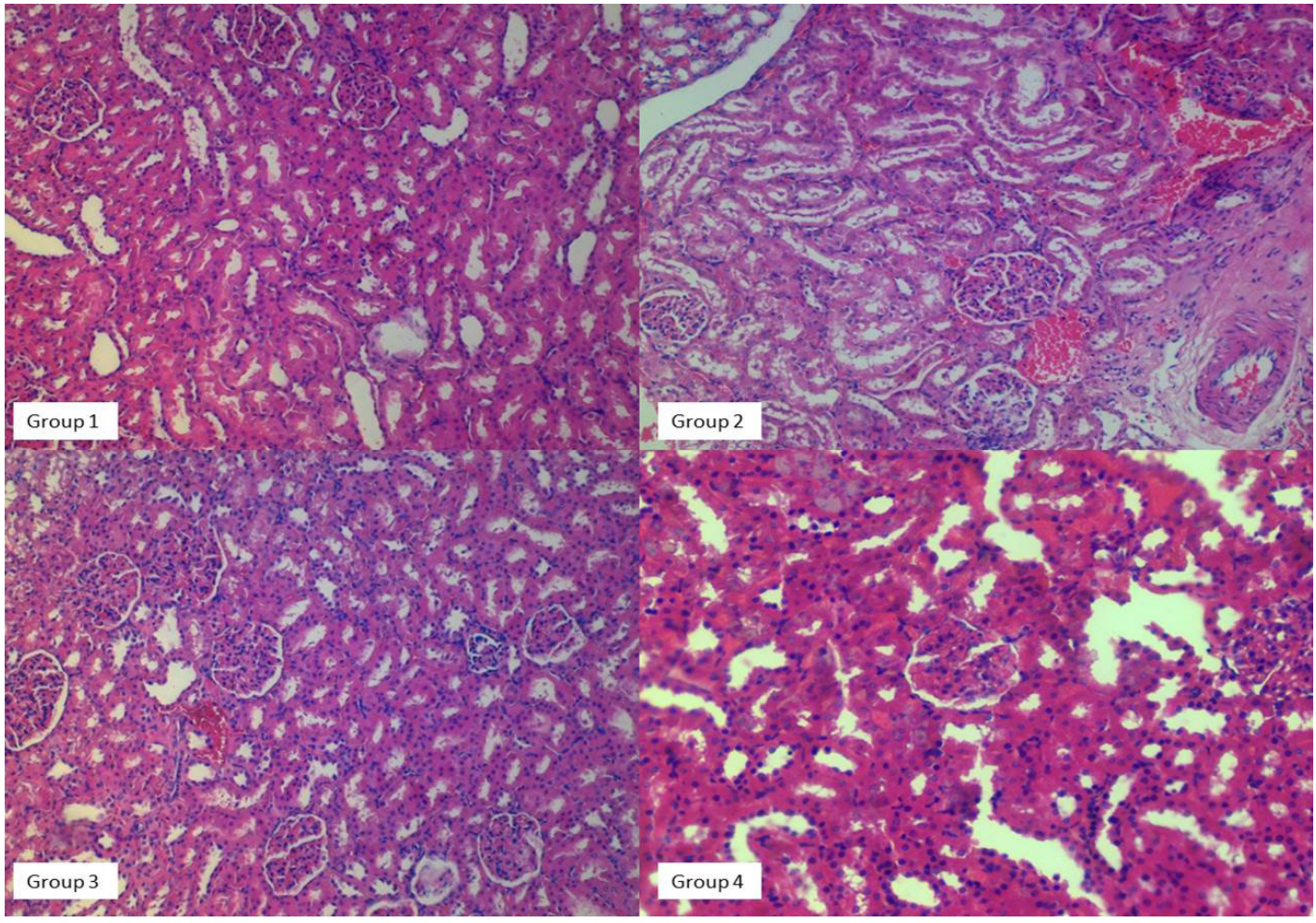

Figure 1. Group 1 (Control Group); Normal kidney tissue, Group 2 (PUUO Group), Kidney tissue specimen of PUUO group, Group 3; Kidney tissue specimen of coenzyme Q group (examination by light microscope X10 magnification). Group 4; Kidney tissue specimen of selenium group (examination by light microscope X20 magnification)

Furthermore, serum PON values statistically significantly increased in Groups 3 and 4, compared to Groups 1 and 2 ($p<0.001$). There was a statistically significant increase in the PON values between Groups 3 and 4 in favor of Group 4.

Histopathological findings

Histopathological examination showed that glomerular atrophy, degeneration of tubules, interstitial inflammation, and congestion decreased in the coenzyme Q group and even more in the selenium group, compared to the PUUO group (Figure 1). In terms of apoptosis, similar to histopathological findings, the number of apoptotic cells decreased which was more prominent in the selenium group (Figure 2).

Discussion

Partial obstruction may occur in the ureters due to several factors such as urinary system stones, ureteropelvic junction stenosis, tumors, ureterovesical junction stenosis, and iatrogenic reasons. Hydronephrosis, renal blood flow variability, and loss of kidney function may develop due to partial obstruction.[13,14] Renal obstruction leads to tubular atrophy and cellular death. When the kidney is obstructed in a rat, apoptosis occurs four days later in the renal tubular cells, and it peaks after 15 days and continues in the interstitial cells during obstruction.[15]

The response to renal tissue damage is a complicated metabolic process and its development takes time. In this case, a single biochemical marker and measurement can be misleading. As distinct from previous publications, in the present study, we evaluated many parameters at the same time and contributed to the early evaluation of kidney damage.

The measurement of TOS provides a sensitive index of lipid peroxidation and oxidative stress.[16] The measurement of TAC

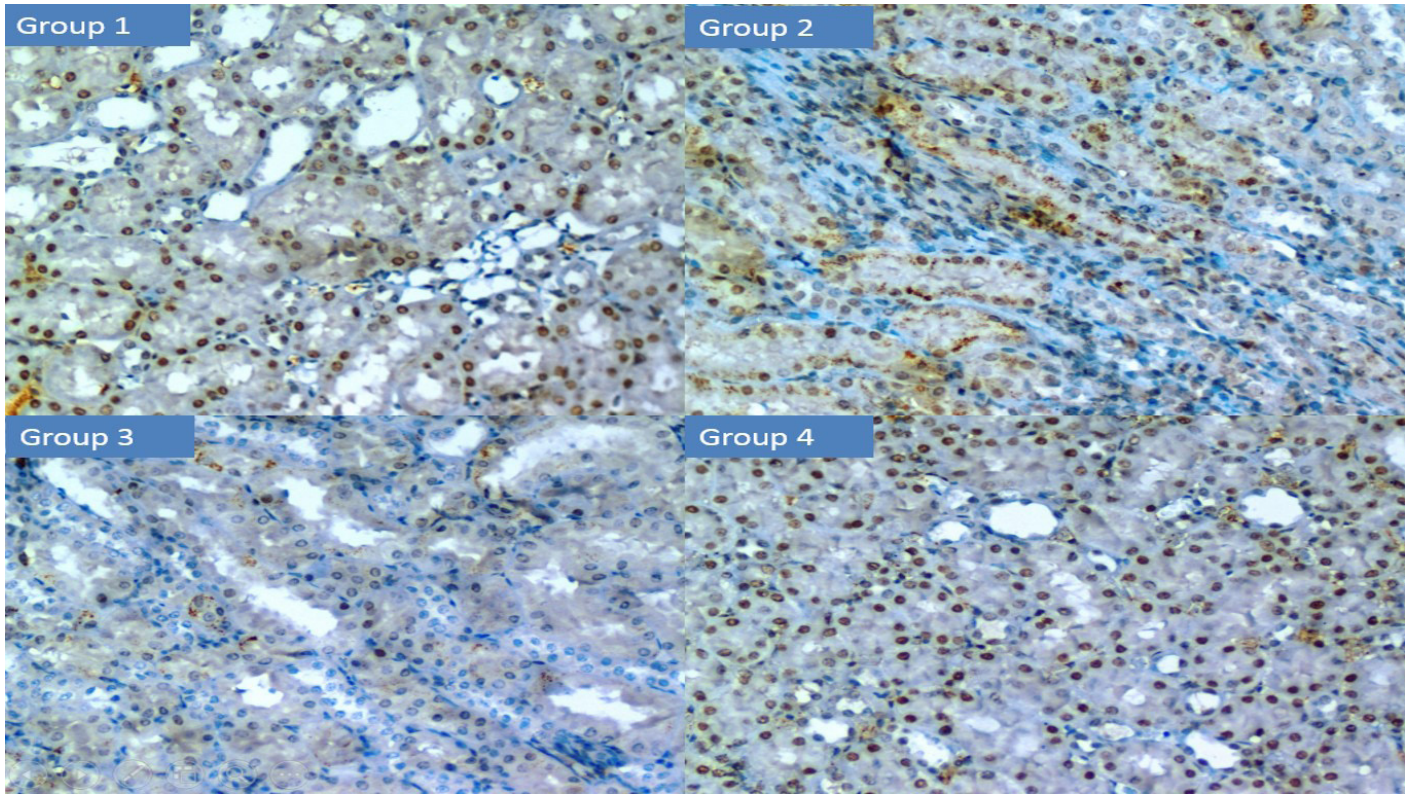

Figure 2. Evaluation of Apoptosis Tissue specimens by immunohistochemical staining method (Group 1 (Control) X200, Group 2 (PUUO) X200, Group 3 (PUUO + Coenzym Q) X200, Group 4 (PUUO + Selenium) X200 magnification)

gives more sensitive information than the individual measurement of antioxidants.[10] Therefore, in the determination of the antioxidant level, the measurement of TAC has become more widespread rather than the measurement of individual antioxidants. In addition, the OSI is a parameter found by dividing the total oxidants by total antioxidants, which indicates whether there is a disruption in balance.[11]

Paraoxonase-1 enzyme protects low-density lipoprotein (LDL) and high-density lipoprotein (HDL) from the effects of oxidative stress by oxidation of lipid peroxides on the oxidized lipoproteins. It is also responsible for some of the antioxidant properties of HDL.[17] It can also be used to evaluate the antioxidant defense system.[18]

To date, numerous studies have reported the beneficial effects of some drugs on renal damage in unilateral partial ureteral obstruction.[19-21] However, the prevention of renal damage due to urinary obstruction is still an unresolved issue.

There are studies in the literature showing the antioxidant effects of coenzyme Q and selenium. Renal function improvement was found in male rats three weeks after heminephrectomy thanks to antioxidant effects of coenzyme Q.[22] In our study, coenzyme Q was found to protect the kidneys at a significant level as demonstrated with the improvement in biochemical antioxidant parameters, compared to the PUUO group, in rats with PUUO (Table 1). The same effect was observed at the histopathological and immunohistochemical levels (Table 2).

In the ischemia-reperfusion studies with selenium, decrease in the levels of nitric oxide and in lipid peroxidase activity, increase in glutathione peroxidase, and PON levels were observed in the selenium treated groups, suggesting the antioxidative effect of selenium.[8]

In the study conducted by Akman et al.[23] selenium was found to prevent oxidative damage in intussusception by increasing antioxidant enzyme activity; however, similar effects were not observed in the histopathological findings. In our study, we found that selenium significantly protected the kidneys in rats with PUUO biochemically, compared to the PUUO group (Table 1), and the same effect was confirmed by histopathological and immunohistochemical analyses (Table 2, 3).

A decrease in the PON-1 levels indicates a decrease in antioxidant activity and an increase in oxidative stress.[24] Previous studies have also shown that PON-1 has a protective effect against oxidative stress and plays an antioxidant role.[25,26] In our groups, an increase in the PON levels, which is a marker of antioxidant

Turk J Urol 2019; 45(Supp. 1): S70–S77
DOI:10.5152/tud.2018.22556

property, was found in Groups 3 and 4, compared to Groups 1 and 2 (Table 1). In our study, coenzyme Q and selenium reduced the TOS and the OSI at the biochemical level. Although this improvement was seen in the control group, it was statistically more significant in the selenium group than in the coenzyme Q group. In histopathological and immunohistochemical analyses, we also found that coenzyme Q and selenium reduced interstitial inflammation, congestion and apoptosis. However, this effect was statistically more significant in the selenium group than the coenzyme Q group.

In conclusion, our study results suggest that coenzyme Q10 and selenium have antioxidative effects on the kidney in rats with PUUO. Although these findings will contribute to the existing literature, further studies are required to support the use of both antioxidants in the clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee Ankara Training and Research Hospital, Animal Care and Investigational Committee (Protocol Number: 276/2014).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.T., M.K.K.; Design – D.T., M.K.K.; Supervision – E.Y., E.B.; Resources – E.Y.U.; Materials – D.T., M.K.K., E.Y.U.; Data Collection and/or Processing – M.B., Ü.K., D.T., M.K.K.; Analysis and/or Interpretation – D.T., M.K.K., E.Y.; Literature Search – D.T., M.K.K.; Writing Manuscript – D.T., M.K.K.; Critical Review – E.Y., E.B., D.T.; Other – M.B., Ü.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that they haven't received any financial support for this study.

References

1. Sampaio FJB. Renal anatomy: endourologic considerations. Urol Clin North Am 2000;27:585-607. [CrossRef]
2. Docherty NG, O'Sullivan OE, Healy DA, Murphy M, O'neill AJ, Fitzpatrick JM, et al. TGF-beta1-induced EMT can occur independently of its proapoptotic effects and is aided by EGF receptor activation. Am J Physiol Renal Physiol 2006;290:F1202-12.
3. Rajiv Saini. Coenzyme Q10: The essential nutrient. J Pharm Bioallied Sci 2011;3:466-7. [CrossRef]
4. Bonakdar RA, Guarneri E. Coenzyme Q10. Am Fam Physician 2005;72:1065-70.
5. Ozbal S, Erbil G, Koçdor H, Tugyana K, Pekcetin C, Ozogul C. The effects of selenium against cerebral ischemia-reperfusion injury in rats. Neurosci Lett 2008;438:265-9. [CrossRef]
6. Ulm AH, Miller F. An operation to produce experimental reversible hydronephrosis in dogs. J Urol 1962;88:337-41. [CrossRef]
7. Fouad AA, Al-Sultan AI, Yacoubi MT. Coenzyme Q10 counteracts testicular injury induced by sodium arsenite in rats. Eur J Pharmacol 2011;655:91-8. [CrossRef]
8. Zendelel A, Gharibi Z, Anbari K, Abbaszadeh A, Khaya K, Khorramabadi RM, et al. Selenium Ameliorate Peripheral Nerve Ischemic-Reperfusion Injury via Decreased TNF-α. Biol Trace Elem Res 2017;176:328-37. [CrossRef]
9. Ozbek E, Ilbey YO, Ozbek M, Simsek A, Cekmen M, Somay A. Melatonin attenuates unilateral ureteral obstruction-induced renal injury by reducing oxidative stress, iNOS, MAPK, and NF-kB expression. J Endourol 2009;23:1165-73. [CrossRef]
10. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. J Clin Biochem 2004;37:112-9. [CrossRef]
11. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103-11. [CrossRef]
12. Toy H, Camuzcuoglu H, Celik H, Erel O, Aksoy N. Assessment of serum paraoxonase and arylesterase activities in early pregnancy failure. Swiss Med Wkly 2009;139:76-81.
13. Vaughan Ed Jr, Sorenson EJ,Gillenwater JY. The renal hemodynamic response to chronic unilateral complete ureteral occlusion. Invest Urol 1970;8:78-90.
14. Ekinci S, Ciftci AO, Atilla P, Muftuoglu S, Senocak ME, Buyukpamukcu N. Ureteropelvic junction obstruction causes histologic alterations in contralateral kidney. J Pediatr Surg 2003;38:1650-5. [CrossRef]
15. Canbay A, Friedman S, Gores GJ. Apoptosis: the nexus of liver injury and fibrosis. Hepatology 2004;39:273-8. [CrossRef]
16. Uzar E, Alp H, Cevik MU, Fırat U, Evliyaoglu O, Tufek A, et al. Ellagic acid attenuates oxidative stress on brain and sciatic nerve and improves histopathology of brain in streptozotocin-induced diabetic rats. Neurol Sci 2012;33:567-74. [CrossRef]
17. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998;101:1581-90. [CrossRef]
18. Topsakal C, Kilic N, Ozveren F, Akdemir I, Kaplan M, Tiftikci M, et al. Effects of prostaglandin E1, melatonin, and oxytetracycline on lipid peroxidation, antioxidant defense system, paraoxonase (PON1) activities, and homocysteine levels in an animal model of spinal cord injury. Spine 2003;28:1643-52. [CrossRef]
19. Yigiter M, Yildiz A, Polat B, Alp HH, Keles ON, Salman AB, et al. The protective effects of metyrosine, lacidipine, clonidine,and moxonidine on kidneydamageinduced by unilateral ureteral obstruction in rats. Surg Today 2012;42:1051-60. [CrossRef]
20. Akin M, Demirbilek S, Ay S, Gurunluoglu K, Turkmen E, Tas E, et al. Attenuation of ureteral obstruction-induced renal injury by polyenylphosphatidylcholine. Int J Urol 2007;14:350-6. [CrossRef]
21. Yasar A, Erdemir F, Parlaktas BS, Atilgan D, Koseoglu RD, Saylan O, et al. The effect of carvedilol on serum and tissue oxidative stress parameters in partial ureteralobstruction induced rat model. Kaohsiung J Med Sci 2013;29:19-25. [CrossRef]
22. Ishikawa A, Kawarazaki H, Ando K, Fujita M, Fujita T, Homma Y. Renal preservation effect of ubiquinol, the reduced form of coenzyme Q10. Clin Exp Nephrol 2011;15:30-3. [CrossRef]
23. Akman H, Somuncu S, Dikmen G, Ayva S, Soyer T, Dogan P, et al. Protective effect of selenium on intussusception-induced isch-

emia/reperfusion intestinal oxidative injury in rats. Turk J Med Sci 2010;40:391-7.

24. Costa LG, Giordano G, Furlong CE. Pharmacological and dietary modulators of paraoxonase 1 (PON1) activity and expression: The hunt goes on. Biochem Pharmacol 2011;81:337-44. [CrossRef]
25. Vasdev S, Gill V, Singal PK. Beneficial effect of low ethanol intake on the cardiovascular system: possible biochemical mechanisms. Vasc Health Risk Manag 2006;2:263-76. [CrossRef]
26. Gur M, Aslan M, Yildiz A, Demirbag R, Yilmaz R, Selek S, et al. Paraoxonase and arylesterase activities in coronary artery disease. Eur J Clin Invest 2006;36:779-87. [CrossRef]