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# Proliferative and apoptotic evaluations of renal preventive effects of coenzyme Q10 in radioiodine-131 induced renal damage

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**Abstract:** The aim of this study was to investigated anti-proliferative and anti-apoptotic effects of coenzyme Q10 (CoQ10) in the prevention of radioiodine-131 (RAI) ($I^{131}$) induced kidney damage. A total of 24 Wistar albino rats were separated into equal three groups (n = 8/group): Group 1 (control): untreated group; Group 2 (RAI): 3 mCi/kg RAI oral route; Group 3 (RAI+CoQ10): 3 mCi/kg RAI oral route and intraperitoneally 30 mg/kg/day CoQ10. CoQ10 treatment was started two days before RAI administration and was continued five days once daily after RAI. Pathomorphological parameters of kidneys were measured using hematoxylin–eosin and Masson's trichrome staining. Immunohistochemically; proliferating cell nuclear antigen (PCNA), caspase 8, caspase 9 and terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick end labeling (TUNEL) were used to determine proliferation and apoptosis. With the exception of the control group, varying degrees of inflammation, degeneration, necrosis, and interstitial/perivascular fibrosis were detected in the kidneys of all rats. This histopathological damage was found to be significantly less in CoQ10 group versus RAI group ($P<0.05$). The all immunohistochemical examinations demonstrated that administration of CoQ10 had reduced proliferation and apoptosis ($P<0.05$). The results of kidney histopathology and immunohistochemistry demonstrated that administration of CoQ10 had reduced inflammation, proliferation, and apoptosis. These findings show CoQ10 can play an important role in the radioprotection of kidneys against RAI-induced damage.

**Keywords:** Antiapoptotic, antiproliferative, coenzyme Q10, kidney, radioiodine-131.

## Radioiodine-131 ile uyarılmış böbrek hasarının önlenmesinde koenzim Q10'un proliferatif ve apoptotik etkilerin değerlendirilmesi

**Özet:** Bu çalışmanın amacı radioioidine-131 (RAI) ($I^{131}$) tedavisine bağlı oluşan böbrek hasarının önlenmesinde koenzim Q10 (CoQ10)'nun anti-apoptotik ve anti-proliferatif etkisinin araştırılmasıdır. Yirmi dört Wistar albino sıçan rastgele olarak üç gruba ayrıldı (n=8/grup): Grup 1 (kontrol): tedavi uygulanmayan grup; Grup 2 (RAI): orogastrik yolla tek doz 3 mCi/kg RAI uygulanan grup; Grup 3 (RAI+CoQ10); tek doz 3 mCi/kg RAI ve intraperitonel olarak 30 mg/kg/gün CoQ10 uygulanan grup. CoQ10 tedavisi RAI uygulamasından 2 gün önce başladı ve RAI sonrası günde bir kez beş gün süreyle uygulandı. Son CoQ10 uygulamasından yirmi dört saat sonra sıçanların böbrekleri alınarak patomorfolojik incelemeler amacıyla hematoksilen-eosin ve Masson'un Trikrom metoduna göre boyandı. İmmunohistokimyasal olarak: proliferasyonun belirlenmesi amacıyla prolifere hücre nükleer antijen (PCNA); apoptozisin belirlenmesi amacıyla Caspase 8 ve Caspase 9; DNA hasarının belirlenmesi amacıyla TUNEL boyaması yapıldı. Çalışma sonucunda; kontrol grubu dışındaki sıçanların böbreklerinde değişen şiddette inflamasyon, ödem, dejenerasyon, nekroz ve fibrozis görülürken bu bulguların CoQ10 ile tedavi edilen grupta istatistiksel olarak belirgin düzeyde daha az olduğu dikkati çekti ($P<0,05$). İmmunohistokimyasal olarak profilerasyonun, apoptozisin ve DNA hasarının CoQ10 grubunda daha hafif olduğu istatistiksel olarak tespit edildi ($P<0,05$). Bu çalışma sonuçlarıyla radyoiyodin'in böbrekler üzerinde yaptığı hasarın önlenmesinde CoQ10'nun başlıca antienflamatuar, antiproliferatif ve antiapoptotik etkiyle radioprotektif olduğu belirlenmiştir.

**Anahtar sözcükler:** Antiapoptozis, antiproliferasyon, böbrek, koenzim Q10, radyoiyodin-131.

## Introduction

Radioiodine–131 (RAI) ($I^{131}$) has been an important component in the treatment of thyroid dysfunction, hyperthyroidism, Graves' disease and differentiated thyroid cancer since the 1940s. It is applied as the continuation of treatment for the prevention of potential recurrences and undetected metastases following total thyroidectomy, particularly in patients with thyroid cancer (10). RAI, which is a radio–isotope, damages tumor cells by irradiating high energy beta (β) (0.61 MeV) and gamma (γ) (0.36 MeV) radiation in these cells and thereby stops tumor development (19).

RAI administered per oral as a part of the treatment (10). It is absorbed by gastrointestinal system cells and then it reaches to target cells through circulation and enters thyroid cells with active transport via Na+/I–Symporter (NIS), which is an integral plasma membrane glycoprotein found in the basolateral membrane of the cells (24). RAI is excreted from the salivary glands, lacrimal gland, mammary gland, and kidneys. Approximately 90% of the RAI administered for treatment is excreted from the kidneys in the first 48 hours (7). This excretion has been seen to continue until the $10^{th}$ week following the administration (30). During the excretion of RAI continue the uptake via NIS at these extrathyroidal tissues. RAI continue to emit ionizing radiation and leads to activation of chemical mediators of inflammation (Interleukin (IL), Tumor Necrosis Factor alpha (TNF-α), etc.) with the increase of reactive oxygen species (ROS) (superoxide, lipid peroxidase and hydrogen peroxide, etc.) in extra–thyroidal and extra–tumoral tissues of the treated patients (2). The ROS in the tissues causes impairment of the control mechanisms of the cell organelles, membrane, DNA and mitochondria and result in genetic destruction, proliferation, apoptosis and inflammation in the kidneys (3, 22). Therefore, there is a need for safe and effective protective agents to protect kidney during $I^{131}$ therapy and prevent secondary renal complications. Recent studies have reported positive results with antioxidant supplements for the prevention of RAI–induced extrathyroidal tissue damage (4, 5, 13, 29).

CoQ10 is a lipid–soluble, nontoxic, vitamin like substance found in many natural foods. CoQ10, which is absorbed by chylomicrons from the gastrointestinal system. Then it goes to tissues which have high metabolic activity, such as the heart, liver, muscle and kidneys through lymphatics and blood. Most of it (40–50%) accumulates in the mitochondria of cells in these tissues, and the remainder accumulates in lysosome, Golgi apparatus, microsome and plasma membrane (11). It primarily acts as an electron transporter of mitochondrial respiratory chain and provides intracellular ion balance. It prevents oxidation and lipid peroxidation in the cell membrane and thereby plays a role in the control of apoptosis. In addition, it shows an anti–inflammatory effect by reducing inflammatory mediators like IL, cytokine and TNF-α (15, 23, 28). CoQ10 has been widely used for the prevention and treatment of various diseases, such as renal (18), cardiovascular (20) and neural diseases (16).

The aim of this study was to investigate the radioprotective effect of CoQ10, an easily available, nontoxic and inexpensive substance, in the prevention of RAI–induced kidney damage.

## Materials and Methods

***Animals:*** All stages of the study were conducted in the Animal Unit Laboratory after national and Local Ethics Committee approval had been obtained for the breeding and use of laboratory animals and accordance with the principles of the experimental ethical principles and animal protection laws according to the rules of EU Directive 2010/63/EU for animal experiments and in compliance with the ARRIVE guidelines and the AVMA euthanasia guidelines 2013 (Approval No: 2020-0059).

The study included a total of 24 male Wistar albino rats aged 4–5 months, each weighing 250–300 g. The sample size of the study was calculated with the G. Power software (ver. 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Germany) statistical analysis. The required total sample was calculated as 24 for 80% power, $\alpha = 0.05$ type I error, and f effect size= 0.80. The animals had a one-week adaptation period to the laboratory environment before the study. The rats were kept in polypropylene cages in room (65–70% humidity and of 21±2 °C temperature) 12–h light/dark cycle and were fed with ad libitum. A sterile pad sheath was used under an absorbable disposable cover to prevent radioactive spread.

***Experimental design:*** The rats were randomly divided into equal three groups (n = 8/group). Group 1 (control) was given no treatment. For treatment-experiment groups (Group 2 and Group 3) were given standard therapy as according to previous similar studies (28). In Group 2 (RAI), radioiodine-131 (Mon–Iyot–131, Eczacıbaşı) was applied at 3 mCi/kg via orogastric route. Group 3 (RAI + CoQ10) was given 3 mCi/kg RAI and 30 mg/kg CoQ10 (Phytopharma, Turkey) via the intraperitoneal (ip) route. CoQ10 was started two days before the RAI, and was continued for five days once daily after RAI administration. At 24 hours after the last dosage of CoQ10, the animals were anesthetized with 50 mg/kg ip propofol and sacrificed. The bilateral kidneys were removed with standard methods for histomorphological and immunohistochemical examination.

***Histopathological examination:*** Tissue samples were fixed in 10% formalin (pH 7.2-7.4) and taken for

routine pathology follow–up as described by Luna et al (17). The tissues, which were dehydrated in increasing degrees of alcohol in an automated tissue follow–up device, were applied with xylol to obtain transparency and embedded in paraffin blocks. Sections of 5–µm were taken with a Leica RM 2125 RT microtome, with the first three and every tenth sections taken onto lams. The preparations were passed through alcohol and xylol series and stained with Hematoxylin–Eosin (HE) and Masson's trichrome stains. All samples were examined under a light microscope (Olympus DP–73, Olympus BX53–DIC microscope; Tokyo, Japan).

All of the stained sections of kidneys were evaluated according to previously published grading system as 0 to 3 (score 0: none, score 1: mild, score 2: moderate and score 3: severe) by the presence and severity of the findings (30).

***Immunohistochemical examination***

***Reagents:*** The reagents used in this study were: PCNA (PCNA15; Invitrogen, USA), Caspase 8 (ab4052; Abcam, USA), Caspase 9 (ab52298; Abcam, USA), and TUNEL assay (InSitu Cell DeathDetection Kit, POD; Roche, Germany); Proteinase K (Roche, Germany), for the chromogens; diaminobenzidine (DAB), 3–amino 9–ethylcarbasole (AEC), and Avidin Biotin Complex (ABC) Immunohistochemical compounds (Histostain Plus Kit; USA).

***Staining:*** Standard Avidin Biotin Complex (ABC) protocol was followed to stain the tissue samples using the Histostain-Plus Kit. After routine deparaffinization and rehydration procedures, the Antigen retrieval was done in a microwave oven 700 W and 10 min with pH 6.0 citrate buffer solution. Endogenous peroxidase activation in the tissues was blocked for 15 min with 0.3% hydrogen peroxide ($H_2O_2$) in 0.01 mol/l Phosphate Buffered Saline (PBS) in methanol. After protein blocking with 5% normal goat serum for 20 min the sections were incubated with PCNA (1:100), caspase 8 (1:50), and caspase 9 (1:100) primer antibodies for one hour. Then, tissues were reacted with secondary antibody for 30 min and stained with DAB chromogen for 5 min. Finally, all of the sections were counterstained with hematoxylin. All steps were carried out at 37 °C and in a damp chamber. PBS was used as a washing solution during all the staining steps.

***TUNEL assay procedures:*** TUNEL marking was performed in accordance with the instructions of the manufacturer. For this purpose, 5 µm sections were treated with Proteinase K (20 mg/ml) at room temperature and damp chamber for 20 min. The washed sections were kept in freshly prepared 50 µL of TUNEL reaction mixture (including TdT&dUTP) solution in the dark, at 37 °C for one hour. Afterwards, the sections were coated with 50 µL of antifluorescein antibody conjugated POD enzyme homogenate and kept at 37 °C for 30 min. Finally, the washed sections were stained with hematoxylin after treatment with AEC for 10 min.

***Method of counting:*** The number of immunopositive cells in the sections were counted under the microscope magnified at 400X in 1 mm2, and ten fields were chosen randomly. The total number of cells in each field were counted. Staining indexes were calculated on the basis of the percentages of the stained nucleus for all markers. The staining intensity was scored from 0 to 3; the distribution of immunoreactive cells 0: for less than 10%, 1: for 10-50%, 2: for 50-80%, and 3: more than 80% of positive cells.

***Statistical analysis:*** Data analysis was performed using Statistical Package for Social Sciences for Windows software (SPSS version 24.0, SPSS Inc. Chicago, IL). Descriptive statistics were used to determine the continuous variables and frequency distributions for categorical variables. The normality of distribution of continuous variables was tested by Shaphiro Wilk test. The groups were compared with nonparametric tests, as the data did not show a normal distribution. Statistical differences between the groups were assessed with the Kruskal Wallis tests. Tukey honestly significant difference or Dunn multiple comparison test was used to determine which group was different from the others. Results were given as Median [minimum–maximum] deviation. P value $< 0.05$ was accepted as statistically significant.

## Results

***Histopathological results:*** The histopathological results of the kidney tissues are summarized in the Table 1. The kidney tissues of the rats in control group were seen to be normal and no pathological changes were found. Whereas, the histopathological changes in tubules, glomeruli, interstitium and vessels were observed to be significantly milder in Group 3, where CoQ10 was applied, compared to Group 2 which was applied with RAI only (Fig. 1) ($P<0.05$). The severity of tubular hyperemia ($P=0.001$), inflammation ($P=0.002$), fibrosis ($P=0.001$), necrosis ($P=0.001$), degeneration ($P=0.002$), vacuolization ($P=0.002$), tubular dilation ($P=0.001$), and hyaline reabsorbs in tubular lumen ($P=0.001$) was found to be significantly lower in Group 3 compared to Group 2 ($P<0.05$). Of the pathological changes in glomerular structures, particularly periglomerular inflammation ($P=0.002$) and periglomerular fibrosis ($P=0.001$) were found to be milder in the group treated with CoQ10 compared to the group treated with RAI only ($P<0.05$). In addition, glomerular wall thickening ($P=0.001$) was found to be milder in Group 3 compared to Group 2 ($P<0.05$). Perivascular inflammation ($P=0.002$) was found to be statistically significantly milder in Group 3 compared to Group 2 ($P<0.05$).

**Table 1.** Distribution of histomorphological parameters in the groups and statistical significance levels.

| Histopathological variables[a] | Group 1 | Group 2 | Group 3 | P |
|---|---|---|---|---|
| Hyperemia | 0[0–0]‡ | 3[2–3] | 0[0–1]‡ | 0.001* |
| Inflammation | 0[0–0]‡ | 2.5[2–3] | 0.5[0–1]‡ | 0.002* |
| Fibrosis | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Degeneration | 0[0–1]‡ | 2.5[2–3] | 0.5[0–1]‡ | 0.002* |
| Necrosis | 0[0–0]‡ | 2[2–2] | 0[0–1]‡ | 0.001* |
| Vacuolization | 0[0–0]‡ | 2.5[2–3] | 0.5[0–1]‡ | 0.002* |
| Tubular Dilatation | 0[0–1]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Reabsorb Drops in tubules | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Periglomerular inflammation | 0[0–0]‡ | 3[2–3] | 0.5[0–1]‡ | 0.002* |
| Periglomerular fibrosis | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Glomerular wall thickening | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Perivascular inflammation | 0[0–0]‡ | 2.5[2–3] | 0.5[0–1]‡ | 0.002* |

[a]Median [minimum–maximum]: 0 (none), 1 (mild), 2 (moderate), 3 (severe). *Significant at 0.05 level (Kruskal–Wallis test). ‡ Significant versus group 2. P shows the differences between all groups. All pairwise multiple comparison test.

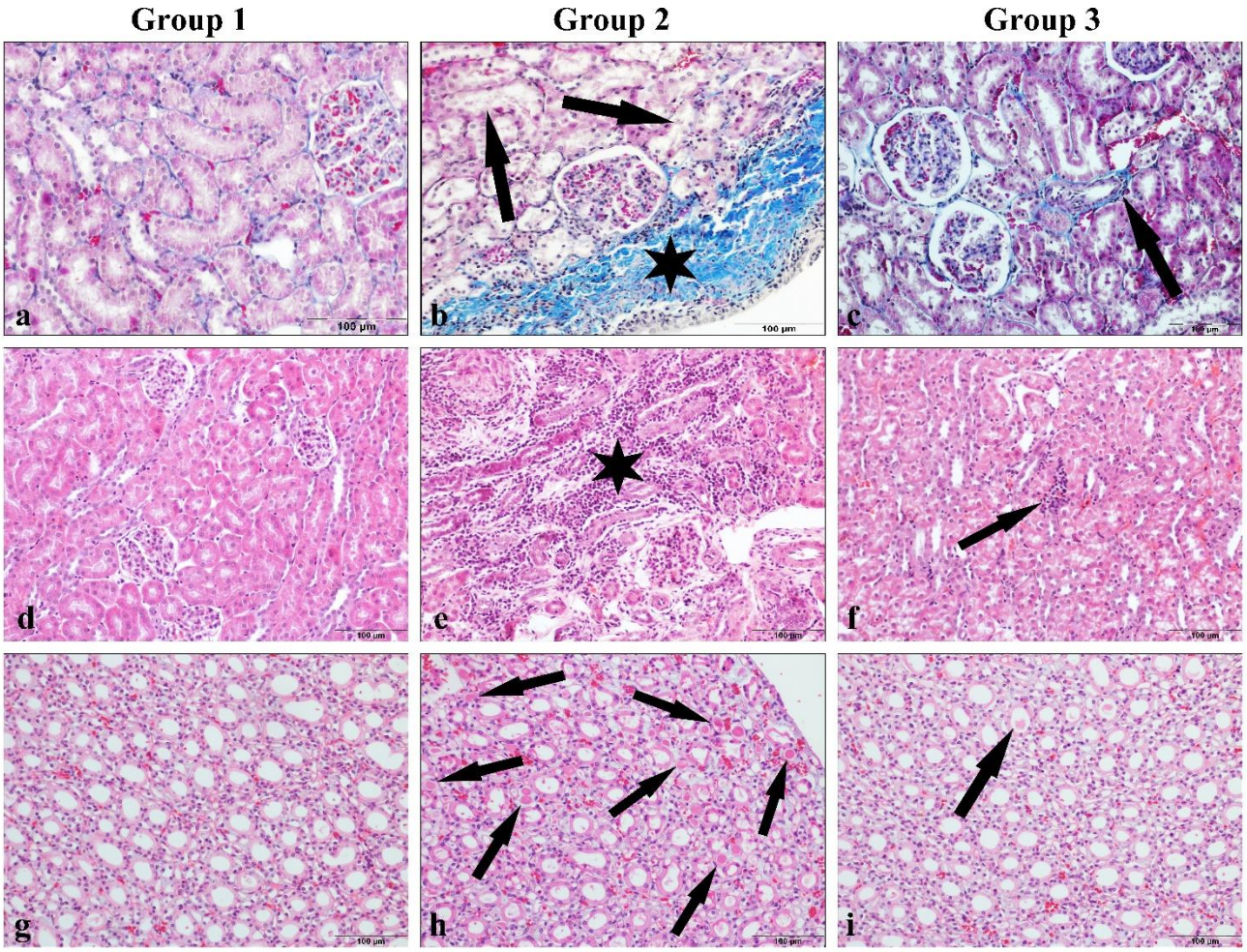


**Figure 1.** The histopathological appearances of the kidneys in different groups.
**a., d., g.** Normal kidney structures in control group. **b.** Diffuse fibrosis and severe inflammation (star), and tubular necrosis (arrows), trichrome. **c.** Mild interstitial fibrosis and inflammation (arrow), trichrome. **e.** Severe inflammation and fibrosis (star), HE. **f.** Few inflammatory cells in interstitium (arrow), HE. **h.** Numerous hyaline casts (arrows) in the collecting ducts, HE. **i.** Few hyaline casts in the ducts (arrow), HE.

**Table 2.** The statistically significant values of proliferation and apoptotic parameters of the kidneys of the groups.

| Immunohistochemical variables[a] | Group 1 | Group 2 | Group 3 | P |
|---|---|---|---|---|
| PCNA | 0[0–1]‡ | 2.5[2–3] | 0.5[0–1]‡ | 0.001* |
| Caspase 8 | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| Caspase 9 | 0[0–0]‡ | 2[2–3] | 0[0–1]‡ | 0.001* |
| TUNEL | 0[0–1]‡ | 2.5[2–3] | 1[0–2]‡ | 0.004* |

[a]Median [minimum–maximum]: 0 (<1% positive), 1 (1–25% positive), 2 (>25–75% positive), 3 (>75% positive) according to the percentage of positive staining cells. *Significant at 0.05 level (Kruskal–Wallis test). ‡ Significant versus group 2. P shows the differences between all groups. All pairwise multiple comparison test.

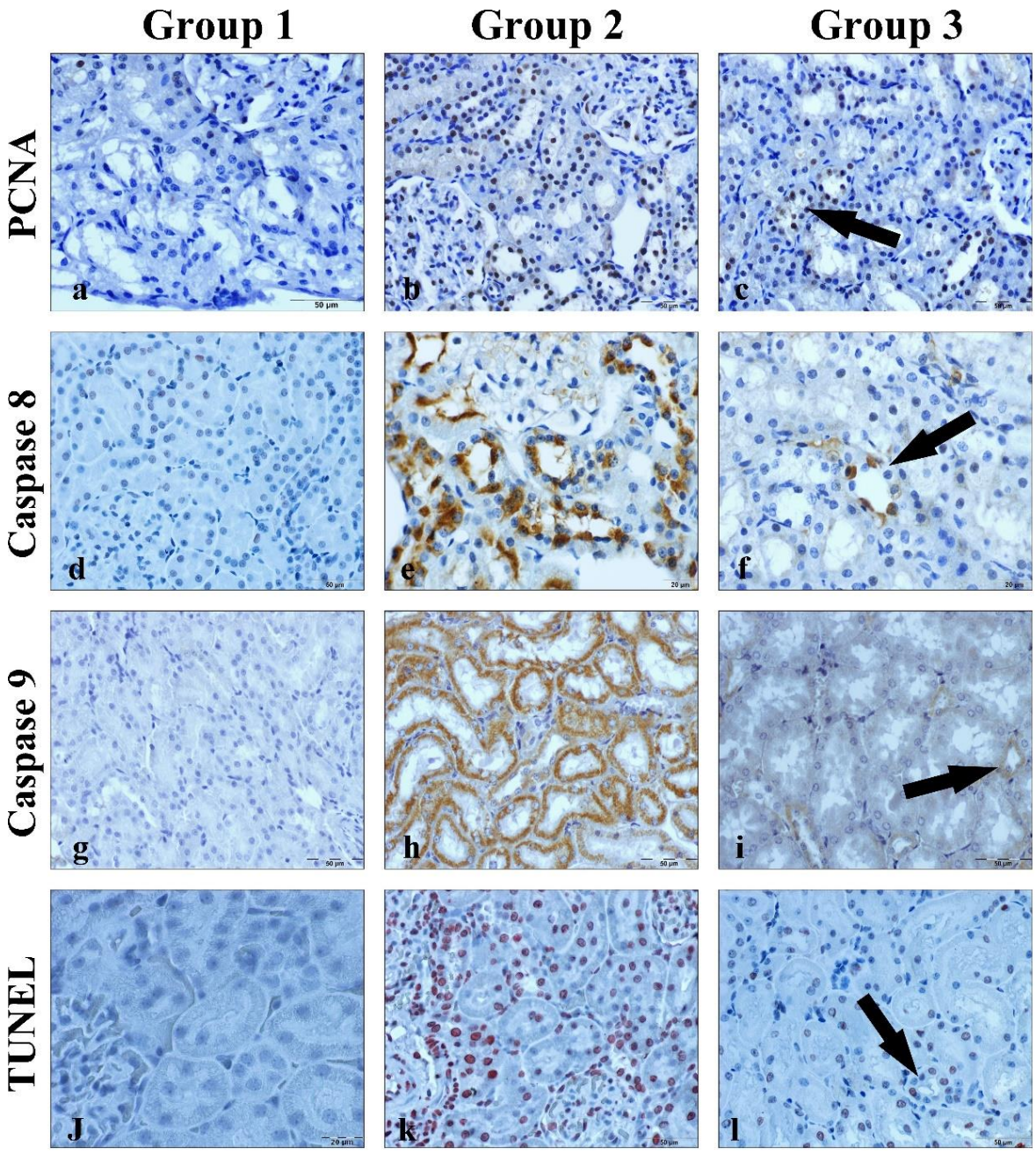


**Figure 2.** Evaluation of immunohistochemistry for cell proliferation and apoptosis.
**a., d., g., j.** All antibodies were immunonegative. Dark nuclear staining was considered to indicate positive immunoreactivity for PCNA; **b.** Severe nuclear immunopositive cells, **c.** Few cells with immunoreactivity, (DAB chromogen). In the caspases staining, yellow cells indicate positivity; **e.** Caspase 8, **h.** Caspase 9 diffuse cellular positivity, **f.** Caspase 8, **i.** Caspase 9 both antibodies were mildly positive, (DAB chromogen). In the TUNEL assay, the red nucleus was considered to indicate positivity; **k.** Severe red nuclear immunopositive cells, **l**. a few little positive immunoreactivity (AEC chromogen).

***Immunohistochemical findings:*** The immunohistochemical findings are summarized in Table 2. The kidney tissues of Group 1 were found to be immune negative in respect of all three antibodies and TUNEL (Fig. 2a, d, g, j). In PCNA staining applied for the detection of tissue proliferation, the intense positive reactions in cell nuclei of the kidney tissues in the rats in Group 3, which were applied with RAI only, were found to be significantly lower compared to those in Group 2 (Fig. 2c) ($P<0.05$). PCNA was found to be more intensely positive in the collecting ducts compared to distal tubules in Group 2 (Fig. 2b). Positive cells in glomerulus were seen to be less intense in Group 3 compared to Group 2.

In the comparison of cytoplasmic marking intensities performed with caspase 8 ($P=0.001$) and caspase 9 ($P=0.001$) antibodies for the detection of apoptosis in the kidneys, a less intensive positive reaction was determined in Group 3 compared to Group 2 (Fig. 2e, h) ($P<0.05$). The staining severity in distal tubules in particular was detected to be more intensive than in proximal tubules in both groups. The staining in collecting ducts were seen to be more severe compared to that in distal and proximal tubules in Group 2 and Group 3. Immune positive cell density for caspase 8 and caspase 9 antibodies was found to be milder in Group 3 compared to Group 2 (Fig. 2f, i). While the glomerulus in Group 2 were detected to be mildly immune positive against both antibodies, mildly positive cells were not observed in the few cells in Group 3. Strong immune positivity was determined in interstitial cells in the kidneys in Group 2, and fewer and milder cytoplasmic positive cells were observed in the same regions in Group 3.

In TUNEL assay marking applied for the detection of DNA damage, positive cell intensity was found to be significantly lower in Group 3, which was applied CoQ10, compared to Group 2, which was applied with RAI only (Fig. 2k, l) ($P=0.004$). TUNEL staining was detected to be intensely positive in the nuclei of the collecting ducts of the kidneys in both groups. Distal tubules demonstrated a more severe reaction compared to proximal tubules. Positive reactions were observed to be less intensive in Group 3 compared to Group 2 ($P<0.05$).

## Discussion and Conclusion

The RAI treatment is successfully used in the treatment of hyperthyroidism and thyroid cancer. Some side effects may occur despite the advantages of being easily applicable, inexpensive and not requiring monitoring after treatment. Particularly the clinical symptoms of nephropathy negatively affect the treatment process and the psychology of the patient (3, 7, 10). There is insufficient available data about RAI–induced nephropathy.

As mentioned earlier, several experimental studies have investigated the pathogenesis of this nephropathy. Yumuşak et al. (30) investigated the pathological findings in the kidneys of rats applied with RAI and detected that degeneration, necrosis, inflammation, proliferation and apoptosis. Kanter et al. (13) reported focal atrophy, cytoplasmic vacuolization and intercellular detachment in renal tubules. Caloğlu et al. (5) vascular congestion and dilation of Bowman's capsule were reported in the acute period. Sürücü et al. (25) reported endothelial destruction and perivascular fibrosis following RAI treatment. The present study also revealed similar histomorphological damage in the rats which were applied with RAI. Pathomorphological changes in tubular, glomerular, interstitial and vascular structures, and intensive hyaline drops in collecting duct lumen were particularly noticeable. Toxicity findings were seen to be more severe in the pelvic canal and medullary region.

The pathogenesis of RAI–induced kidney damage has not been completely explained to date. The general sense is that RAI increases the release of inflammatory mediators and many ROS by entering renal cells via NIS during its excretion (5, 13). The increased ROS leads to cellular proliferation by damaging organelles. Proliferation induces apoptosis by activating DNA breaks and caspase pathways. The caspase pathway mechanism mainly occurs in two ways as mitochondrial (intrinsic) and death receptor (extrinsic) cell death (22). The mitochondrial pathway, which is controlled by caspase 9, is initiated when activated by various forms of cellular stress such as hypoxia, ischemia, oxidative stress, anticancer drugs and DNA damage. The death receptor pathway, which is controlled by caspase 9, is activated by death ligands such as cytochrome and TNF-α (27).

In the present study, severe cell proliferation and DNA damage were seen to occur in the kidneys of the rats which were applied with RAI. It has been suggested that caspase 8 and caspase 9 positive intensity in these regions leads to significant damage in the mitochondria and is an indicator of activation of chemical inflammatory mediators in the tissue. These findings indicate that RAI leads to apoptosis both by mitochondrial and death receptor pathways. The more severe histomorphological and immunohistochemical damage in the pelvic canal and collecting ducts than in the medullary and cortical tubules are thought to develop in parallel with urinary excretion. It has been suggested that the pelvic canal and medulla are exposed to radiation for longer as RAI contaminated urine remains for a longer period in these structures. Tissue damage in these structures may lead to hyaline accumulation in tubule lumen due to impaired urinary excretion and urine accumulation in ducts.

Many animal models and human trials in recent years have indicated that CoQ10, a potent antioxidant,

suppressed inflammatory mediator release and prevented damage in the mitochondria and cell membrane (23). Therefore, it has begun to be commonly prescribed for the prevention and treatment of renal diseases. Zahed et al. (31) reported that CoQ10 administration in chronic kidney disease patients undergoing hemodialysis significantly reduced of inflammatory markers. Ishikawa et al. (12) detected that CoQ10 significantly reduced the urinary albumin level and superoxide anion in the prevention of salt–induced chronic kidney disease. Carrasco et al. (6) reported that CoQ10 regulated the serum albumin/creatinine ratio and beta 2 microglobuline levels against kidney damage and showed an anti–inflammatory effect by reducing mediators such as IL6 and cytokine in patients treated for urolithiasis. In a rat model experimental study by Fatima et al. (8), it was reported that CoQ10 reduced oxidant levels, cytokine levels such as TNF-α and IL6, and significantly reduced caspase activity immunohistochemically. In another study by Fatima et al. (9) CoQ10 was shown to be effective in the prevention of tubular necrosis, glomerular congestion and cast formation in diabetic nephropathy. Saiki et al. (21) conducted a study of PDSS2 deficient mice and reported that CoQ10 had protective effects against proteinuria, interstitial inflammation, tubular dilation and glomerular crescents. Abitoğlu et al. (1) also stated that CoQ10 had anticongestive and anti-necrotic effects in the prevention of septic damage in the kidneys of mice. Kırdağ et al. (14) determined that CoQ10 prevented oxidation, particularly interstitial inflammation, glomerular atrophy, degeneration and apoptosis in kidneys in an experimental ureteral obstruction study in rats. Üstüner et al. (26) reported significant success of CoQ10 in the prevention of tubular necrosis and hyaline accumulation and in the prevention of apoptosis detected with TUNEL in gentamicin–induced kidney damage. In the present study, histomorphological damage was seen to be significantly prevented by CoQ10. In particular, fibrosis and inflammation seen in perivascular and interstitial regions were significantly prevented by CoQ10. These results demonstrated that CoQ10 prevented inflammatory reactions and inhibited fibrosis formation. In addition, hyaline drops were seen to form less in tubule lumens. The most important findings of the study were that cell proliferation, DNA damage and apoptosis were suppressed with CoQ10 and CoQ10 showed an anti–apoptotic and anti–proliferative effect.

In conclusion, severe proliferative, apoptotic and histomorphological damage was seen to develop in the kidneys of rats applied with RAI. In the present study, an important antioxidant CoQ10, was determined to have a radioprotective effect through histomorphological and immunohistochemical examinations. These results demonstrated that especially anti–proliferative, anti–apototic, and anti–inflammatory activities are involved in the mechanism underlying the radioprotective effects of CoQ10.

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## Ethical Statement

All stages of the study were conducted in the Animal Unit Laboratory after national and Local Ethics Committee approval had been obtained for the breeding and use of laboratory animals and accordance with the principles of the experimental ethical principles and animal protection laws according to the rules of EU Directive 2010/63/EU for animal experiments and in compliance with the ARRIVE guidelines and the AVMA euthanasia guidelines 2013 (Approval No: 2020-0059).

## Conflict of Interest

The authors are declared that there is no conflict of interest.

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