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ORIGINAL ARTICLE

Evaluation of the protective effect of coenzyme Q10 against x-ray irradiation-induced ovarian injury

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Abstract

Aim: This study focused on the anti-oxidant and anti-apoptotic effects of CoQ10 in ovaries exposed to pelvic radiation.

Methods: Thirty-two female rats were randomly assigned into four groups. Group I (control group), Group II: Only 2 Gy pelvic x-ray irradiation (IR) was administered as a single fractioned dose. Group III: 30 mg/kg CoQ10 was administered by oral gavage +2 Gy pelvic IR. Group IV: 150 mg/kg CoQ10 was administered by oral gavage +2 Gy pelvic IR. CoQ10 treatment was started 7 days before pelvic IR and completed 7 days later. The rats in Group III and IV were treated with CoQ10 for a total of 14 days.

Results: Histopathological analysis showed severe damage to the ovarian tissue in the radiation group, while both doses of CoQ10 showed normal histological structure. Likewise, while there was a high level of staining in the IR group for necrosis and apoptosis, the CoQ10 treated ones were like the control group. Tissue Malondialdehyde (MDA) levels were like the control group in the low-dose CoQ10 group, while the MDA levels of the high dose CoQ10 group were similar to the radiation group.

Conclusion: Usage of low-dose CoQ10 has a radioprotective effect on radiation-induced ovarian damage. Although the use of high doses is morphologically radioprotective, no antioxidative effect was observed in the biochemical evaluation.

KEYWORDS
apoptosis, coenzyme Q10, ionizing radiation, ovary, oxidative stress

INTRODUCTION

Radiotherapy is one of the common cytotoxic treatment modalities used in cancer patients. Although ionizing radiation increases long-term survival, it has iatrogenic effects on fertility ranging from decreased fertility to premature ovarian failure and sterility. It has been shown that acute ovarian failure develops in 70%–85% of young reproductive-age women after abdominopelvic radiotherapy in a dose- and age-related manner.[1]

Adult ovarian tissue has a pool of follicles containing limited oocytes. With aging, primordial follicles forming the ovarian reserve undergo atresia and gradually decrease during folliculogenesis. Growing follicles are associated with oocyte development and mitotic growth in follicular cells. The oocyte pool cannot be regenerated, and gonadotoxic exposure such as radiation dramatically accelerates physiological changes in fertility.

Ovarian follicles are embedded in a microenvironment of extracellular matrix and stroma. This complex

structure includes fibroblasts, theca-interstitial cells, and endothelial and immune cells. Granulosa cells are the first cell group to be affected by radiation injury, and significant cell death is observed within hours after exposure.[2] The oocyte is also affected by apoptosis and oxidative stress in the follicular environment. Oocyte is highly sensitive even to doses >2 Gy and radiosensitivity varies according to the growth phase.[3]

It was shown that primordial follicular oocytes were affected by low-dose radiotherapy while developing follicle oocytes were affected by high-dose radiotherapy. It has been determined that small follicles waiting in the follicle pool are 80 times more sensitive to radiation dose than developing follicles.[4] Radiation damage to the stroma both affects vascularization and leads to atrophy and fibrosis. Many factors such as age, ovarian reserve, combined treatments, total radiation dose, application area, and fraction scheme affect the radiation damage that develops in the ovary.

Oxidative stress and the formation of free oxygen radicals are the most important causes of radiotherapy-induced infertility. Its toxic effect occurs by damage to DNA, protein, and lipids with free radicals formed due to water radiolysis of the cell.[5] Induction of apoptosis by intrinsic mitochondrial pathways results in p53 activation, cytochrome c release, and caspase activation. Activated caspase cleaves DNA damage repair enzymes to block DNA repair and accelerate apoptosis. Radiation dose >2 Gy causes apoptosis and chromosomal damage in follicular cells, losing half of the ovarian reserve.[6]

CoQ10 plays a key role in mitochondrial membranes as an electron and proton carrier in aerobic cellular respiration. It functions as an antioxidant in the cell membrane and plasma. It also takes part in cell signaling systems, metabolic reactions, and transport systems.[7] CoQ10 plays a role in the etiopathogenesis of many diseases such as oxidative stress, carcinogenetic process, neurodegenerative diseases, diabetes, cardiovascular diseases, and fibromyalgia.[8]

CoQ10 carries electrons in the mitochondrial respiratory chain that are involved in ATP synthesis. The role of CoQ10 in oxygen metabolism is making a superoxide anion radical derivative as one of the main oxygen reactive species. The presence of both prooxidant and antioxidant capacity enables it to play a key regulatory role in the oxidative state balance.[9] The reduced form of CoQ10 is ubiquinol, which transforms vitamin E and protects biological membranes from lipid peroxidation.[10] The dual function of CoQ10 makes it indispensable for the control of mitochondrial functions and cellular mechanisms.[11]

This study aimed to examine the radioprotective effect of CoQ10 in an experimental rat model using histological and immunohistochemical methods. At the same time, we determined the oxidant-antioxidant status biochemically. In the literature, there are studies evaluating the radioprotective effect of antioxidants against ovarian damage, but there is no treatment agent that has entered clinical use yet. As far as we know, there is no study in the literature investigating the effect of CoQ10 on ovarian damage due to ionizing radiation. In addition, we examined two different doses of CoQ10 (30 vs. 150 mg/kg) to observe whether there is a dose-dependent effect. This study is exploratory research since it does not produce a statistical hypothesis despite a null hypothesis.

MATERIALS AND METHODS

This study is a prospective, randomized experimental animal model study conducted at Recep Tayyip Erdoğan University Experimental Animals Application and Research Center, Rize. Prior to the study, ethical approval was obtained from the Ethics Committee (Approval No: 2019/44). The study was carried out with the funds of the Scientific Researches Project Support Unit of Recep Tayyip Erdogan University (project number: 2020–1221).

Experimental animals

Thirty-two female adult Sprague–Dawley rats (3- to 4-month-old), weighing 200–250 g, were used in the study. The rats were kept in standard conditions at 22° constant room temperature, 50%–60% humidity, 12 h of light and 12 h of darkness, in a ventilated environment with lighting and air conditioning. Standard daily diet and water consumption were provided.

The rats were randomly allocated into four groups: Group I: control group, Group II: only pelvic irradiation (IR) was administered, Group III: 30 mg/kg CoQ10 (Solgar, New Jersey, USA) was administered by oral gavage + IR, Group IV: 150 mg/kg CoQ10 (Solgar, New Jersey, USA) was administered by oral gavage + IR. CoQ10 therapy was started 7 days before pelvic irradiation.

The fertility protective effect of CoQ10 has been frequently used in rat testicular experimental models and the standard dose used was 10 mg/kg.[12] The number of publications in the literature showing the protective effect of CoQ10 on the ovary is limited and variable dosages has been used. Dosages of CoQ10 were chosen based on previous experimental studies taking into account preservation of ovarian reserve.[13–16] Özcan et al. determined the ovarian protective CoQ10 dose against oxidative stress caused by cisplatin as 150 mg/kg. Our study aimed to evaluate the effect of different doses of CoQ10 on ovarian tissue. For this reason, 150 mg/kg[16] was determined as the high dose and 30 mg/kg was determined as the low dose. In experimental studies, CoQ10 application generally lasts 14 days.[13,17,18] Additionally, Özcan et al stated earlier initiation of CoQ10 supplementation prior to cisplatin exposure may better demonstrate the possible protective role of CoQ10.[16]

TABLE 1 Histopathological damage score (HDS).

	Grade			
Histologic area	**0**	**1**	**2**	**3**
Degenerative follicle Hemorrhage Inflammation	≤5%	6%–25%	26%–50%	>51%

TABLE 2 Apoptosis score (AS).

Grade	Score
0	Less than ≤5%
1	Between 6% and 25%
2	Between 26% and 50%
3	More than 51%

X-ray irradiation procedure

Radiotherapy was administered at Recep Tayyip Erdogan University Radiation Oncology Radiotherapy Unit. X-ray beam (Elekta Synergy; Elekta, Crawley, United Kingdom) was applied with a digital linear accelerator at 6 MV and 4 Gy/min. Radiotherapy planning was done using the CMS-XIO system (version 13.2). Rats received radiation to the pelvic region with a single dose of 2 Gy beam, which was sufficient to induce ovarian injury.[19] Before radiotherapy, all rats were anesthetized with 20–30 mg/kg ketamine hydrochloride and fixed in the supine position by the legs and tail. Rats were irradiated with bolus 1 cm and 0° to 180° by the isometric method in a $20 \times 40\ cm^2$ area from front to back with 6 MV.

CoQ10 was continued for 7 days after pelvic irradiation and rats were sacrificed 7 days after pelvic radiotherapy. For the scarification process, 50 mg of ketamine and 7 mg/kg of xylazine was administered intraperitoneally, and bilateral ovarian tissues were removed by laparotomy. The right ovarian tissue was stored at −80° for biochemical examination, and the left ovarian tissue was fixed in 10% formaldehyde for histological examination.

Histopathological analyses

After tissue follow-up procedures, ovarian tissues were embedded in paraffin blocks and then serial sections were taken and stained with Hematoxylin-Eosin (H-E). By using semi-quantitative analysis, histopathological damage score (HDS) was designed in accordance with previous studies[20–22] and calculated as shown in Table 1. Twenty-seven different areas of each ovary tissue section in the groups were measured by two blind histopathologists. Histopathologists were double blinded to the study groups.

Immunohistochemical analyses

Apoptosis was evaluated by applying immunohistochemical staining steps. TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling) antibodies were used to detect apoptotic cells in ovarian sections. Sections were placed on positively charged slides and blocked with deparaffinized endogenous peroxidase for 15 min with 3% H_2O_2. Sections were blocked for 20 min to prevent nonspecific binding and then a primary antibody was applied. After incubation with a secondary antibody, chromogen (diaminobenzidine chromogen) was added, and sections were sealed after counterstaining with hematoxylin.

Apoptosis score

Immune-positive apoptotic cells marked by the TUNEL method were scored as shown in Table 2. Twenty randomly selected different areas were measured in each apparatus by two blinded histopathologists whose scoring process was blinded to the study groups.

Biochemical analyses

Malondialdehyde (MDA) values were checked to determine the oxidative stress level in ovarian tissues. MDA level was measured using Draper and Hadley's double heating technique. The color formed after the reaction was measured spectrophotometrically. MDA levels are given in μmol/L.

Statistical analyses

SPSS Statistics version 18.0 software program was used for statistical analysis (IBM Corporation, Armonk, NY, USA). Categorical variables are given as numbers and percentages, and continuous variables as mean ± standard deviation. A value of $p < 0.05$ was considered significant. The normality distribution of the groups was performed with the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) test was applied, and the post hoc Tukey test was used to evaluate the mean differences between the groups.

RESULTS

Histopathological analyses

When the ovarian tissue sections of the control group (Group I) were examined under a light microscope;

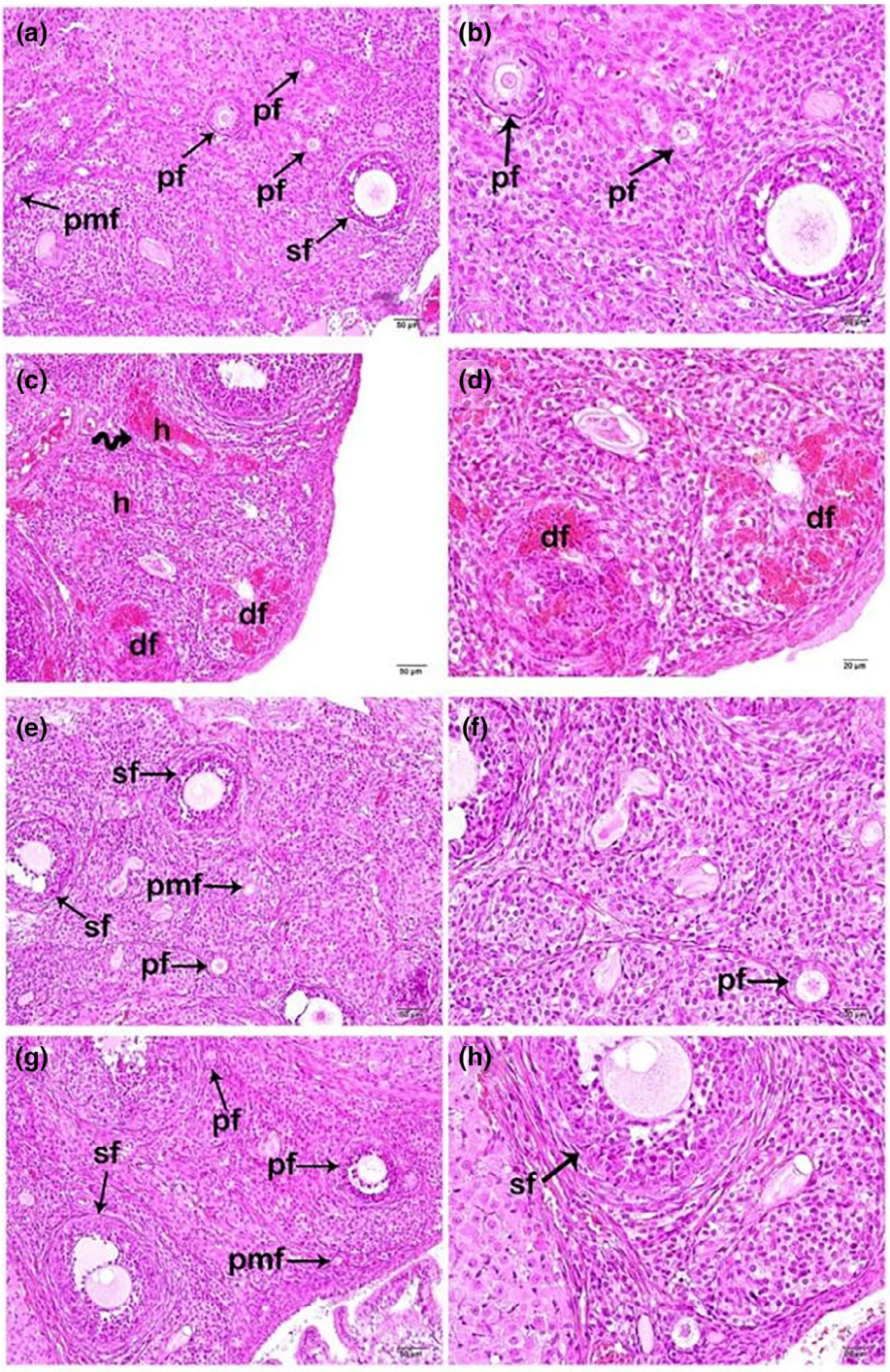

FIGURE 1 H + E-stained sections of the ovarian tissues of the study groups under light microscope. A (H + E ×200), B (H + E ×400): Group I (control group) normally structured secondary follicle with granulosa cells and primary oocyte. C (H + E ×200), D (H + E ×400): Group II (irridation group) disseminated degenerative follicles, hemorrhagic areas and inflammation (spiral arrow). E (H + E ×200), F (H + E ×400): Group III (low dose group) decreased degenerative follicle, hemorrhage and inflammation. G (H + E ×200), H (H + E ×400): Group IV (high dose group) normally structured ovarian follicles with decreased degeneration. pmf: primordial follicle, pf: primary follicle, sf: secondary follicle, h: hemorrhage, df: degenerative follicle.

primordial, primary, and secondary follicles containing normal granulosa cells in the cortex of the ovary were observed (Figure 1a, b, HDS: 0.5 [0–1] mean [min–max]). On the contrary, there were hemorrhagic degenerative follicles in the cortex of the ovarian tissue belonging to the irradiation group (Group II). In addition, hemorrhagic and infiltrative areas were observed in the medulla and cortex of the ovary (Figure 1c, d, HDS 7 [6–7] mean [min–max]). Degenerative follicles, hemorrhagic areas and inflammation were found to be decreased in the low-dose CoQ10 group (Group III) (Figure 1e, f, $p = 0.001$, HDS: 2 [1–2] mean [min–max]). Similarly, degenerative follicles were decreased in the high-dose CoQ10 group (Group IV), and the presence of many typical preantral follicles was detected (Figure 1g, h, $p = 0.001$, HDS: 1 [0–2] mean [min–max]).

Immunohistochemical analyses

TUNEL method was used to mark apoptotic cells. Sections of Group I consisted of primordial, primary, and

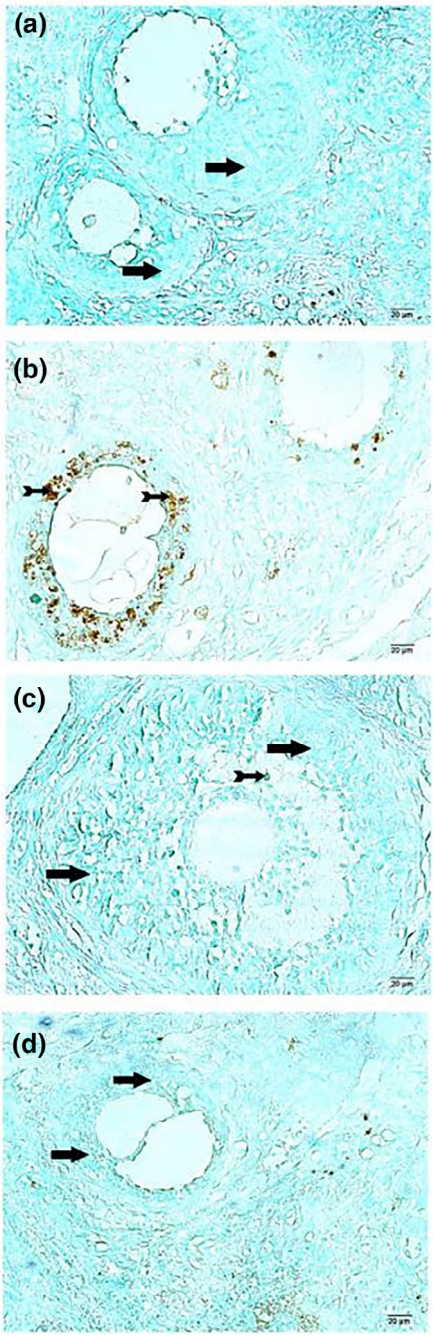

FIGURE 2 Apoptotic assessment of ovarian tissues with TUNEL. (a) Group I—a normally structured secondary follicle with granulosa cells (arrow) (×400). (b) Group II—secondary follicle with numerous intensely immunoreactive granulosa cells (tailed arrow) (×400). (c) Group III—decreased immunoreactive granulosa cells in secondary follicle (tailed arrow) (×400). (d) Group IV—secondary follicle with typical granulosa cells (arrow) (×400).

secondary follicles containing normal immune-negative granulosa cells (Figure 2a, Apoptosis score [AS]: 0 [0–0] mean [min–max]). In contrast, cross-sections of group II had degenerative follicles containing dense immune-positive granulosa cells in the cortex of the ovarian tissue. (Figure 2b; AS 3 [3–3] mean [min–max]). Apoptotic

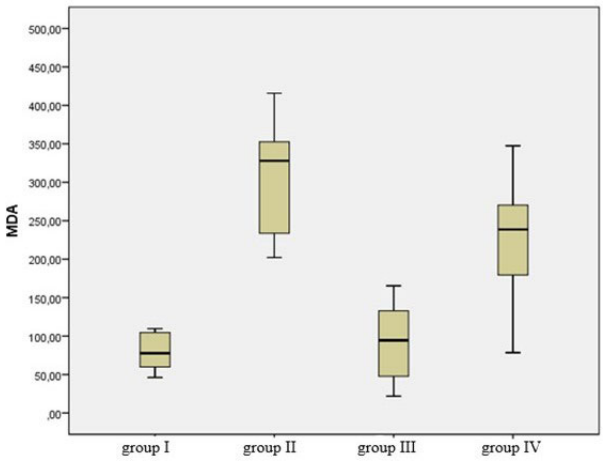

FIGURE 3 Comparison of the malondialdehyde (MDA) levels of study groups. Groups I and III have significantly lower MDA levels than Groups II and IV.

granulosa cells showing TUNEL-positiveness were found to be decreased in Group III (Figure 2c, $p = 0.001$, AS: 0 [0–0.5] mean [min–max]). Similarly, in the preantral follicles of group IV, TUNEL-positive granulosa cells were decreased, and there were preantral follicles containing many typical granulosa cells (Figure 2d, AS 0 [0–0.5] mean [min–max]).

Biochemical analyses

In the biochemical evaluation, the MDA values of the groups were compared. The MDA values were 89.56 ± 44 μmol/L (Group I), 305.77 ± 76 μmol/L (Group II), 92.19 ± 53 μmol/L (Group III), and 225.36 ± 81 μmol/L (Group IV), respectively. Since the data were normally distributed ($p > 0.05$), the One-way ANOVA test was performed to determine the difference between the groups, and a statistically significant difference was found ($F = 20.048$, $p < 0.01$, df = 3). According to the Tukey HSD test, Groups I and III had low MDA values (89.56 and 92.19 μmol/L), while Groups II and IV had high MDA values (225.36 and 305.77 μmol/L). The difference between the groups was statistically significant ($p < 0.05$) (Figure 3).

DISCUSSION

The present study investigated the possible radioprotective effect of CoQ10 in ovarian tissue exposed to ionizing radiation using two different CoQ10 doses, with histopathological, immunohistochemical, and biochemical methods. It was observed that the ovarian tissue was damaged due to pelvic ionizing radiation as reported in the literature.[4] However, CoQ10 administration partially or completely restored the histological architecture of

ovarian tissue damaged by ionizing radiation. In addition, the low dose of CoQ10 provided greater protection than the high dose.

Even at low doses, ionizing radiation creates breaks in DNA, increases free oxygen radicals, and causes damage to cellular lipid membranes.[23] MDA is the most important indicator of lipid peroxidation. The lipid peroxidation products formed as a result of damage to the cell membrane cause cellular apoptosis and necrosis by activating the NF-κB pathway and caspase cascade.[24] The increase in MDA levels and TUNEL positivity in the ovarian tissue in the radiation group of our study confirm the oxidative and apoptotic effects of radiation. However, CoQ10 acts as an antioxidant by protecting membrane phospholipids, proteins, and DNA. CoQ10 has antioxidant and antiapoptotic effects by capturing free radicals in lipid and mitochondrial membranes. It has been shown to be a strong radio-protector.[25] Lipid peroxidation leads to a decrease in the endogen CoQ10 pool and mitochondrial respiratory chain activity. In the case of oxidative stress, dietary CoQ10 intake may be necessary as the endogenous CoQ10 pool is depleted. It has also been shown that dietary CoQ10 supplementation does not cause accumulation in tissues and is safe.[26] Exogenous CoQ10 supplementation has been shown to prevent oxidative stress and preserve mitochondrial respiratory functions. The antioxidant effect of CoQ10 supplementation has been demonstrated in clinical and experimental studies in cardiovascular diseases, kidney diseases, neurodegenerative diseases, and oxidative stress caused by chemotherapeutic agents.[27] It was shown that total antioxidant capacity elevated, MDA levels decreased, and superoxide dismutase levels increased with CoQ10 supplementation.[28] In addition, CoQ10 supplementation has β-cell protective effects against β-cell damage caused by oxidative stress in diabetics.[29] In the literature, there is a study showing that the damage is reduced with the use of exogenous CoQ10 against the functional and structural damage in the ovarian tissue due to the use of methotrexate.[30]

There are limited studies in the literature about ovarian reserve preserving effect of CoQ10, administered dosages of CoQ10 are not standard. Ben-Meir et al.[15] showed that age-related ovarian reserve decline can be prevented with 22 mg/kg of CoQ10 supplementation. In another study, the protective effect of CoQ10 was exerted via the antioxidant and proliferative properties on cyclophosphamide induced ovarian damage with the same dosage.[14] On the other hand, Lee et al.[13] demonstrated 150 mg/kg CoQ10 reduced oxidative stress levels and improved ovarian function and oocyte quality. Similarly, Özcan et al showed higher dosage CoQ10 supplementation may protect against oxidative stress induced ovarian damage.[16] As far as we know, there is no study in the literature evaluating the protective effect of CoQ10 against radiotherapy-induced ovarian injury. In this sense, our study is a pilot study. In this experimental model, irradiation was applied at a level that would cause irreversible damage to the ovarian tissue and it was aimed to evaluate the protective effect and dose-dependent curative effect on the ovarian tissue by using two different doses of CoQ10. In our study, low dose (30 mg) CoQ10 was given to one group and high dose (150 mg) CoQ10 to the other group in order to determine the dose-dependent variability of the effect of CoQ10 on rats given 2 Gy radiation.

Our histopathological analysis showed severe damage to the ovarian tissue in the radiation group, while both doses of CoQ10 showed normal histological structure in the ovarian tissue. Likewise, while there was a high level of staining in the radiation group in which we applied the TUNEL method to show necrosis and apoptosis, the positivity levels of both groups that received CoQ10 were similar to the control group. However, tissue MDA levels, which we measured biochemically, were similar to the control group in the low-dose CoQ10 (30 mg) group. Interestingly, the tissue MDA levels of the group in which we applied high-dose CoQ10 (150 mg) were found close to the radiation group. This situation made us think that high-dose CoQ10 intake caused a decrease in antioxidant activity. In order to understand whether this is due to the decrease in antioxidant activity of high-dose CoQ10 or the potential for toxic effects of high-dose CoQ10 alone, it may be explanatory to create an experimental group given only high-dose CoQ10. As is known, CoQ10 is an agent that acts as a regulator with both prooxidant and antioxidant properties. CoQ10 forms a superoxide anion radical derivative as one of the main oxygen-reactive species. The use of high doses of CoQ10 disrupts the regulatory function and causes the balance to shift to the prooxidant side. This is an important finding as evidence that the use of high doses of CoQ10, unlike low doses, worsens oxidative stress instead of improving it.

CoQ10 is one of the most popular antioxidant agents used in the treatment of many diseases. There are approximately 16 680 articles about CoQ10 in the literature. From cancer to neurodegenerative diseases, from aging to infertility, these studies have focused on the protective effect of CoQ10.[27] However, there are very few studies comparing the dose of CoQ10 and in this sense, our study fills an important gap in the literature. At the same time, although there are many studies investigating the chemoprotective effects of CoQ10, the number of studies evaluating its radioprotective activity is limited. In our study, ovarian tissue with high radiosensitivity was examined. In addition, two different doses of CoQ10 were used to find the effective dose of CoQ10. In light of the data obtained, it has been proven that CoQ10 is an effective radioprotective agent for the ovary, and this effect is more pronounced when used in low doses such as 30 mg. The use of high-dose CoQ10 showed radioprotective activity histologically similar to that of low-dose administration but did not exhibit a sufficient antioxidative effect.

Our study has some limitations. Firstly, the study was conducted in experimental animals. The administration of CoQ10 to humans may be considered after studies in

higher primates and mammals. The second limitation is the evaluation of short-term complications of radiotherapy. Although the positive effects of CoQ10 used in the early period were observed morphologically and biochemically, longer-term effects were not assessed. On the other hand, we mentioned usage of high doses of CoQ10 disrupts the regulatory function and causes the balance to shift to the prooxidant side, one of limitation of our study was lack of control groups with CoQ10 intake 30 and 150 mg/kg without using 2 Gy of irradiation. Another limitation is that functional tests are not used in the evaluation of ovarian reserve. However, within the scope of the study, we determined that the ovarian tissue was preserved morphologically, and hormonal evaluation was not performed.

In conclusion, this study showed that the use of low-dose CoQ10 has a radioprotective effect on radiation-induced ovarian damage. Although usage of high doses of CoQ10 is morphologically radioprotective, the oxidative stress level in the ovary was found similar to only the radiotherapy receiving group at biochemical evaluation. Further research with larger groups and wider CoQ10 ranges are required in advanced primates or mammals.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by (Yesim Bayoglu Tekin, Levent Tumkaya, Tolga Mercantepe, Zehra Suzan Topal, Tuğba Celik Samanci, Hulya Kilic Yilmaz, Sema Rakici and Atilla Topcu). The first draft of the manuscript was written by (Yesim Bayoglu Tekin) and (Levent Tumkaya, Tolga Mercantepe) commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interest to disclose.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author upon reasonable request. ScholarOne upload is not viewed favorably as data sharing jeopardizes ethical standards or legal requirements. However, it will be shared with the journal editor in the case of necessity.

ETHICS STATEMENT

Animal experimentation procedures were performed in accordance with the National Health Sciences Institute's guidelines. The study protocol was approved by the Recep Tayyip Erdoğan University Animal Experiments Local Ethical Committee (Rize, Turkey; Decision No: 2019/44).

REFERENCES

1. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab. 2006;91:1723–8.
2. Reiser E, Bazzano MV, Solano ME, Haybaeck J, Schatz C, Mangesius J, et al. Unlaid eggs: ovarian damage after low-dose radiation. Cells. 2022;11:1219.
3. Duncan FE, Kimler BF, Briley SM. Combating radiation therapy-induced damage to the ovarian environment. Future Oncol. 2016; 12:1687–90.
4. Puy V, Barroca V, Messiaen S, Ménard V, Torres C, Devanand C, et al. Mouse model of radiation-induced premature ovarian insufficiency reveals compromised oocyte quality: implications for fertility preservation. Reprod Biomed Online. 2021;43:799–809.
5. Kimler BF, Briley SM, Johnson BW, Armstrong AG, Jasti S, Duncan F. Radiation-induced ovarian follicle loss occurs without overt stromal changes. Reproduction. 2018;155:553–62.
6. Onder GO, Balcioglu E, Baran M, et al. The different doses of radiation therapy-induced damage to the ovarian environment in rats. Int J Radiat Biol. 2021;97:367–75.
7. Raizner AE. Coenzyme Q10. Methodist Debakey Cardiovasc J. 2019;15:185–91.
8. Brandmeyer EA, Shen Q, Thimmesch AR, Pierce JD. Using coenzyme Q10 in clinical practice. Nursing. 2014;44:63–6.
9. Genova ML, Lenaz G. New developments on the functions of coenzyme Q in mitochondria. Biofactors. 2011;37:330–54.
10. Wang Y, Hekimi S. Understanding ubiquinone. Trends Cell Biol. 2016;26:367–78.
11. Rodríguez-Varela C, Labarta E. Clinical application of antioxidants to improve human oocyte mitochondrial function: a review. Antioxidants (Basel). 2020;9:1197.
12. Said RS, Mohamed HA, Kamal MM. Coenzyme Q10 mitigates ionizing radiation-induced testicular damage in rats through inhibition of oxidative stress and mitochondria-mediated apoptotic cell death. Toxicol Appl Pharmacol. 2019;383:114780.
13. Lee HJ, Park MJ, Joo BS, Joo JK, Kim YH, Yang SW, et al. Effects of coenzyme Q10 on ovarian surface epithelium-derived ovarian stem cells and ovarian function in a 4-vinylcyclohexene diepoxide-induced murine model of ovarian failure. Reprod Biol Endocrinol. 2021;19(1):59.
14. Delkhosh A, Delashoub M, Tehrani AA, Bahrami AM, Niazi V, Shoorei H, et al. Upregulation of FSHR and PCNA by administration of coenzyme Q10 on cyclophosphamide-induced premature ovarian failure in a mouse model. J Biochem Mol Toxicol. 2019; 33(11):e22398.
15. Ben-Meir A, Burstein E, Borrego-Alvarez A, Chong J, Wong E, Yavorska T, et al. Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging. Aging Cell. 2015; 14(5):887–95.
16. Özcan P, Fıçıcıoğlu C, Kizilkale O, Yesiladali M, Tok OE, Ozkan F, et al. Can coenzyme Q10 supplementation protect the ovarian reserve against oxidative damage? J Assist Reprod Genet. 2016;33(9):1223–30.
17. Botelho AFM, Lempek MR, Branco SEMT, Nogueira MM, de Almeida ME, Costa AG, et al. Coenzyme Q10 cardioprotective effects against doxorubicin-induced cardiotoxicity in Wistar rat. Cardiovasc Toxicol. 2020;20(3):222–34.
18. Ramadan LA, Abd-Allah AR, Aly HA, Saad-el-Din AA. Testicular toxicity effects of magnetic field exposure and prophylactic role of coenzyme Q10 and L-carnitine in mice. Pharmacol Res. 2002;46(4):363–70.
19. Zhao J, Zhang S, Chen L, Liu X, Su H, Chen L, et al. Sphingosine 1-phosphate protects against radiation-induced ovarian injury in female rats-impact on mitochondrial-related genes. Reprod Biol Endocrinol. 2020;18(1):99.

20. Saber M, Eimani H, Soleimani Mehranjani M, Shahverdi A, Momeni HR, Fathi R, et al. The effect of verapamil on ischaemia/reperfusion injury in mouse ovarian tissue transplantation. Biomed Pharmacother. 2018;108:1313–9.
21. Kim TH, Choi JH, Jun Y, Lim SM, Park S, Paek JY, et al. 3D-cultured human placenta-derived mesenchymal stem cell spheroids enhance ovary function by inducing folliculogenesis. Sci Rep. 2018;8:1–11.
22. Taskin O, Birincioglu M, Aydin A, Buhur A, Burak F, Yilmaz I, et al. The effects of twisted ischaemic adnexa managed by detorsion on ovarian viability and histology: an ischaemia-reperfusion rodent model. Hum Reprod. 1998;13:2823–7.
23. Marci R, Mallozzi M, Di Benedetto L, et al. Radiations and female fertility. Reprod Biol Endocrinol. 2018;16:112.
24. Pietraforte D, Paulicelli E, Patrono C, Gambardella L, Scorza G, Testa A, et al. Protein oxidative damage and redox imbalance induced by ionising radiation in CHO cells. Free Radic Res. 2018;52:465–79.
25. Yakin M, Eksioglu U, Sadic M, Koca G, Ozkan-Uney G, Yumusak N, et al. Coenzyme Q10 for the protection of lacrimal gland against high-dose radioiodine therapy-associated oxidative damage: histopathologic and tissue cytokine level assessments in an animal model. Curr Eye Res. 2017;42:1590–6.
26. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, et al. Clinical applications of coenzyme Q10. Front Biosci (Landmark Ed). 2014;19:619–33.
27. Gutierrez-Mariscal FM, Arenas-de Larriva AP, Limia-Perez L, Romero-Cabrera JL, Yubero-Serrano EM, López-Miranda J. Coenzyme q_{10} supplementation for the reduction of oxidative stress: clinical implications in the treatment of chronic diseases. Int J Mol Sci. 2020;21:7870.
28. Akbari A, Mobini GR, Agah S, Morvaridzadeh M, Omidi A, Potter E, et al. Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials. Eur J Clin Pharmacol. 2020;76:1483–99.
29. Luo K, Yu JH, Quan Y, Shin YJ, Lee KE, Kim HL, et al. Therapeutic potential of coenzyme Q_{10} in mitochondrial dysfunction during tacrolimus-induced beta cell injury. Sci Rep. 2019;9:7995.
30. Kiremitli T, Kiremitli S, Akselim B, Yilmaz B, Mammadov R, Tor IH, et al. Protective effect of Coenzyme Q10 on oxidative ovarian and uterine damage induced by methotrexate in rats. Hum Exp Toxicol. 2021;40:1537–44.

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