Original Article

The Effect of Coenzyme Q10 on Dexamethasone-Induced Oxidative Stress in Rats Testes

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Abstract

Background: Oxidative stress is a contributing factor in 30%–80% of infertile men. **Objective:** The aim of this study was to investigate the impact of coenzyme Q10 on dexamethasone-induced oxidative stress in rats testes. **Materials and Methods:** Sixteen male Wistar rats were divided into four groups of four: group 1 (control) received 1 mL of distilled water daily orally; group 2 received dexamethasone 0.2 mg/kg/day intraperitoneally; group 3 received coenzyme Q10 30 mg/kg/day orally; and group 4 received dexamethasone and coenzyme Q10 via the same routes. Testicular total antioxidant capacity (TAC), superoxide dismutase (SOD), and catalase (CAT) activities as well as testicular histopathological changes were compared among groups. **Results:** Although testicular SOD was lower in groups 3 and 4, dexamethasone and coenzyme Q10 treatment did not significantly alter TAC, SOD, CAT, or histopathological features of rats testes. **Conclusion:** Dexamethasone (0.2 mg/kg/day) and coenzyme Q10 (30 mg/kg/day) may have no impact on gonadal oxidative stress, antioxidant capacity, or spermatogenesis in rats testes with these doses.

Keywords: Antioxidants, coenzyme Q10, dexamethasone, oxidative stress, rats testes

Introduction

Infertility affects approximately 50–80 million couples globally with psychological, sociocultural, physical, and financial issues to families.[1] Male factors contribute for 20%–50% of infertility cases.[2] These factors could include genetic, endocrine, infections, varicocele, and environmental factors. However, in approximately 25% of male infertility cases, the underlying semen abnormalities cannot be explained and referred to as an idiopathic infertility. One of the proposed mechanisms for an idiopathic male infertility is the oxidative stress (OS), which could be a contributing factor in 30%–80% of infertile men.[2,3]

OS is defined as an imbalance between pro-oxidants and antioxidants leading to a redox paradox.[4] Excessive reactive oxygen species (ROS) generation overwhelms the endogenous antioxidants (enzymatic and nonenzymatic) in the seminal plasma leading to oxidative damage in macro biological molecules.[5] OS has been linked to altered sperm structure, motility,[6] mitochondrial DNA damage, sperm nuclear DNA fragmentation,[7,8] epigenetic abnormalities,[2] recurrent miscarriages, congenital diseases, neurological and psychiatric disorders, and childhood malignancies.[9] Early and accurate detection of OS could be a potential diagnostic and therapeutic target for idiopathic male infertility.[10] Previous studies have reported higher ROS levels and/or decreased antioxidants levels in infertile men and in animal models.[11] Other studies, however, demonstrated no differences between patients and fertile controls.[12] Assessing OS can help identify subsets of infertile men who might benefit from antioxidant treatment and improve fertility treatment outcomes.[3]

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Coenzyme Q10 (CoQ10) is a component of the mitochondrial respiratory with antioxidant properties. CoQ10 found endogenously in the mitochondria of spermatozoa and human seminal plasma in its reduced and oxidized forms (ubiquinone and ubiquinol, respectively).[13] Low levels of CoQ10 have been reported in elderly people and have been linked to the cardiovascular diseases, cancer, diabetes, and neurodegenerative diseases via oxidative-stress mediated mechanism.[14] Previous randomized placebo-controlled trial studies have illustrated an association between CoQ10 supplementation and improved sperm concentration, motility, and morphology[15] in animals and in men suggesting a potential therapeutic role. In these studies, patients also had higher catalase (CAT) and superoxide dismutase (SOD) levels in comparison to the control group. These findings were augmented by recent meta-analysis, which reported an increment in all seminal fluid parameters but not in conception rates following CoQ10 therapy.[16] Although the antioxidant properties of CoQ10 are well-recognized, studies on the effect of CoQ10 on seminal enzymatic and nonenzymatic antioxidant capacities are limited.[17]

Dexamethasone, long-acting synthetic member glucocorticoids, is widely used as an anti-inflammatory and immunosuppressive drug. Long-term administration of dexamethasone is, however, associated with significant side effects including osteoporosis and immunosuppression.[18] The mechanism by which glucocorticoids provoke testicular dysfunction is unknown; however, one of the proposed mechanisms is OS.[19] Dexamethasone can increase ROS production, which ultimately induces mitochondrial dysfunction and cellular apoptosis.[20] A study reported that dexamethasone treatment altered oxidants/antioxidants balance and decreased CAT activity with increment in malondialdehyde (MDA) levels in the muscular tissues of chickens.[21] Another study demonstrated that high levels of dexamethasone significantly increased MDA and hydrogen peroxide and reduced total antioxidant capacity (TAC) and SOD activity, resulting in OS.[22]

Dexamethasone has been used to induce OS for experimental studies; however, studies exploring the effects of dexamethasone therapy on gonadal redox system are limited. To our knowledge, this study is the first study to assess CoQ10/dexamethasone interaction on OS in rats testes. Therefore, this study aimed to investigate the impact of coenzyme Q10 on dexamethasone-induced OS in rats testes.

Materials and Methods

Chemicals

Coenzyme Q10 was purchased from America Medic and Science (AMS) (WA, USA), and dexamethasone was purchased from T and D Pharma GmbH (Lemgo, Germany). Other chemicals were received from standard commercial supplies.

Experimental design

Sixteen male Wistar rats (150–180 g) of 8 weeks' age were used in this experimental study. The study was conducted at the College of Science, University of Babylon, in August 2018. Animals were purchased from Animal Research Facility, College of Science, University of Babylon. Animals were housed inside plastic cages at room temperature (25°C ± 2°C) with a 12-h light/dark cycle and received standard pellet diet and water *ad libitum*.

After the acclimation time, rats were randomly allocated into four equal groups of four each as follows: group 1 (control) received 1 mL of distilled water daily orally; group 2 (coenzyme Q10) received 30 mg/kg/day coenzyme Q10 orally; group 3 (dexamethasone) received 0.2 mg/kg/day dexamethasone intraperitoneally (i.p); and group 4 (coenzyme Q10 + dexamethasone) received 30 mg/kg/day coenzyme Q10 orally and 0.2 mg/kg/day dexamethasone (i.p.). All treatments were administered for 14 days. We have used doses used in previous studies.[23,24]

At the end of the treatment period, the animals were anesthetized with chloroform, killed, and testis tissue was collected. Right testis specimen was quickly excised, weighed, and then homogenization was accomplished with phosphate-buffered saline (10% w/v) and centrifuged at 4000 rpm for 15 min. The supernatant was stored at −20°C for antioxidants assays. Other testis specimen was fixed in 10% buffered formalin for histopathological assessment.

Biochemical analysis

Total antioxidant capacity

TAC was assessed using CUPRAC (cupric reducing antioxidant capacity) spectrophotometric method as described by Apak *et al.* (2008).[25]

Superoxide dismutase activity

(Cu-Zn) SOD activity was determined by a colorimetric method, based on the ability of the enzyme to inhibit the auto-oxidation of pyrogallol as described by Magnani *et al.* (2000).[26]

Catalase activity

CAT activity was determined by a colorimetric method, based on the reactions of ammonium metavanadate with H_2O_2 under acidic conditions as described by reference [27].

Histopathological study

Left testis from all animals was fixed in 10% formaldehyde solution for 72 h, dehydrated in increasing concentration ethanol solutions, and embedded in paraffin. Five µm

sections were then obtained, stained with hematoxylin–eosin (H & E) stain, and assessed by a consultant pathologist using light microscope.

Statistical analysis

Statistical analysis of data was performed with SPSS (v. 24) software. Data normality was explored with Shapiro-Wilk test and relevant histograms. The results were presented as mean ± standard deviation, and Kruskal–Wallis test was used to compare the means of different groups. $P < 0.05$ was considered as statistically significant.[28]

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and animal handling procedure reviewed and approved by University of Babylon, Iraq, local ethics committee according to the document number 302 on 28-03-2022.

Results

TAC did not differ significantly among control, coenzyme Q10, dexamethasone, and coenzyme Q10 + dexamethasone treated groups (1310.8 ± 153.6, 1186.8 ± 170.8, 1244.3 ± 175.8, and 1156.4 ± 75.8, μM respectively, $P > 0.05$) [Figure 1]. CAT activity was also comparable between four treatment groups (0.123 ± 0.02, 0.137 ± 0.04, 0.110 ± 0.013, and 0.117 ± 0.02 KU/mL respectively, $P > 0.05$) [Figure 2]. As for SOD activity, although it was lower in dexamethasone and coenzyme Q10 + dexamethasone groups, these differences were not statistically significant (0.630 ± 0.20, 0.570 ± 0.28, 0.309 ± 0.15, and 0.222 ± 0.07 U/mL respectively, $P > 0.05$) [Figure 3].

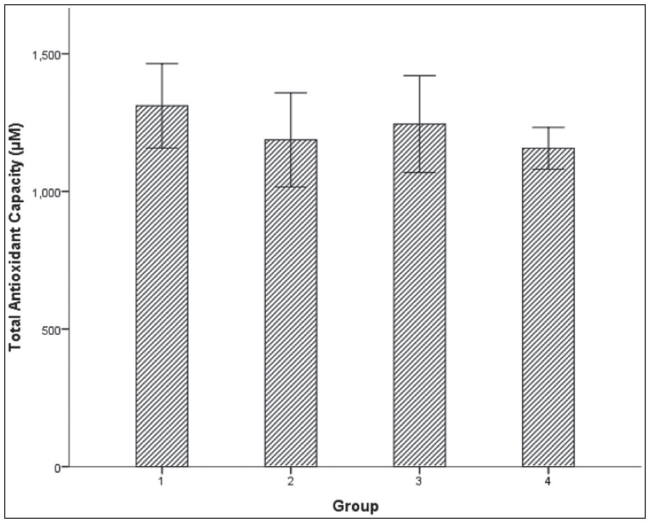

Figure 1: TAC among controls (group 1), coenzyme Q10 (group 2), dexamethasone (group 3), and coenzyme Q10 + dexamethasone (group 4) groups ($P > 0.05$)

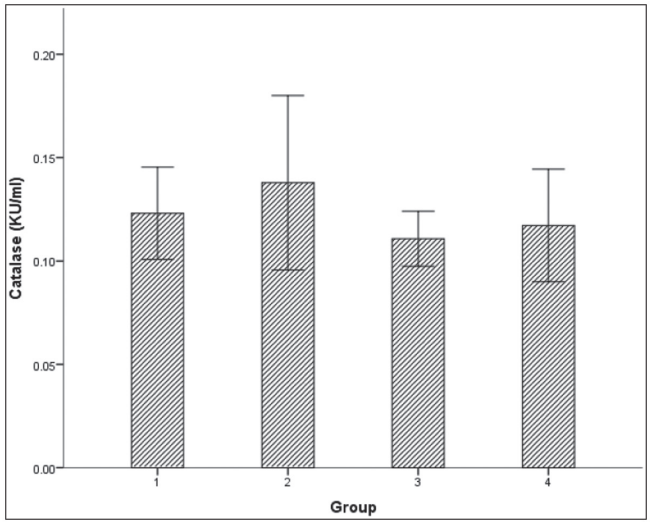

Figure 2: CAT activity among controls (group 1), coenzyme Q10 (group 2), dexamethasone (group 3), and coenzyme Q10 + dexamethasone (group 4) groups ($P > 0.05$)

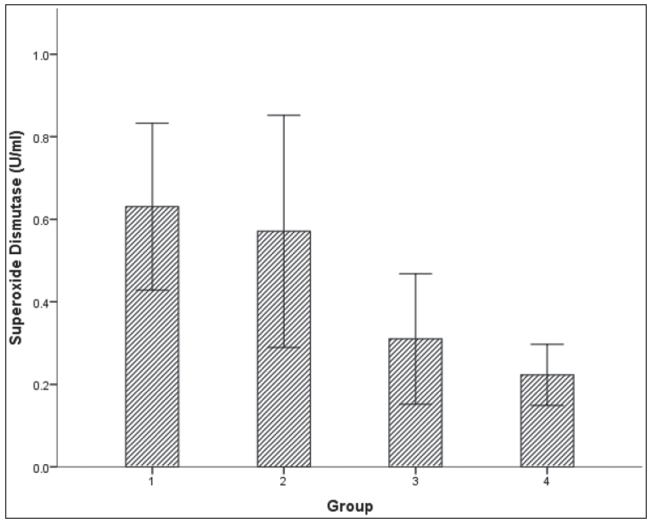

Figure 3: SOD activity among controls (group 1), coenzyme Q10 (group 2), dexamethasone (group 3), and coenzyme Q10 + dexamethasone (group 4) groups ($P > 0.05$)

Figure 4 illustrates histopathological findings of rats testes of four treatment groups. All groups demonstrated normal development of spermatogonia, spermatocytes, spermatids, and spermatozoa as well as normal basement membrane of seminiferous tubules.

Discussion

Immunosuppressive, anti-inflammatory, and OS induction properties of acute and pharmacological doses of glucocorticoids have been recognized.[21] Although ROS are required for certain physiological processes such as acrosome reaction and capacitation, excessive production of ROS and reduced antioxidant capacity

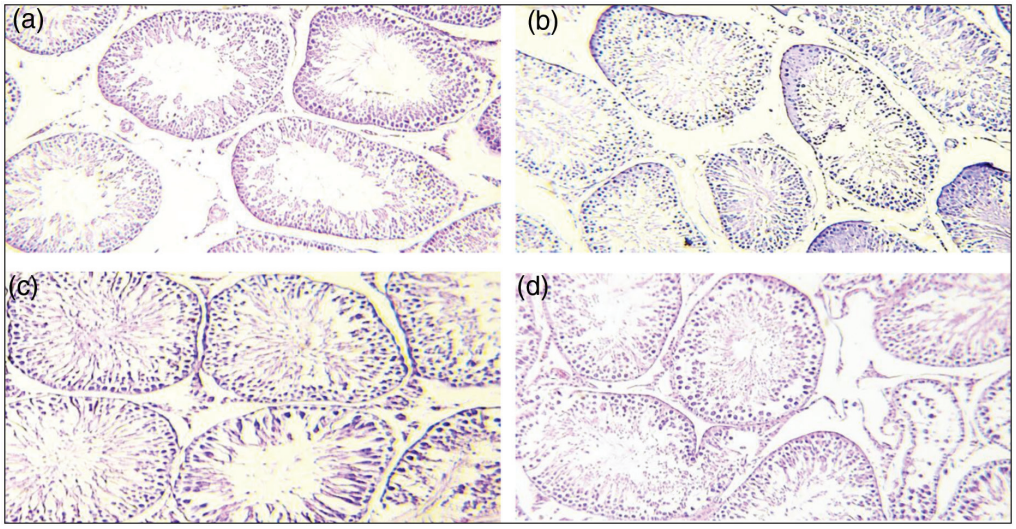

Figure 4: Microphotographs of rats testes showing normal spermatogenesis and basement membrane of seminiferous tubules in (a) control, (b) coenzyme Q10, (c) dexamethasone, and (d) coenzyme Q10 + dexamethasone-treated groups (H&E, ×200)

are detrimental for spermatogenesis and fertilization.[29] In the present study, dexamethasone treatment did not significantly alter the TAC, CAT, and SOD activities in rats testes although SOD activity in rats testes was lower in dexamethasone and CoQ10 + dexamethasone groups. Our results contradict the results of previous studies, which showed increased OS and reduction in antioxidant capacity following dexamethasone administration.[20] Mukherjee *et al.* showed that dexamethasone treatment (7 mg/kg/day) decreased testicular OS via reducing SOD, CAT, glutathione peroxidase (GSH-PX) activity, plasma melatonin, and melatonin receptor expression in golden hamster.[30] Further, a dose of dexamethasone of 10 mg/kg/day caused an increase in MDA levels in serum and lipid profile measures, and these changes were reduced by hydroalcoholic extract of Allium elburzense.[31] A possible explanation for the lack of dexamethasone's effect on TAC, CAT, and SOD activities could be the lower dose used here comparing with the does used in the previous studies.[23,32] However, there is a lack of agreement on the dose of dexamethasone used in experimental studies on rats. Smaller sample sizes used in the current study could also mask the potential differences from being appeared among studied groups.

In our study, CoQ10 alone or in combination with dexamethasone therapy did not show positive effects on antioxidant measures. Dexamethasone-induced OS can be ameliorated by various antioxidants. Pretreatment of mice with betulinic acid for 2 weeks significantly reduced dexamethasone-induced OS and increased TAC and SOD activity in serum, liver, spleen, and thymus. Dexamethasone was administered i.p. at dose of 25 mg/kg, and these effects were attributed partially to c-Jun N-terminal kinase and P38 mitogen-activated protein kinase pathway modulation.[20] Hasona explored the effect of grape seed extract on dexamethasone-associated oxidative injury in male albino rats. In their study, rats received dexamethasone subcutaneously (0.1 mg/kg) three times per week for 1 month, resulted in decrease in CAT, and reduced glutathione (GSH) activity in testes. These changes were ameliorated by grape seed extract.[33] Moreover, coadministration of dexamethasone and vitamin E protected against varicocele-induced reduction in SOD, CAT, GSH-PX, and increment in MDA in rats testis.[34] Similarly, pretreatment with antioxidants such as mangiferin protected against MC3T3-E1 osteoblast cell line apoptosis, OS, and secretion of tumor necrosis factor-alpha, interleukin-6, and macrophage colony-stimulating factor associated with dexamethasone treatment.[35]

A body of the literature revealed an increment in TAC, CAT, and SOD activities in rats following CoQ10 treatment. Sun *et al.* explored the effect of CoQ10 (20 mg/kg orally) and metformin (250 mg/kg orally) alone or in combination with diabetic rats and demonstrated an increment in SOD and CAT activity.[36] Coenzyme Q10 (10 mg/kg/day oral) alone or in combination with fish oil suppressed aluminum chloride-induced inhibition of testicular steroidogenesis in rats.[37] In addition, CoQ10 administration (10 mg/kg/day for 8 days) counteracted doxorubicin-associated testicular OS via the upregulation of caspase 3 and P-glycoprotein expression in rats.[38] Conversely, Beharry *et al.* reported that CoQ10 (0.35 mg/day oral) reduced SOD and GSH but not CAT in rats models of neonatal intermittent hypoxia.[32] Because of poor bioavailability, some studies tried nanoformulations of CoQ10 and demonstrated better therapeutic efficacy and reduction of OS in rats.[39] Several studies have reported a positive effect for CoQ10 on one more of seminal fluid parameters in infertile men.[29] However, in the line with our findings, a study found that the serum CoQ10 level

was not different in fertile and infertile men who had lower levels of serum TAC.[40] In addition, coenzyme Q10 counteracted doxorubicin-induced testicular OS and apoptotic effect by upregulating the efflux pump P-glycoprotein in rats.[38] Lipophilic properties of CoQ10 offer protection against lipid peroxidation in tissues with high lipid content such as liver and nervous tissue, which are targets for lipid peroxidation.

Histopathological findings of rats testes were congruent with biochemical tests results in our study. All study groups demonstrated normal spermatogenesis and normal basement membrane of seminiferous tubules following dexamethasone and coenzyme Q10 therapy. Previous study demonstrated that dexamethasone treatment was associated with the separation of germ cells and basement membrane with intratubular debris in seminiferous tubules, and these changes were ameliorated by grape-seeds extract.[33] Limitations of our study include a small sample size and a lack of the comparison of different doses of CoQ10 and dexamethasone. However, we have used a study design and doses similar to previous studies.

Conclusions

The present study demonstrated that dexamethasone (0.2 mg/kg/day) and coenzyme Q10 (30 mg/kg/day) did not alter testicular TAC, CAT, and SOD activities or histopathology of rats testes. This study may help identify the therapeutic as well as the toxic doses and effects of coenzyme Q10 and dexamethasone on spermatogenesis. Further studies using higher doses of dexamethasone and coenzyme Q10 are recommended to assess their impact on markers of gonadal oxidative damage and their potential therapeutic efficacy in male infertility.

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Conflicts of interest

There are no conflicts of interest.

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