

Impact of Ciprofloxacin and Coenzyme Q10 on Spermatogenesis in Mice

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Abstract

Background: Ciprofloxacin is commonly used to treat many bacterial infections. There are controversial reports regarding abnormalities in sperm parameters in laboratory animal and human studies after ciprofloxacin administration. Coenzyme Q10 is a fat-soluble vitamin-like substance that is concentrated in sperm mitochondria, where it acts as an antioxidant and an energy promoter. Various studies found that coenzyme Q10 can improve sperm parameters, whereas other studies showed no significant improvement in sperm parameters. This study aimed at investigating the effect of ciprofloxacin and coenzyme Q10 on spermatogenesis and sperm morphology in male mice. **Materials and Methods:** Twenty eight-week-old male albino mice were randomly divided into four equal groups: control group, group 1 that received ciprofloxacin (102.78 mg/kg), group 2 that was given coenzyme Q10 (20.56 mg/kg), and group 3 that was given both ciprofloxacin and coenzyme Q10. The drugs were given twice daily for 35 days. On day 36, the mice were sacrificed; sperm were harvested, analyzed for sperm morphology, and stained for detection of sperm abnormalities. Testes were taken to evaluate spermatogenesis histopathologically. Data were statistically analyzed, and a *P* value of ≤ 0.05 was considered significant. **Results:** Sperm morphology showed no significant alteration in the groups treated with ciprofloxacin, coenzyme Q10, and a combination of ciprofloxacin and coenzyme Q10 compared with the control. However, histopathological lesions showed a mild decrease in spermatogenesis that was accompanied by mild vein congestion in the testicular tissue sections of mice treated with ciprofloxacin only. **Conclusion:** Ciprofloxacin had no significant negative impact on sperm morphology; however, it induced mild histopathological alterations in testicular tissue that was ameliorated by the coadministration of coenzyme Q10. This effect should be taken into consideration during ciprofloxacin therapy in males.

Keywords: Ciprofloxacin, coenzyme Q10, fertility, sperm, spermatogenesis

INTRODUCTION

The use of antimicrobial agents is of great importance in the treatment of male genital tract infections, and such infections may affect fertility.^[1,2] Fluoroquinolones are routinely used to control male reproductive infections in assisted conception.^[3] Ciprofloxacin is a second-generation fluoroquinolone exhibiting broad-spectrum antibacterial activity.^[4] The antibacterial mechanism of action of ciprofloxacin is based on the inhibition of bacterial DNA gyrase enzyme and type II topoisomerase enzyme, which is equivalent to topoisomerase II in mammalian cells.^[5]

Ciprofloxacin displays good bioavailability after oral administration; it exhibits good to excellent tissue penetration, which makes this antibiotic a gold standard candidate for treating urogenital infections.^[6] In prostatic

tissue and seminal fluid, ciprofloxacin can be detected in a high concentration, where it may adversely affect sperm cells, resulting in physiological, metabolic, and/or genetic changes.^[7] Impairment of the histological structure of the epididymis, testicles, seminal vesicles, and prostate has been reported in laboratory animal studies conducted with ciprofloxacin.^[8-10]

Coenzyme Q10 in sperm cells is mostly concentrated in the mitochondria of the midpiece; it is required in energy-dependent processes depicting sperm cells availability.

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A direct correlation between coenzyme Q10 and semen parameters has been observed.^[11] Supplementation with coenzyme Q10 has been used for an improvement in reproductive outcomes in men with fertility problems.^[12]

The molecular activity of ciprofloxacin observed in human cells remains unclear in many aspects, and the induction of oxidative stress was reported in patients after ciprofloxacin administration.^[13]

Based on human and animal studies that showed that ciprofloxacin induces oxidative stress and has a negative impact on sperm parameters and that depicted coenzyme Q10 as having a therapeutic role in improving sperm parameters, this study was undertaken to find out the impact of ciprofloxacin and coenzyme Q10 on spermatogenesis in mice.

MATERIALS AND METHODS

Twenty eight-week-old male albino mice, weighing 25 ± 5 g, were used in the study. The mice were housed in the laboratory animal house (College of Medicine, Hawler Medical University) under controlled room temperature (25°C) and a 12h/12h light/ dark cycle; they were given water and feed pellets freely. The mice were randomly selected and divided into control ($n = 5$) and experimental ($n = 15$) groups. The experimental groups were subdivided equally into three groups. The control group received placebo (0.1ml saline solution orally). The treatment group 1 received ciprofloxacin (ciprofloxacin tablet as hydrochloride, Bayer) at 102.78mg/kg. The treatment group 2 was given coenzyme Q10 (Nature Company, USA) at 20.56mg/kg. The treatment group 3 was given both ciprofloxacin at 102.78mg/kg and coenzyme Q10 at 20.56mg/kg.

The dose of ciprofloxacin given was intended to imitate the therapeutic human dose equivalent to 500 mg, and the dose of coenzyme Q10 was chosen based on infertility studies conducted in humans.^[14]

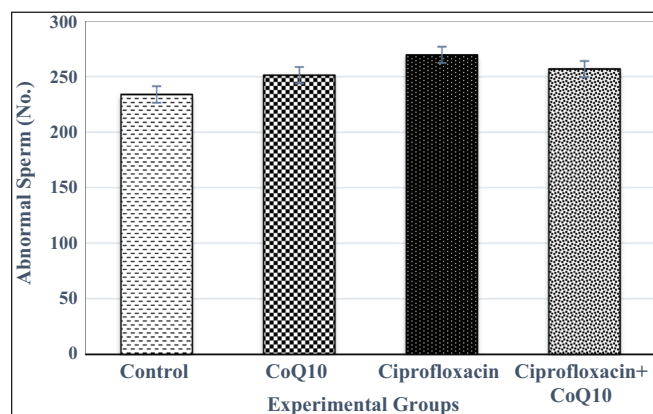


Figure 1: Number of morphologically abnormal sperm in different experimental groups

The drugs were given twice daily for a period of 35 days, corresponding to the duration of spermatogenesis in mice. On day 36, the mice were anesthetized with ketamine at 100mg/ kg and sacrificed by cervical dislocation. The testis and epididymis were immediately removed; the epididymal spermatozoa were harvested after dissecting the caudal part of the epididymis, smeared onto slides, fixed in Methanol: Glacial acetic acid (3:1 v/v), and stained with eosin. A total of 800 spermatozoa were examined (at $400\times$ magnification) for the presence of abnormal spermatozoa morphology in each group. The percentage of abnormal spermatozoa was expressed as a fraction of the total counted spermatozoa. The testes were fixed in 10% formalin solution, and slides for histopathological examination were prepared and stained with eosin and hematoxylin.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 44 (including the number and the date in 11/6/2020) to get this approval.

Data are expressed as mean $\pm$ SE and statistically analyzed by Professor Namir Al-Tawil (College of Medicine, Hawler Medical University) using SPSS software version 18 (SPSS, IBM Company, Chicago, IL 60606, US). A P value of ≤ 0.05 was considered significant.

RESULTS

The number of morphologically abnormal sperm in different experimental groups is shown in Figure 1. No statistically significant ($P \geq 0.05$) differences were observed in the morphology of sperm between the different treatment groups compared with the control.

Abnormalities, including changes in the normal morphology of the head, neck, and tail region of the sperm in the groups treated with either ciprofloxacin or coenzyme Q10 or a combination of ciprofloxacin and coenzyme Q10, are shown in Figure 2.

Although the changes observed in normal sperm morphology were statistically not different ($P \geq 0.05$), the highest percent of abnormality was shown in the tail of sperm in the ciprofloxacin group and in the group that received both ciprofloxacin and coenzyme Q10 (45.99% and 38.94%), respectively; however, the head abnormality was the highest (38.69%) in the coenzyme Q10 group [Table 1].

The histopathological study showed normal seminiferous tubules, spermatogenesis, and normal interstitial tissue in control and coenzyme Q10 treated mice ([Figure 3]; A, B respectively). A mild to moderate decrease in the number

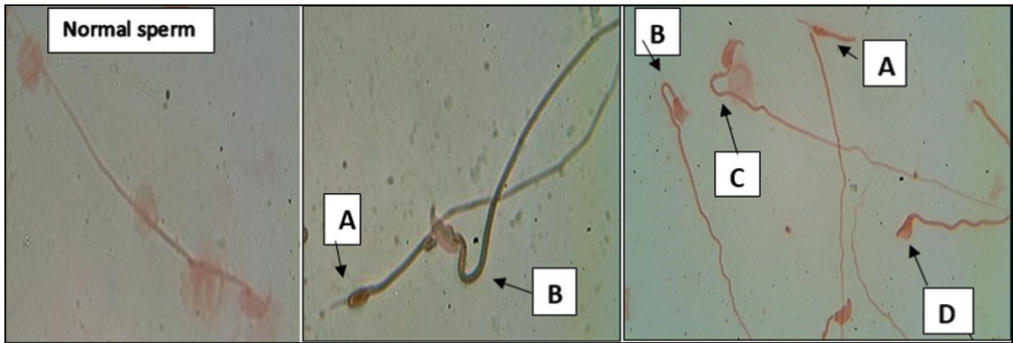


Figure 2: Abnormalities in sperm morphology in different experimental groups: (A) sperm with pin head, (B) bent neck, (C) amorphous sperm with bent neck, and (D) amorphous sperm

Table 1: Effect of ciprofloxacin, coenzyme Q10 alone or in combination on the morphology of sperm in different experimental groups			
Group	% Abnormality		
	Head	Neck	Tail
Control	41.02	17.09	41.88
Ciprofloxacin	21.36	32.64	45.99
Co enzyme Q10	38.69	29.45	31.85
Ciprofloxacin + coenzyme Q10	33.72	27.34	38.94

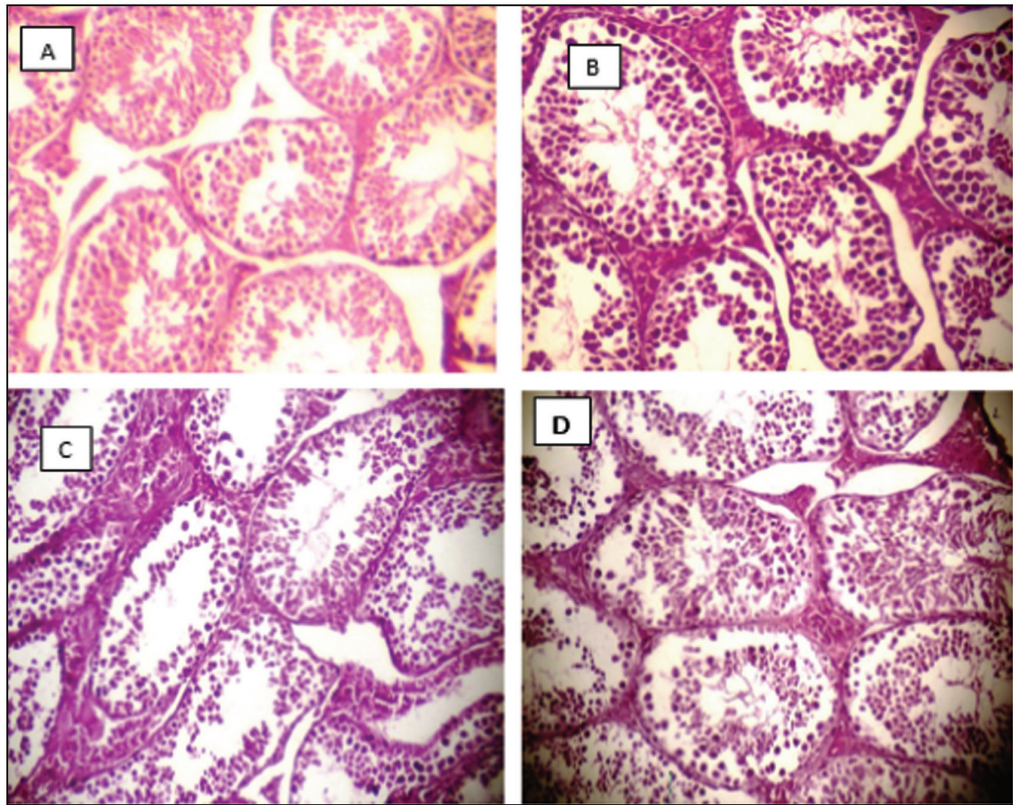


Figure 3: Histopathological section through the testis of control mice showing normal seminiferous tubules, normal spermatogenesis, and normal interstitial tissue (A). Coenzyme Q10-treated mice show normal seminiferous tubules, normal spermatogenesis, and normal interstitial tissue (B). Ciprofloxacin-treated mice show a mild-to-moderate decrease in the number of spermatogenic cells (spermatogonia, spermatocyte, spermatid, and sperm) in the seminiferous tubules with intertubular spaces and mild vein congestion (C). Ciprofloxacin + coenzyme Q10 treated mice show a focal mild decrease in the number of spermatogenic cells in the seminiferous tubules with mild vein congestion (D). (H&E, x40)

of spermatogonia, spermatocyte, spermatid, and sperm in the seminiferous tubules with intertubular spaces and mild vein congestion was found in the testicular tissue section of the mice treated with ciprofloxacin [Figure 3C]; these testicular alterations were attenuated in the mice that were coadministered ciprofloxacin and coenzyme Q10 [Figure 3D].

DISCUSSION

In the present study, the administration of ciprofloxacin for 35 days produced no significant ($P \geq 0.05$) adverse effects on sperm parameters, including abnormalities in the head, neck, or tail of the sperm of male mice. These results are in agreement with studies conducted in patients.^[15,16] However, they are in contrast to the studies conducted in the case of laboratory animals, which reported the deleterious effects of ciprofloxacin on certain sperm parameters.^[9,10,17,18]

These discrepancies may be related to the differences between *in vivo* and *in vitro* studies, dose, route of administration of ciprofloxacin (orally or IP), duration of drug administration, and different drug formulations (pure powder or patent pharmaceutical formulation) or they could be related to the small number of mice used in the present study.

It seems that the dose of ciprofloxacin used (akin to the therapeutic dose) did not attain high enough concentrations in the sperm cells to inflict significant damage on the sperm cells. This explanation is based on the findings of Bulitta *et al.*,^[19] as ciprofloxacin attains lower concentrations in the sperm cells whereas it achieves high concentrations in the prostate acini and seminal fluid, a property exhibiting its potent antibacterial efficacy; therefore, it may not induce direct adverse effects on sperm parameters.

Plasma membranes of spermatozoa contain low concentrations of scavenging enzymes in the cytoplasm, so they are particularly susceptible to the damage induced by excessive ROS.^[20] The mild-moderate reduction in number of spermatogenic cells shown within seminiferous tubules and other histopathological changes in the testicular tissues of male mice in the present study most probably are related to the oxidative stress effects induced by ciprofloxacin.^[13]

This finding indicates that the administration of therapeutic doses of ciprofloxacin may adversely influence male fertility through inducing oxidative stress and it may also induce defective spermatogenesis, as proposed by others.^[21]

Although these histopathological findings do not reflect the nonsignificant ($P \geq 0.05$) abnormality in sperm morphology, they shed light on the negative impact on male fertility that might be induced with ciprofloxacin treatment.

These mild to moderate histopathological alterations that were observed in testicular tissues after ciprofloxacin administration in this study are in contrast to the significant testicular damage reported in different studies,^[8-10] which could be related to differences in the settings of the studies and the type of drug formulations used.

The nonsignificant ($P \geq 0.05$) alterations in sperm parameters depicted by coenzyme Q10 administration and a combination of coenzyme Q10 and ciprofloxacin compared with the control group illustrate that the administration of coenzyme Q10 imposes no hazard to sperm cells and supports the beneficial role of coenzyme Q10 administration in male fertility, which has been demonstrated by many studies.^[22] This is because the administration of coenzyme Q10 along with ciprofloxacin reduced the histopathological alteration in testicular tissues induced by ciprofloxacin administration. This result supports the notion that coenzyme Q10 is capable of attenuating oxidative stress in the seminal plasma and of improving testicular damage, as has been demonstrated by other studies.^[2,11,12]

CONCLUSION

The administration of ciprofloxacin induced mild histopathological alterations in testicular tissue and subsequent sperm parameters; the coadministration of coenzyme Q10 is useful for those patients on long-term ciprofloxacin therapy to maintain successful male fertility, normal spermatogenesis, normal sperm transport, and normal accessory gland function.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Perletti G, Marras E, Wagenlehner FM, Magri V. Antimicrobial therapy for chronic bacterial prostatitis. *Cochrane Database Syst Rev* 2013;12:CD009071.
2. Onyije FM. Drug: A major cause of infertility in male. *Asian J Med Pharm Res* 2012;2:30-7.
3. Calogero AE, Condorelli RA, Russo GI, La Vignera S. Conservative nonhormonal options for the treatment of male infertility: Antibiotics, anti-inflammatory drugs, and antioxidants. *Biomed Res Int* 2017;2017:4650182.
4. Oliphant CM, Green GM. Quinolones: A comprehensive review. *Am Fam Physician* 2002;65:455-64.
5. Lica K. ZX. DNA gyrase topoisomerase IV and the 4-Quinolones. *Microbiol Mol Biol Rev* 1997;61:377-392.

6. Cao D, Shen Y, Huang Y, Chen B, Chen Z, Ai J, *et al.* Levofloxacin versus ciprofloxacin in the treatment of urinary tract infections: Evidence-based analysis. *Front Pharmacol* 2021;12:658095.
7. Charalabopoulos K, Karachalios G, Baltogiannis D, Charalabopoulos A, Giannakopoulos X, Sofikitis N. Penetration of antimicrobial agents into the prostate. *Chemotherapy* 2003;49:269-79.
8. Elias A, Nelson B. Toxicological effect of ciprofloxacin on testicular function of male guinea pigs. *Asian J Exp Biol Sci* 2012;3:384-90.
9. Zobeiri F, Sadrkhanlou RA, Salami S, Mardani K, Ahmadi A. The effect of ciprofloxacin on sperm DNA damage, fertility potential and early embryonic development in NMRI mice. *Vet Res Forum* 2012;3:131-5.
10. Khaki A. Assessment on the adverse effects of aminoglycosides and flouroquinolone on sperm parameters and male reproductive tissue: A systematic review. *Iran J Reprod Med* 2015;13:125-34.
11. Torres-Arce E, Vizmanos B, Babio N, Márquez-Sandoval F, Salas-Huetos A. Dietary antioxidants in the treatment of male infertility: Counteracting oxidative stress. *Biology* 2021;10:241.
12. Salvio G, Cutini M, Ciarloni A, Giovannini L, Perrone M, Balercia G. Coenzyme Q10 and male infertility: A systematic review. *Antioxidants* 2021;10:874-90.
13. Talla V, Veerareddy P. Oxidative stress induced by fluoroquinolones on treatment for complicated urinary tract infections in Indian patients. *J Young Pharm* 2011;3:304-9.
14. Festa R, Giacchi E, Raimondo S, Tiano L, Zuccarelli P, Silvestrini A, *et al.* Coenzyme Q10 supplementation in infertile men with low-grade varicocele: An open, uncontrolled pilot study. *Andrologia* 2014;46:805-7.
15. Zhang ZC, Jin FS, Liu DM, Shen ZJ, Sun YH, Guo YL. Safety and efficacy of levofloxacin versus ciprofloxacin for the treatment of chronic bacterial prostatitis in Chinese patients. *Asian J Androl* 2012;14:870-4.
16. Fakhridin MB, Selman MO, Najim DA. Effect of different antibiotics administered to infertile men with leucocytospermia on the sperm parameters. *World J Pharm Res* 2015;4:144-9.
17. Khaki A, Heidari M, Novin MG, Khaki AA. Adverse effects of ciprofloxacin on testis apoptosis and sperm parameters in rats. *Iran J Reprod Med* 2008;6:71-6.
18. Zobeiri F, Salami S, Sadrkhanlou R, Peirouvi T. Role of mitochondria in ciprofloxacin-induced apoptosis in murine sperm cells. *Reprod Sci* 2013;20:1090-5.
19. Bulitta JB, Kinzig M, Naber CK, Wagenlehner FM, Sauber C, Landersdorfer CB, *et al.* Population pharmacokinetics and penetration into prostatic, seminal, and vaginal fluid for ciprofloxacin, levofloxacin, and their combination. *Chemotherapy* 2011;57:402-16.
20. Agarwal A, Makker K, Sharma R. Clinical relevance of oxidative stress in male factor infertility: An update. *Am J Reprod Immunol* 2008;59:2-11.
21. Zobeiri F, Sadrkhanlou RA, Salami S, Mardani K. Long-term effect of ciprofloxacin on testicular tissue: Evidence for biochemical and histochemical changes. *Int J Fertil Steril* 2013;6:294-303.
22. Nadjarzadeh A, Sadeghi MR, Amirjannati N, Vafa MR, Motevalian SA, Gohari MR, *et al.* Coenzyme Q10 improves seminal oxidative defense but does not affect on semen parameters in idiopathic oligoasthenoteratozoospermia: A randomized double-blind, placebo controlled trial. *J Endocrinol Invest* 2011;34:e224-8.