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Research Article

The protective role of CoQ10 against cisplatin-induced cytotoxicity in male albino mice

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Abstract
This study aimed to investigate the protective effect of CoQ10 against cisplatin-induced cytotoxicity in male albino mice. The study was divided into two phases. In the first phase, the optimum dose of CoQ10 was selected by using gradual concentrations of the coenzyme Q10 (100, 200, 400mg/kg). The concentration of 100mg/kg showed a significant difference in reducing the abnormalities in the sperm heads. In the second stage, the interaction of the optimal concentration of CoQ10 with the mutagenic drug cisplatin [Cis-Diammine Dichloride Platinum] (CDDP) on two treatments (before and after the use of the mutagenic drug) performed to find out the mechanism by which the coenzyme works in preventing or reducing the genotoxic effect of the mutagenic drug CDDP in the event of abnormalities in the heads of the sperm, and both of the interaction treatments had a significant decrease. The results the ability of coenzyme Q10 (CoQ10) to counteract the damage caused by cisplatin by abnormalities in the sperm heads. The interaction treatment (before) was less than the interaction treatment (after) in the rate of abnormalities of the sperm heads. In addition, the results showed that the enzymatic compound has a clear protective role because of its important vital activities in protecting sperm from malformations when given before and after cisplatin.

Keywords: Sperm, Cisplatin, Protective effect, CoQ10.

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Introduction

Coenzyme Q10, a lipid-soluble compound, is found in nearly all cell membranes. It is essential for transporting electrons in the mitochondrial respiratory chain for cellular energy production in the inner mitochondrial membrane. The reduced form of CoQ10, known as ubiquinol, acts as an antioxidant in cellular metabolism by inhibiting lipid peroxidation, protein, and DNA oxidation, removing free radicals and maintaining genome stability (Santos-Ocaña et al. 2002; McCarthy et al. 2004). It supports the regeneration of other antioxidants, affecting membrane stability and permeability, stimulating cell growth, and inhibiting apoptosis (DiNicolantonio et al. 2015). CoQ10 deficiency can damage mitochondrial bioenergetics and cause oxidative stress, as evidenced by decreased ATP generation, increased reactive oxygen species (ROS) production, and cell death (Ben-Meir et al. 2015; Bokov et al. 2022). Therefore, this study aimed to investigate the protective effect of CoQ10 against cisplatin-induced cytotoxicity in male albino mice.

Materials and methods

Coenzyme Q10: CoQ10 is a gelatin capsule manufactured by Newton-Everett Nutraceuticals.

One capsule contains 200mg of CoQ10 dissolved in corn oil. The mice were dosed orally using a gavage needle for 35 days (Nyariki et al. 2019). Three concentrations of CoQ10 (100, 200, and 400mg/kg/day) were prepared depending on the average body weight of the animal to obtain the optimal concentration (appropriate dose) from the above concentrations. The maximum tolerated oral dose of CoQ10 has been estimated to be more than 4000mg/kg in mice and rats (Hidaka et al. 2008).

Solutions

Phosphate buffered saline (PBS): The following components were dissolved in 500ml of distilled water, and then the volume was increased to 1000ml: Potassium chloride (KCL) 0.20g, sodium chloride (NaCl) 8.00g, sodium monohydrogen phosphate (Na2HPO4) 1.15g, dihydrogen phosphate (KH_2PO_4) 0.20g, pH fixed at (7.2) and sterilized by Autoclave and kept in 4ºC refrigerator (Hudson & Hay 1980).

Eosin Stain: The solution was prepared by dissolving 1g of Eosin Yellowish stain in 100ml of distilled water. The solution was put in an opaque vial and stored in the incubator at 37°C (Wyrobek & Bruce 1975).

Cisplatin (CDDP): Cisplatin (CDDP) in the form of a solution is manufactured by the American company Pfizer. The vial contains 50mg of Cisplatin in 50ml of the solution (every 1ml contains 1mg of CDDP). The other substances in the solution are sodium chloride, hydrochloric acid (to adjust the pH), and water. According to Sawhney et al. (2005), the dose was prepared at a 1mg/kg concentration by taking 1ml of cisplatin (one injection in the chelate membrane intraperitoneal injection).

Experimental animals: Swiss white male mice (*Mus musculus*) Balb/C were used in this study. The number of animals was 45, distributed over all treatments, with an average age of 12-14 weeks and a weight of 25-30g, which were prepared by the animal house in the College of Science/University of Al-Qadisiyah. They were distributed in plastic cages with a metal clip in the form of groups, according to the experiment's needs, in a room in which the temperature ranged 23-25°C and the duration of illumination was 12L and 12D. These animals were given water and a complete nutritional value diet produced locally at the infertility institute.

Experiment design

First experiment: The experiment included 25 adult male mice distributed into five groups, where each group had five mice for 35 days, after which the optimum concentration of CoQ10 was selected as follows (1) negative control treatment (T1): mice were given an injection of 0.9% saline solution every seven days, and corn oil orally as 0.1ml daily, (2) positive control treatment (T2): CDDP was injected intraperitoneally (i.p.) every seven days, (3) the first treatment of coenzyme Q10 (T3): CoQ10 is administered orally at a concentration of 100mg/kg of body weight, (4) the second treatment of coenzyme Q10 (T4): Q10 is administered orally at a concentration of 200mg/kg of body weight, and (5) the third treatment of Coenzyme Q10 (T5): Q10 is administered orally at a concentration of 400mg/kg of body weight.

Second experiment: The experiment included 20 adult male mice distributed into four groups, where each group included five mice for 35 days, during which the optimal concentration of CoQ10 was overlapped with CDDP as following (1) negative control treatment (T1): an injection of 0.9% saline solution was given every seven days, and corn oil was dosed orally as 0.1ml per day throughout the second experiment, which also amounted to 35 days, (2) positive control treatment (T2): CDDP was injected into the i.p. every seven days of the second experiment, (3) treatment of the interaction between CoQ10 and Cisplatin (before) (T3): Cisplatin is injected intravenously at a 1 mg/kg every seven days, and the CoQ10 conjugate is given orally at a concentration of 100 mg/kg/day. The dose begins one day before administration. Cisplatin is continued throughout the second trial, and (4) treatment of the interaction between CoQ10 and Cisplatin (after) (T4): Rats are injected with cisplatin into the i.p. at a concentration of 1 mg/kg every seven-day coenzyme

Table 1. The effect of the mutagenic drug CDDP and the different concentrations of CoQ10 on the percentage of abnormalities in the sperm heads of mice.

Treatment	Abnormal sperm %	Normal sperm%	Total number rate	Percentage of sperm head abnormalities
T1	48±3.16	152±3.16	200	24±1.78
T2	133.8±3.11	66.2±3.11	200	66.9±1.98
T3	37.2±1.64	162.8±1.64	200	18.6±1.14
T4	39.6±1.14	160.4±1.14	200	19.8±1.02
T5	43.4±2.07	156.6±2.07	200	21.7±1.08
$LSD_{0.05}$	3.122	3.122	----------	2.34

Number of replicates is 5 for each treatment.

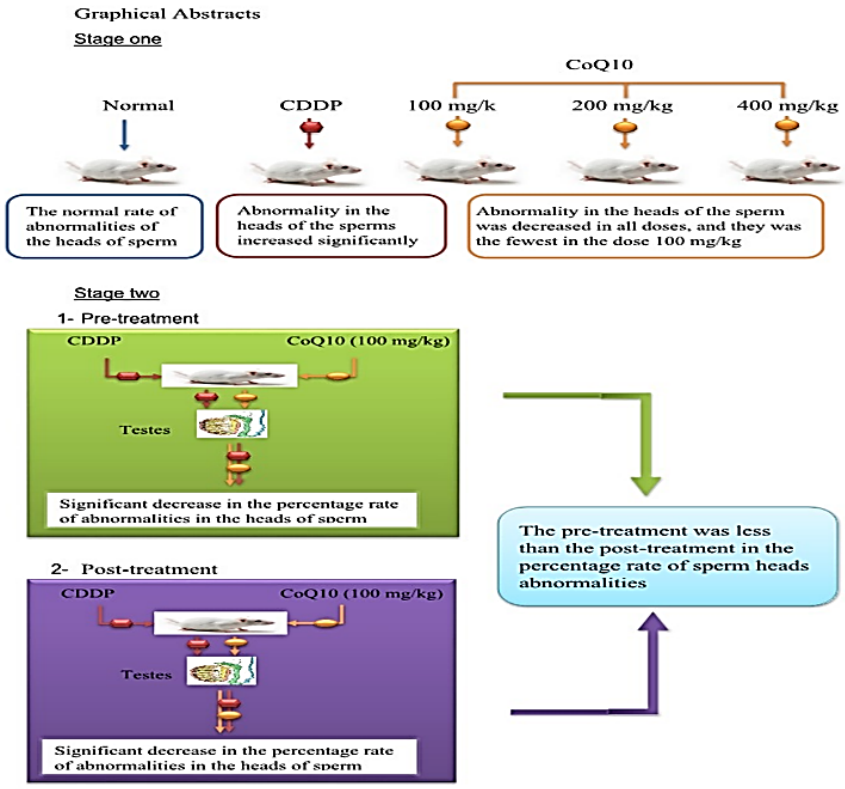

Fig.1. The study design**.**

is given orally at a concentration of 100mg/kg/day. CoQ10 starts after a day of cisplatin administration and continues throughout the second trial.

Sperm head abnormality assay: Mice were dissected, and sperm was extracted from the epididymis, according to Wyrobek & Bruce (1975). The epididymis was cut and placed in a petri dish containing 5ml PBS solution. Using a sharp blade and fine forceps, the epididymis was cut into very small pieces, and the solution containing these parts was placed in a clean test tube. Clean slides were prepared by spreading a drop of the solution in the tube on the glass slide, then leaving the slides on a hot plate (50ºC) to dry. The dry glass slides were stained with Eosin 1% stain for 1-3 minutes, after which the excess dye was removed by washing the slides with distilled water. Then, the slides were examined with a light microscope using an oil lens. The percentage of abnormalities of the sperm heads was calculated by examining (1000 sperm) and

Table 2. Effect of Cisplatin and CoQ10 Interaction (before and after) on the percentage of sperm head abnormalities in mice.

Treatment	Abnormal sperm%	Normal sper %	Total number rate	Percentage of sperm head abnormalities
T1	61.2±2.28	138.8±2.28	200	30.6±2.02
T2	125±1.22	75±1.22	200	62.5±0.78
T3	72.8±5.16	127.2±5.16	200	36.4±3.12
T4	98.4±6.65	101.6±6.65	200	49.2±3.36
$LSD_{0.05}$	5.909	5.909	----------	2.95

The number of replicates is 5 for each treatment.

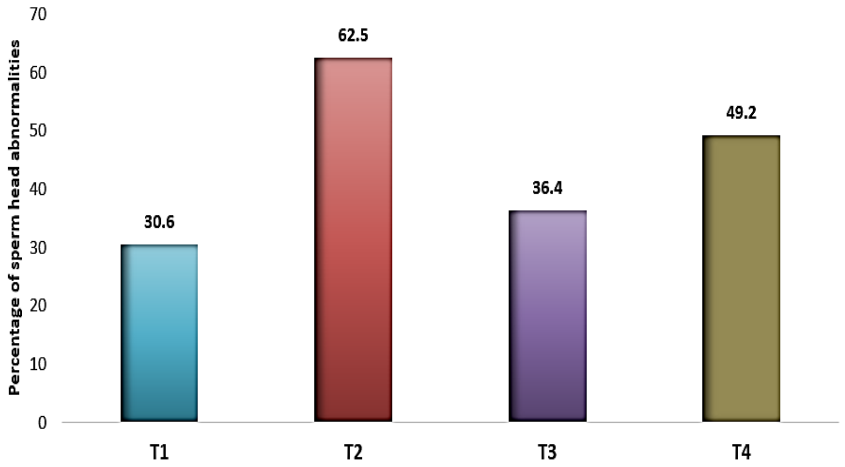

Fig.2. The effect of the interaction between Cisplatin and CoQ10 on the percentage of sperm head abnormalities in mice.

comparing the shapes of those sperm with the normal shape of the head of the mouse sperm from the Balb/C.

Statistical analysis: The results were analyzed using Statistical Package of Social Science (SPSS version 26). The One Way ANOVA was used with the Least Significant Difference (LSD) value to compare the averages of the transactions included in the study. The significant differences were determined at the 5% probability level.

Results

First experiment: The study showed some deformations in the sperm heads, including the narrow head, broken hook head, missing head, giant head, micro head, and hammerhead. The percentage of sperm head abnormalities in the positive control treatment (66.9) was significantly higher (P<0.05). There was a significant difference (P<0.05) as a decrease in the rate of denatured sperm heads between the coenzyme treatments (T3 = 100mg/kg and T4 = 200mg/kg) (18.6 and 19.8), respectively. There was no significant difference (P>0.05) between the fifth treatment (T5) (21.7) and the negative control treatment (24) in the percentage rate of sperm head abnormalities. All CoQ10 treatments were characterized by a significant decrease (P<0.05) compared with the positive control one (Table 1).

Second experiment: The results indicated a significant increase (P<0.05) in the percentage of sperm head abnormalities in the positive control treatment (62.5) than in the negative control treatment (30.6). This percentage was decreased significantly (P<0.05) in the interaction treatments of CoQ10 (before/after) compared to the positive control treatment, as the percentage of sperm head abnormalities in these two treatments was (36.4 and 49.2), respectively. The interaction treatment (before) was the closest of the two interference treatments with a percentage of sperm abnormalities than the negative control treatment despite the significant difference (P<0.05) (Table 2).

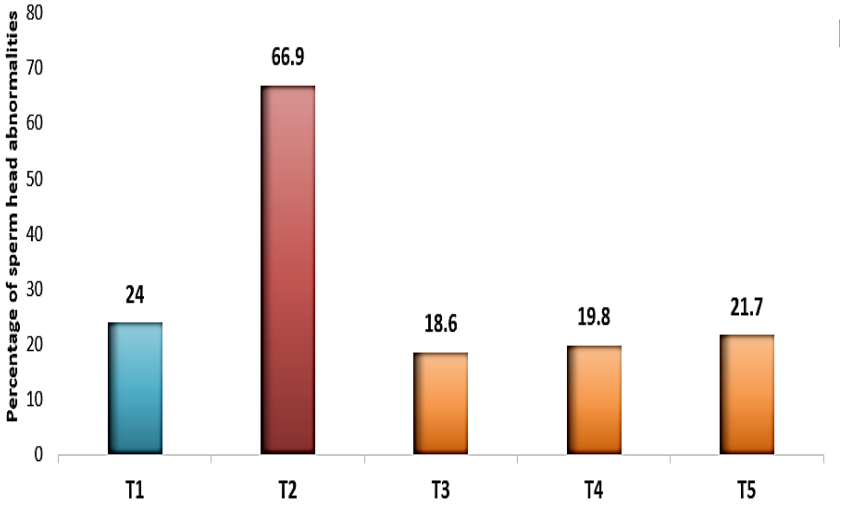

Fig.3. The effect of the mutagenic drug CDDP and the different concentrations of CoQ10 on the percentage of sperm head abnormalities in mice.

Discussion

First experiment: The sperm head abnormalities provide clear and rapid evidence in the safety assessment of chemicals in detecting the carcinogenic and/or genotoxic activity of some mutagens or carcinogens that may cause abnormalities in the morphological shape of the sperm head due to a defect in its differentiation as a result of the interference of these substances in the process of sperm differentiation (interference with DNA/RNA/protein) (Topham 1980). The results showed a significant increase in the average sperm head abnormalities in the T2 positive control treatment, indicating cisplatin's toxicity effect. This was in agreement with the findings of Prasad & Prasad (2020) that showed cisplatin causes testicular/genital toxicity in male mice. The results of this toxicity are an increase in the number of abnormally shaped sperm, in addition to abnormalities in sperm chromosomes, a decrease in the weight of the reproductive organs, and a decrease in the number and motility of sperm (Prasad & Prasad 2020). The use of cisplatin leads to oxidative stress (OS) due to an increase in ROS, which has the ability to, directly and indirectly, damage sperm DNA by substances resulting from the lipid peroxidation process, the products of which are carbonyl-containing substances such as malondialdehyde (MDA), 4-hydroxynonenal, and 2-alkenals, which are genetically genotoxic and cancerogenic, and have an effect on fertility and cause an increase in the rate of distorted sperm (Marnett 2002; Aksu et al. 2017).

Based on the results, the deformations in the sperm heads in the third and fourth coenzyme Q10 treatments significantly decreased, and there was no significant difference in the fifth treatment of CoQ10 treatments. These results agree with some studies conducted on some experimental animals (Güleş et al. 2019; Kobayashi et al. 2021). The significant decrease in the abnormalities of the sperm heads of the two treatments i.e. T3, and T4, is due to the strong properties of CoQ10 as an antioxidant in counteracting oxidative stress by reducing the production of ROS in the sperm mitochondria and protecting their membranes from the process of lipid peroxidation. Polyunsaturated fatty acids (PUFA) in sperm membranes are susceptible to ROS attack and lipid peroxidation formation, increasing ROS production and inducing DNA fragmentation and sperm apoptosis (Salvio et al. 2021). Alleva et al. (1997) showed a negative relationship between CoQ10 coenzyme, and the concentration of lipid peroxide products, i.e. CoQ10 prevents peroxide formation in the semen and the plasma membrane of

sperm and thus reduces the oxidative stress to which sperm may be exposed. Its role in improving the state of total antioxidants in semen is one of the most protective systems for sperm from the effects of ROS (Nadjarzadeh et al. 2011). As seen in the T5 treatment, despite the decrease in the percentage of abnormalities in the head of sperm, there was no significant difference with the negative control treatment, but the abnormalities in it increased in T3 (significant difference) and T4 (insignificant difference). The reason for the high rate of abnormalities in T5 treatment may be because increasing the dose of CoQ10 had a prooxidant effect, as many studies indicate that some antioxidants have the impact of prooxidants at high doses, such as flavonoids like quercetin, myricetin, kaempferol, and curcumin (Sahu & Gray 1996; Tanwar et al. 2010), In the study ofthe effects of CoQ10 on the nephrotoxicity caused by Doxorubicin (Dox), El-Sheikh et al. (2012) confirmed that administration of high doses of CoQ10 *in vivo* results in clear oxidative stress through reduced levels of Glutathione (GSH) and Catalase (CAT) Renal.

Second experiment: The results showed a decrease in the distorted sperm heads in the two intervention treatments (before and after), and this decrease was significant in the two treatments, where the abnormalities in the intervention (before) treatment were the lowest. The interaction treatment (after) indicates that coenzyme Q10 to experimental animals (rats) before the mutagenic drug had a clear protective effect in reducing the percentage of abnormalities in the sperm heads.

Treating animals with CoQ10 before using CDDP: Pre-treatment with CoQ10 significantly reduced spermatozoa malformations caused by CDDP administration due to the protective activity of coenzyme Q10 in providing protection against the harmful effects of cisplatin. CoQ10 reduces oxidative stress by decreasing the level of MDA and increasing the levels of total antioxidants, or CAT, Superoxide dismutase (SOD), and GSH of the testicle (El-Sheikh et al. 2014), which could be affected under cisplatin-induced toxicity conditions. Nadjarzadeh et al. (2011) showed that CoQ10 supplementation for three months increased CAT and SOD in semen, and there was a significant positive correlation between the concentration of CoQ10 and normal sperm morphology, as well as CAT and SOD concentrations. These antioxidants neutralize free radical activity and protect sperm from ROS, whose high levels cause DNA damage (Ahmadi et al. 2016). Sperm cells are capable of producing ROS, in which a mismatch between ROS production and antioxidant mechanisms could potentially lead to cell damage (Miesel et al. 1997).

Treating animals with CoQ10 after using CDDP: This treatment gave a high sperm heads abnormality when compared to the interventional treatment (before), but the percentage was low and significant compared to the positive control. The reason for the increase in sperm head abnormalities in this treatment (after) compared to the intervention treatment (before) is due to two reasons. The first is that mitochondria, which are abundantly present in sperm, are a major source of reactive oxygen species production through the NADH-dependent redox system or through the NADPH oxidation system in the seminal membrane, as well as in white blood cells in semen, which are another source of ROS (Henkel 2011). As a result of the increased metabolic activity and high blood flow in the epididymis region, this region is more susceptible to oxidative stress. If there is less antioxidant capacity in this area, the chance of getting morphological abnormalities will be greater because the sperm reach full maturity in this location (Güleş et al. 2019). The second reason is that treatment with the mutagenic drug (cisplatin) leads to an increase in the production of reactive oxygen species as a result of damage to the mitochondria of the sperm and a defect in the self-defense systems, which leads to oxidative stress and thus affects the process of sperm formation and destruction of its DNA and may lead to apoptosis (Ko et al. 2014; Hu et al. 2021; Mohammed & Qasim 2021). The percentage of abnormalities in the heads of sperm

was low when comparing this treatment (after) and this is due to the effectiveness of the antioxidant CoQ10 that reduces the accumulation of ROS and alleviates the resulting mitochondrial dysfunction (Zhao 2019). Yaripour et al. (2018) and Alahmar (2019) found improvement in sperm characteristics after administration of fat- or water-soluble enzymatic antioxidants alone or in combination.

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