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Original Article

The Effects of Coenzyme Q10 on Hormonal and Histopathological Changes in Female Wistar Rats with Polycystic Ovary Syndrome

Mohammad Pak-Hashemi[1], Zahra Taghipour[2], Iman Fatemi[3*], Mahsa Hassanipour[4,5*]

[1]Student Research Committee, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2]Department of Anatomy, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[3]Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran
[4]Physiology-Pharmacology Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[5]Department of Physiology and Pharmacology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Abstract

Background: Polycystic ovary syndrome (PCOS) is one the most common diseases in women in the fertility age. PCOS alters ovarian follicles and affects blood lipid profiles, liver enzymes and hormones. In this study, we tried to investigate the effects of coenzyme Q10 (CoQ10) on PCOS pathological conditions.

Methods: Twenty-four female rats were randomly divided into the three groups; 1: control group, 2: PCOS group (received 1 mg/kg letrozole daily for 21 days, PO) and 3: PCOS + CoQ10 group (received 1 mg/kg letrozole with 10 mg/kg of CoQ10 for 21 days orally). Blood lipid profiles, liver enzymes, blood glucose and testosterone levels were measured and ovarian histopathology was evaluated.

Results: Histological examination showed reduced number of antral follicles in PCOS + CoQ10 group as compared with PCOS group ($P<0.001$). PCOS increased the alanine aminotransferase (ALT) enzyme by acting on the liver ($P<0.01$). Administration of CoQ10 during PCOS induction was able to reduce ALT levels ($P<0.01$). PCOS increased the cholesterol ($P<0.05$), fasting blood sugar (FBS) ($P<0.05$), triglyceride ($P<0.001$), low-density lipoprotein (LDL) ($P<0.05$) and testosterone levels ($P<0.001$) compared to the control group. However, CoQ10 treatment significantly reduced the above-mentioned parameters compared to the PCOS group.

Conclusion: The results of the present study confirm that CoQ10 has a therapeutic potential for PCOS-induced lipid and hormonal changes and ovarian tissue damages. CoQ10 supplementation and its concomitant use with letrozole could inhibit the development of PCOS in rats. Testosterone reduction could be an important mechanism for CoQ10 beneficial effects.

Keywords: Polycystic ovary syndrome, Letrozole, Coenzyme Q10, Ovary, Rat

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Introduction

Polycystic ovary syndrome (PCOS) is a major health concern for the women in childbearing age (1). This endocrine disorder affects many body systems and causes different complications such as infertility, menstrual dysfunction, acne, obesity, hirsutism, and metabolic syndrome (2,3). PCOS has strong association with hyperlipidemia, fatty liver, type 2 diabetes, hypertension and central nervous system diseases (4). Chronic PCOS leads to cardiovascular disorders, endometrium carcinoma and kidney diseases (4,5). There is no specific or single treatment option for PCOS and some medical strategies such as insulin sensitizers, like metformin, has been used and other pharmacotherapeutic approaches are selected based on the symptoms (6,7).

PCOS causes histopathological morphology changes in the ovary and also affects the lipid profile and blood glucose levels (8). Obesity which is common in PCOS patients may be the reason for insulin resistance and dyslipidemia (9). Lipid disorders in PCOS include high total cholesterol and low-density lipoprotein (LDL) levels, high triglycerides and low high-density lipoprotein (HDL) (10). Another aspect of PCOS is the association with metabolic syndrome which results in the different abnormalities in metabolism of fat, sugar and proteins, and metabolic dysfunctions have been reported in PCOS

*Corresponding Authors: Iman Fatemi, Email: i.fatemi@kmu.ac.ir and Mahsa Hassanipour, Email: mhasanipoor@gmail.com

patients (9,11). Chronic inflammation and oxidative stress probably have a role in PCOS pathophysiology (12). Furthermore, this endocrinopathy plays a role in the liver disease development such as nonalcoholic fatty liver disease (13). There are also reports of the higher risk for kidney injury in PCOS (14).

Coenzyme Q10 (CoQ10) is a lipid-soluble micronutrient with antioxidant and anti-inflammatory properties (15). The evidence reported that supplementation with CoQ10 and silymarin could reduce CCl4-induced oxidative stress and liver and kidney injury in ovariectomized rats (16). Recently it has been shown that CoQ10 is a protective therapeutic approach for ovaries and PCOS complications (17). Data exhibited that CoQ10 supplementation is accompanied by mental health improvement and regulation of inflammatory or oxidative parameters (18). El Refaeey et al showed that combination of CoQ10 and clomiphene citrate improved ovulation and clinical pregnancy rates in the infertile women with PCOS resistant to clomiphene (19). Shokrpour et al revealed that CoQ10 intake (100 mg daily for 3 months) in patients with PCOS is associated with anti-Müllerian hormone reduction (20). Izadi et al investigated the effects of CoQ10 and vitamin E on the cardiometabolic parameters in patients with PCOS and found it as a beneficial treatment in reduction of serum triglycerides, total cholesterol and LDL and enhancement of HDL levels as well as decreasing atherogenic coefficient visceral adiposity index (17). Studies indicated that 24 weeks of CoQ10 treatment improves glucolipid profile in dyslipidemic patients (21) and also exhibited that 8 weeks CoQ10 supplementation is beneficial against inflammatory and endothelial dysfunction in overweight and obese PCOS patients (22). Based on the recent evidence, the protective mechanisms of CoQ10 in PCOS is related to improving the insulin resistance, changes of sex hormone levels and blood lipids improvement (23).

As the clinical or experimental studies about the possible protective role of CoQ10 on PCOS is limited and the biochemical and histologic assessments need more clarifications, in the current study we aimed to investigate the CoQ10 effects in an animal model of letrozole-induced PCOS in order to find a safe adjuvant inhibitor for pathological process during PCOS induction.

Material and Methods

Animals and grouping

Female Wistar rats (160–200 g) were purchased from the animal house of Rafsanjan University of Medical Sciences (Rafsanjan, Iran). Animals were kept at standard conditions of 12 hours light/12 hours darkness and temperature of 22 ± 2°C. Animals had free access to food and water. The principles of care and treatment of laboratory animals were performed according to the guidelines of the National Institutes of Health (NIH). The female rats were randomly divided into the 3 experimental groups (8 animals per group):

1. Control group: healthy animals
2. PCOS group: These animals received letrozole 1 mg/kg orally (for 21 days).
3. PCOS + CoQ10 group: The animals in this group received 10 mg/kg of CoQ10 in addition to 1 mg/kg letrozole for 21 days (both drugs orally).

PCOS induction and treatments

Letrozole was used to induce PCOS in laboratory animals. Letrozole is in the pharmacological class of non-steroidal aromatase inhibitors. This drug was administered orally [suspended in 0.5% carboxymethylcellulose (CMC)] at a dose of 1 mg/kg, and 21 days of letrozole gavage was sufficient for this standard model. Letrozole was obtained from Aburaihan Pharmaceutical Co. /Iran (24-27). Control animals received only the vehicle (0.5% CMC). CoQ10 was purchased from Zahravi Pharmaceutical Co./ Iran and was suspended in CMC for a dose of 10 mg/kg. Rats were treated with CoQ10 by a gavage needle once daily for 21 days after letrozole administration (25,28-30).

Biochemical, hormonal and histological evaluation

Blood samples were prepared from the retro-orbital sinus under anesthesia with diethyl-ether (day 22), 24 hours after the last administration of drugs. The animals were fasted for performing the biochemical assessments. The serums were separated via centrifugation at 3000 rpm for 10 minutes and stored at -20°C until the related analysis. Blood serums were evaluated for lipid profile (triglyceride, cholesterol, LDL, HDL), liver enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), glucose and testosterone, by ELISA and based on the manufacturer's instructions (31-34). Then, rats were sacrificed and both ovaries were detached and ovarian tissue samples were fixed in 10% neutral buffered formalin. Four ovary paraffin-embedded tissues of each group were selected. Then, they were sectioned serially at 5 μm. Four sections of slices were selected for hematoxylin and eosin staining (with a distance of 10 slices between). The stained slides were assessed under a light microscope (Olympus BX51, at X4 magnification) equipped with camera, by two blind students. Finally, the mean of antral and primary follicles was evaluated (8,35,36).

Statistical analysis

Values were stated as mean ± SEM in this study. One-way analysis of variance (ANOVA) was used to determine the statistical difference ($P < 0.05$) between the groups, followed by post hoc Tukey's test. The SPSS software (version 22) and GraphPad Prism version 6.01 and publisher 2016 were used for data analysis.

Results

Ovarian histology

According to the Figure 1, it can be concluded that in the PCOS group compared to the control group, the number of antral follicles had an increasing pattern and the number of primary follicles showed a decrease. After concomitant administration with CoQ10, the number of antral follicles decreased and was almost the same as the control group.

Examination of antral follicles

Figure 2 shows that the number of antral follicles increased significantly ($P<0.001$) compared to the control group due to PCOS induction. Moreover, PCOS + CoQ10 treatment significantly ($P<0.001$) reduced the number of antral follicles compared to PCOS group.

Liver enzymes

There was a significant increase ($P<0.01$) of ALT in the PCOS group compared to the control group. CoQ10 treatment significantly ($P<0.01$) reduced ALT levels in the PCOS + CoQ10 group compared to the PCOS group. No change in the levels of other liver enzymes (ALP, AST) was observed (Table 1).

Glucose and lipid evaluation

In the PCOS group, significant increases in the levels of cholesterol and fasting blood sugar (FBS) ($P<0.05$) as well as triglyceride ($P<0.001$) were observed compared to the control group. CoQ10 administration caused significant reduction of cholesterol and FBS levels ($P<0.01$) as well as triglyceride level ($P<0.001$) compared to the PCOS group (Table 1). According to Table 1, there is a significant increase in LDL levels ($P<0.05$) in the PCOS group compared to the control group. However, in PCOS + CoQ10 treatment group, a significant decrease in LDL level ($P<0.05$) was observed.

Hormonal assay

Examination of testosterone levels has been shown in table 1. In the PCOS-induced group, a significant increase in testosterone level was observed compared to the control group ($P<0.001$). However, after the treatment protocol, a significant decrease in testosterone level was obtained in the PCOS + CoQ10 group compared to the PCOS group ($P<0.001$).

Discussion

In the current investigation, we evaluated the protective properties of CoQ10 against deleterious effects of PCOS on biochemical, hormonal and histopathological indices in female Wistar rats. We found that letrozole-induced PCOS (1 mg/kg daily for 21 days, orally) increases the number of antral follicles in ovary as well as the levels of ALT, cholesterol, FBS, triglyceride, LDL and testosterone in serum. On the other hand, CoQ10 administration (10 mg/kg for 21 days, orally) alongside with letrozole decreases all of the above-mentioned indices in animals.

PCOS is the most common gynecological endocrine disease which increases the body weight and the risk of type 2 diabetes mellitus and atherosclerosis (37,38). In agreement with our results, Mohammadi et al showed that ovaries develop histological changes after treatment with letrozole for 21 days and reported neurological impairment in rats with PCOS (24).

In our study, concurrent administration of CoQ10 to the PCOS animals led to reduction of antral follicles in ovaries. Our data exhibited that CoQ10 could protect ovaries from PCOS-induced damages. There is evidence indicating that CoQ10 is capable to reverse PCOS deleterious effects. Taghizadeh et al, via a randomized double-blind, placebo-controlled clinical trial showed that chronic administration of CoQ10 for 8 weeks has beneficial effects against inflammatory and endothelial dysfunctions in obese PCOS patients (22). Al-Qadhi et al reported that PCOS patients receiving CoQ10 for 3 months showed a decreased levels of body mass index, malondialdehyde and testosterone compared with baseline (39).

Our data also revealed that animal supplementation with CoQ10 for 21 days decreases the testosterone level when compared with PCOS group which is in line with a

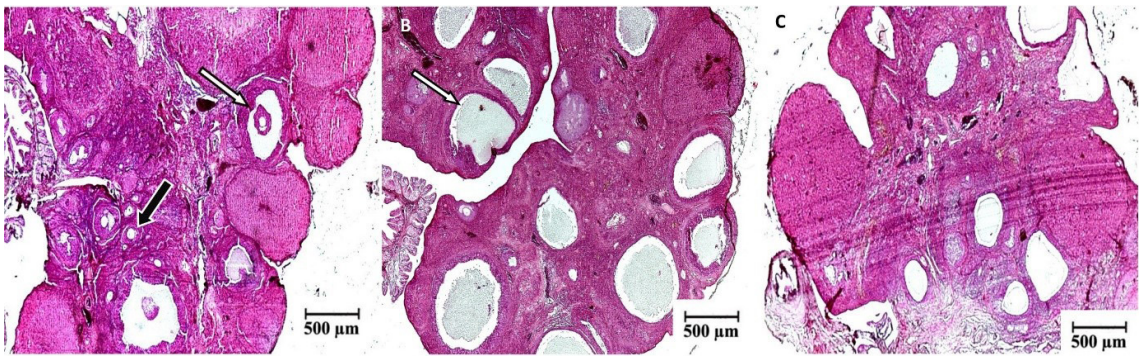

Figure 1. The effect of PCOS induction and CoQ10 administration on ovarian tissue: A: Control, B: PCOS, C: PCOS + CoQ10. Black arrow: Primary follicle, White arrow: Antral follicle

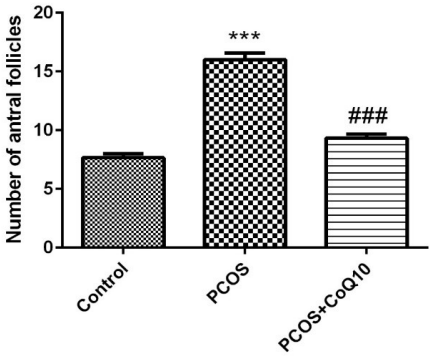

Figure 2. The effect of PCOS and CoQ10 on the number of antral follicles. Results are illustrated as mean ± SEM. One-Way ANOVA was used to compare the values obtained from different experimental groups. *** $P<0.001$ vs Control, ### $P<0.001$ vs PCOS

Table 1. The mean ± S.E.M. of ALP, ALT, AST, Cholesterol, FBS, Triglyceride, HDL, LDL and Testosterone levels

	Control	PCOS	PCOS + CoQ10
ALP (U/L)	412 ± 62.19	541.8 ± 56.66	369.4 ± 10.4
ALT (U/L)	57 ± 3.19	73.60 ± 3.12 **	58 ± 2 ##
AST (U/L)	151.8 ± 6.64	193.2 ± 19.85	195.2 ± 11.93
Cholesterol (mg/dL)	60.40 ± 2.20	71.80 ± 1.68 *	52.60 ± 4.43 ##
FBS (mg/dL)	154.8 ± 7.01	190.8 ± 9.86 *	147.6 ± 6.15 ##
Triglyceride (mg/dL)	53.8 ± 1.35	78.80 ± 2.08 ***	52.20 ± 2.81 ###
HDL (mg/dL)	39.60 ± 1.72	32.60 ± 0.60 *	36 ± 2.21
LDL (mg/dL)	16.80 ± 0.91	21.40 ± 1.69 *	15.80 ± 0.86 #
Testosterone (ng/dL)	1.2 ± 0.10	3.2 ± 0.12 ***	1.4 ± 0.33 ###

One-Way ANOVA was used to compare the values in different experimental groups.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs Control, # $P<0.05$, ## $P<0.01$, ### $P<0.001$ vs PCOS group.

previous study. It has been demonstrated that approaches diminishing the androgens could be effective for PCOS because several complications of PCOS could be related to excessive androgens including cardiovascular diseases, diabetes mellitus type 2, obesity and kidney diseases through different signaling pathway (40). Moreover, Han et al showed that androgen-induced gut microbiota dysbiosis aggravates endocrine and metabolic and malfunctions in PCOS (41). Zhang et al showed that oral nutritional agents such as CoQ10, inositols, vitamin E, and vitamin D improve endocrine profiles in PCOS women and reported the advantages of these nutraceuticals (42). Therefore, testosterone decreasing effect of CoQ10 in the animals with letrozole-induced PCOS could be considered as an important mechanism for CoQ10 protection against PCOS.

Moreover, our data indicated that CoQ10 administration could reduce the ALT level, FBS, triglyceride, total cholesterol and LDL levels in PCOS animals. Studies reported that PCOS may injure the liver and the prevalence of nonalcoholic fatty liver disease is high in women and girls with PCOS (43,44). Furthermore, CoQ10 has protective effects on liver in different pathological conditions. Alqarni et al reported that co-administration of CoQ10 with valproic acid in epilepsy not only increases the antiepileptic activity, but also reduces the hepatotoxicity of valproic acid (45). Furthermore, Fatima et al confirmed protective effects of CoQ10 against cisplatin-induced hepatotoxicity in animals (46).

This study has the following limitations: first, the serum levels of sex hormone-binding globulin, prolactin, luteinizing hormone and follicle-stimulating hormone were not determined. Second, CoQ10 could be administered for longer period of time. Third, in this study the effects of CoQ10 were assessed on the induction of PCOS, and we suggest CoQ10 acute and chronic treatment after induction of PCOS for future studies.

Conclusion

In the current study, CoQ10 administration reduced the histological, hormonal and biochemical impairments in the animals with letrozole-induced PCOS. We suggest chronic administration of CoQ10 as a potential therapeutic approach in women with PCOS. However, additional experimental studies and clinical trials for identifying the exact mechanisms of action are required.

Authors' Contribution

Conceptualization: Mahsa Hassanipour, Iman Fatemi.
Data curation: Iman Fatemi, Zahra Taghipour.
Formal analysis: Iman Fatemi.
Funding acquisition: Mahsa Hassanipour.
Investigation: Mohammad Pak-Hashemi.
Methodology: Mahsa Hassanipour, Iman Fatemi.
Project administration: Mahsa Hassanipour.
Resources: Mahsa Hassanipour, Mohammad Pak-Hashemi.
Software: Iman Fatemi, Mohammad Pak-Hashemi.
Supervision: Mahsa Hassanipour.
Validation: Zahra Taghipour.
Visualization: Zahra Taghipour, Mahsa Hassanipour, Iman Fatemi.
Writing–original draft: Mohammad Pak-Hashemi, Zahra Taghipour.
Writing–review & editing: Mahsa Hassanipour, Iman Fatemi, Zahra Taghipour.

Competing Interests

No conflict of interest.

Ethical Approval

The study procedures were approved by Rafsanjan University of Medical Sciences ethics committee with ethical code: IR.RUMS.REC.1397.236.

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