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ORIGINAL ARTICLE

Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial

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Summary

Low seminal plasma concentrations of coenzyme Q10 (CoQ10) have been correlated with impaired sperm parameters, but the exact mechanism remains of dominating interest. This randomised, placebo-controlled study examined the effect of CoQ10 on catalase, superoxide dismutase (SOD) and F_2-isoprostanes in seminal plasma in infertile men and their relation with CoQ10 concentration. Sixty infertile men with idiopathic oligoasthenoteratozoospermia (OAT) were randomised to receive 200 mg d^{-1} of CoQ10 or placebo for 3 months. 47 persons of them completed the study. Semen analysis, anthropometric measurements, diet and physical activity assessment were performed for subjects before and after treatment. Independent and paired *t*-test, chi-square test and ANCOVA were compared outcomes of supplementation between two groups. CoQ10 levels increased from 44.74 ± 36.47 to 68.17 ± 42.41 ng ml^{-1} following supplementation in CoQ10 ($P < 0.001$). CoQ10 group had higher catalase and SOD activity than the placebo group. There was a significant positive correlation between CoQ10 concentration and normal sperm morphology ($P = 0.037$), catalase ($P = 0.041$) and SOD ($P < 0.001$). Significant difference was shown between the mean of changes in seminal plasma 8-isoprostane in two groups ($P = 0.003$) after supplementation. Three-month supplementation with CoQ10 in OAT infertile men can attenuate oxidative stress in seminal plasma and improve semen parameters and antioxidant enzymes activity.

Introduction

Male factor has a role in up to half of all cases of infertility and affects 5% of men of general population (Mclachlan & De Kretser, 2001). Several studies represent that reactive oxygen species (ROS)-mediated damage to spermatozoa has a significant contribution in male infertility (Agarwal & Saleh, 2002; Saleh & Agarwal, 2002). Therefore, the role of antioxidant such as vitamins A, C, E, selenium and glutathione in male infertility has been studied extensively in recent years (Rolf *et al.*, 1999; Keskes-Ammar *et al.*, 2003; Greco *et al.*, 2005; Aliabadi *et al.*, 2012). Coenzyme Q10 (CoQ10) is a critical intermediate of the mitochondrial electron transport chain that regulates cytoplasmic redox potential (Crane, 2001). It is a more powerful antioxidant than vitamin E, so it can neutralise tocopheroxyl radicals and regenerates its reduced form (Nagaoka *et al.*, 2000). Its beneficial effects have been shown in diabetes mellitus, hypercholesterolaemia, hypertension, neurodegenerative diseases and lipid peroxidation (Leibovitz *et al.*, 1990; Watts *et al.*, 2002; Shults *et al.*, 2002; Rosenfeldt *et al.*, 2007; Hamilton *et al.*, 2009;). Besides, its deficiency has been found in infertile men with sperm disorders (Mancini *et al.*, 1998, 2005). Low seminal plasma/sperm concentra-

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tions of CoQ10 have been correlated with impaired sperm parameters such as motility (Balercia *et al.*, 2004). Accordingly, some clinical trials have shown that CoQ10 could improve semen quality in subfertile men (Balercia *et al.*, 2009; Safarinejad, 2009). However, till now, no studies have been reported regarding the effect of CoQ10 on antioxidant enzyme activities of semen such as catalase, superoxide dismutase (SOD) and 8-isoprostane concentration as a biomarker of oxidative stress in seminal plasma.

The purposes of this randomised, double-blind placebo-controlled trial were to determine the effects of 3-month supplementation with CoQ10 on antioxidant enzymes activities and isoprostane concentration in seminal plasma and evaluate the relationship between these parameters and CoQ10 concentration in seminal plasma in a group of infertile men with idiopathic oligoasthenoteratozoospermia.

Materials and methods

Sixty infertile men (25–40 years) with idiopathic oligoasthenoteratozoospermia (OAT) were enrolled in this parallel clinical trial between November 2008 and December 2009 (Fig. 1). The infertile men were selected at the andrology Unit of the Avicenna infertility clinic, Tehran, Iran. All subjects with the history of primary infertility more than one year and underwent clinical and laboratory screening for the causes of their infertility. Subjects with infectious genital disease, leucocytospermia (WBC $>1 \times 10^6$ ml^{-1}), genital tract abnormalities such as varicocele, cigarettes smoking, alcohol abusing, antioxidant supplementation during last 3 months, drug addiction and occupational chemical exposure were excluded from the study. Informed written consent was obtained from all participants. Once eligibility criteria were met, participants were randomly allocated to take either CoQ10 in the form of 100-mg capsules (Nutraceutical Science Institute, NC, USA) or an identical in appearance placebo (lactose). Patients were instructed to take two capsules per day (200 mg d^{-1}) with their food. The quantity of dose was based on the previous studies (Balercia *et al.*, 2009). The containers of supplement and placebo were identical and were labelled with special codes before the study took place by one of the staff who had no contact with participants. Patients, researchers and laboratory staff were kept blinded to treatment assignment during the entire study. Subjects were instructed to maintain their usual diet and lifestyle during the study. At the baseline and after 3 months of supplementation, the semen analysis, anthropometric measurements, diet analysis using 3 days 24-h dietary recall, physical activity assessment by completing International Physical Activity Questionnaire were performed for all subjects. Compliance was assessed by counting remaining tablets at the follow-up visits. The study protocol was reviewed and approved by the Institutional Review Board in the school of Health, Tehran

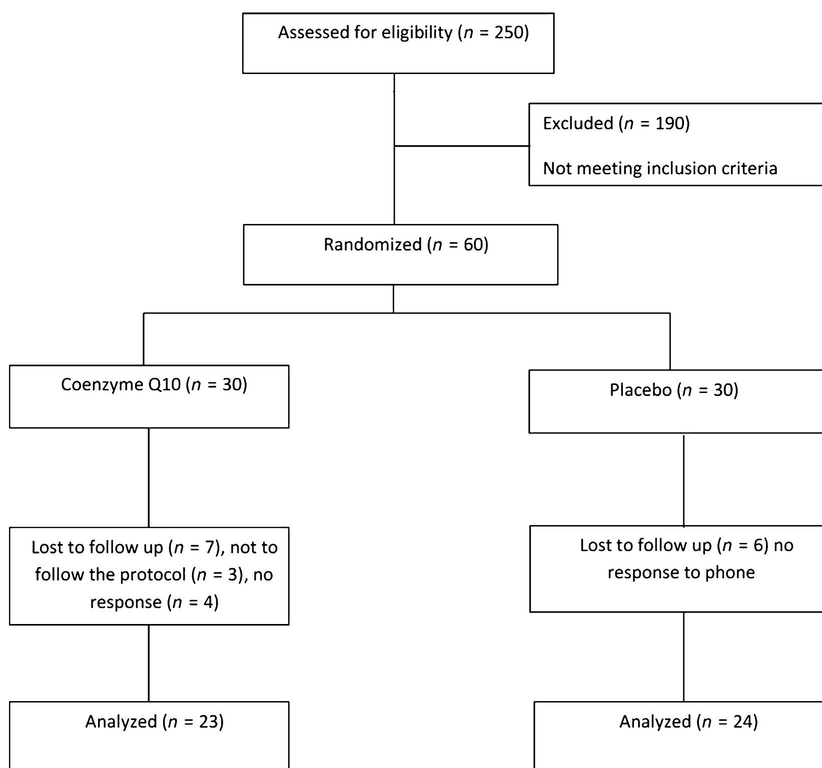

Fig. 1 Flow diagram of the participants.

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University of Medical Sciences and ethical committee of Avicenna Research Institute, Tehran, Iran.

Semen samples were obtained by masturbation after 3–7 days of sexual abstinence at andrology unit of Avicenna infertility clinic, Tehran, Iran. All semen was held at 37 °C to liquefy. After liquefaction, the samples were analysed according to the World Health Organization (1999). Remnants of liquefied semen samples were immediately centrifuged at 300 ***g*** for 10 min. The seminal plasma was divided into several aliquot and kept frozen at −80 °C for further biochemical analysis. Catalase activity of seminal plasma was determined by spectrophotometric method through established method (Aebi, 1984). The catalase activity is expressed as specific activity (K ml^{-1} of seminal plasma). Superoxide dismutase (SOD) activity was determined using commercial kit (RanSOD, Randox Laboratories, Crumlin, UK).

Free form of 8-isoprostane was measured in seminal plasma by sensitive combined affinity chromatography–ELISA method. At first, all samples were centrifuged at 15000 ***g*** to precipitate all of cell debris and clots. Subsequently, the supernatant was diluted 1 : 5 with affinity buffer and slowly loaded to the column. Free 8-isoprostane was purified by commercially available affinity column (Cayman Chemical, Ann Arbor, MI, USA). Other procedures were carried out according to the instructions provided by the manufacturer. To measure eluted free 8-isoprostane from affinity column, the elution solution was evaporated using nitrogen steam, which was followed by measurement of the free 8-isoprostane concentration by a commercially available EIA kit (Cayman Chemical, Ann Arbor, MI, USA). The EIA procedure for measurement of the free 8-isoprostane was carried out according to the instructions provided by the manufacturer. The levels of free 8-isoprostane were presented as pg ml^{-1}.

Seminal plasma CoQ10 was measured by HPLC using UV–visible detector with detection at 275 nm (Li *et al.*, 2006). A 0.5-ml aliquot of the seminal plasma was added to a chemically clean screw-capped glass tube without light exposure, and 50 μl of retinyl acetate solution (20 μg ml^{-1}) was added to the seminal plasma as internal standard and mixed for 30 s. Then, 1 ml of HPLC grade of methanol (ROMIL) was added to the tube and mixed for 1 min and it followed with addition of 2.5 ml n-hexane (ROMIL) as an extracting solvent and vortex-mixed for 5 min. After 10 min of centrifugation at 4000 rpm, the organic layer was collected and evaporated using a water bath at 40 °C and nitrogen stream. Finally, 50 μl isopropanol was added to dissolve the residue, and the resulting solution was injected into the HPLC system (Younglin 9000). Chromatographic separations were carried out on a C18 column (Intersil, 25 × 4.6 cm. particle size 5 μm).

Statistical analysis

We based our sample size estimates on data and sample sizes used in other studies of CoQ10 administered as an antioxidant (Balercia *et al.*, 2004). The distribution of the data was evaluated by the Kolmogorov–Smirnov test. Due to normal distribution of variables, the independent *t*-test and the paired *t*-test were applied to analyse differences in semen variables between and within groups. The chi-square test was applied to compare categorical variables between groups. To adjust the effect of confounders, such as BMI, dietary intakes and baseline concentrations, the ANCOVA was performed. The data were expressed as the mean ± SD. Statistical computations were calculated using SPSS 12.5 for windows software (SPSS Inc., Chicago, IL, USA).

Results

During the supplementation period, 13 men of 60 (21%) dropped out of the study for personal reasons and only 47 men with idiopathic oligoasthenoteratozoospermia (iOAT) completed the study (Fig. 1). There were no side effects reported with CoQ10 supplementation. The mean age of all participants in two groups was 34.43 ± 5.67 years. There were no significant differences among two groups in respect of age, BMI, physical activity, seminal characteristics (Table 1), energy intake and macro/micro nutrients intake at baseline (Nadjarzadeh *et al.*, 2011). Following 3-month supplementation, although there was an increase in sperm forward and total motility, the changes in other sperm parameters such as sperm concentration, motility and morphology were not significant (Table 2). As shown in Table 3, CoQ10 levels increased in seminal plasma following supplementation and it rose from 44.74 ± 36.47 ng ml^{-1} at baseline to 68.17 ± 42.41 ng ml^{-1} after 3 months of CoQ10 supplementation ($P = 0.0001$). There was a significant positive correlation between CoQ10 concentration and normal

Table 1 Baseline characteristics of the participants

Group	Placebo (*n* = 24)	CoQ10 (*n* = 23)	*P*-value
Age (yrs)	34.67 ± 6.69	34.17 ± 4.52	0.77
BMI (Kg m^{-2})	23.29 ± 3.98	22.91 ± 3.31	0.70
Physical activity			
Low (%)	41.7	39.1	0.86
Moderate (%)	58.3	48.9	
Concentration (10^6 ml^{-1})	19.77 ± 11.1	16.13 ± 10.7	0.24
Forward motility (%)	26.29 ± 13.1	25.91 ± 16.5	0.6
Total motility (%)	37.79 ± 15.9	36.13 ± 17.9	0.81
Normal morphology (%)	6.08 ± 5.6	7.43 ± 5.1	0.31

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Table 2 Mean and SD of changes of seminal characteristics in P (placebo) and Q (CoQ_{10}) groups

	Group		
Semen parameters	Placebo ($n = 24$)	Coenzyme Q10 ($n = 23$)	P^a
Concentration ($\times 10^6$ ml^{-1})	−3.56 ± 14.96	1.34 ± 13.66	0.5
Forward motility (%)	−1.95 ± 16.09	3 ± 15.17	0.2
Total motility (%)	0.54 ± 20.19	5.78 ± 15.63	0.3
Normal morphology (%)	0.21 ± 3.62	−0.91 ± 4.45	0.5

[a]Differences between two groups compared using ANCOVA with baseline values as covariate.

morphology of spermatozoa ($r = 0.44$, $P = 0.037$) (Fig. 2). Furthermore, the correlation between CoQ10 and forward motility was at a marginal level of significance ($P = 0.058$). With respect to antioxidant enzymes activity, the men in CoQ10 group had higher catalase and SOD activity than those in the placebo group subsequent to supplementation (Figs 3 and 4). The concentration of CoQ10 in seminal plasma was significantly correlated with SOD ($r = 0.6$ $P < 0.005$) and catalase ($r = 0.3$ $P < 0.05$) after supplementation. Seminal plasma 8-isoprostane concentration was decreased significantly ($P = 0.012$) following CoQ10 supplementation in treatment group compared with the corresponding change in placebo ones (Table 3). Its concentration was significantly decreased ($P = 0.025$) after 3-month supplementation compared with baseline in treatment group. Considering its baseline level as covariate, ANCOVA showed significant difference between two groups regarding 8-isoprostane concentration following supplementation ($P = 0.003$). Although there was an inverse correlation between seminal plasma 8-isoprostane and sperm parameters including normal morphology and motility, this correlation was not statistically significant. Furthermore, there was the same situation for correlation between CoQ10 concentration and 8- isoprostane in seminal plasma.

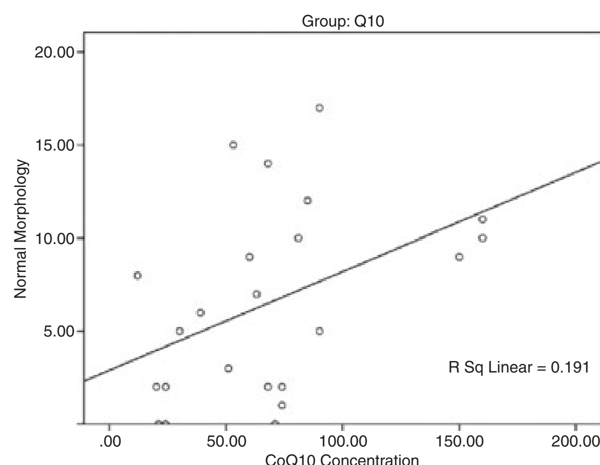

Fig. 2 Correlation between CoQ10 concentration in seminal plasma with normal spermatozoa ($r = 0.44$, $P = 0.037$).

Discussion

The sperm plasma membrane is rich in polyunsaturated fatty acids (PUFA), which provide favourable ability for its function during fertilisation process. At the same time, it makes the sperm membrane vulnerable to lipid peroxidation following oxidative stress. Previous data indicate that oxidative stress impaired sperm functions and has a significant role in male infertility (Saleh & Agarwal, 2002; Tremellen, 2008).

Coenzyme Q10 is broadly used as an antioxidant supplement for oxidative stress conditions associated with a wide range of diseases such as cardiovascular, neurodegenerative, neuromuscular and infectious diseases. Numerous studies indicate that coenzyme Q10 also plays an important role in overall health and maintenance of the normal functions of cells, tissues and organs (Sandor *et al.*, 2005; Marcoff & Thompson, 2007; Hamilton *et al.*, 2009; Lee *et al.*, 2012). According to the results of this study, CoQ10 concentration in seminal plasma significantly increases following 3 months of supplementation. Observational studies showed significant differences between basal levels of CoQ10 in seminal plasma of infertile men with abnormal semen parameters and healthy controls (Mancini *et al.*, 1998, 2003, 2005). Several clinical trial studies showed that 3 and 6 months of supplementation with CoQ10 increase its concentration in blood and seminal plasma (Hodgson *et al.*, 2002;

Table 3 Ubiquinone and isoprostane levels in seminal plasma of OAT in two groups following 3 months of CoQ10 supplementation[a]

	Placebo ($n = 24$)		Coenzyme Q10 ($n = 23$)	
Parameters	Before supplementation	After supplementation	Before supplementation	After supplementation
Ubiquinone (ng ml^{-1})	50.75 ± 36.41	52.71 ± 37.44	44.74 ± 36.47	68.17 ± 42.41[b]
Isoprostane (pg ml^{-1})	34.91 ± 24.32	42.54 ± 29.57	31.04 ± 20.62	22.86 ± 12.84[c]

[a]All values are mean ± SD.
[b]Significantly different after supplementation within the group, $P < 0.001$.
[c]Significantly different after supplementation within the group $P < 0.03$, and between groups $P < 0.006$.

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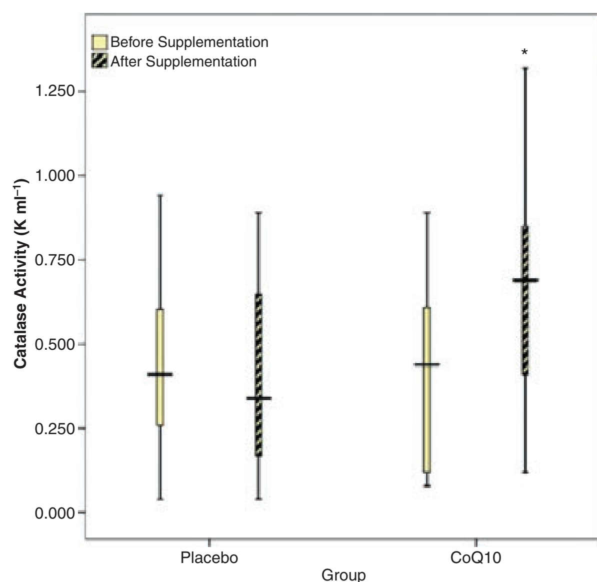

Fig. 3 Catalase activity in seminal plasma of two groups before and after supplementation * *P*-value 0.001 between groups, 0.02 within groups.

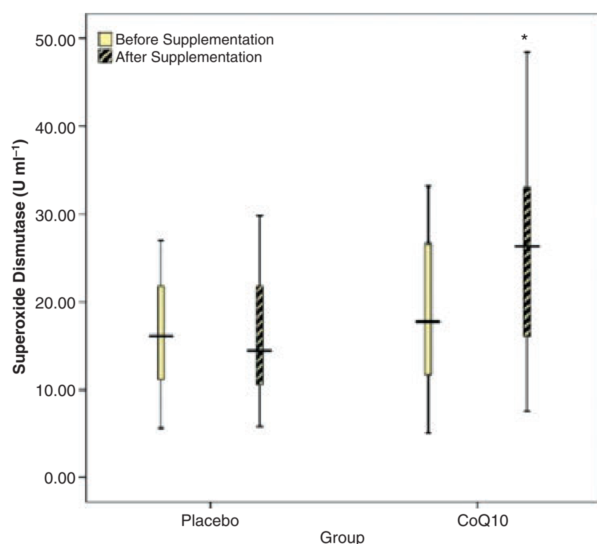

Fig. 4 Superoxide dismutase activity in seminal plasma of two groups before and after supplementation * *P*-value 0.002 between groups, 0.03 within groups.

Safarinejad, 2009). According to their results, 3-month intervention is sufficient to increase the steady level of CoQ10 in seminal plasma. In this study, CoQ10 levels in seminal plasma had significant correlation with sperm motility and morphology. Mancini *et al.* (2003, 2005) found the same correlation with sperm count and motility in seminal fluid. In the present study, the decrease in plasma 8-isoprostane concentrations suggests that supplementation of oligoasthenoteratozoospermic infertile men with 200 mg day^{-1} of coenzyme Q10 may attenuate oxidative stress and subsequently deleterious effects of reactive oxygen species (ROS) on sperm and male fertility.

Catalase and superoxide dismutase are the first line of enzymatic defence against ROS (Florence, 1995). The activity of these enzymes was significantly increased after 3 months of CoQ10 supplementation at a dose of 200 mg day^{-1}. As presented in this trial, the seminal plasma CoQ10 level was significantly correlated with their activity. Lee *et al.* showed increase in catalase and SOD activities in plasma of patients with coronary artery disease subsequent to 12-week supplementation with 150 mg day^{-1} of CoQ10. The decreased activity of superoxide dismutase in the seminal plasma failed to convert superoxide radical to hydrogen peroxide and subsequently its reduction to water. The increased level of superoxide anion could damage the vital macromolecules such as lipids, proteins and DNA. This anion may react with itself in a dismutation reaction to generate hydrogen peroxide (H2O2). In the presence of transition metals such as iron and copper, H2O2 and superoxide anion can interact to produce the extremely dangerous hydroxyl radical (•OH) (Haber–Weiss reaction). Further, the hydroxyl radical can be generated from hydrogen peroxide (Fenton reaction). This radical can induce the lipid peroxidation cascade and impair sperm membrane integrity, leading to the complete inhibition of motility and energy metabolism of spermatozoa (Florence, 1995). Despite the significant correlation between catalase and SOD with CoQ10, we could not find such a correlation between semen parameters with these two antioxidant enzymes before and after supplementation. It is hypothesised that this increase in the concentration of CoQ10 could somehow affect antioxidant enzyme activities. However, its increase was not high enough to neutralise the deleterious effects of ROS on spermatozoa and improve the sperm parameters. It is well known that oxidative stress impairs sperm functions and plays a negative role on male fertility (Agarwal *et al.*, 2004). So, decrease in 8-isoprostane concentrations in seminal plasma as shown in our study may conceivably benefit for subfertile men. At present, isoprostane is the more valuable biomarker for lipid peroxidation. Many evidences indicate that the quantification of F_2-isoprostanes provides a reliable and useful biomarker to assess oxidative stress and lipid peroxidation *in vivo* (Montuschi *et al.*, 2000; Kinnula *et al.*, 2007). F_2-Isoprostanes are specific end products of arachidonic acid peroxidation that formed in situ on phospholipids and subsequently released in free form through function of phospholipase enzymes (Roberts & Morrow, 2002). According to the results of one study, seminal level of 8-isoprostane

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increased in oligoasthenoteratozoospermic men and it had a negative correlation with sperm motility and normal morphology (Khosrowbeygi & Zarghami, 2008). But, to our knowledge, this was the first study to determine the effects of CoQ10 supplementation on isoprostane level in semen. There are some results showing the positive effect of antioxidants on isoprostane concentration in urine or plasma (Dietrich *et al.*, 2002). On the other hand, in some studies, antioxidants supplementation did not decrease urinary isoprostane excretion (Meagher *et al.*, 2001; Wood *et al.*, 2003). Some factors such as differences in the health, smoking status, small numbers of participants, fatty acids and antioxidant intakes, interval of CoQ10 supplementation, and its dose and form may contribute to discrepancies in results.

It is well established that CoQ10 is synthesised de novo in all tissues, so under normal circumstances, most tissues are not dependent on an exogenous supply of CoQ10 (Bhagavan & Chopra, 2006). However, under certain conditions such as oxidative stress and ageing, endogenous production may not meet the demands for CoQ10. In this study, despite of increasing the seminal plasma CoQ10 and decreasing isoprostane levels, CoQ10 supplementation did not alter sperm parameters. But there was a positive correlation between ubiquinone levels of seminal plasma with sperm morphology ($P = 0.037$) and sperm motility ($P = 0.058$). The limitation of our study was the small sample size of participants. Larger sample size is required to determine the effects of ubiquinone on 15-F_{2t}-isoprostane in oligoasthenoteratozoospermic males or other groups of infertile men and its correlation with sperm parameters.

The design of this study, repeated assessment of diet and physical activity, exclusion of subjects using tobacco or acute inflammatory disease and control for covariates were strengths of our study. Further studies are needed to establish the effect of higher doses and longer durations of CoQ10 in larger sample size.

In conclusion, the semen of most oligoasthenoteratozoospermic men is accompanied with increased oxidative stress, which impairs semen parameters and potentiates failure of sperm functions and men fertility in OAT men. At least three months of supplementation with coenzyme Q10 can attenuate oxidative stress in seminal plasma and improve antioxidant enzymes activity in oligoasthenoteratozoospermic men.

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