Effects of the Reduced Form of Coenzyme Q_{10} (Ubiquinol) on Semen Parameters in Men with Idiopathic Infertility: a Double-Blind, Placebo Controlled, Randomized Study

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Purpose: We investigated the effects of the administration of ubiquinol (a reduced form of coenzyme Q_{10}) on semen parameters and seminal plasma antioxidant capacity in infertile men with idiopathic oligoasthenoteratozoospermia.

Materials and Methods: A total of 228 men with unexplained infertility were randomly assigned 1:1 into 2 groups. Group 1 (114) received 200 mg ubiquinol daily by mouth for 26 weeks and group 2 (114) received a similar regimen of placebo. After completion of the 26-week treatment phase, all participants were followed for another 12-week off-drug period. Primary outcomes were improvement in sperm density, sperm motility and sperm strict morphology.

Results: At the end of 26-week treatment period mean ± SD sperm density in the ubiquinol and placebo groups was $28.7 \pm 4.6 \times 10^6$/ml and $16.8 \pm 4.4 \times 10^6$/ml ($p = 0.005$), sperm motility was 35.8% ± 2.7% and 25.4% ± 2.1% ($p = 0.008$), and sperm strict morphology was 17.6% ± 4.4% and 14.8% ± 4.1% ($p = 0.01$) of normal sperm, respectively. During the treatment period serum follicle-stimulating hormone levels decreased significantly ($p = 0.02$) and serum inhibin B concentrations increased significantly ($p = 0.01$). During the off-drug period semen parameters gradually returned to baseline values but the differences were still significant for sperm density ($p = 0.03$) and sperm motility ($p = 0.03$). The correlation coefficients analysis revealed a positive association between the duration of treatment with ubiquinol and sperm density ($r = 0.74$, $p = 0.017$), sperm motility ($r = 0.66$, $p = 0.024$) and sperm morphology ($r = 0.57$, $p = 0.027$).

Conclusions: Ubiquinol was significantly effective in men with unexplained oligoasthenoteratozoospermia for improving sperm density, sperm motility and sperm morphology.

Key Words: ubiquinol; randomized controlled trial; infertility, male; antioxidants

Abbreviations and Acronyms

AE = adverse event
AZF = azoospermia factor
CAT = catalase
CoQ_{10} = coenzyme Q_{10}
FSH = follicle-stimulating hormone
LH = luteinizing hormone
OAT = oligoasthenoteratozoospermia
OS = oxidative stress
ROS = reactive oxygen species
SOD = superoxide dismutase

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Approximately 8% of men of reproductive age seek help for infertility.[1] The current treatment of idiopathic male factor infertility is empirical. Many pharmacological agents have been used with varying degrees of efficacy. Oxidative stress is one of the main issues associated with male infertility.[2] ROS significantly and adversely affect sperm function at high concentrations.[3] An imbalance between antioxidant capacity in seminal plasma and the production of ROS results in OS.

Coenzyme Q_{10} (2,3-dimethoxy-5-methyl-6-deca-69 prenyl-1,4-benzoquinone, CoQ_{10}) is an isoprenylated benzoquinone which transports electrons from complexes I and II to complex III in the

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mitochondrial respiratory chain.[4] There is a direct correlation between seminal plasma CoQ_{10} concentration and semen parameters.[5] It has been shown that exogenous administration of CoQ_{10} in infertile men with idiopathic OAT had beneficial effects on semen parameters.[6,7] In a recent study the effects of CoQ_{10} administration were also shown to be beneficial to the pregnancy rate.[8] The 2 forms of CoQ_{10} are reduced (ubiquinol) ($CoQ_{10}H_2$) and oxidized (ubiquinone) forms. Ubiquinol is a strong lipophilic antioxidant, and can recycle and regenerate other antioxidants such as tocopherol and ascorbate.[9] Decreased serum CoQ_{10} concentrations as well as a decrease in the $CoQ_{10}H_2$-to-ubiquinone ratio have been demonstrated in diseases associated with OS.[10] A strong correlation among sperm count, motility and ubiquinol-10 levels in seminal fluid has also been reported.[11] In this study, the first on this subject to our knowledge, we determined the effects of the exogenous administration of ubiquinol in the improvement of semen parameters.

MATERIALS AND METHODS

Study Design

This randomized, double-blind, placebo controlled trial was performed from June 2010 to January 2011. The study was performed in accordance with the Declaration of Helsinki on good clinical practice and the local medical ethics committee at the site approved the study protocol. All subjects provided informed consent before beginning the screening procedure.

Study Population

A total of 264 infertile men with poor semen quality were selected for screening. They were between 25 and 44 years old, and had primary infertility for at least 2 years. Poor semen quality was defined by the Kruger strict criteria with less than 14% normal forms, oligozoospermia by a sperm concentration of less than 20×10^6 spermatozoa per ml and asthenozoospermia by less than 50% of motile spermatozoa with forward progression according to WHO criteria. All of the participants had oligoasthenozoospermia. Male infertility was diagnosed when abnormal semen parameters were seen in at least 2 semen samples. All of the participants were naïve for treatment.

Evaluations

All men underwent a thorough physical examination, a detailed history, serum biochemical and hematological laboratory tests, and measurement of serum sex and thyroid hormone levels. A questionnaire was used to collect information on demographic characteristics. Two semen samples 1 month apart were obtained after 3 to 5 days of sexual abstinence and processed within 1 hour of ejaculation. The mean of 2 was used for statistical analysis. Semen analyses were performed using WHO recommended methods.[12] Seminal plasma antioxidant capacity was assessed using the measurement of CAT-like and SOD-like activity. Genetic analyses included peripheral blood lymphocyte karyotype, and Y chromosome microdeletion in the AZFa, AZFb and AZFc regions.

Inclusion/Exclusion Criteria

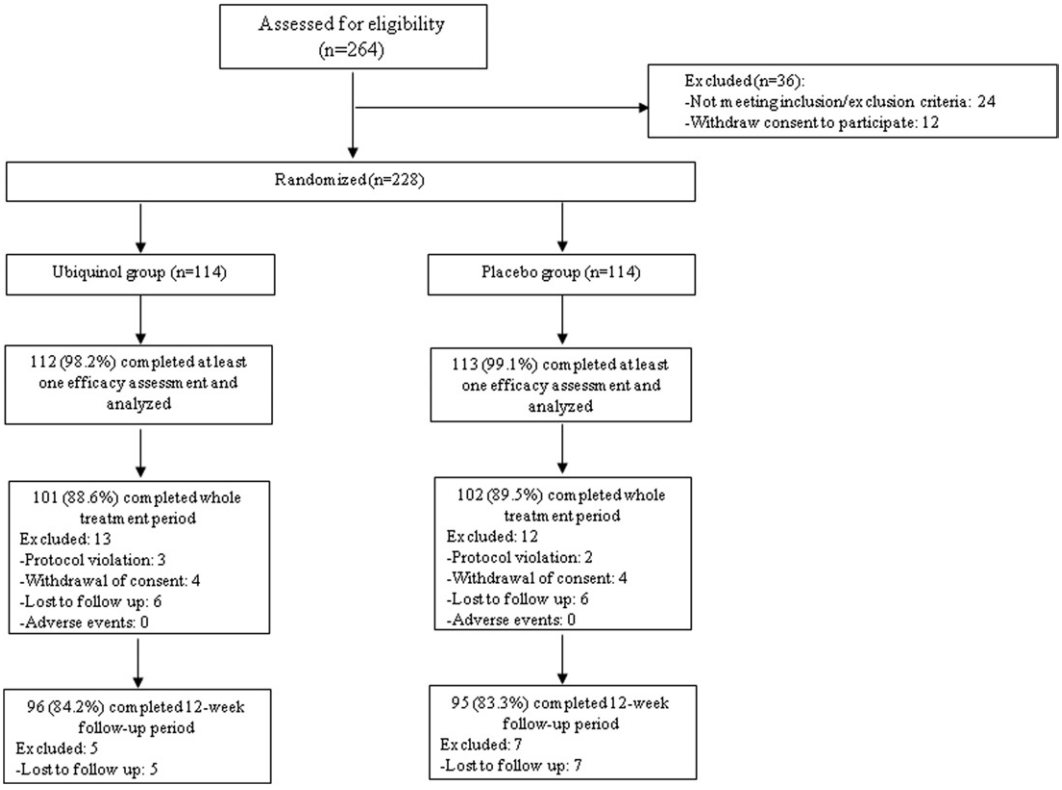
Patients were recruited in the study if they satisfied the criteria of history of primary infertility of more than 2 years, abnormal sperm count and motility according to WHO criteria, wife age between 20 and 40 years, documentation of fertile female partner, and no known medical or surgical condition which can result in infertility. Our exclusion criteria were a history of cancer chemotherapy or radiotherapy; a history of genital disease such as cryptorchidism and varicocele; a history of genital surgery; body mass index 30 kg/m^2 or greater; any endocrinopathy; Y chromosome microdeletions or karyotype abnormalities; leukocytospermia (more than 10^6 white blood cells per ml); drug, alcohol or substance abuse; tobacco use; use of anticonvulsants, androgens or antiandrogens; significant liver (serum bilirubin greater than 2.0 mg/dl) or renal function (serum creatinine greater than 2.0 mg/dl) impairment; and occupational and environmental exposure to reproductive toxins. Patients with severe oligozoospermia (less than 5×10^6/ml), azoospermia and testicular volume less than 12 ml were also excluded from study.

Randomization and Treatment Protocol

The study consisted of a 4-week screening phase, a 26-week treatment phase and a 12-week treatment-free period. A total of 228 patients who met the study criteria were selected and recruited into the study. Of these subjects 36 did not meet the inclusion/exclusion criteria or withdrew consent to participate in the study (see figure). F1
Randomization codes were provided by the first investigator (MRS) using a computer generated random number table. The randomization codes were centrally assigned by the coordination center after checking the main eligibility criteria. Eligible subjects were randomized 1:1 to 200 mg ubiquinol (New Life CoEnz QH, Istanbul, Turkey) orally once daily after a meal (group 1, 114) or to a similar regimen of placebo (group 2, 114). Study medications were over-encapsulated so that ubiquinol and placebo appeared identical. All investigators and study staff were blinded to treatment allocation during the whole study period, and the treatment code was unblinded at the end of the study. The participants were informed not to take other medications that could affect spermatogenesis during the study period.

Outcome Measures

The primary outcome measure was percent change from baseline at the end of the 26-week treatment period. Efficacy was assessed every 4 weeks after the initial dose of ubiquinol on the first day, at the end of the 26-week treatment period and at the end of treatment-free period. At each followup point 2 semen analyses were performed 1 week apart. The results were averaged to minimize variability. Blood samples for hormonal (testosterone, LH, FSH, inhibin B), biochemical and hematological assays were collected at weeks 12 and 26 of treatment. Seminal plasma CAT-like and SOD-like activity was measured every 4 weeks, at the end of the 26-week treatment period and at the end of the treatment-free period.



Participant flow diagram. Of patients in ubiquinol and placebo groups 101 and 102 completed 26-week intervention period, and 96 and 95 completed 12-week treatment-free period, respectively. Intent to treat population included all randomized patients who took at least 1 dose of assigned study medication and who had at least 1 valid assessment (4-week) after baseline of primary outcome measure (112 in ubiquinol group and 113 in placebo group).

Safety Assessment

An adverse event was defined as any symptom, sign or condition that appeared during the study or, if present at the beginning of the study, worsened throughout the study, with the exception of the suspected cause of the event. The relatedness and severity of AEs with study medications were assessed by the investigator (MRS). Treatment emergent AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA® version 8.0). Compliance with consumption of the study medications during the intervention period was monitored by pill counts at each followup visit.

Statistical Analysis

The study was powered to detect an increase of 15% in sperm with normal morphology. The clinical improvement of sperm with normal morphology of at least 10% was expected for 1 spermatogenesis cycle according to our previous study.[7] Therefore, P1 was calculated as 0.25. The value of P2 was set to be 0.10. It was estimated that 90 patients in each group would be an adequate sample number to achieve an 80% power of detection of differences at a significance level (α) of 0.05 using a 2-sided Z test. Assuming an overall dropout rate of 20%, the total number of subjects required for each arm was determined to be 112. The efficacy results were determined at the end of the 26-week treatment period. Values were expressed as mean $\pm$ SD. The normal distribution of the variables was checked by the Kolmogorov-Smirnov test for goodness of fit. Where necessary, the data were logarithmically transformed before analysis to obtain normal distributions. Qualitative data were compared by the chi-square test or Fisher's exact test when necessary. The Mann-Whitney test was used to compare quantitative data. Statistical analysis of outcomes was done using intent to treat analysis. The intent to treat population included all randomized subjects who took at least 1 dose of the assigned study medication and who had at least 1 valid assessment (4 weeks) after baseline. Missing values for the patients who withdrew from the study before the 4-week treatment phase were imputed using the last observation carried forward method. Correlations were determined by Spearman's rank correlation test. After univariate analysis, multivariate logistic regression was performed with adjustment for age, occupational status, infertility duration, abstinence period and body mass index with p less than 0.05 considered statistically significant. Data were entered into and analyzed with SPSS® (version 18.0 for Windows).

RESULTS

Baseline Characteristics

On average, participants were 31 and 32 years old in the ubiquinol and placebo groups, respectively. The

demographic variables, and disease related and baseline outcome parameters of the 2 groups did not differ significantly at baseline. The 26-week study completion rates were 88.6% for the ubiquinol group and 89.5% for the placebo group (see figure). Among the 25 subjects who discontinued prematurely, the most common reason in both treatment groups was withdrawal of consent.

Semen Parameters for 26-Week Treatment Period

Semen volume and sperm density. Mean semen volume did not differ significantly between the 2 groups ($p = 0.1$). At the end of the 26-week treatment period a significant increase in sperm density was observed in group supplemented with 200 mg ubiquinol daily ($28.7 \pm 4.6 \times 10^6$/ml) compared to T1 placebo ($16.8 \pm 4.4 \times 10^6$/ml, $p = 0.005$, table 1). Sperm density improved in 62% of patients, remained unchanged in 27% and deteriorated in 11% in the ubiquinol group. The average percentage of increased sperm density in group 1 at weeks 8, 16 and 26 was 15.2%, 43.7% and 81.6%, respectively.

Sperm motility. A significant increase in the percentage of motile sperm was observed in the ubiquinol group (35.8% ± 2.7%) by 26 weeks of treatment compared to the placebo group (25.4% ± 2.1%) ($p = 0.008$). The percentage of patients in the treatment group who showed improvement and deterioration in sperm motility was 57% and 16%, respectively. Compared to baseline there was a statistically significant increase in the number of motile sperm in the ubiquinol group from week 12 onward. The average percent increase in the number of motile sperm during weeks 12, 20 and 26 was 18.0%, 26.5% and 31.7%, respectively.

Sperm morphology. At the end of the 26-week treatment phase ubiquinol (17.6% ± 4.4%) was significantly more effective than placebo (14.8% ± 4.1%) in improving strict morphology ($p = 0.01$, table 1). Strict morphology improved in 52%, remained unchanged in 25% and deteriorated in 23% of patients in the ubiquinol group. Similar results for the comparison of ubiquinol vs placebo were obtained when the percent change from baseline was assessed. Compared with placebo, supplementation with ubiquinol for 16, 20 and 26 weeks conferred 18.3%, 21.1% and 24% increases in strict morphology, respectively.

Seminal plasma antioxidant status. Time duration related increases were evident in the activities of both antioxidant enzymes. At 26 weeks of treatment mean levels of seminal plasma CAT-like and SOD-like activity were significantly higher in the ubiquinol group (422 ± 17 and 54.7 ± 1.7 U/ml) than in the placebo group (311 ± 12 and 36.5 ± 1.4 U/ml, both $p = 0.002$, table 1). At the end of the treatment period seminal plasma CAT-like and SOD-like activity increased by 35.7% and 51.1%, respectively.

Serum hormones. Ubiquinol treatment produced a slight and statistically nonsignificant increase in serum testosterone at week 26 (percent change from baseline 19.5 vs 3.7, $p = 0.08$). This increase in serum testosterone was associated with a statistically significant ($p = 0.03$) mean decrease of 33.9% in serum LH, which remained well within the normal limit. These changes in serum testosterone and LH with 200 mg oral ubiquinol daily were associated with significant effects in serum FSH compared to placebo (table 1). Mean serum FSH at the end of the on-drug period decreased by 37.7% (9.6 ± 3.6 IU/l) in

Table 1. *Summary of semen parameters, reproductive hormones and CoQ_{10} concentrations*

	26-Wk Ubiquinol	p Value*	26-Wk Placebo	p Value*	38-Wk Ubiquinol	p Value†	38-Wk Placebo	p Value†	p Value‡
Mean ± SD semen parameters:									
Ejaculate vol (ml)	2.6 ± 1.4	0.1	2.7 ± 1.6	0.1	2.7 ± 1.4	0.1	2.7 ± 1.3	0.1	0.1
Total sperm count (10^6)	62.6 ± 15.8	0.006	44.7 ± 11.8	0.22	54.3 ± 11.7	0.01	45.1 ± 11.5	0.17	0.02
Sperm density (10^6/ml)	28.7 ± 4.6	0.005	16.8 ± 4.4	0.67	22.4 ± 4.2	0.03	16.2 ± 3.7	0.65	0.03
Sperm motility (% motile)	35.8 ± 2.7	0.008	25.4 ± 2.1	0.17	31.2 ± 2.4	0.04	25.8 ± 2.2	0.32	0.03
Strict morphology (% normal)	17.6 ± 4.4	0.01	14.8 ± 4.1	0.76	15.2 ± 4.1	0.03	14.4 ± 4.8	0.91	0.09
Mean ± SD serum hormones:									
Testosterone (nmol/l)	19.6 ± 4.6	0.08	16.7 ± 4.4	0.25	17.3 ± 4.8	0.14	15.8 ± 4.1	0.34	0.08
LH (IU/l)	8.2 ± 2.4	0.03	13.1 ± 2.4	0.64	9.1 ± 2.3	0.08	12.8 ± 2.2	0.78	0.03
FSH (IU/l)	9.6 ± 3.6	0.02	16.4 ± 4.2	0.27	12.4 ± 3.8	0.03	16.6 ± 4.2	0.31	0.03
Prolactin (pmol/l)	361 ± 111	0.1	372 ± 124	0.1	366 ± 127	0.1	364 ± 110	0.1	0.1
Inhibin B (ng/l)	191 ± 32	0.01	158 ± 22	0.1	174 ± 28	0.03	151 ± 24	0.34	0.02
Mean ± SD seminal plasma antioxidant status:									
CAT-like activity (U/ml)	422 ± 17	0.002	311 ± 12	0.1	321 ± 14	0.08	307 ± 11	0.1	0.08
SOD-like activity (U/ml)	54.7 ± 1.7	0.002	36.5 ± 1.4	0.09	38.4 ± 1.3	0.004	36.1 ± 1.4	0.1	0.18

* Versus baseline.
† Versus 26-week values.
‡ Versus 38-week ubiquinol values.

the ubiquinol group and increased by 5.1% in the placebo group (16.4 ± 4.2 IU/l). At week 26 in subjects treated with ubiquinol serum inhibin B increased by 25.2% from baseline (191 ± 32 ng/l, p = 0.01).

Semen Parameters for 12-Week Treatment-Free Period

The improvement in semen parameters gradually reversed with the discontinuation of ubiquinol. At the end of the 12-week followup the mean sperm concentration in the ubiquinol and placebo groups was 22.4 ± 4.2 × 10^6/ml and 16.2 ± 3.7 × 10^6/ml (p = 0.009), mean sperm motility was 31.2% ± 2.4% and 25.8% ± 2.2% (p = 0.04), and mean sperm morphology was 15.2% ± 4.1% and 14.4% ± 4.8% of normal sperm, respectively (p = 0.08). The differences were still significant for sperm density (p = 0.03) and sperm motility (p = 0.03). After treatment cessation, serum FSH concentration gradually increased but remained statistically significantly decreased (p = 0.03). At the end of the no-drug period the differences in seminal plasma CAT-like and SOD-like activity and serum inhibin B concentration were no longer significant between the 2 groups.

Correlations

The correlations were assessed at the end of the 26-week treatment period after the codes were broken. Correlation coefficients analysis revealed a positive association between the duration of the treatment with ubiquinol, and sperm density (r = 0.74, p = 0.017), sperm motility (r = 0.66, p = 0.024) and sperm morphology (r = 0.57, p = 0.027, table 2). A significant correlation was found between CAT-like and SOD-like activity (r = 0.49, p = 0.0001). CAT-like activity was significantly correlated with sperm density (r = 0.64, p = 0.007), sperm motility (r = 0.62, p = 0.008) and strict morphology (r = 0.51, p = 0.031). Positive correlations were also observed between seminal plasma SOD-like activity and semen parameters. CAT-like and SOD-like activity was significantly negatively correlated with leukocytospermia (r = −0.28, p = 0.01, and r = −0.32, p = 0.01, respectively). Treatment duration had a significant impact on study variables. In terms of adverse events, ubiquinol was well tolerated by all participants in terms of taste and the absence of any serious side effects.

Table 2. *Correlation between semen parameters and leukocytospermia with seminal plasma CAT-like and SOD-like activity, and duration of treatment with ubiquinol*

	CAT-Like Activity (p value)	SOD-Like Activity (p value)	Treatment Duration (p value)
Sperm density	0.64 (0.007)	0.78 (0.001)	0.74 (0.017)
Sperm motility	0.62 (0.008)	0.73 (0.004)	0.66 (0.024)
Sperm morphology	0.51 (0.031)	0.48 (0.034)	0.57 (0.027)
Leukocytospermia	−0.22 (0.042)	−0.25 (0.036)	−0.38 (0.027)

DISCUSSION

The results of this study demonstrate that ubiquinol supplementation significantly improves semen parameters in infertile men with idiopathic OAT. Coenzyme Q_{10}, an endogenous enzyme cofactor, is a crucial component of the mitochondrial respiratory chain and confers protective benefits as an antioxidant.[13] More than 90% of the CoQ_{10} content in serum and biological tissues[13] presents in the reduced form ubiquinol-10,[14] a potent lipid soluble antioxidant. In our previous study CoQ_{10} administration in same setting resulted in a 30.7%, 24.3% and 33.3% increase in sperm density, sperm motility and sperm morphology, respectively.[7] In the present study ubiquinol supplementation for 26 weeks resulted in 81.6%, 31.7% and 24.0% improvement in sperm density, sperm motility and sperm morphology, respectively. Ubiquinol was more effective than CoQ_{10} in improving sperm count and motility. Sperm density increased more than 2.5-fold with ubiquinol compared to CoQ_{10}. On the other hand, ubiquinol was less effective than CoQ_{10} in improving sperm morphology. Various medications with various degrees of effectiveness have been used for the treatment of male infertility, including gonadotropin-releasing hormone, gonadotropins, antiestrogens, aromatase inhibitors, a variety of vitamins, nutritional supplements and anti-inflammatory agents.[15] In recent decades interest has increasingly focused on the use of antioxidants to scavenge excessive seminal plasma ROS.[16–19] Overall, considering the important role of OS in semen quality, antioxidants deserve further attention from pharmaceutical companies and researchers. It seems that pharmaceutical companies have more interest in providing medications for assisted reproductive technique protocols than for OAT itself.

The present study is not without limitations. Our study lacked a long followup evaluation. In addition, improved semen quality does not translate into an improved pregnancy rate. In infertility treatment the ultimate outcome would probably be the pregnancy rate but we did not address pregnancy rate during the whole study period. This study was also limited to infertile men actively seeking medical care. Finally, we should acknowledge that a statistical significance level of 0.05 will not account for all the multiple testing.

CONCLUSIONS

In infertile men with idiopathic OAT, ubiquinol administration significantly improves sperm density, sperm motility and sperm strict morphology.

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