

Antioxidant cosupplementation therapy with vitamin C, vitamin E, and coenzyme Q10 in patients with oligoasthenozoospermia

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Summary *Objective: Overproduction of reactive oxygen species results in oxidative stress, a deleterious process that damages cell structure as well as lipids, proteins, and DNA. Oxidative stress plays a major role in various human diseases, such as oligoasthenozoospermia syndrome.*

Materials and methods: We evaluated the effectiveness of antioxidant co-supplementation therapy using vitamin C, vitamin E, and coenzyme Q10 in men with oligoasthenozoospermia. Overall, 169 infertile men with oligoasthenozoospermia received antioxidant therapy with 80 mg/day vitamin C, 40 mg/day vitamin E, and 120 mg/day coenzyme Q10. We evaluated spermogram parameters at baseline and at 3 and 6 months of follow-up.

Results: Significant improvements were evident in sperm concentration and motility following coenzyme Q10 therapy. Treatment resulted in 48 (28.4%) partner pregnancies, of which 16 (9.5%) were spontaneous. Significant improvements in sperm cell concentration and sperm motility were observed after 3 and 6 months of treatment.

Conclusions: Vitamin C, vitamin E, and coenzyme Q10 supplementation resulted in a significant improvement in certain semen parameters. However, further studies are needed to empirically determine the effect of supplementation on pregnancy rate.

KEY WORDS: Vitamin C; Vitamin E; Coenzyme Q10; Male infertility.

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INTRODUCTION

There is much evidence to show that oxidant radicals and reactive oxygen species play a harmful role in human reproduction and male infertility (1).

Testicular oxidative stress is important in a number of conditions known to be detrimental to male infertility. These include a broad spectrum of diseases and conditions due to lifestyle factors such as smoking, alcohol, and obesity (2), environmental hazards such as pesti-

cides, plasticizers, and heavy metals (3), systemic infections (4), chronic diseases and inflammation such as diabetes, chronic renal failure, and varicocele (5), and a number of iatrogenic or idiopathic causes (6).

A previous open, controlled pilot study of a cohort of infertile men with idiopathic asthenozoospermia showed that exogenous administration of coenzyme Q10 (CoQ10) increases the level of both CoQ10 and ubiquinol (QH2) in semen and is effective in improving sperm kinetics (7). In addition, administration of vitamins E and C significantly reduced hydroxyguanine levels in spermatozoa and led to an increased sperm count (8).

We previously found that a relatively low intake of CoQ10 (30-60 mg/day) improved semen parameters (unpublished data).

These data encouraged us to assess the possible effectiveness of this therapeutic approach by conducting a 6-month trial of cosupplementation antioxidant therapy (vitamin C, vitamin E, and CoQ10) in a cohort of infertile men with idiopathic oligoasthenozoospermia.

Change in semen parameters and achievement of pregnancy were evaluated after 6 months of treatment.

MATERIALS AND METHODS

Patients

A total of 169 consecutive patients (mean age 36, range 25-58 years) with idiopathic oligoasthenozoospermia were enrolled in the study. All presented with infertility after at least 2 years of unprotected intercourse. Male infertility was diagnosed if one or more standard semen parameters were below the cutoff levels according to the criteria of the *World Health Organization, 1999* (sperm concentration < 20 × 10⁶/ml, sperm motility < 50%, normal morphology < 30%, and/or semen volume < 2 ml) based on at least two semen analyses performed 3 months apart to eliminate accidental and possible adverse effects of exogenous factors on spermatogenesis. After providing a complete medical and reproductive history exploring all aspects that might be related to fertility, patients underwent physical examination and

serum chemical and hematological laboratory tests. Testicular volume was measured using an orchidometer. Serum follicle stimulating hormone, luteinizing hormone, and testosterone levels were measured in all patients. Patients with infection, liver dysfunction, renal dysfunction, or a metabolic disease (e.g., diabetes mellitus) were excluded, as were patients with malignant neoplasm and those with spouses with diseases or conditions that may affect conception.

Study design

All patients underwent antioxidant therapy with 120 mg CoQ10, 80 mg vitamin C, and 40 mg vitamin E daily (two tablets of *SO support; Partners, Yokohama, Japan*). Semen parameters were evaluated before and at 3 and 6 months of treatment with co-supplementation. Pregnancy outcome and use of assisted reproduction technology was evaluated after 3 and 6 months of treatment.

Ethics

All patients provided informed consent. The study design was approved by the institutional review board.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL). Data are expressed as mean ± SD values. Differences between groups were estimated using the paired t-test. P < 0.05 was considered statistically significant for hypothesis testing.

RESULTS

Baseline patient characteristics are shown in Table 1. The mean duration of infertility was 2.3 years.

Table 2 shows mean (± SD) semen parameters before and at 3 and 6 months of treatment. The t-test performed on single variables for the homogeneity at baseline showed that there were no significant differences regarding atypical sperm cells and semen volume. On the contrary, significant improvements in sperm cell concentration and sperm motility were observed after 3 and 6 months of treatment.

A total of 48 (28.4%) pregnancies were achieved, including 16 (9.5%) spontaneous pregnancies as follows: seven

after 3 months, eight after 6 months, and one after 9 months of treatment. Overall, 32 pregnancies were achieved using assisted reproductive technology.

Six couples used *artificial insemination by husband* (AIH), eight couples used conventional *in vitro fertilization* (IVF) and 18 couples used *intracytoplasmic sperm injection* (ICSI).

Oral administration of CoQ10, vitamin C, and vitamin E was generally well tolerated, and no adverse effects or laboratory abnormalities were observed.

DISCUSSION

Several approaches have been proposed for the management of infertility caused by oxidative stress. Once an individual has been identified as having oxidative stress-related infertility, treatment should be aimed at identification and amelioration of the underlying cause before considering antioxidant treatment. Lifestyle behaviors such as smoking, poor diet, alcohol abuse, pollution and environmental toxins, obesity, and psychological stress have all been linked to oxidative stress. While the effectiveness of eliminating these lifestyle triggers on oxidative stress has not been formally tested, it is likely that

Table 1.

Baseline patient demographics, serum hormone levels, and semen parameters.

Characteristic	Range	Mean ± SD
Age (yrs)	25-58	36 ± 9
Age of wife (yrs)	22-44	34 ± 8
Serum hormones		
Testosterone (ng/dl)	169-988	406 ± 88
LH (IU/l)	1.1-11.5	3.5 ± 2.4
FSH (IU/l)	1.6-26.8	5.0 ± 4.1
Testicular volume (ml)		
Right	8-26	18 ± 5
Left	4-26	16 ± 5

FSH: follicle stimulating hormone; LH: luteinizing hormone

Table 2.

Descriptive statistics of sperm variables throughout the study.

Sperm variable	Baseline Mean ± SD	3 months Mean SD	6 months Mean SD
Sperm concentration (n x 10 ⁶ /ml)	26.3 ± 36.0	37.5 54.0	49.0 ± 59.0
<i>P value</i>		0.03	< 0.001
Sperm motility (%)	25.2 ± 18.1	39.1 ± 20.3	41.3 ± 22.1
<i>P value</i>		< 0.001	< 0.001
Atypical sperm cells (%)	25.4 ± 10.0	22.6 ± 10.3	23.4 ± 12.0
<i>P value</i>		0.43	0.44
Semen volume (ml)	3.1 ± 1.9	3.1 ± 2.2	4.3 ± 2.9
<i>P value</i>		0.78	0.08

making positive lifestyle changes such as changing to a diet high in fruit and vegetables, maintaining normal weight, and reducing smoking or alcohol intake would have at least some beneficial effects on sperm health. Several studies have reported that levels of reactive oxygen species within semen can be reduced by augmenting the scavenging capacity of seminal plasma using oral antioxidant supplements.

Vitamin E is a major chain-breaking antioxidant in sperm membranes and this effect appears to be dose dependent. Vitamin E scavenges the three major types of free reactive species, namely superoxide, hydrogen peroxide, and hydroxyl radicals. In a randomized, double-blind, placebo-controlled trial (9), *in vitro* functional tests of human spermatozoa improved after 3 months of vitamin E (600 mg/day) therapy. While some studies suggest a potential role for vitamin E in the management of male infertility, another randomized trial failed to confirm these findings (10).

Vitamin C is another important chain-breaking antioxidant and is present at a higher concentration in seminal fluid than in plasma as well as being present in low but detectable amounts in sperm cells (11). Vitamin C neutralizes hydroxyl, superoxide, and hydrogen peroxide reactive species and prevents sperm agglutination, while preventing lipid peroxidation, recycling vitamin E, and protecting against DNA damage induced by hydrogen peroxide radicals (12). It has been suggested that oral administration of vitamin C with vitamin E significantly reduces hydroxyguanine levels in spermatozoa and also leads to an increased sperm count (8).

CoQ10 is a component of the mitochondrial respiratory chain and plays a crucial role in energy metabolism and as a liposoluble chain-breaking antioxidant for cell membranes and lipoproteins (13).

Recently, the role of CoQ10 as a gene inducer has also been investigated (14). CoQ10 biosynthesis is markedly active in the testis (15), and high levels of its reduced form, QH₂, are present in sperm (16), suggesting a protective antioxidant role. Levels of CoQ10 and QH₂ in seminal plasma and sperm cells of infertile men with idiopathic and varicocele-associated asthenozoospermia were reduced significantly (17). On the basis of this finding, CoQ10 likely contributes to the total antioxidant buffer capacity of semen, and a decrease in levels is deleterious in terms of dealing with oxidative stress. The mode of action of CoQ10 in male infertility is not clear but may be useful for vitalizing cells by providing greater energy to mitochondria, thereby improving motility and preventing oxidative damage through its actions as a free radical scavenger. CoQ10 recycles vitamin E and prevents its pro-oxidant activity (18). QH₂ also acts as an antioxidant by preventing lipid peroxidation, whereas CoQ10 inhibits hydrogen peroxide formation in the seminal fluid and seminal plasma of infertile men (19). In a randomized, double-blind, placebo-controlled trial, the exogenous administration of CoQ10 increased the level of both CoQ10 and QH₂ in semen and was effective in improving sperm kinetics in patients with idiopathic asthenozoospermia (17).

When a molecule of vitamin E neutralizes a free radical it loses its antioxidant ability which is subsequently

restored by the actions of other antioxidants such as vitamin C and CoQ10 (20).

The synergy provided by combination supplementation may improve the qualitative and quantitative parameters of the seminogram in patients with oligoasthenozoospermia.

CONCLUSION

Co-administration of vitamin C, vitamin E, and CoQ10 may play a positive role in the treatment of oligoasthenozoospermia, possibly mediated by the mitochondrial respiratory chain and by its antioxidant effects. However, further studies are needed to draw firm conclusions; the effect of such supplementation on pregnancy rate is currently being investigated in a randomized, double-blind, placebo-controlled trial.

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