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ORIGINAL ARTICLE

# Effect of Vitamin C, Vitamin E, Zinc, Selenium, and Coenzyme Q10 in Infertile Men with Idiopathic Oligoasthenozoospermia

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## ABSTRACT

**Introduction:** Accumulating evidence suggests that oxidative stress plays an important role in the development of male infertility and recently antioxidants have been tried to treat men with idiopathic infertility.

**Objective:** To assess the effect of treatment with vitamin C, vitamin E, zinc, selenium, and coenzyme Q10 on seminal fluid parameters in infertile men with idiopathic oligoasthenozoospermia.

**Materials and methods:** A prospective randomized trial was conducted on 32 infertile men with idiopathic oligoasthenozoospmia who received a daily supplement of one caplet containing vitamin C (90 mg/day), vitamin E (15 mg/day), coenzyme Q10 (4 mg/day), selenium (30 µg/day), and zinc (5 mg/day) for 3 months. Semen analysis was performed at baseline and 3 months after treatment using World Health Organization (WHO) 2010 guidelines.

**Results:** Significant improvement in sperm concentration was observed after combination therapy (9.13 ± 4.29 *vs* 11.3 ± 6.05 × $10^6$/mL, $p < 0.05$). Sperm progressive motility (18.1 ± 8.68 *vs* 24.6 ± 10.2%, $p < 0.01$) and total motility (28.4 ± 8.71 *vs* 34.4 ± 11.7%, $p < 0.01$) also increased significantly following treatment. No change, however, was observed in semen volume or the proportion of sperms with normal morphology.

**Conclusion:** The combination of vitamin C, vitamin E, zinc, selenium, and coenzyme Q10 can significantly improve sperm concentration and motility in infertile men with idiopathic oligoasthenozoospermia, which could be attributed to their synergistic antioxidant action.



**Keywords:** Coenzyme Q10, Idiopathic, Male infertility, Oligoasthenozoospermia, Selenium, Vitamin C, Vitamin E, Zinc.

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## INTRODUCTION

Infertility is defined as the inability of a couple to conceive after 1 year of regular, unprotected sexual intercourse. Around 15% of all couples trying to conceive are affected by infertility and in 50% of infertile couples, it is possible to identify a male factor infertility.[1] It is known that some conditions, such as varicocele, cryptorchidism, hypogonadism, and genetic factors, can cause infertility. However, no underlying cause can be identified for primary or secondary infertility in approximately 25% of couples. Such idiopathic male infertility and oligoasthenozoospermia is a condition in which sperm concentration and the percentage of progressively motile sperms are below the WHO reference values.[2] As many environmental, genetic, and physiological factors including oxidative stress have been implicated in idiopathic male infertility,[3] the pathogenesis of suboptimal semen quality remains to be elucidated.

Accumulating evidence suggests that oxidative stress plays an important role in the development of male infertility. High reactive oxygen species (ROS) level and oxidative stress have been implicated in the etiology of male factor infertility. Further, ROS have been linked to sperm deoxyribonucleic acid (DNA) damage, altered sperm motility, poor fertilization, and embryo development.[4,5] The adverse effects of ROS stem from their ability to alter normal sperm function as they damage lipids, other macromolecules, and DNA of the spermatozoa. The abundance of plasma membrane polyunsaturated fatty acids in spermatozoa makes them particularly susceptible to the adverse effects of oxidative stress. Normal function of these fatty acids is essential for the acrosome reaction, sperm–egg interaction, and sperm motility.[6]

The human ejaculate contains a number of potential sources of ROS. These comprise germ cells, abnormal sperms, and leukocytes.[2] On the contrary, human body is empowered with highly organized and sophisticated antioxidant defence system that provides protection against ROS. The system involves a synergy between various endogenous and exogenous components to scavenger-free radicals.[7] These antioxidants are divided into enzymatic antioxidants (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic antioxidants (like glutathione, vitamin E, vitamin A, vitamin C, ascorbate, urate, coenzyme Q10, and L-carnitine) which eliminate free radicals produced during normal cellular metabolism. However, during pathological conditions, when generation of ROS is exceeded, the balance between free radical production and the protective antioxidant defence system shifted to the increase in free radical-mediated oxidative stress.[8] Moreover, many studies have revealed that the antioxidant capacity of seminal fluid is suppressed in infertile men in comparison with fertile men.[6,9]

Based on the integral role of oxidative stress in the pathogenesis of male infertility, treatment strategies that target the reduction of seminal oxidative stress have become a probable therapeutic window to improve reproduction potential and pregnancy rates.[10] In fact, little is known about how usual levels of intake of various antioxidants and how antioxidant intake from food sources relate to sperm production and function. Recently, the relationship between antioxidants, such as vitamins A, C, E, selenium, and glutathione and the development of male infertility has been investigated.[2,11,12] Several antioxidants and micronutrients, such as vitamin C, vitamin E, selenium, astaxanthin, glutathione, pentoxifylline, arginine, zinc, L-carnitine, and coenzyme Q10, have been shown to improve seminal fluid parameters in infertile men.[2,5,13,14]

A study investigating the effect of selenium and vitamin E in asthenoteratospermic patients reported improvement in sperm motility, morphology, and pregnancy rate.[3] Another controlled study revealed higher semen volume, sperm count, and progressive motility after receiving zinc sulfate supplement.[10] Further, asthenozoospermic patients who received 200 mg of coenzyme Q10 for 6 months showed increment in sperm motility and spontaneous pregnancy rate.[12] The majority of studies reported beneficial effect of different antioxidants on at least one of the seminal fluid indices and the main influence was on sperm motility.[2] Further, several studies suggest improved pregnancy rates using combination therapies.[15] All these potential therapeutic agents have been tried to treat male infertility; however, there is no well-defined therapeutic protocol for antioxidants in the treatment of male infertility.

The aim of this study was to evaluate the effect of treatment with a combination of vitamin C, vitamin E, selenium, zinc, and coenzyme Q10 on seminal fluid parameters in infertile men with idiopathic oligoasthenozoospermia.

## MATERIALS AND METHODS

A prospective randomized study was conducted on 32 infertile men with idiopathic oligoasthenozoospermia who met the inclusion criteria. The patients were recruited at our Fertility Clinic in Hilla, Iraq, and the study was conducted from December 2016 to May 2017. Inclusion criteria comprised history of infertility of at least 12 months despite regular unprotected intercourse and seminal fluid analysis showing abnormal sperm concentration (<15 million/mL), progressive motility (<32%), and total motility (<40%) as defined by WHO manual for semen analysis 2010.[16] Exclusion criteria comprised azoospermia, varicocele, genital tract infection, cryptorchidism, testicular trauma or scrotal surgery, endocrine disorder, systemic illness, and smoking. All participants consented for participation in the study and the study adhered to the local ethical protocol.

All patients received a daily supplement of one caplet containing vitamin C 90 mg, vitamin E 15 mg, coenzyme Q10 4 mg, selenium 30 µg, and zinc 5 mg (Hansal A–Z Vital, Hansal Pharm GmbH, Germany) for 3 months. Semen samples were obtained at baseline and after 3 months and analyzed in accordance with WHO manual for semen analysis 2010.[16] Following abstinence of 2 to 3 days, semen sample was obtained by masturbation and incubated in the lab at 37°C. The liquefied semen sample was then assessed for the following parameters: Semen volume (mL), sperm concentration (million/mL), sperm progressive motility (%), sperm total motility (%), and normal sperm morphology (%) using WHO criteria.

GraphPad Prism v.6.01 (GraphPad Software, Inc, CA 92037 USA) software for Windows was used for statistical analysis. Data were assessed for normality distribution by Shapiro–Wilk test and histograms where appropriate. Nominal variables were expressed as proportions, whereas continuous variables were presented as mean and standard deviation. Paired Student's t-test was used to compare seminal fluid parameters before and after supplement; $p < 0.05$ was considered statistically significant.

## RESULTS

In this study, the mean of patients' age was 27.66 ± 7.42 years. Patients with primary infertility constituted 71.8%, whereas those with secondary infertility formed 28.2%, with a mean of duration of infertility of 4.54 ± 2.61 years.

Seminal fluid parameters before and after 3 months of combined treatment with vitamin C, vitamin E, selenium, zinc, and coenzyme Q10 are shown in Table 1. There was no significant change in semen volume after treatment (2.6 ± 0.91 *vs* 2.8 ± 0.68 mL respectively). Sperm concentration increased in patients with idiopathic oligoasthenozoospermia after 3 months of treatment with

**Table 1:** Seminal fluid parameters before and after 3 months of treatment

| | *Before treatment (n = 32)* | *After treatment (n = 32)* | *p-value* |
|---|---|---|---|
| Semen volume (mL) | 2.6 ± 0.91 | 2.8 ± 0.68 | >0.05 |
| Sperm concentration (×$10^6$/mL) | 9.13 ± 4.29 | 11.3 ± 6.05 | <0.05 |
| Sperm progressive motility (%) | 18.1 ± 8.68 | 24.6 ± 10.2 | <0.01 |
| Sperm total motility (%) | 28.4 ± 8.71 | 34.4 ± 11.7 | <0.01 |
| Normal sperm morphology (%) | 33.8 ± 8.33 | 34.5 ± 6.50 | >0.05 |

Results are expressed as mean ± standard deviation

means of sperm concentration of 9.13 ± 4.29 and 11.3 ± 6.05 × $10^6$/mL respectively ($p < 0.05$). Progressive sperm motility significantly increased in patients after treatment (18.1 ± 8.68 *vs* 24.6 ± 10.2% respectively, $p < 0.01$). Moreover, total sperm motility also increased from 28.4 ± 8.71 to 34.4 ± 11.7% after treatment ($p < 0.01$). Normal sperm morphology, however, did not alter significantly in infertile patients after treatment (33.8 ± 8.33 *vs* 34.5 ± 6.50% respectively).

## DISCUSSION

The current study demonstrated an improvement in sperm concentration, progressive motility, and total motility in infertile patients with idiopathic oligoasthenozoospermia after 3 months of combined treatment with vitamin C, vitamin E, zinc, selenium, and coenzyme Q10. Due to the diversity of the underlying causes for infertility in men with oligoasthenozoospermia, various medications with different degrees of effectiveness have been tried for the treatment of male infertility. Recently, interest has been increasingly focused on the role of excessive ROS production in infertile men and the use of antioxidants to scavenge excessive seminal plasma ROS.[17]

In the current study, there was no significant change in semen volume after treatment. This observation is congruent with the findings of other studies which demonstrated no change in semen volume in infertile men following treatment with coenzyme Q10 (200 mg)[17] or vitamin E (400 mg).[15] In contrast, semen volume increased after combined antioxidant treatment for 3 months.[18] Sperm concentration significantly increased after 3 months of combined antioxidant treatment. These results are consistent with previous reports which showed an increment in sperm concentration after antioxidant supplement.[10,17-20] A recent study investigated the effect of combined micronutrients including vitamin E, zinc, selenium, and coenzyme Q10 for 3 months and reported increased sperm concentration in men with infertility.[18] Another study observed higher sperm density in men with idiopathic oligoasthenozoospermia after 6 months of treatment with vitamin E (400 mg/day) with or without clomiphene citrate.[20] Further, total sperm motility in infertile men was higher than those of fertile controls following daily administration of zinc sulfate for 3 months[10] and zinc correlated with sperm density in another study.[21] A placebo-controlled trail of 200 mg of coenzyme Q10 for 26 weeks reported increased sperm density in men with unexplained infertility.[17] Interestingly, sperm density returned to baseline values within 12 weeks of off-drug period, suggesting a coenzyme Q10-mediated effect. Nevertheless, our findings are in contrast with a study which showed no improvement in sperm concentration in infertile men after 12 weeks period of treatment with coenzyme Q10, albeit a reduction in oxidative stress was observed.[22]

Both sperm progressive motility and total motility were significantly higher in infertile patients after 3 months of antioxidant treatment. Our findings are consistent with previous studies which demonstrated higher sperm motility in patients with idiopathic infertility following vitamin C,[23] vitamin E,[3,18,20] zinc,[10,18,24] selenium,[3,18] and coenzyme Q10[8,18,25] administration. A recent study has compared the effect of L-carnitine *vs* a combination of zinc, vitamin E, selenium, coenzyme Q10, glutathione, and L-carnitine and reported improvement in all seminal fluid measures after 3 months of combined treatment.[18] Another study explored the effect of daily supplement of selenium (200 Ug) and vitamin E (400 units) in idiopathic asthenoteratospermia and showed an increase in total sperm motility and spontaneous pregnancy rates following 100 days of treatment.[3] Similarly, daily zinc supplement of 440 mg for 3 months improved progressive and total sperm motility in infertile men with asthenozoospermia as compared with fertile controls.[10] Another experimental study, however, reported a paradoxical reduction in sperm motility in male rats after supplementation with vitamin C, E, and astaxanthin.[19] Moreover, a daily supplement of coenzyme Q10 (200 mg) did not improve seminal fluid parameters including sperm motility in infertile men in one study.[22] The proportion of sperm with normal morphology did not alter following treatment. Nadjarzadeh et al[26] also reported no correlation between dietary intake of vitamin C, vitamin E, zinc, and selenium with the proportion of normal sperm morphology. Our results, however, are in contrast with those of Safarinejad[27] who reported improvement of normal sperm morphology in men with idiopathic infertility who received coenzyme Q10 for 12 months.

In men with infertility, there is evidence of imbalance between ROS production and seminal fluid antioxidant capacity, creating a condition of oxidative stress that negatively impacts sperm quality.[28] Dietary intake of antioxidants[11] and seminal fluid total antioxidant capacity[25,28] have been also shown to be reduced in patients with idiopathic male infertility. Other studies have also reported lower levels of antioxidants in seminal plasma of infertile men.[21,24] The effect of the combination of micronutrients in this study could be attributed to the sum of the partly augmentative effects of each compound. Coenzyme Q10 counteracts free radicals and is required for male follicle-stimulating hormone and luteinizing hormone production, which ultimately results in improvement of sperm concentration, motility, and morphology.[27] Antioxidant properties of dietary zinc protects against excessive oxidative stress during sperm production that may counteract against copper excess, improving sperm cell concentration and motility.[29] Zinc supplementation also improves the synthesis of zinc-binding proteins, such as metallothioneins in infertile men with asthenozoospermia.[10] Selenium mediates protection against ROS by binding to a structural element in the sperm cell membrane in the form of the enzymes selenoprotein mGPx4 and snGPx4.[3] Moreover, it augments thyroid hormone effects which are important for sperm production.[30] Vitamin E protects against lipid peroxidation, therefore, improving seminal fluid quality and sperm motility significantly.[20] Similarly, vitamin C also counteracts oxidative stress and improves semen quality in man and animal models.[19]

The diversity of target for the five micronutrients used in this study and their partially synergistic action on the male reproductive system could explain their selective superiority as compared with the monotherapy.[18] Recently, two articles[2,5] reviewed published articles on the effect of antioxidants in male infertility and the main improvement was related to sperm motility. The two reviews, however, emphasized the lack of agreement on the daily dosage, combination formula, and treatment protocol in infertile men. The variability of dosage and protocol could partially explain the differences of our results from other studies. It is still unclear whether improvement in sperm concentration and motility observed in the current study exerted by combined compound is due to suppression of ROS action or to the sum of the specific unidentified effects of each individual compound on gonadal sperm production and function. The limitations of our study comprise the relatively small sample size, unreported pregnancy rates, and the absence of placebo group.

## CONCLUSION

The combined formulation of vitamin C, vitamin E, zinc, selenium, and coenzyme Q10 improved sperm concentration, progressive and total sperm motility in infertile men with idiopathic oligoasthenozoospermia. These effects could be due to synergistic antioxidant action of the compounds or other unidentified mechanisms which affect gonadal sperm production and seminal fluid antioxidant capacity. Further studies are warranted to augment the evidence provided in this work.

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