Randomized, triple-blind, placebo-controlled clinical trial examining the effects of alpha-lipoic acid supplement on the spermatogram and seminal oxidative stress in infertile men

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Objective: To evaluate effects of supplementation with alpha-lipoic acid (ALA) on the spermatogram and seminal oxidative stress biomarkers.
Design: Randomized, triple-blind, placebo-controlled clinical trial.
Setting: Infertility clinic.
Patient(s): Infertile men.
Intervention(s): ALA (600 mg) or placebo for 12 weeks.
Main Outcome Measure(s): Semen analysis, anthropometric, dietary, and physical activity assessments, total antioxidant capacity, and malondialdehyde.
Result(s): At the end of study, the total sperm count, sperm concentration, and motility in the intervention group were significantly higher than in the control group. In the ALA group, the total sperm count, sperm concentration, and motility levels were also significantly increased at the end of study compared with baseline values. However, there were no significant differences in ejaculate volume, normal morphology percentage, and live sperm between groups. ALA supplementation also resulted in a significant improvement in seminal levels of total antioxidant capacity (TAC) and malondialdehyde compared with the placebo.
Conclusion(s): According to the results, medical therapy of asthenoteratospermia with ALA supplement could improve quality of semen parameters. However, further investigation is suggested in this regard.
Clinical Trial Registration Number: IRCT2013111010181N3. (Fertil Steril® 2015;104:318–24. ©2015 by American Society for Reproductive Medicine.)
Key Words: Alpha-lipoic acid, asthenospermia, spermatogram, oxidative stress, infertile men

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Infertility is defined as conception failure after regular sexual activities in the absence of contraception for at least 1 year (1). Infertility is a major clinical concern, affecting 15% of married couples (2). Causes of infertility in couples are varied, but the main causes are attributable to the male partner (3). Although certain cases of male infertility are due to anatomic abnormalities, such as varicocele, ductal obstructions,

and ejaculatory disorders, an estimated 40%–90% of cases are due to deficient sperm production of unidentifiable origin (4). Recently, a special concern has been raised about the low sperm concentration and poor quality of semen found in young men in some countries (5). At the present time, the etiology of suboptimal semen quality is not well understood, and many physiologic, environmental, and genetic factors, such as oxidative stress, have been suggested (6).

Reactive oxygen species (ROS) can have beneficial or detrimental effects on sperm function, depending on the nature and the concentration of the ROS as well as the location and length of exposure to ROS (7). During epididymal transit, sperm acquire the ability to move progressively; however, they acquire the ability to fertilize in the female tract through a series of physiologic changes called "capacitation" (8). Under physiologic states, spermatozoa make little amounts of ROS, which are needed for capacitation and acrosomal reaction. Superoxide anion appears to play a role in this process (9). It is known that spermatozoa are susceptible to oxidative damage because their plasma membranes are rich in polyunsaturated fatty acids and have low concentrations of scavenging enzymes (10). Studies have indicated that male germ cells at various stages of differentiation have the potential to generate ROS. Excessive generation of ROS in semen by leukocytes as well as by abnormal spermatozoa could be a cause of infertility (11). It has been reported that moderately elevated concentrations of ROS do not affect sperm viability but cause sperm immobilization, mostly via depletion of intracellular adenosine triphosphate (ATP), and decreased phosphorylation of axonemal proteins (12). High concentrations of hydrogen peroxide, the main ROS producer, also prompt lipid peroxidation and result in cell death (13). In several studies, ROS levels were higher and levels of seminal antioxidants significantly lower in subfertile patients than in normal fertile men (14). A simple tool to assay the effect of lipid peroxidation on the spermatozoa is the evaluation of seminal levels of malondialdehyde (MDA), which is a stable lipid peroxidation product (15).

Dietary antioxidants may also have a positive effect on semen quality (16). Recently, Buhling et al. reported that a lower intake of some antioxidant nutrients, such as vitamins A, C, and E, carnitine, folate, zinc, and selenium, is associated with male infertility (17). In a cross-sectional study of 97 healthy male subjects, a higher intake of vitamins C, E, and β-carotene was associated with a higher sperm count and motility (18).

Alpha-lipoic acid (ALA; also called thioctic acid) acts as the coenzyme for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in the mitochondria (19). Exogenous ALA supplementation results in increased unbound ALA levels, which can act as a strong antioxidant and improve oxidative stress status both in vitro and in vivo. Inside cells and tissues, ALA is reduced to dihydrolipoic acid (DHLA), which is even more potent as an antioxidant (20). ALA or its reduced form, DHLA, quenches a number of oxygen-free radical species in both lipid and aqueous phases, chelates transition metals, and prevents membrane lipid peroxidation and protein damage via interactions with glutathione (21). Recent studies results have also suggested that ALA is a main factor in the Krebs cycle and contributes to ATP biosynthesis, which is crucial for the sperm viability (22).

Based on the above facts, the present study was conducted to study the effect of daily oral supplementation of ALA on the quality of semen parameters and seminal markers of oxidative stress, including MDA, and total antioxidant capacity (TAC) levels in infertile men. As such, the results of this study may have wide clinical importance in fertility clinics and laboratories.

MATERIAL AND METHODS

Subjects

This randomized, triple-blind, placebo-controlled clinical trial was conducted on 44 infertile men with idiopathic asthenozoospermia in the infertility clinic of Ahvaz Jundishapur University of Medical Sciences, Iran, in 2014. After laboratory investigations, if the mobility of sperm was $<$50% and rapid mobility in the direct path of sperm was $<$25%, the diagnosis was idiopathic asthenozoospermia (23). Patients were recruited in the study after fulfilling certain criteria, including unwilling childlessness at least 24 months in duration with a female partner, no medical condition that could account for infertility, and a normal fertile female partner according to investigations. All patients were needed to have stopped all medical therapy $\geq$12 weeks before study initiation. Exclusion criteria included the history of epididymo-orchitis, prostatitis, genital trauma, testicular torsion, inguinal or genital surgery, urinary tract infection, or previous hormonal therapy; another genital disease (cryptorchidism, current genital inflammation or varicocele); severe general or central nervous system disease and endocrinopathy; use of cytotoxic drugs, immunosuppressants, anticonvulsants, androgens, or antiandrogens; and a recent history of sexually transmitted infection. Patients were also excluded from analysis if they had psychologic or physiologic abnormalities that would impair sexual performance or the ability to provide semen samples; drug or alcohol abuse; hepatobiliary disease; significant renal insufficiency; occupational and environmental subjections to possible reproductive toxins (24); a body mass index of ≥ 30 kg/m^2; participation in another investigational study; and unlikely availability for follow-up. The study was approved by Medical Ethical Committee of the Ahvaz Jundishapur University and recorded by the identification code of IRCT2013111010181N3 in the clinical trials registry of Iran. Written consent was obtained from each of the participants. The work was financially supported by a grant from the Vice-Chancellor for Research Affairs of Jundishapur University of Medical Sciences, Ahvaz, Iran.

Study Design

At the beginning of the study, patients were randomized to group 1, who received 600 mg ALA once daily, and group 2, who received matching placebo for 12 weeks. Each eligible patient received a randomization number which was determined by a computer-generated schedule. Then a randomization table was generated by the method of random permuted blocks. Persons who were operationally independent from the

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