

Is there a place for nutritional supplements in the treatment of idiopathic male infertility?

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Summary *Objective: Infertility affects 15% of couples in fertile age. Male factor is a cause of infertility in almost half of cases, mainly due to oligoasthenoteratozoospermia (OAT). The purpose of this study is to review the effects of nutritional supplements as medical treatment for idiopathic male infertility.*

Material and methods: A Pub Med and Medline review of the published studies utilizing nutritional supplements for the treatment of male infertility has been performed.

Results: Clinical trials on Vitamin E, Vitamin A, Vitamin C, Arginine, Carnitine, N-Acetyl-Carnitine, Glutathione, Coenzyme Q10, Selenium and Zinc were reviewed. Although there is a wide variability in selected population, dose regimen and final outcomes, nutritional supplements both alone and in combination seems to be able to improve semen parameters (sperm count, sperm motility and morphology) and pregnancy rate in infertile men.

Conclusions: There are rising evidences from published randomized trials and systematic review suggesting that nutritional supplementation may improve semen parameters and the likelihood of pregnancy in men affected by OAT. This improvement, however, is not consistent and there is a wide variation in the treatment regimens used. Well designed and adequately powered RCTs are needed to better clarify the role of nutritional supplements as treatment for male infertility.

KEY WORDS: Phytotherapy; Male fertility; Oligoasthenoteratozoospermia; N-Acetyl-Carnitine; Vitamin E; Semen parameters.

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INTRODUCTION

Almost 15% of all couples trying to conceive are affected by infertility and seek treatment for this condition (1). In a 50% of childless couples, it is possible to recognize a male-infertility-associated factor (2). Male infertility could be consequence of some definable conditions (varicocele, cryptorchidism, hypogonadism, genetic abnormalities), but in 30-40% of infertile male no cause may be determined. Such idiopathic infertility is characterized by a decreased number of spermatozoa, decreased sperm motility and abnormal sperm morphology in men with no history of diseases impairing fertility and with normal findings on physical examination and laboratory testing (3). Idiopathic oligoasthenoteratozoospermia is supposed to be determined by several causes, including endocrine disorders, genetic abnormalities or reactive oxygen species (4).

High ROS level and oxidative stress have been implicated in the pathophysiology of male infertility (5) and correlated with sperm DNA damage, reduced sperm motility, impaired fertilization and embryo development (6, 7). ROS affect sperm function as they damage lipids, amino acids, carbohydrates, protein, and DNA of the spermatozoa (8). In human ejaculate there are some endogenous antioxidants, but many studies have shown that seminal antioxidant capacity is suppressed in infertile men with high ROS levels compared to men with normal levels of ROS (9, 10).

Many medical therapies have been historically used for male fertility, including herbs, vitamins, and nutritional supplements, and many of them rely on antioxidant properties. According to EAU Guidelines on male infertility there is little scientific evidence for an empirical approach and medical therapy should be reserved only in case of hypogonadotropic hypogonadism (4).

The aim of this manuscript is to accurately review the role of nutritional supplements in the treatment of male infertility, evaluating their effect on semen parameters and pregnancy rate.

MATERIALS AND METHODS

The MEDLINE database was searched using PubMed with various keywords, including various combinations of search terms. "Male infertility", "nutraceuticals", "nutritional supplements", "antioxidants" and "antioxidant therapy" were the most relevant search terms, combined via Boolean operators. From the numerous search results, studies were selected on the basis of their quality: studies that were biased, incomplete or otherwise considered untrustworthy were excluded. Data were analyzed in order to provide a complete overview of the literature.

RESULTS

Vitamin E

Vitamin E is a fat-soluble vitamin belonging to the tocopherol family. It acts inhibiting free-radical-induced damage to cell membranes, preventing lipid peroxidation and improving the activity of other antioxidants. (11, 12). It has been demonstrated that Vitamin E is able to decrease seminal ROS in infertile males and there are some epidemiological data that support a direct correlation between improvement of seminal parameters and increased dietary intake of vitamin E. (13-15). Vitamin E has been widely used for the treatment of male infertility and many randomized controlled trials have been performed to assess the effect of this compound in infertile men. Pre-clinical evidences demonstrated that Vitamin E alone or in combination with Vitamin C is able to reduce lipid peroxidation, improve DNA fragmentation and improve binding of the spermatozoa to the zona pellucida (13, 16, 17). However, often these data "in vitro" do not correlate with clinical evidences. *Suleiman et al.* demonstrated increased sperm motility, with 21% of couples treated with 300 mg of Vitamin E achieved pregnancy compared with 0% in the placebo group, but *Kessopoulou et al.* failed to demonstrate an improvement in semen parameters or seminal ROS levels compared to placebo. A recent trial assessed the synergic effect of Vitamin E, Coenzyme Q10 and Vitamin C in men with OAT. Authors demonstrated an improvement of sperm count and sperm motility after 3 and 6 months of treatment with a pregnancy rate of 28%. The big limitation of this trial is the lack of a control group. (18).

Vitamin C

Vitamin C is a water soluble vitamin that act as a potent antioxidant. It is involved in the synthesis of collagen, proteoglycans, and components of the intercellular matrix (19). Few studies have been published using vitamin C alone in the treatment of male infertility. So any possible effect on semen parameters could be the effect of synergistic combinations of vitamin C and other antioxidants like Vitamin E, beta carotene, zinc, selenium, etc (15, 20, 21). In vitro studies demonstrated that Vitamin C plays a

crucial role in preserving sperm from oxidative damage and reducing DNA fragmentation (17, 22, 23). Dawson et coll. demonstrated the effectiveness of high dose supplementation of vitamin C (1000 mg/die), compared to placebo, in improving sperm quality (count and viability, motility and morphology) in heavy smokers (24).

Vitamin A

Vitamin A is a fat-soluble vitamin with a slight antioxidant activity (25). There is a lack of studies investigating the effect of Vitamin A alone in male fertility. Combined treatment with Vitamin A and other nutraceuticals (vitamin E, zinc, selenium, vitamin C) can improve sperm motility up to 30% in infertile man (26) and sperm count after varicocele repair (27).

Arginine

Arginine is a semi-essential amino acid which is involved in various human biochemical process as ammonia detoxification, hormone secretion and immune modulation. It is also a precursor of nitric oxide (NO) (28) and it is necessary for the synthesis of putrescine, spermidine, and spermine, which are thought to be essential to sperm motility (29). Many studies have been carried out to investigate the role of arginine supplementation in male infertility, but to date it is not possible to give evidence-based recommendation on its use. Some historical studies have reported that arginine can improve sperm concentration and motility (30-32), while others have failed to demonstrate any improvement in semen parameters or pregnancy rates (33, 34). There is a lack of recent, well-designed studies on arginine supplementation in male infertility, so it is difficult to conclude definitively that arginine supplementation improves male fertility.

Carnitine

Carnitines are amines derived from the synthesis of lysine and methionine. Carnitines stimulate both fatty acid breakdown and glycolysis in Sertoli cells (35) and have an antioxidant effect protecting cells from ROS. L-carnitine and L-acetylcarnitine are concentrated in the epididymis, spermatozoa, and seminal plasma (36). Carnitines are the most studied nutritional supplements for the treatment of idiopathic male infertility. Lenzi et al. demonstrated an increase in all sperm parameters and in pregnancy rate after combined carnitine treatment (2 g/d L-carnitine and 1 g/d L-acetyl-carnitine for 6 months) in 60 men suffering from OAT, compared to placebo. The most significant improvement was observed in sperm motility in patients who had lower initial absolute values of motile sperm (37). Similarly, Balercia et al showed a significant improvement in both sperm motility and morphology in men treated with L-Carnitine or L-Acetyl-Carnitine supplementation, for 24 weeks compared to placebo (38). The role of carnitines in patient with varicocele-associated OAT has been investigated by *Cavallini et al.* in a placebo controlled randomized study (39). Pregnancy rates increased in patients treated with carnitine alone or in combination with cinnocicam, over the placebo arm. In addition, improvements in sperm concentration, motility and

morphology were observed in patients with no varicocele or small or moderate-grade varicoceles treated with carnitine, alone or in combination with cinnocicam, while no improvement was noted in those with large varicoceles. The combination of carnitine and nonsteroidal anti-inflammatory drugs resulted effective also in improving semen parameters in men with abacterial prostatovesiculopididymitis and elevated seminal leukocyte concentrations (36). Other studies confirmed the positive effect of carnitine therapy on sperm count and motility (40-44). Nevertheless *Sigman et al.* in a randomized placebo controlled trial showed no improvements of semen parameters in men treated with carnitines (45). More recently, *Busetto et al.* demonstrated the beneficial effect of an antioxidant complex containing carnitines (L-carnitine, acetyl-L-carnitine, fructose, citric acid, selenium, coenzyme Q10, zinc, ascorbic acid, cyanocobalamin, folic acid) in improving sperm progressive motility compared to baseline (46).

Coenzyme Q-10

Coenzyme Q-10 (CoQ10) acts as an electron carrier in the mitochondrial respiratory chain (*Hidaka et al.*, 2008) and therefore it is involved in mitochondrial bioenergetics, which is important in sperm maturation (47). Some studies in the past showed a positive effect of CoQ10 in improving sperm concentration and motility, although no differences in pregnancy rate were found (48-50). A more recent small trial demonstrated the effectiveness of CoQ10 in improving semen parameters in men with varicocele (51). Two big randomized placebo-controlled trials confirmed that CoQ10 and its reduced form, ubiquinol, are safe and effective in improving sperm density, sperm motility and sperm morphology in men with unexplained infertility compared to placebo arm. Patients treated with CoQ10 and ubiquinol presented higher catalase and SOD, higher inhibin B levels and lower FSH if compared to placebo (52, 53). *Safarinejad et al.* found also a partner pregnancy rate of 34% in infertile men with idiopathic OAT treated with CoQ10, but this study lack of a control group (54). A recent meta-analysis concluded that there is no evidence in the literature that CoQ10 increases either live birth or pregnancy rates, but there is a global improvement in sperm parameters (55).

Glutathione

Glutathione plays a significant role in the antioxidant defences of the spermatogenic epithelium, the epididymis, and perhaps in ejaculated spermatozoa. It is produced endogenously in the liver and is one of the most abundant antioxidants found in the body (56). Few and dated studies have been published on the role of glutathione in male infertility. These data showed improved sperm motility, sperm concentration and decreased sperm DNA fragmentation in infertile men treated with glutathione or a combination of glutathione and other antioxidants (56-58). Intramuscular glutathione therapy resulted effective in increasing sperm motility in patients suffering from varicocele (57). Glutathione is not well adsorbed in gastrointestinal tract and the parenteral use represents the major limitation for this therapy.

N-Acetylcysteine

NAC is an amino acid precursor to glutathione and acts as ROS scavenger (59) (*Zembron-Lacny et al.*, 2009). In vitro data showed a positive effect of NAC in improving total sperm motility and reducing ROS levels (60). In a randomized placebo-controlled trial, conducted in 120 men with idiopathic infertility, has been demonstrated that NAC therapy (600 mg/daily for 3 months) significantly increase seminal volume, sperm motility and viscosity (61). Another randomized trial confirmed the beneficial role of NAC alone or in combination with selenium in improving all semen parameters if compared to baseline and placebo treatment (62). Combination therapy with selenium resulted in a significant improvement of sperm count, motility and morphology, suggesting a synergistic effect.

Selenium

Selenium is an essential trace element which is involved in antioxidant reactions (63) and it seems to be necessary for normal testicular development, spermatogenesis, and the process of sperm capacitation (64). As previously described, selenium alone or in combination with other antioxidants can ameliorate sperm count, motility, and morphology (62) and many other studies confirmed the synergic activity of Selenium combined with other nutraceuticals like Vitamin E (65-67). Selenium demonstrated positive effects on male infertility, which appear synergistic when used with other supplements. Optimal dosing appears to be between 100 and 210 mg on the basis of the studies above.

Zinc

Zinc is a trace mineral essential for normal functioning of the male reproductive system. It plays a role in testicular steroidogenesis, testicular development, spermatozoa oxygen consumption, nuclear chromatin condensation, the acrosome reaction, acrosin activity, sperm chromatin stabilization, and conversion of testosterone to 5 α -dihydrotestosterone (68). Many biochemical mechanism are zinc-dependent and it acts as cofactor for more than 200 enzyme in the whole body, including those involved in DNA transcription and protein synthesis (68). Zinc deficiency is related to oligospermia, hypogonadism and compromised immune system function (69). In addition, zinc deficiency is involved in the pathogenesis of oligoasthenospermia in diabetic patients (70). A prospective randomized controlled study was carried out to investigate the effects of zinc sulfate, folic acid and combination of both on sperm quality, protamine content and acrosomal integrity after surgical treatment of varicocele. Researchers concluded that co-administration of zinc and folic acid significantly improved sperm parameters and increased varicocelelectomy outcomes (71). More recently, *Raigani et al.* investigated in a randomised, double-blind, placebo-controlled clinical trial, the effects of folic acid and zinc sulphate supplementation on the improvement of sperm function in subfertile oligoasthenoteratozoospermic men. This study failed to demonstrate that zinc sulphate and folic acid supplementation ameliorate sperm quality in infertile men with severely compromised sperm parameters (72).

DISCUSSION

Despite the big amount of studies published on nutraceuticals and male infertility, to date it is not possible to give any recommendation about their use as therapy in infertile male. A significant number of studies lack randomization and placebo-controlled arms and in many cases the pregnancy rate is not the primary endpoint. Additionally, many studies have been unable to control or account for dietary intake of potential fertility-affecting food sources. In fact, usually a balanced diet cannot make it necessary the supplementation. Another limitation of the proposed studies is the inherent tendency of biological fluctuation in consecutive semen samples from the same individual, the geographical variation in semen quality, the lack of standardization in carrying out the tests used in assessing semen variables and the intra-observer and inter-observer semen assessment bias. Nevertheless, based upon the results of the selected studies, it seems that selective supplementation with nutritional supplements could have beneficial consequences on sperm parameters, even if there is a wide range of dosing regimens used across the different trials. Unfortunately, the clinical heterogeneity of the included studies meant a meta-analysis of their results could not be performed.

A systematic review published by Ross *et al.* in 2010, selected 17 randomized trial to evaluate the effects of oral antioxidants on sperm quality and pregnancy rate in infertile men. Their results showed that treatment of infertile men with oral antioxidants reduces seminal oxidative stress and could improve sperm motility, but has a less predictable impact on sperm concentration and morphology. Furthermore, oral antioxidant therapy was associated with a significant improvement in spontaneous and assisted conception pregnancy rates in 6 out of the 10 randomized studies included in the analysis (14).

The role of antioxidants therapy for the treatment of male infertility has been reviewed extensively by the *Cochrane Collaboration* (73). The primary end point of this review was to identify whether supplementation with oral antioxidants would improve outcomes of assisted reproductive techniques when used in male partners of couples undergoing assisted reproduction techniques (ART), while secondary endpoint was to assess how antioxidants may influence pregnancy rate, sperm parameters and sperm DNA fragmentation. 34 trials were included in the pooled analysis with 2876 couples in total. Antioxidants therapy is associated with a statistically significant increase in live birth rate (OR 4.85, 95% CI 1.92 to 12.24; $P = 0.0008$) and in pregnancy rates (OR 4.18, 95% CI 2.65 to 6.59; $P < 0.00001$), if compared with the men in control group. However, authors stated that it is not possible to draw conclusions on the effect of antioxidants on sperm parameters, due to the very poor quality of evidence in the reviewed trials and concluded that antioxidant supplementation might improve live birth and pregnancy rate outcomes for subfertile couples undergoing ART. In addition, data from this review are not sufficient to draw any conclusions from the head to head comparisons between antioxidants. So, to date, one antioxidant did not appear to have any effect on pregnancy rate per couple or sperm parameters over those of another antioxi-

dant (73). Starting from 2013, EAU Guidelines changed their recommendation according to these findings (4).

More recently, Clark *et al.* reviewed 37 RCTs on complementary and alternative medicine, including antioxidant and nutritional supplements, for the treatment of male infertility. They concluded that despite some preliminary evidences of the effectiveness of CAM interventions among infertile patients, there is a need for further investigation before they can be considered for routine clinical use (74). The same conclusions have been reached by Imamovic Kumalic *et al.* They reviewed 32 studies from 2000 to 2013 and found that the majority of these studies confirmed beneficial effect of antioxidants on at least one of the semen parameters, with the most relevant effect on sperm motility, confirming a possible role of nutritional supplements for the treatment of idiopathic oligoasthenoatozoospermia (75).

Comhair *et al.* evaluated the clinical efficacy of different treatment for male infertility by calculating the numbers needed to treat (NNT) in 4143 infertile couples, based on controlled trials. Antioxidant therapy resulted in a NNT of 7.8, while varicocele treatment yielded a NNT of 6.3. The NNT of the combination of varicocele treatment with nutraceuticals supplementation was 2.6 and combination of nutraceuticals and IVF had a NNT of 4.0. So authors concluded that there may be a trend for the use of NFS to improve the success rate of varicocele treatment and of IVF (76). Nutritional supplements are usually well tolerated and must be considered safe, nevertheless there are some possible dose-related adverse events that must be taken into consideration (Table 1).

CONCLUSIONS

Even if it is not possible to give any firm recommendation about nutritional supplementation for the treatment of idiopathic male infertility, rising evidences from randomized trials and systematic review suggests that oral antioxidant supplementation may improve semen parameters and the likelihood of pregnancy. This improvement, however, is not consistent and there is a wide variation in the treatment regimens used. There is therefore a need to plan further large randomized controlled studies, with clear inclusion/exclusion criteria, to evaluate the effect of standardized doses of specific antioxidants on both spontaneous and assisted conception pregnancy rates, in order to select the population that could benefit from oral antioxidants therapy.

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Table 1. Potential adverse events of nutritional supplements.

Vitamin E	GI distress Fatigue Muscle weakness Headache Blurry vision Rash Bruising Bleeding complication (> 800 IU/d) Cardiovascular complications (> 400 IU/d)	<i>Lonn et al. 2005</i> <i>Miller et al. 2005</i> <i>Alpers et al. 2008</i> <i>Mousa et al. 2010</i>
Vitamin C (> 2000 mg/die)	Dyspepsia Headache Increased risk of nephrolithiasis	<i>Alpers et al. 2008</i>
Vitamin A (> 50.000 IU/d)	Fatigue Irritability Mental status change Visual disturbances Vertigo Anorexia GI distress Excessive sweating Myalgia/Arthralgia Hepatotoxicity Hypoplastic Anemia	<i>Oversen et al. 1984</i>
Arginine	GI discomfort Hypotension Electrolyte abnormalities Renal insufficiency Increased bleeding risk Elevated glucose levels Worsening symptoms of sickle cell disease and asthma	<i>Appleton et al. 2002</i>
Carnitine (> 4 g/die)	GI distress Seizures Malodorous body secretion	<i>Rubin et al, 2001; Alpers et al, 2008</i>
Coenzyme Q10	GI distress Loss of appetite Headache Skin rash	<i>Ko EY, Sabanegh ES Jr.</i> <i>The role of over-the-counter supplements for the treatment of male infertility-fact or fiction?</i> <i>J Androl. 2012 May-Jun; 33(3):292-308</i>
Glutathione	Not adsorbed within GI tract	<i>Witschi et al. 1992</i>
N-Acetyl-Cysteine	GI distress Rash Fever Headache Drowsiness Hypotension Hepatic toxicity	<i>Holdiness et al. 1991</i>
Selenium (uncommon)	GI distress Nail changes Fatigue Irritability Hair loss Garlic breath odor Metallic taste Muscle tenderness Tremors Facial flushing Hematologic changes Hepatic and renal insufficiency	<i>Yang et al. 1983;</i> <i>Standing Committee, 2000b</i>
ZINC (> 200 mg/die)	GI distress Loss of appetite Dehydration Gastric ulceration Rash Headache	<i>Alpers et al. 2008</i>
(> 450 mg/die)	Altered iron function Low copper levels Sideroblastic anemia Reduced immune function Reduced HDL levels	<i>Maret and Sandstead, 2006</i>

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