REVIEW ARTICLE

Is there a Definitive Therapeutic Role of Vitamin E in the Prevention and/ or Treatment of Human Male Infertility?

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Abstract

Male factors are involved in the majority of infertile human patients worldwide. Free radicals and Reactive oxygen species (ROS)-mediated oxidative damage have been linked to male infertility by causing increased membrane lipid peroxidation, excessive DNA fragmentation, increased apoptosis, and reduced motility in human spermatozoa. Vitamin E, which is a potent lipophilic substance, has been tested alone or in combination with some of the other antioxidant nutrients for the management of infertility in men. Results of *in vitro* experiments indicated that incubating human semen from infertile patients with vitamin E decreased ROS levels, reduced oxidative stress-induced sperm DNA damage, and improved acrosomal integrity in these samples. Some previous studies have demonstrated that when vitamin E was administered in combination with other antioxidants (vitamin C, coenzyme Q, or selenium) to infertile men, it resulted in significantly reduced sperm DNA damage and improved sperm concentration and motility. However, some of the recent clinical trials failed to illustrate statistically significant changes in semen quality after vitamin E therapy in the infertile patients. Thus, clear evidence on the positive clinical outcomes of vitamin E therapy in human male infertility is still debatable. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to ensure a robust, transparent search process that minimizes bias and maximizes the retrieval of pertinent studies for review.

Keywords: *Reactive oxygen species, oxidative stress, antioxidants, human semen, male infertility, vitamin E.*

INTRODUCTION AND BACKGROUND

Human infertility is quite prevalent all over the world, and male factors are suggested to contribute to approximately 50% of all cases of human infertility globally [1]. Prevalence of male infertility is high in China, India, Indonesia, and some West African countries [2, 3]. Male infertility refers to a sexually mature male's inability to impregnate a fertile female even after 1 year of regular unprotected intercourse [4]. Human male infertility is primarily due to hormonal or anatomical disorders, which may be congenital or acquired (*e.g.*, endocrine disorders, sperm transport disorders, testicular defects, *etc.*). However, many cases of male infertility have an idiopathic etiology [5]. World Health Organization (WHO) laboratory manual (2022) indicates that the risk of infertility increases significantly in a male, if his semen analysis persistently shows a sperm count of less than $15x10^6$ per ml of ejaculate, significantly decreased sperm motility, sperm vitality less than 58%, or a combination of these as compared to their respective values in a normal human semen [6, 7]. The objective of this review is to study and analyze in detail the published research articles that discussed the possible therapeutic role of vitamin E (if any) in the prevention and/or treatment of free radical-mediated human male infertility.

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METHODS

In this review, the authors studied and analyzed in detail the research studies published between 1970 and 2024 related to the effects of vitamin E treatment on the levels of free radicals and reactive oxygen species in human semen, and on various semen parameters in patients suffering from male infertility. The literature searches for the published data were performed using PubMed, Google Scholar, and Web of Science. The selected articles and some of their linked references were also reviewed to obtain relevant information. The search strategy adopted was a published article title/ keywords/abstract-based search using key terms such as 'free radicals', 'human semen', 'male infertility', and 'vitamin E'. The reviewed published articles include single- and double-masked placebo-controlled randomized studies, case-control studies, pilot studies, retrospective cohort studies, comparative studies, case reports, registered clinical trials, and systematic reviews. Inclusion criteria were: human subjects and adult infertile males. Exclusion criteria were: non-English articles, animal studies, and females. A total of about 315 published articles were reviewed and analyzed for this manuscript to explore any evidence of a possible positive role of vitamin E in treating male infertile patients. The PRISMA guidelines were followed to conduct an efficient search, aiming to minimize bias and maximize the retrieval of pertinent studies for review [8]. The study selection process is visualized in **Fig. (1).**

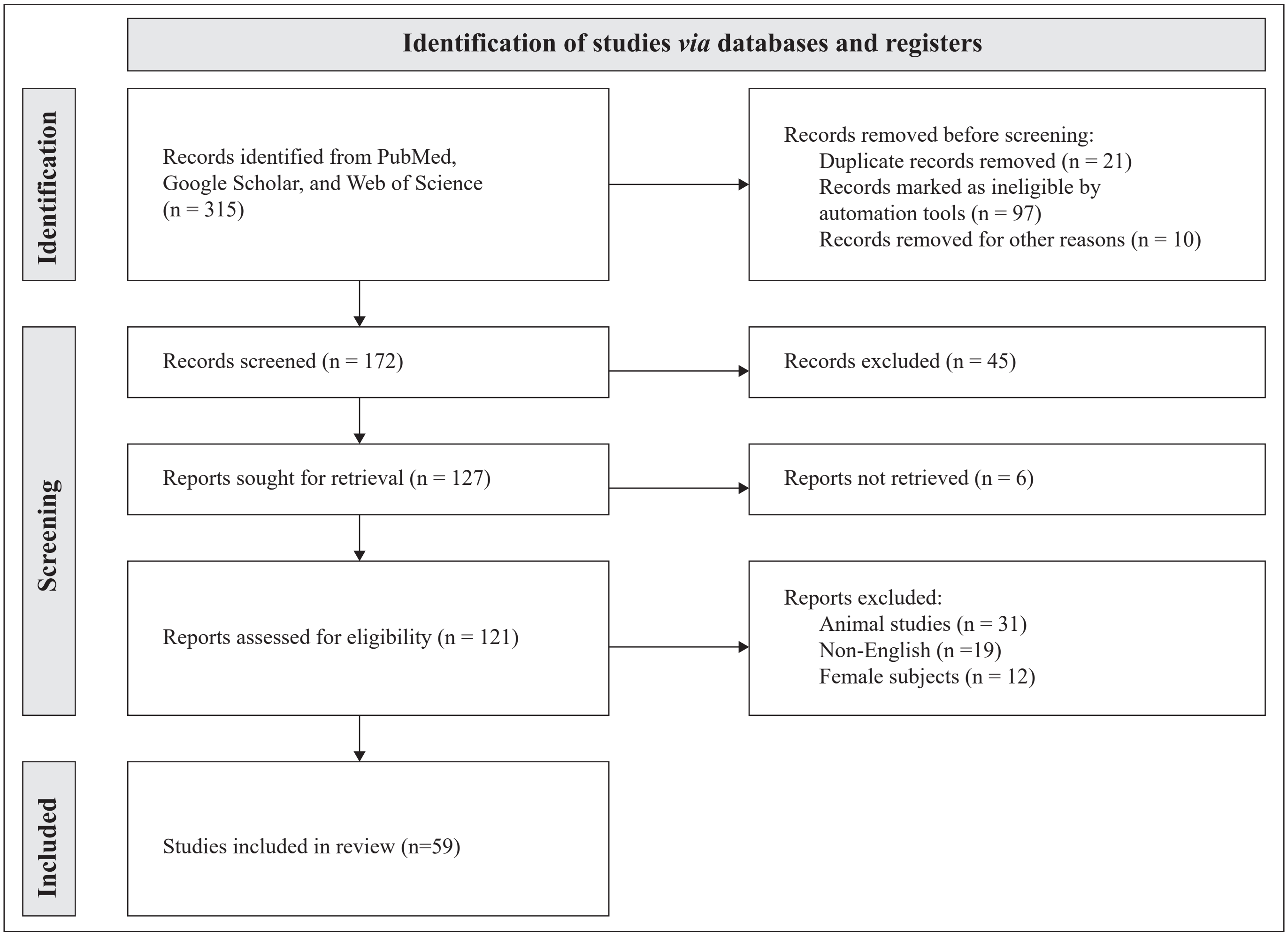

Fig. (1): A flow diagram depicting the study selection process.

RELATIONSHIP BETWEEN FREE RADICALS AND MALE INFERTILITY

There is usually a well-maintained balance between pro-oxidants and antioxidants in apparently healthy people. The primary antioxidants present in the normal human semen include vitamin E, vitamin C, catalase, superoxide dismutase, glutathione peroxidase, and zinc [9]. Environmental factors (*e.g.*, chronic cigarette smoking, heavy alcohol consumption, continuous exposure to heavy metals or radiation, zinc deficiency, certain insecticides, *etc.*) and nutritional antioxidant deficiencies have been suggested to significantly increase ROS levels in human semen [10-12]. The presence of excessive free radicals/ROS in the human semen has been linked to oxidative stress-mediated damage to spermatozoa. Thus, there is some evidence of oxidative stress (OS) role in human male infertility [13, 14].

Numerous studies have shown that ROS and OS contribute to the pathophysiology of human male infertility by causing:

a. injury to sperm membrane through lipid peroxidation,
b. fragmentation of sperm's DNA,
c. a significant decrease in sperm motility,
d. an increase in apoptosis in spermatozoa, *etc.* [15-18].

EFFECTIVENESS OF ANTIOXIDANT THERAPY IN CASES OF MALE INFERTILITY

Antioxidants are suggested to maintain and enhance normal sperm integrity and promote male reproductive function[18]. The potential therapeutic use of some antioxidants, alone or in combination, for the treatment of human male infertility has become popular over the last two decades [19-21]. However, more well-planned placebo-controlled clinical trials are needed to get further clear evidence of a positive effect of antioxidants on post-supplemental changes in semen parameters in infertile male patients [22-24].

ROLE OF VITAMIN E IN NORMAL MALE REPRODUCTION AND FERTILITY

Vitamin E is an exogenously required powerful lipid-soluble chain-breaking antioxidant, which is well known to protect human cells from ROS and free radical-mediated lipid peroxidation and proteolysis. In the Pakistani diet, vitamin E is mainly found in oils of palm, soybean, corn, canola, sunflower, olive, cotton, flax, safflower, linseed, cod liver, wheat germ, and almonds, hazelnut, peanut, walnut, chestnut, salmon fish, shrimps, egg yolk, broccoli, avocado, and spinach, *etc.* [25]. Vitamin E is present in natural and synthetic forms. The natural forms of vitamin E include alpha-, beta-, gamma-, and delta-tocopherols and tocotrienols. Synthetic vitamin E is a racemic mixture of all eight natural forms of vitamin E, each in equal proportions, with different potencies. However, only alpha-tocopherol is found in abundance and is primarily retained well within the human body [26, 27]. Vitamin E was first reported in the literature in 1922 by Evans and Bishop as an unrecognized and newly discovered essential dietary factor for animal reproduction [28].

An extensive literature search has revealed that there are very few reported studies evaluating the possible role of vitamin E in reproduction in apparently healthy, fertile men [29]. Over the last three decades, the use of vitamin E to prevent and/or treat various human diseases has become common [26]; however, its potential for treating ROS-associated infertility in human males has not been thoroughly evaluated.

POTENTIAL USE OF VITAMIN E AS A THERAPEUTIC AGENT FOR INFERTILITY TREATMENT IN MALES

Some clinical trials carried out during the last few years have indicated that the low levels of vitamin E in the seminal fluid can be a contributing factor in human male infertility [30, 31]. There is little research on oral vitamin E supplementation/ treatment alone without antioxidant combinations in human male infertile patients. Results of some earlier studies indicated that *in vitro* incubation of semen samples obtained from patients with a provisional diagnosis of infertility with vitamin E significantly decreased free radical-induced DNA damage and increased acrosomal integrity in their spermatozoa [32, 33].

The *in vivo* use of a combination of antioxidant supplements to improve overall human sperm quality has become increasingly popular worldwide during the last two decades [34]. Results from multiple studies demonstrated that *in vitro* supplementation with vitamin E, in combination with other antioxidants, decreased the production and/or accumulation of ROS in human semen samples [35, 36]. Studies conducted during the last two decades indicated that co-supplementation therapy of vitamin E (40 mg/day)/, vitamin C (80 mg/day), and coenzyme Q (180 mg/day) given for 6 months to infertile men significantly increased their post-supplemental sperm concentration and motility [37, 38]. In an earlier randomized, placebo-controlled clinical trial, a combined therapy of vitamin E and vitamin C, each at a dose of 1 g/day for 2 months, in patients with unexplained infertility resulted in a significantly reduced quantity of DNA-fragmented spermatozoa compared with pretreatment values [39]. However, in another study by Rolf *et al.* (1999), during a combination treatment with vitamin E and vitamin C at 800 mg and 1000 mg, respectively, each day continuously for about 2 months in infertile patients, no significant changes in semen parameters were observed [40].

A clinical case-control study conducted in 2005 showed that co-supplementation of vitamin E with vitamin C resulted in significant improvement in post-supplemental sperm counts and a significant decrease in sperm damage in male infertile patients [41]. An *in vitro* study published in 1996 found that treating asthenospermic patients with vitamin E significantly decreased lipid peroxidation in spermatozoa and improved sperm motility [42].

Some earlier studies suggested a positive association between high dietary and supplemental intake of vitamin E and increased sperm motility in semen samples from apparently healthy, non-smoking men [43]. A study by Matorras *et al.* (2020) showed that 400 mg/day of vitamin E given orally for three months to infertile male patients significantly increased their sperm motility compared with the respective pretreatment values [44]. In another study, oral vitamin E supplementation, along with selenium, given for 3 months resulted in significantly decreased post-supplement lipid peroxidation and improved sperm count and motility in these patients [45]. A clinical trial carried out by Elsheikh *et al.* (2015) suggested that vitamin E therapy given along with clomiphene citrate to infertile patients continuously for six months caused a significant ($p= 0.001$) increase in their sperm concentration and motility [46]. However, few recent clinical research studies using oral vitamin E therapy to treat human male fertility did not demonstrate any significant change in post-therapy sperm parameters in these patients [47, 48]. The minimal or no impact of vitamin E treatment in these studies may be due to the relatively short treatment duration, the lower vitamin E dosage used, or the lower post-supplemental vitamin E concentration achieved in the patients' semen. Therefore, a clear consensus on the clinical efficacy of oral vitamin E in human male infertility remains debatable (**Fig. 2**). The findings are summarized in Table **1**.

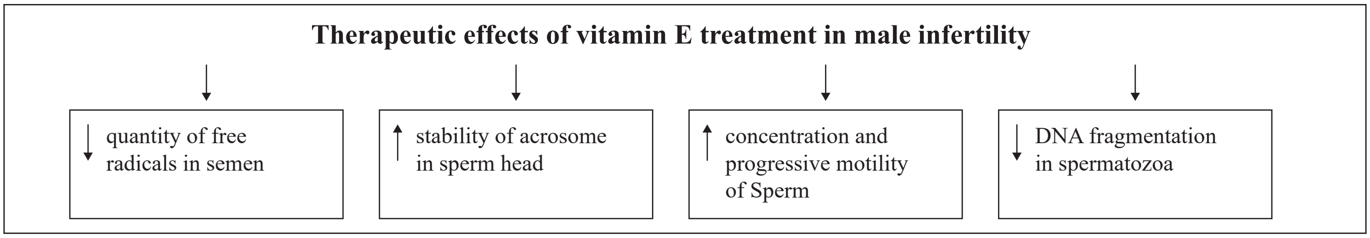

Fig. (2): Suggested vitamin E mechanisms of action on human spermatozoa.

Table 1: Summarized findings of research studies in which Vitamin E therapy was given for the treatment of male infertility.

Study	Active Agents	Sample Size	Outcomes
Greco *et al.* [39]	Vitamin E and Vitamin C	64	Significant decrease in the quantity of fragmented DNA inside their spermatozoa as compared with the pretreatment values
Kodama *et al.* [41]	Vitamin E, Vitamin C, and Glutathione	36	Significant increase in sperm concentrations, with a substantial reduction in sperm DNA injury in these patients
Sulieman *et al.* [42]	Vitamin E	285	Significantly decreased lipid peroxidation and improved sperm motility in these patients.
Eskenazi *et al.* [43]	Vitamin E	97	Progressive motility of sperm in semen samples from apparently healthy non-smoking men
Matorras *et al.* [44]	Vitamin E	101	Significant increase in progressive motility compared with the respective pretreatment values
Keskes-Ammar *et al.* [45]	Vitamin E and Selenium	54	Significant decrease in post-supplement lipid peroxidation and increased sperm motility and sperm concentration in these patients
ElSheikh *et al.* [46]	Vitamin E and Clomiphene	90	Increase in their total sperm motility and sperm concentration

COMPARISON OF VITAMIN E TO OTHER NUTRACEUTICALS USED IN THE TREATMENT OF OLIGOASTHENOSPERMIA

Nutraceuticals are food constituents that provide health benefits beyond basic nutrition, often with a possible role in the prevention and/ or treatment of various diseases. Oligoasthenospermia is defined as a condition in which a male suffers from both a low sperm count and decreased sperm motility. Some nutraceuticals, including zinc, selenium, N-acetyl-cysteine, and carnitine, have been evaluated as potential treatments for male oligoasthenospermia. In a previous study, there was an increased volume of semen, progressive sperm motility, and total normal sperm count in 60 oligoasthenospermic infertile men after three months of zinc supplementation (440 mg/day) as compared to age-matched fertile subjects [49]. In an earlier study, 600 mg/day of selenium alone or 220 µg of selenium plus 600 N-acetyl-cystine/day supplements for 26 weeks significantly improved sperm concentration, sperm motility, and percent normal morphology in infertile men with idiopathic oligoasthenospermia [50]. In a study conducted by Balercia *et al.*, sperm motility increased in patients aged 20 to 40 years with asthenozoospermia who were administered L-acetyl-carnitine for 6 months, alone or in combination with L-carnitine [51].

There are very few reported studies that have assessed the role of vitamin E alone or in combination with other nutraceuticals in the management of oligoasthenospermia. In a case-control study, treatment with vitamin E (300 mg/day) for three months was shown to significantly improve the concentration and percentage of progressively motile sperm in infertile patients with oligoasthenospermia [52]. In another controlled randomized trial, there was no statistically significant increase seen in sperm motility after three months of vitamin E (300 mg/day) plus vitamin C (300 mg/day) supplementation given to control group patients with oligoasthenozoospermia in contrast to significant increase in sperm motility in the test group oligoasthenozoospermic test group patients who received L-carnitine (4 gm/day) and acetyl-L-carnitine (2 gm/day) for three months [53]. Thus, well-controlled clinical trials with optimal dosages, combinations, and long-term effects of vitamin E in combination with these nutraceuticals are needed to solidify the evidence further.

VITAMIN E POLYMORPHISMS AND MALE INFERTILITY

Variations in genes that affect vitamin E metabolism and transport (*e.g.*, genes involved in hepatic uptake and transport *via* the α-tocopherol transport protein) are termed vitamin E polymorphisms. Most of these genetic variants related to vitamin E are due to single-nucleotide polymorphisms (SNPs) [54]. Vitamin E gene polymorphism is common in the South Asian population [55]. In a recent study, some SNPs in the vitamin E carrier protein gene were suggested to be associated with infertility in men with oligoasthenospermia [56].

PHOSPHODIESTERASE-5 (PDE5) INHIBITORS' ROLE IN INFERTILITY

The effects of nitric oxide (NO) signaling are terminated by phosphodiesterase enzymes, which break down cGMP to GMP. Inhibiting phosphodiesterase enzymes allows cGMP to persist longer and accumulate to higher levels. Type 5 phosphodiesterase is present in vascular smooth muscle and lung, as well as other tissues, and is especially enriched in the corpus cavernosa of the penis. Inhibitors such as sildenafil allow NO-induced cGMP elevations to reach higher cytosolic levels and to be prolonged in these tissues [57]. Erectile dysfunction (ED) leads to impaired fertility through natural conception when a severe problem is present, such as absent erection or insufficient erection for penetration, and ED is an independent risk factor for a reduced frequency of sexual intercourse, with an apparent adverse effect on fertility [58]. PDE5 inhibitors are effective in treating men with ED [59]. Some of the earlier studies have used the PDE5 in patients with male infertility to improve sperm quality [60, 61]. However, more stringent clinical trials and case-control studies are needed to establish a clearer, more well-defined role for PDE5 inhibitors in the treatment of male human fertility [62].

FUTURE IMPLICATIONS

More large-scale randomized clinical trials with a larger number of patients and controls, and sufficient evidence are necessary to prove the 100% % efficacy of vitamin E indication in human male fertility disorders. Moreover, well-designed, long-term research studies are needed to determine the optimal dose and duration of vitamin E therapy for male infertility.

CONCLUSION

ROS and OS significantly impact human male fertility. For this reason, vitamin E has potential therapeutic value in the treatment of infertility. However, due to a lack of clear and consistent clinical trial results, the therapeutic application of vitamin E in human male infertility is limited. Therefore, additional prospective studies and randomized placebo-controlled clinical trials with more appropriate dosage and duration are needed to clearly establish and define vitamin E-based therapies for human male fertility.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

TJ: Conceptualization, Literature search, Writing of initial manuscript.

SP: Critical revision of manuscript, editing.

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