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RESEARCH ARTICLE

The Levels of Vitamin E in Seminal Fluids and their association with Male Infertility: Short Review

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ABSTRACT:
Background: Vitamin E is one of four fat-soluble vitamin with antioxidant property consists oftocopherols and tocotrienolswith α-tocopherol the most bioactive member of this family. Aim: This study aims to assess always almosteach potential deals withthe effect of consuming vitamin E on seminal fluids properties in asthenospermic patients. **Methods:** This review reports the modern state of knowledge and ambiguities about the oral treatment of infertile male with vitamin E. The current study illustrates the best obtainable information from randomized clinical trials, investigational studies, and systematic reviews. **Results:** Data extracted from the previous publicationsclarify that treatment of idiopathic infertile males with vitamin E supplementation can lead to a considerable enhancement in semen quality; however large-scale studies will be of great benefit to achieve such conclusions. **Conclusions:**The vitamin E therapy is an effective choice for the management of idiopathic infertile maleswith asthenozoospermia.

KEYWORDS: Vitamin E, infertility,asthenozoospermia, oxidative stress; antioxidant.

INTRODUCTION:
World Health Organization (WHO) describes infertility as the "disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse[1]. Infertility affects approximately 15% couples in the reproductive-aged worldwide, half of this percent attributed to infertility male factors, of which there are about 50% of cases yet of idiopathic origin[2,3].

Oxidative stress and infertility:
Oxidative stress (OS) is a critical pathophysiological factor in the causation of a male infertility of idiopathic origin[4]. It is a consequence ofincreasegeneration of reactive oxygen and/ornitrogen specieswhich collectively called free radicals, or produced by decreased antioxidant production.

The balance between reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) with antioxidants is strictly maintained in a fertile male,and their imbalance is implicated in various pathological conditions concern sperm morphology and function, as well as their adverse effect on sperm genomic integrity[5]. OS is highly susceptible to induce damage in spermatozoadue to the presence of high content of polyunsaturated fatty acids (PUFA) in the seminal plasma membrane, low levels of seminal defense enzymes[6] and high levels of free radicals[7]. OS disables normal sperm function and induces mitochondrial genome mutations by the action of peroxidation process to PUFA especially docosahexaenoic acid; one of the components of sperm plasma membrane[8,9]. The lipid peroxides formation affects sperm membrane fluidity and flagellar motion, leading to sperm dysfunction. Mitochondrial mutations impair metabolism within spermatozoa resulting in an energy crisis, which in turn lead to the spermatozoa functional impairment[10].

Progress of infertility:

Accumulating medical reports confirmed a great decrease in sperm count in the last fifty years, where Carlsen*et al.*,[11] found after the analysis of data of the mean seminal volume and sperm density in 14947 males cases subjected to sixty-one studies extended from 1938 to 1991. Carlsen*et al.*,[11] study found a significant depletion in seminal quantity from 3.4 ml to 2.75 ml and sperm density from 113 million/ml to 66 million/ml in the comparison between 1940 and 1990. This shows that there is 20% decrease in seminal volume and 58% decrease in sperm density in the last five decades. Other studies confirmed this results carried out in the last two decades also show a decrease in semen quality and they attributed their finding to the multifactor such as diet, lifestyle and environmental factors which may in combination interfere with spermatogenesis[12,13].

Chemistry of vitamin E

Fat soluble vitamins like vitamin E and A which are naturally occurring in diet have a preservative properties make them ideal excipients materials used many industries including in drug industries[14]. The name vitamin E is colligative term involves eight relative compounds, each of them consists of a phytol side chain attach to chromanol ring; four tocotrienols compounds categorized as (α, β, γ, and δ) and four tocopherols compounds categorized as (α, β, γ, and δ)[15]. The prefixes α, β, γ, and δ attach to tocopherols give to distinguish among the position of methyl groups substituted on chromanol ring[16]. α-Tocopherol is the widely distributed among natural sources and is the most active member of tocopherol family and has the ability to quench a couple of peroxyl radicals that responsible for triggering lipid peroxidation process[17]. For this reason vitamin E protect lipid found in membrane against free radical attack[18], and thus stabilize membrane[19]. The digestion of vitamin E is analogous to that of carotenoids and vitamin A, and the deficiency in its level may occur in fat malabsorption case with neurological symptoms. These symptoms result from the decrease in nerve conduction, which may be reversed by E vitamin supplementation[17].

The absorption of vitamin E occurs in the gut via lymph system and intestine via chylomicron to reach liver as chylomicron remnants. It is then distributed by very low density lipoprotein (VLDL) to required tissue, and can transfer to low density lipoprotein (LDL) or scavenges by high density lipoprotein (HDL)[20].

Among deferent types of tocopherol, α-tocopherol represents the predominant and more active form of vitamin E that present in the leaves of plants with an antioxidant property. Several studies were reported that vitamin E plays a crucial role in the protection of plant photosynthetic apparatus against oxidative stress[21,22]. Vitamin E also has a key role in the amino acids and lipids transportation in the intestine[22]. Other function of vitamin E includes its role in steroidogenesis and iron metabolism[23], as well as its role in the stimulation of hormonal response and the response of cellular immune system against infection threatening[24]. Vitamin E deficiency symptoms and disorders are vary depending on the species affected[25,26].

Vitamin E as treatment:

Vitamin E represents the first line of the chain-breaking antioxidant present in the cell membrane. It is well-documented as a lipid-soluble antioxidant and it has an inhibitory effect on ROS and/or RNS that may produce damage when attack cell membrane including seminal membrane. The product of lipid peroxidation process as result of oxidative stress in the seminal specimens is malondialdehyde (MDA) found to be significantly decreased after vitamin E supplementation, as well as notable enhancement in sperm motility[27]. A clinical trial carried out by Kessopoulou*et al.*[28] shows that supplementation of 600 mg per day of vitamin E enhances sperm function, in the term of the sperm ability to penetrate the female egg in vitro. Another clinical trial was reported that after taken vitamin E in combination with the trace element selenium, the volunteers status with altered sperm motility and low sperm count were improved after four months of an experiment in the term of total percent of normal spermatozoa and sperm motility[29].

The role of vitamin E in infertility:

Vitamin E has an advantage of competing for peroxyl radicals much faster than PUFA, therefore, a small amount of vitamin E is sufficient to protect a large amount of PUFA against oxidative stress. It has been found that one molecule of vitamin E corresponds to thousands of lipid molecules in biological membranes [30]. During this process, vitamin E transformed into vitamin E radical which unless is regenerated by other chain breaker antioxidant like vitamin C, it must be replenished from diet or from body storage, or it will be consumed eventually[31], as shown in Figure 1.

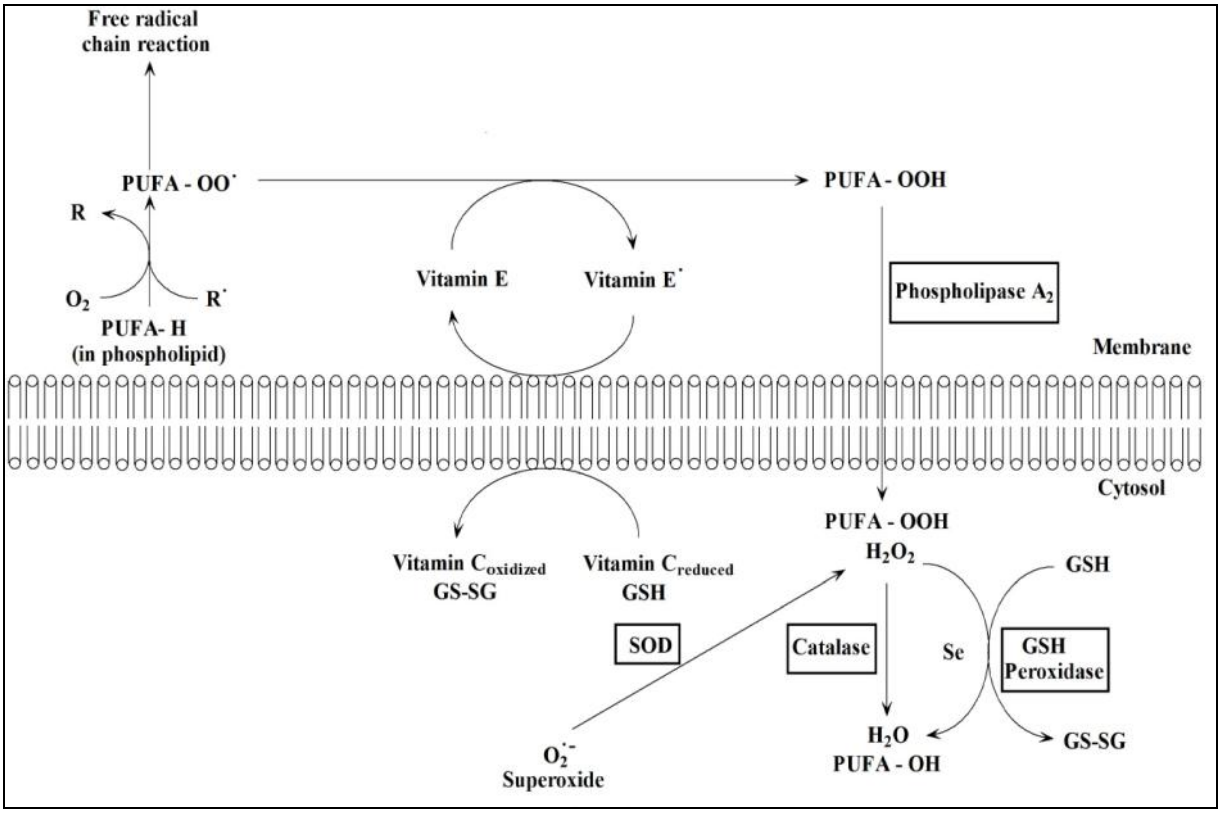

Figure 1 Mechanism of antioxidant defense system. Modified from (Alta'ee et al., 2015) (R• = free radical; PUFA-OO• =peroxyl radical of PUFA; PUFA-OOH=hydroperoxy PUFA; PUFA-OH=hydroxy PUFA;vitamin E• = vitamin E radical; GSH= reduced glutathione; GS-SG= oxidized glutathione; Se= selenium).

Vitamin E as treatment:

Many organs and tissues like adipose tissue may reveal a deficiency of vitamin E accompanied with a number of disorders such as ischemic heart disease, male infertility, breast cancer and increase the predisposing to infections [16,32], as well as the promotion of environmental and dietary stress in both animals and humans[22,24,33].Animal clinical trial show low toxicity of vitamin E and no carcinogenic, mutagenic, or teratogenic effect in comparison to human clinical trials which were found many symptoms associated with vitamin E toxicity such as nausea, stupor, and loss of appetite, as well as enhancement of calcium absorption, which in turn may lead to increase deposition and precipitation of Ca in several organs like kidney and arteries[21].

Studies carried out on human and animals show a positive effect for vitamin E on fertility as a dietary essential factor in both genders[33,34]. In spite of the fact that vitamin E has multifunction in the body, it possesses a characteristic role in the fertility of human and many types of animals species. Poultry farmers add vitamin E to the feed to enhance male and female fertility, which in turn increases the net income of poultry production[35].

Numerous studies reported the antioxidant properties of vitamin E for improvement of sperm motility and count [36,37,38]. Other studied demonstrated positive effect for the usage of high doses of vitamin E on improving fertility [28,29], whereas opposite result is obtained by another study, in which no such advantage for the usage of high doses of combination of vitamin C and E[39].

Male with idiopathic infertility treated with vitamin E found to have a rate of 15% of seminal live birth compared with 0% of the control group in meta-analysis clinical trials[28,40,41]. However, the usage of different doses of vitamin E in these studies range from 300 mg to 600 mg making the determination of optimum dose is a matter under discussion. Moreover, interesting results were presented by Rolf et al.,[41] study which investigates the defense mechanism of vitamin E as an antioxidant in infertile men after treating with a high dose of E vitamin (800 mg) for a period of eight weeks. This randomized, placebo-controlled trial advice to measure the seminal ROS levels before and after treating with vitamin E, due to the uselessness of this type of therapy in infertile men

don't suffer from oxidative stress. This is very important because the high level of vitamin E may act as pro-oxidant in the semen of infertile men without oxidative stress[42].

Several reports focused upon the combinations of the mixture of antioxidants in the treatment of idiopathic infertile males. The pharmaceutical companies also started to produce combinations of such antioxidants as the mixture of vitamin C and vitamin E in the therapy of such patients. However, the data of such reports found to be fluctuated, where[43] study which uses a daily pill of one gram of vitamin E and one gram vitamin C for two months for treatment of infertile males was found a significant reduction in DNA fragmentation in semen of infertile males when compared with placebo group, however, this study found no effect on other seminal fluid parameters. Another study[41] was found a comparable result, in which one gram of vitamin C and 800 gram of vitamin E were used daily for eight weeks. This study didn't find an improvement in seminal fluid parameters in males and the rate of pregnancy in females. Another study[44] use the same combination in addition to vitamin A and found the same results in the idiopathic infertile men. In a placebo-control clinical trial carried out on sixty idiopathic infertile men, the combination of 400 mg vitamin E and 25 mg clomiphene citrate was used daily for six months, and the results shown significant improvement in sperm count and motility in treated group in the comparison group [45]. Patankar et al.[46] investigates the role of clomiphene citrate on primary infertile males and shows significant improvement in seminal fluid parameters. Furthermore, the supplemented of E vitamin was studied alone in another clinical trial and this study was also shows a significant improvement in seminal fluid analysis and the pregnancy rate[27]. The usage of combination therapy of vitamin E with other antioxidants were studied in six clinical trials[41,44,47-50] and show significant improvement of sperm motility in the first three studies and significant improvement of sperm count in one of them[50,51].

From all of above, the subject of vitamin E supplementation for the treatment of infertility of both genders is a controversial issue that needs further investigation in studies that extend for longer time and require a larger sample size.

CONCLUSIONS:

The present literature review shows that E vitamin is required for the function and development of the reproductive tissues in both sexes, possibly due to its key role in the modulation of antioxidant balance.The excessive generation of ROS makes biological systems subject to continuous exposer to oxidative stress. The excessive production ROS may contributes in several pathogenic conditions including cancer, diabetes mellitus, aging, and several diseased affecting reproduction systems in both sexes. The presence of active antioxidant defense mechanism may contributes to prevent or decrease the oxidative induced injury.

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