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REVIEW PAPER

Vitamins and male infertility: role of various vitamins versus oxidative stress

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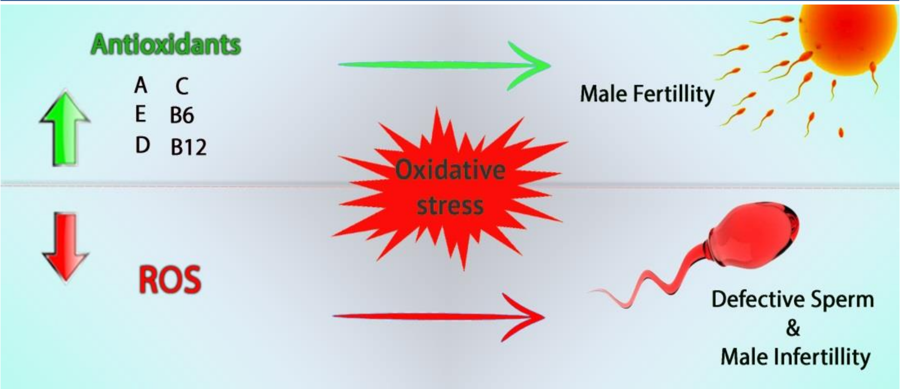
Highlights

- A high amount of reactive oxygen species can be harmful to function of sperm.
- Compared to other cells, the sperm cell is more susceptible to oxidative attacks.
- Various vitamins can affect male infertility induced by oxidative stress.

Graphical Abstract



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Abstract

Reactive oxygen species (ROS) are necessary for regular functions of spermatozoa including acrosome reaction, capacitation, fertilization, etc. But its high amount can be harmful to the function of the sperm cell. Compared to other cells, the sperm cell is more susceptible to oxidative attacks because of the extreme concentration of unsaturated fatty acids in the plasmalemma and the minor level of the cytoplasm. A chief factor of sperm genome damage, which is involved in most kinds of infertility in men, is increased oxidative stress. Some micronutrients, such as vitamins C, E, D, B6, B9, B12, selenium, iron, zinc, and essential fatty acids could have a direct effect on fertility by reducing the ROS level and its detrimental influences on sperm parameters. In humans, the most active form of vitamin E is alpha-tocopherol and the strongest antioxidant, and its most important task is to fight lipid oxidation by free radicals. High concentration of ascorbic acid in seminal plasma probably points to its role in protection of spermatozoa from ROS attacks and preventing oxidative DNA damage. Quality of semen and specific sperm motility seem to be related to vitamin D. Vitamin A plays an important role in spermatogenesis due to its oxidative activity. Vitamins B are cofactors for the main metabolic enzymes of sperm and their deficiency can affect male fertility. The purpose of this study is to describe the role of vitamins in overcoming oxidative stress in male infertility.

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Introduction

One out of every six couples of reproductive age has an infertility problem (1). The injury induced by reactive oxygen species (ROS) could be a central factor in male infertility. Reduced sperm motility (asthenospermia) is a factor contributed to male infertility. The factors that cause the reduction of sperm motility in many cases are still not fully known. One of the factors that can reduce sperm motility is oxidative stress caused by ROS (2). Between 30 and 80% of male infertility patients overproduce reactive oxygen species in their ejaculate. There is a strong association between oxidative stress (OS) and infertility in men, which has led researchers to suggest the term "male oxidative stress infertility (MOSI)" to define OS-related infertility in men (3). ROS are necessary for regular functions of sperm including acrosome reaction, capacitation, fertilization, etc. Compared to other cells, the sperm cell is more susceptible to oxidative attacks because of the extreme concentration of unsaturated fatty acids in the plasmalemma and the minor level of the cytoplasm. A main factor in damage ofsperm DNA, which has harmful effects in most kind of infertility in men, is the increase in the level of oxidative stress (4).

Several researches have shown that there is a relationship between oxidative stress conditions in semen and spermatozoa dysfunction. Natural semen contains enzymatic antioxidants including catalase and superoxide dismutase and non-enzymatic antioxidants including ascorbate, α-tocopherol, and pyruvate, which support sperm against OS. Therefore, one of the reasons for creating OS conditions in semen is the imbalance between ROS generation and its inactivation by antioxidants (5, 6). Sperm, similar to all of cells that live in aerobic situation, on the one hand, need oxygen for their survival, and on the other hand, oxygen metabolites such as ROS might be damaging for the cell. Therefore, the ROS produced for the survival of the cell must be continuously deactivated so that its concentration always remains at a very low level that is essential for the usual cell functioning. Therefore, the imbalance between the generation and elimination of ROS in sperm results in the creation of OS conditions. In fact, due to the low amount of mature spermatozoa cytoplasm and the low level of ROS-destroying enzymes in sperm, this cell is more prone to oxidative stress than any other cell. In addition, because of the high levels of unsaturated fatty acids in the sperm plasmalemma, its vulnerability to oxidative stress is high (7).

Based on the available evidence, antioxidants can reduce DNA fragmentation due to oxidative stress. Antioxidants including glutathione, vitamins C and E, N-acetylcysteine, catalase, SOD, taurine, albumin, and hypotaurine, and mainly N-acetylcysteine and coenzyme Q10 not only prevent the decrease of sperm motility but also increase sperm motility (8, 9). So, protective agents *vs*. reactive oxygen species, including antioxidants, can be considered effective therapeutic agents for male infertility (10). So that the potential role of antioxidants against male infertility has attracted the attention of many researchers. Nowadays, it is believed that enriching the environment around sperm with antioxidants will probably lead to the protection of sperm *vs*. damage induced by OS. Based on this, many researchers investigated the role of antioxidants in vitro conditions. The aim of this study is to describe the role of vitamins in overcoming oxidative stress in male infertility.

Therapeutic strategies to deal with oxidative stress

Oxidative stress causes from excessive generation of ROS or defects in the antioxidant defense mechanism (Figure 1). Studies have shown that some micronutrients, such as vitamins C, E, D, B6, B9, B12, selenium, iron, zinc, and essential fatty acids can have a direct effect on fertility by reducing the ROS level and its damaging impacts on sperm parameters (8). Although several studies have been done to prove this hypothesis, there is little information on how much of each type of food antioxidant can be effective in the production and function of sperms. Reducing the intake of antioxidants such as carotenoids, antioxidant vitamins, and minerals with antioxidant properties can be effective against damaging sperm (9). Researchers tried to use antioxidants to prevent decreased mobility and increased sperm DNA damage by oxidative stress conditions in infertile people. Antioxidants are the main protective mechanisms *vs*. oxidative stress. Metal-binding proteins as well as metal chelators that prevent the production of new ROS are categorized as preventive (11). Antioxidants including β-carotene and vitamins C and E and other supplements of antioxidant nutrition, and enzymes act by eliminating reactive oxygen species that has previously been produced by cell function (12).

Antioxidants in semen could be divided into two overall classes, scavenger, and preventive antioxidants. Preventive antioxidants including metal chelators and transition metal-binding proteins including lactoferrin inhibit the new ROS formation (13) and scavenger antioxidants including vitamin C and E, β-carotene, enzymatic antioxidants, etc. destroy ROS produced in cell. In fact, preventing the production of ROS is the main line of protection of antioxidants *vs*. oxidative stress (14). Antioxidants in nutrition, metal-binding proteins, and endogenous antioxidants are considered as three defense mechanisms against OS in men (15). Antioxidants in spermatozoa and seminal plasma are the endogenous antioxidants. Semen comprises three key enzyme antioxidants including catalase, superoxide dismutase (SOD), and glutathione peroxidase/glutathione reductase. These antioxidants neutralize a large number of ROS and prevent damage to the cell structure and reduce the reduction of hydrogen peroxide to H_2O and alcohol (16).

Antioxidants in nutrition are found in the form of vitamin E, vitamin C, β-carotene, etc. Metal-binding proteins include myoglobin, metallothionein, albumin, transferrin, ceruloplasmin, and ferritin, which act via deactivating the transport of metal ions. Metal chelators including ceruloplasmin, lactoferrin, transferrin, and which are in the seminal plasma, also regulate the peroxidation of lipid in the plasma membrane of sperm and participate in maintaining its structural integrity (17). Studies have shown that antioxidants reduce the fragmentation of DNA induced by OS. The daily use of 1g of vitamin E and C orally for two months reduced the number of spermatozoa with DNA damage from 22.1 to 9.1%. Antioxidants (mainly glutathione, vitamin C and E, N-acetylcysteine, catalase, SOD, taurine, albumin, and hypotaurine), not only inhibit the decrease of sperm mobility but also increase sperm motility (8). So, protective agents *vs*. reactive oxygen species, including antioxidants, can be considered effective therapeutic agents for male infertility (10). So that the potential advantages of antioxidants in helping reproduction have attracted the attention of many researchers. Nowadays, it is believed that enriching the environment around sperm with antioxidants will probably lead to the defense of sperm *vs*. damage induced by oxidative stress (18).

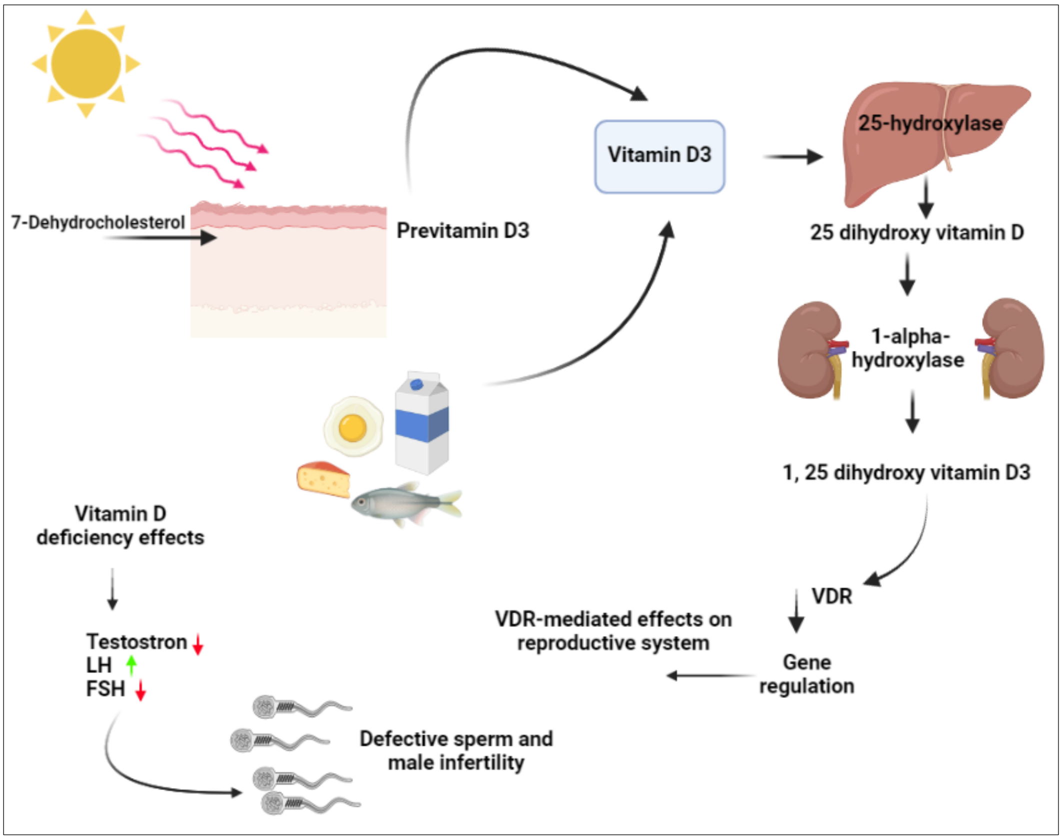

Figure 1. Role of oxidative stress in male infertility.

Oxidative stress is caused by excessive generation of ROS or defects in the antioxidant defense mechanism. In other words, the imbalance between antioxidants including catalase, glutathione, superoxide dismutase, peroxidase, vitamins A, B, C, D, E, and ROS leads to oxidative stress, which causes DNA damage caused by oxidative stress is a main reason in the incomplete function of sperm and may cause infertility in men.

Due to the fact that the cytoplasm of spermatozoa has small amounts of ROS neutralizing enzymes, it turns to seminal liquid antioxidant systems to protect itself (14). Selected sperms for assisted reproductive techniques (ART) and intracytoplasmic sperm injection (ICSI) are usually taken from an environment with OS, peroxidative injury on sperm plasmalemma and genome prevent successful fertilization of sperm and egg. So that spermatozoa with damaged DNA that are used in the ICSI method could endanger the fertilization procedure and the development of the embryo, which has not yet been determined (19). So, defensive agents *vs*. oxidative stress, including antioxidants, can be considered effective therapeutic agents for male infertility (10).

The influence of vitamin deficiency on male infertility

Increased OS and generation of ROS cause injury to proteins, membrane lipids, and DNA integrity of sperms (20). Therefore, sufficient consumption of antioxidants in the diet is essential to decrease ROS and maintain the quantity and quality of spermatozoa. Vitamin C, a water-soluble vitamin, has strong antioxidant impacts (21). In the study of Eskenazi et al., it was shown that this vitamin has a helpful impact on the sperm quality of elderly people (22). Vitamin C could increase the level of glutathione (GSH) and the function of antioxidant enzymes including superoxide dismutase and catalase in testicle (which play a key role in sperm viability) by decreasing the damage caused by OS. Also, vitamin C has a role in increasing testosterone generation by improving the function of testicular enzymes (23). Also, Almbro et al., stated that the consumption of vitamin E meaningfully increases sperm motility (24). Also, this vitamin and selenium improve the quality of sperm and have defensive impacts on spermatozoa in male infertility condition (25).

Vitamin D is necessary for the normal sperm nucleus formation and helps maintain the quality of semen and the number of sperms. Deficiency of vitamin D reduces the motility of sperm and the amount of normal morphologic sperm and also causes osteoporosis in infertile men (26). Vitamin E (tocopherol) is a potent non-enzymatic antioxidant that could prevent the peroxidation of lipid reaction in plasmalemma by restricting the action of ROS, therefore protecting plasmalemma from injury stimulated by them (27). In the male reproductive system, the antioxidant share of this vitamin in preventing the damaging impacts of ROS in the testis (28) and sperm (29) has been reported. In addition, vitamin E with the mentioned ability is able to power the antioxidant protection system of testicular as well as sperm (30). Various studies have shown that the ROS levels of seminal fluid are reduced with the use of oral supplemental antioxidants, by strengthening the free radical scavenging capacity. Oral antioxidant Astaxanthin, carnitine, or a antioxidants combination including vitamin E, B-carotene, N-acetylcysteine, and essential fatty acids directly reduce ROS levels in semen (31).

The role of vitamin E on male infertility

Tocopherols protect cell membrane components from oxidation, act as an anti-inflammatory in people with immunodeficiency, and are also neuroprotective. These vitamins are fat-soluble and their deficiency becomes apparent months after the onset of deficiency. Since selenium is essential for the male body to produce sperm, some research has shown that a combination of selenium and vitamin E could improve semen quality and sperm motility (25). Selenium, a key compound for numerous metabolic conditions. In the field of oncology, it is considered the main share of treatment. Physiologically, it is an effective factor in the thyroxine conversion to active triiodothyronine, thereby ultimately affecting thyroid function. Also, due to the relationship between selenium and thyroid hormones, as a result of selenium depletion, spermatogenesis is disturbed (32, 33).

Vitamin E (VE), a main lipophilic chain-breaking antioxidant, could prevent lipid peroxidation in tissue enriched by polyunsaturated fatty acids. This feature that can be useful in physiology of male reproductive system due to the cell membrane of sperm are highly susceptible to lipid peroxidation (34). Antioxidant therapy of VE is strongly dependent on the dose of the vitamin. Therefore, more clinical and laboratory researches with improved specific circumstances should be done to determine the effectiveness of vitamin E in vitro conditions and in vivo for male infertility in humans (35). It was shown that vitamin E intake significantly increases sperm motility (24). In a clinical trial Moslemi et al., displayed that the simultaneous use of selenium and vitamin E improves the quality of sperm and has defensive impacts on spermatozoa in male infertility condition (25).

In humans, alpha-tocopherol is the strongest biological antioxidant and the most active form of vitamin E, and its most important task is to fight lipid oxidation by free radicals. In the structure of this antioxidant, the -OH group of the aromatic ring could play antioxidant features, and its hydrogen is delivered to the free radical to convert the radical into a stable form (36). Coenzyme Q10 is located in all plasmalemma and in the adjacency of unsaturated chains. Coenzyme Q10 acts as an intracellular antioxidant and is in the middle part of the sperm, which regenerates vitamin E and protects the phospholipid membrane, and inhibits its peroxidative activity (37).

Melatonin is obtained from Trp amino acid and, in vertebrates, is mainly generated through the pineal gland. Melatonin secretion happens in a circadian form that the maximum release of it occurs in the night. Melatonin is a multifunctional molecule and as a strong antioxidant, it exerts a unique fight against oxidative stress. Evidence shows that this compound could defend the cell membrane *vs*. peroxidation of lipid and its effect is twice the effect of vitamin E (38). A series of studies suggest that for the treatment of infertility in infertile couples, after examining vitamin C and E deficiency, before starting the treatment process with ovulation stimulation, these vitamins should be consumed with the doctor's prescription and with the appropriate dose, so that the egg and sperm samples in these people have better quality and a higher chance of conception (33, 39).

The role of vitamin C on male infertility

Vitamin C is a key and influential antioxidant that acts in the body in aqueous conditions and makes up about 65% of the total capacity of intracellular and extracellular antioxidants in semen. Vitamin C neutralizes H_2O_2, superoxide, and hydroxyl, and inhibits sperm coagulation also blocks peroxidation of lipid, regenerates vitamin E, and prevents genome damage by hydrogen peroxide (40). Also, this vitamin is important for biosynthesis of collagen. This result is particularly vital for the follicles growth in ovary, ovulation, and luteal phase. In ovary, the concentration of this vitamin is high (41).

In a study by Kodama and colleagues, they observed that orally administering 200 milligram of ascorbic acid with glutathione and vitamin E meaningfully decreased concentrations of 8-hydroxy-2-deoxyguanosine (8-OHdG) in spermatozoa and increases sperm count (42). 8-OHdG is considered as a marker of DNA damage induced by oxidative stress. The high levels of vitamin C in semen probably points to its role in protection of spermatozoa from ROS attacks and preventing oxidative DNA damage. Ascorbic acid is able to catalytically reduce the active transport of oxidizing metal ions and free radicals so that at first ascorbic acid oxidizes itself and forms Ascorbate Free Radical (AFR) (43). Contrary to other free radicals, AFR is partly inactive so that it can be converted into dehydroascorbic acid and vitamin C during inhomogeneous reactions, and as a result, it prevents the spread of chain breakage reactions (44).

Measuring plasma ascorbic acid and white blood cell levels is the most accurate and reliable test to check vitamin C status. Experimental and epidemiological investigations have revealed that the plasma level of ascorbic acid is related to the intake of ascorbic acid and its amount in white blood cells. Vitamin C may act wonders for motility in old sperm. Numerous investigations have displayed that eating vitamin C could give new life to sperm. Experiments on animals have shown that the lack of this vitamin in the blood definitely damages the ovaries and also reduces the production of active sperm. In the case of humans, research shows that the consumption of ascorbic acid is efficient in increasing the fertility of male sperm, and in experiments, it has been noticeably observed that men who have more than 25% of this type of immobile sperm cannot have children, but according to a research, it was prescribed 1000 mg of this vitamin per day to his patients, and after two months, he had a remarkable positive result in these patients and the number of active sperm (45).

Many investigations have displayed that antioxidants including ascorbic acid, vitamin E, N-acetyl cysteine, superoxide dismutase enzyme, catalase enzyme, hypotaurine, albumin, and taurine prevent the decrease of sperm mobility, and coenzyme Q10 leads to the increase of sperm motility (46). Due to the fact that ascorbic acid is a most plentiful antioxidants in human body, seminal plasma is very sensitive to a decrease in the level of ascorbic acid in the body. An accurate method for measuring vitamin C is the HPLC technique. There are several HPLC methods to determine the quantity and quality of ascorbic acid in semen (44).

The role of vitamin D on male infertility

Many studies addressed the role of vitamin D in fertility (27, 47). Vitamin D is a vital nutrient whose main and important role is to maintain calcium homeostasis and the health of the body's skeletal system (48). Physiologically, exist two active forms of vitamin D, termed calciferol, and they are vitamin D2 and D3. Vitamin D2 or ergocalciferol produced by plants, while vitamin D3 or cholecalciferol is converted from 7-dehydrocholecalciferol under the effect of UV rays made in the skin (49). Vitamin D is available as D2 and D3, and vitamin D3 is several folds more efficient than vitamin D2 (50, 51). Both vitamin D2 and vitamin D3 have the same metabolism; so that it is first hydroxylated in the liver and then it becomes 25-hydroxyvitamin D or (calcidiol) and then it becomes 1 and 25-dihydroxyvitamin D or calcitriol in the kidneys in response to the levels of parathyroid hormone (52).

The circulating form of vitamin D is 25-hydroxyvitamin D3. By 1-alpha hydroxylase in the kidneys, 25-hydroxy vitamin D3 is changed to the active form of 1-25-dihydroxy vitamin D3 by the enzyme 1-alpha hydroxylase. In addition to kidneys, this enzyme exists in many tissues and causes the conversion of 1-25 dihydroxy vitamin D3 in different tissues. The vitamin D active form attaches to its receptor (VDR) in various tissues and affects the expression of more than 200 genes, thereby exerting various effects on organs such as the parathyroid, pituitary, pancreas, ovary, colon, immune system, and skin (53). Vitamin D is also present in tissues such as the placenta, ovarian cells, and endometrium and affects the function of ovarian granulosa cells. It also has an effective role in steroidogenesis, fertility, and regulation of the immune system (54, 55) (Figure 2).

Recently, the vitamin D role in the expression of the anti-Mullerian hormone gene has been proven in vitro (56, 57). In ovary of human, cholecalciferol induces the generation of progesterone (13%), estradiol (9%), and estrogen (21%). Vitamin D is essential in biosynthesis of estrogen in gonads of male and female. In this regard, the study of Paffoni et al., (2014), which was conducted with the aim of determining vitamin D deficiency and infertility, showed that this vitamin is an effective factor in women's fertility and the result of in vitro fertilization (IVF) (58).

The important role of vitamin D serum level in reproductive functions has been shown for a long time in various animals (59), but various studies have also proven this relationship in humans (60). The results of the study by Bloberg Jensen and colleagues showed a positive association between the percentage of motile sperm and the serum level of vitamin D. It was also observed that the stimulation of human sperm cells by active vitamin D in vitro can promote their forward movement and increase the amount of intracellular calcium in human sperm cells (61). In men with vitamin D deficiency (< 25 nmol), the number of motile spermatozoa, and sperm cells with typical morphology were lower than in males with high levels of vitamin D (more than 75 nmol) (54).

It was once thought that the expression of enzymes involved in metabolizing of vitamin D including CYP24A1, CYP27B1, and CYP2R1 are exclusively restricted to the liver and kidney (62). The mentioned enzymes are existent in several tissues, including male reproductive organs (63). Enzymes involved in metabolizing of vitamin D and also VDR are expressed in some human tissues including prostate, sperm, seminal vesicle, testis, and epididymis (54). Also, the VDR presence in germ cells shows the vitamin D role in sperm (64). Most in vivo investigations have shown that the quality of semen and specific motility of sperm seem to be related to this vitamin (61). VDR might directly influence the function of germ cell whereas having an indirect influence on reproductive tissues via the control of other endocrine elements with a reproductive function including osteocalcin (65).

Deficiency of vitamin D plays a role in the functions of reproductive system including uterine fibroids, polycystic ovary syndrome, inappropriate sperm parameters, and failure of IVF, thus supplementation of this vitamin is recommended in the female and male infertility treatment. Serum vitamin D level above 50 nmol/L, in women, have a higher chance of becoming pregnant, and vitamin D supplementation is especially important in cases where there is a vitamin deficiency, such as obese people, insulin-resistant women, and people with low levels of AMH, as well as in oligospermia and asthenospermia is recommended (66).

Nowadays, assisted reproductive techniques for treating all types of infertility and increasing its success rate have received more attention than before. Various factors affect the success rate of an ART-induced pregnancy. Many factors are effective in the process of follicle and embryo development (67). The dietary effect on the process of the embryo development is confirmed, the absence of several nutrients and vitamins could decrease the chances of normal fertility. Insufficient vitamin D levels have been of attention to IVF scientists for several years.

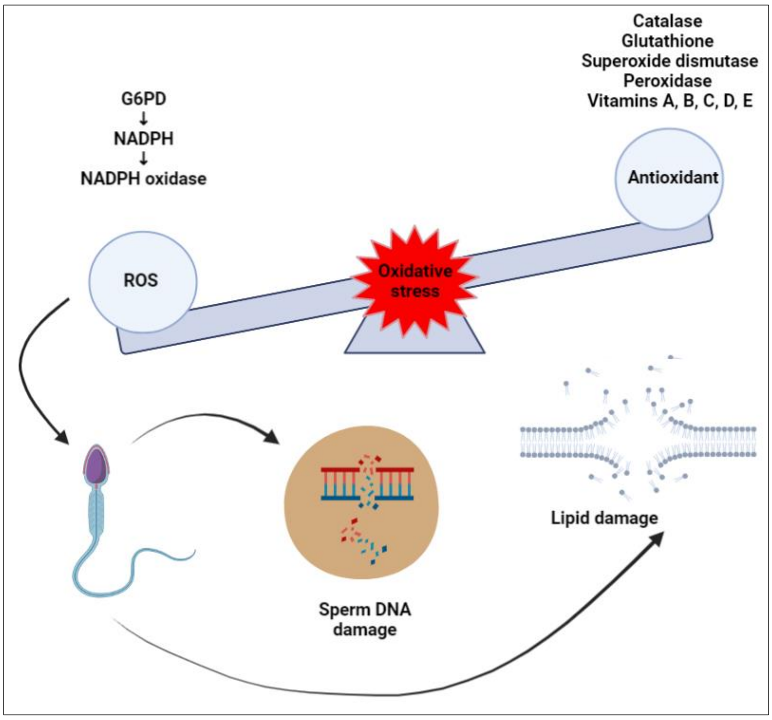

Figure 2. Vitamin D and male infertility.

The circulating form of vitamin D is 25-hydroxyvitamin D3. In the kidneys, 25-hydroxyvitamin D3 is converted into the active form of 1-25-dihydroxyvitamin D3 by the enzyme 1-alpha hydroxylase. In addition to the kidneys, this enzyme exists in many tissues of the body and causes the conversion of 1-25-dihydroxyvitamin D3 in different tissues, which binds to its receptor (VDR) and affects the expression of target genes. Vitamin D deficiency may cause a reduction in FSH and Testosterone hormones and an increase in LH hormone, which affects the number of sperms able to move, and the forward movement of sperms, and ultimately may cause infertility.

The role of vitamin A on male infertility

Vitamin A contains retinol esters and retinol. The absorption amount of this vitamin is around 30%, which could be elevated by consuming a lot of fat. Vitamin A, as a fat-soluble vitamin, plays a role in the creation and action of mucous membranes. This vitamin A has an important function in spermatogenesis due to its oxidative activity (36). In this regard, the study of Paradiso Galatioto et al., (2008) displayed that treatment with a combination of antioxidants comprising 0.06IU/kg (units/kg) of vitamin A increases the number of sperms (68).

Vitamin A (Retinol) is necessary for male reproduction. Vitamin A, an antioxidant, has a function in neutralizing free radicals and eliminating oxidative stress (69). The role of vitamin A as a protector of the testicular tissue as well as improving the function of the testicle against the destructive effects of prednisolone is quite evident, and the impact of this element on the process of spermatogenesis and sperm parameters is well visible, and in confirmation of this study, Brown and colleagues also showed that antioxidants are essential for spermatogenesis (70).

In overall, the function of vitamin A in the testicle is carried out through the transportation, processing, and destruction of retinoids and its activation of receptors in nucleus. Because Retinoic acid (RA) is not well transported through serum, vitamin A oxidation in diet to RA usually occurs in tissues. The liver could store the Retinol and transport it to different tissues (71), which produce the essential intracellular binding-proteins as well as retinoid-metabolizing enzymes to tightly regulate RA production and degradation (72).

The vitamin A role in the differentiation of mammalian spermatogonia and initiation of meiosis is emerging. Vitamin A has been known to be required for normal spermatogenesis since 1925 (73), as when retinol is deficient, spermatogenesis ceases in male rodents. Assessment of the testes of retinol-deficient rodents shows just spermatogonia and undifferentiated Sertoli cells in the spermatogenic epithelium (74, 75). Therefore, vitamin A deficiency leads to blocking the capability differentiation of spermatogonia (76).

The combined effects of retinoic acid, testosterone, and FSH are necessary for regular spermatogenesis in mammalian. Action of FSH on Sertoli cells could influence the population of spermatogonia. Action of RA on both germ cells and Sertoli cells and directs undifferentiated spermatogonia to the path of differentiation and finally prophase of meiosis. Also, testosterone affects Sertoli cells and is essential for formation of spermatid. Vitamin A deficiency, which leads to several human diseases, occurs in several regions of the world, but little is known about its effect on human reproductive capacity (77).

The role of vitamin B on male infertility

The increase of homocysteine (Hcy) is related to OS. Vitamins B group, vitamin B12 and B6, folate influence the efficiency of methyltetrahydrofolate reductase (MTHFR, the enzyme that converts homocysteine to methionine) and cystathionine B-synthase, which are accountable for eliminating homocysteine from the bloodstream. The use of group B vitamins may be considered in men with homocysteinemia and OS because this therapy is cheap and has fewer side effects (15). Considering that many publications about the influence of different antioxidants on parameters of sperm and pregnancy rate, it seems that oral antioxidants can have useful impacts on spermatozoa function and pregnancy rate (16).

Homocysteine amino acid have a function in two important metabolic paths: the GSH synthesis pathway, which is responsible for regulating redox balance, and transmethylation pathway, which regulates gene expression and cell growth. Also, an extreme increase of this substance can have negative impacts on the quality of spermatogenesis, and its accumulation in the ejaculate affects fertility. The one-carbon pathway is an important pathway in which the occurrence of defects causes an elevation in the concentration of endogenous glutathione and an increase in the free homocysteine level and affects the methylation process. Therefore, by activating this pathway, the food supplement strengthens the antioxidant factors and at the same time protects the growth of the tissues, leading to better sperm differentiation and maturation (78).

The right food supplement to stimulate the one-carbon cycle and the transsulfuration cycle must contain a wide kind of vitamins B (B2, B3, B6, B9, and B12) to carry out the recovery process of homocysteine and zinc as essential cofactors. On the other hand, include N-acetylcysteine is the only oral precursor with strong absorption for glutathione synthesis and improving sperm and oxidative parameters, which is easily converted into cysteine inside the cell (79).

Folate, a water-soluble vitamin, could be found in potatoes, grains, and green vegetables. Taking folate with vitamins B12 and B6 at the same time reduces blood homocysteine levels. Homocysteine, an amino acid, is indirectly essential for protein metabolism. According to studies, low levels of folate and increased levels of homocysteine cause frequent miscarriages. Folic acid is one of the important and necessary vitamins for women of reproductive age (35).

The study of Najafipour et al., in 2017, which was done with the purpose of the influence of taking vitamins B12 and B9 on men with methylene tetrahydrofolate reductase polymorphism, showed that taking these two vitamins has a positive and significant effect on semen parameters (80). In confirmation of these contents, in the study of Schmid et al., (2012), men receiving high amounts of vitamin E, vitamin C, zinc, beta-carotene, and folate supplements will have less DNA damage than men receiving the fewer matters (81).

Idiopathic male infertility is a chief factor in infertility in general. Irregular metabolism of folate has been suggested as an issue in male infertility. This is mechanically reasonable because folate pathway is essential in synthesis of DNA and methylation of DNA which involved in transcription process, two main procedures in spermatogenesis (82, 83).

B vitamins are cofactors for the main metabolic enzymes of sperm and their amount depends on their daily absorption and this also applies to zinc. In addition, it has been proven that vitamin B9 (folic acid) and zinc either in combination with each other or alone (orally) has a positive effect on the nucleus and acrosome of sperm (84). Folate together with Hcy and methionine help to carry out the typical procedure of spermatozoa maturation and chromatin condensation and keep sperm against ROS (85). Metabolism of folate, Hcy, and methyl groups are interrelated procedures. Folate deficiency followed by Hcy accumulation results in an increase in homocysteine concentration. Accumulation of cytokines, which is the result of increased homocysteine levels, increases the possibility of disturbances in sperm parameters and male infertility. Homocysteine is recovered by the one-carbon cycle, which recovery requires the correct functioning of enzymes and the main cofactors of the pathway (86). N-acetyl cysteine, which is soluble in water, is certainly absorbed and, in the cell, is transferred to cysteine by the reaction of deacetylation, and with its antioxidant properties, it improves the level of sperm parameters in infertile men (87).

Conclusion

Various vitamins can have a direct effect on fertility by reducing the ROS level and its damaging influences on sperm parameters. Antioxidants such as vitamins E and C act by scavenging ROS that have already been generated by cellular oxidation. Vitamin C as a water-soluble vitamin has a helpful impact on the sperm quality of elderly people. This vitamin could elevate the levels of glutathione and the action of antioxidant enzymes such as superoxide dismutase and catalase and then reduce the damage caused by oxidative stress in testicle. In addition, vitamin C has a role in increasing the production of testosterone by improving the function of testicular enzymes. Also, the consumption of vitamin E significantly increases the movement of sperms. This vitamin and selenium improve the quality of sperm and has protective impacts on spermatozoaj in men. Vitamin D is necessary for the normal formation of the sperm nucleus and helps maintain the quality of semen and the number of sperms. Vitamin D deficiency reduces sperm motility. Vitamin E is a potent non-enzymatic antioxidant that could prevent the peroxidation of lipid in plasmalemma by restricting the action of ROS and thus protect the membrane of cells from the injury stimulated by them. In the reproductive system of men, the antioxidant function of this vitamin has been identified in inhibiting the damaging impacts of ROS in the testicles and spermatozoa. In addition, vitamin E with the mentioned ability could strengthen the antioxidant protection system of testicle and spermatozoa. Vitamin A has a central role in sperm production because of its oxidative activity. Vitamins B are cofactors for the main metabolic enzymes of sperm and their deficiency can affect male fertility. According to the mentioned cases, knowing the exact role of vitamins in neutralizing oxidative stress in the male reproductive system can provide useful therapeutic solutions based on various vitamins.

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