REVIEW ARTICLE

The Role of Antioxidant Supplementation in Male Infertility

Annika Sinha[1], **Sajal Gupta**[2]

[1]Case Western Reserve School of Medicine, 10900 Euclid Ave., Cleveland, OH, USA 44106, [2]American Center for Reproductive Medicine, Cleveland Clinic, 10681 Carnegie Ave., X11 Cleveland, OH, USA 44195

ABSTRACT

With nearly 15% of all couples facing this problem, the health-care burden is profound. While infertility can be due to either female or male factors, nearly 50% of cases are due to semen abnormalities. These can result from conditions, such as varicocele, cryptorchidism, and hypogonadism; however, more commonly, the cause of infertility is unknown. This idiopathic infertility is hypothesized to be due to excessive reactive oxidative species (ROS). Although normal functioning of sperm requires ROS, high levels of ROS negatively affect DNA structure, causing dysfunction in these cells. Due to this, antioxidant supplementation has emerged as a possible. The goal of this study is to examine common causes of ROS accumulation, discuss currently used antioxidant agents, and analyze the effectiveness of these treatments. Articles from 2014 to 2017 were found using PUBMED search criteria "male infertility" and "antioxidant supplementation." Relevant abstracts were reviewed, and 32 articles were chosen. Antioxidant supplementation has shown to improve sperm health and reduce oxidative stress, which is hypothesized to mediate infertility.

Key words: Antioxidant supplementation, antioxidants, infertility, male, reactive oxidative species

INTRODUCTION

With 15% of all child-bearing age couples facing infertility, up to 80 million people are currently affected worldwide.[1] One in two of these cases can be attributed to malefactors.[1] Pathologies, such as varicocele, cryptorchidism, and hypogonadism, are often easily identifiable causes; however, in approximately a quarter of the cases, no definable source is found.[1] This idiopathic infertility is often categorized by abnormalities in sperm morphology, motility, and concentration.[1] These irregular findings are characterized as teratospermia, asthenospermia, and oligospermia, respectively.

Despite ongoing research, the pathogenesis of sperm dysfunction has yet to be completely elucidated. Current hypotheses suggest that elevated reactive oxidative species (ROS) may contribute abnormal semen profiles. Physiologic concentrations of ROS are vital for normal spermatozoa functioning in processes, such as capacitation, activation, acrosome reaction, and fusion[2]. The main sources of ROS include immature spermatozoa and leukocytes.[2] Developing sperm is exceptionally susceptible to the detrimental effects of ROS.[2] Comparison of semen from fertile and infertile men revealed that infertile men have high levels of ROS.[2] To counteract the effects of ROS, human ejaculate contains antioxidant sources, which protect developing sperm.[1]

Due to this, the use of antioxidant supplementation has emerged as a therapy for idiopathic male infertility. However, there is controversy surrounding this treatment. Due to the physiological role of ROS in sperm function, antioxidant supplementation has the potential to further hinder normal sperm processes. Despite this possibility, multiple antioxidant supplementation trials have shown promising results with improvement in at least one sperm parameter.[1] The objective of this study is to describe causes of ROS-mediated

Address for correspondence:
Sajal Gupta, 10681 Carnegie Ave., X11 Cleveland, OH 44195. E-mail: guptas@ccf.org

infertility and examine the role of common antioxidants in this condition.

SPERM FUNCTION

As previously described, ROS have a role in normal sperm development. These ROS are mainly produced as by-products of oxidative metabolism in sperm cells and aid maturation. Agarwal *et al.* described seminal leukocytes and immature spermatozoa as the major contributors of ROS.[2] The mechanism of ROS-mediated sperm damage is hypothesized to be lipid peroxidation. Lipid peroxidation is the process by which free radicals interact with polyunsaturated lipids of the cell membrane to form bioactive compounds.[3] These radical molecules not only affect the integrity of the lipid bilayer but also can affect DNA structure. Changes in DNA structure can target cells for premature apoptosis, impair fertilization, and affect embryo formation, leading to unsuccessful conception, and pregnancies. Of the two ROS-producing components, leukocytes, such as polymorphonuclear lymphocytes and macrophages, cause three-fold more ROS production.[2]

Especially during episodes of infection, leukocytes increase superoxide concentrations, which can easily cause excessive ROS accumulation.[2] In a 2016 systemic review of 11 randomized controlled trials centered on the treatment of leukocytospermia, Jung *et al.* found that eight of these studies reported resolution of leukocytospermia after antibiotic treatment.[4] Although only one study showed a statistically significant increase in pregnancy rate, all four studies that reported pregnancy rates did have overall higher numbers of pregnancies in the treated group in comparison those to the untreated group.[4] From this work, antibiotic therapy appeared successful with limited adverse events, which included gastrointestinal issues and hypersensitivity.[4] However, current literature also suggests that reactive leukocytosis and ROS-production can occur due to pathologies other than infection.

CAUSES OF MALE INFERTILITY

In addition to infection, Asadi *et al.* reviewed other potential causes of infertility.[5] Asadi *et al.* discussed factors that increase testicular oxidative stress, disturbing the physiological antioxidant balance.[5] This review examined the impact of testicular torsion, varicocele, diabetes, and hyperthyroidism.[5] These conditions have all been reported to increase ROS production through various mechanisms, leading to sperm damage and subsequent infertility. These findings are further described in Table 1.[5] In addition to defects in physiological processing caused by these pathologies, extrinsic factors, such as temperature, radiation exposure, and drug exposure, can also impact ROS-production.[5]

Even components of foods prominently featured in the American diet can increase ROS. In rabbit model, El *et al.* demonstrated that exposure to N-nitrosamine, a common environmental toxin found in smoked or barbecued meat products, increase radical levels, and decreased antioxidant levels in testes of rabbits.[6] In addition, histological analysis of seminiferous tubules of exposed rabbits showed deterioration, nuclear atypia, and basement membrane dysfunction.[6] Finally, as a result of harmful diets, body habitus (body mass index [BMI] 25 and more) can also enhance lipid peroxidation.[3] In a 2015 case–control study, the dietary fat intake of infertile and fertile men was compared. The findings showed that increased dietary fat was directly related to sperm dysfunction, particularly affecting sperm motility.[7] Weight loss in patients with BMI of 25 or greater showed beneficial changes in sperm volume and motility.[8] Because many of these internal and external contributors are relatively common in the US population, the prevalence of male infertility could potentially increase dramatically without appropriate intervention, leading to more thought and consideration to antioxidant therapy as a viable solution.

ANTIOXIDANT SUPPLEMENTATION

To combat the negative effects of ROS, antioxidant supplementation has become an important treatment option for idiopathic male infertility. Current literature on this topic is centered on the efficacy of antioxidant supplementation and its effect on sperm parameters. Antioxidants form two distinct categories: Enzymatic compounds and non-enzyme molecules.[9] Enzymatic compounds are often found physiologically within the cell. These include proteins, such as catalase, glutathione, and superoxide dismutase. These endogenous compounds cannot typically be supplemented; however, supplementation of non-enzymatic compounds often enhances the activity and effectiveness of the enzymes. Non-enzymatic compounds include certain vitamins, metals, non-metallic chemicals, and commercial homeopathic formulations. These have shown promise in improving and restoring sperm functioning with short-term use (<1 year) in infertile men. While there is limited data on the sustained long-term effect of this type of antioxidant use, sperm characteristics do statistically significantly improve. The results of these studies are summarized in Table 2.

VITAMINS

Commonly used vitamin supplements include fat-soluble vitamins, including Vitamin A, Vitamin C, Vitamin E, and non-fat soluble vitamins, such as Vitamin B12 and Vitamin B9. While broadly, these vitamins increase the likelihood of normal spermatic growth, each of them utilizes a different mechanism to enact this outcome. For example, retinol, a major component of Vitamin A, aids with the differentiation

Table 1: Common pathologies causing male infertility

Cause of infertility	Mechanism of ROS production
Testicular torsion	Can cause testicular ischemia, which increases oxidative stress. It also reduces antioxidant enzyme functioning[5] Even short episodes of ischemia (3 h or fewer) have been associated with high levels of ROS[5]
Varicocele	Characterized by a spermatic vein dilation Not only does varicocele induce ROS but also increases testicular temperature[5]
Diabetes mellitus	Causes free-radical amplification[5] Associated with DNA destruction[5]
Infection	Introduces ROS through inflammatory and immune mechanisms[5] Decreases testosterone levels, impairing sperm development[5] Bacterial components such as lipopolysaccharide, and propagate lipid peroxidation[5]
Hyperthyroidism	Proper testicular function is hypothesized to be closely related to thyroxine[5] Increased thyroxine can cause ROS production[5]
Aging	Increased age is associated with lower antioxidant levels, disrupting the ROS-antioxidant balance[5]

ROS: Reactive oxidative species

and maturation of many cell types, including gonadal cells. In a comparison study of men with either normospermia or idiopathic infertility, infertile men had lower levels of retinol and high rates of sperm DNA fragmentation.[10] Vitamin E, however, works by preventing lipid peroxidation of spermatic membranes; thereby, improving sperm motility.[9] Elsheikh *et al.* studied the effects of 6-month supplementation of Vitamin E (400 mg/day) in men with oligoasthenozoospermia.[11]

Due to its synergistic effect with Vitamin E, Vitamin C also prevents oxidative damage of DNA and has important roles in sperm morphology. 3-month supplementation of Vitamin C (1000 mg/daily) for 5 days a week showed statistically significant improvement in sperm motility, total count, and morphology in the control group (n = 120), and the lead-exposed experimental group (n = 120).[12] Given the size of this study, it offered promising results on the effect of Vitamin C on sperm parameters. However, it appears that the consistency of Vitamin C use is important for this effect. In a 6-month study, 50 control patients and 100 experimental patients were given 1000 mg of Vitamin C every other day.[8] Although there was an improvement in sperm motility, there were no significant findings in either sperm volume or morphology in this study.[8] Like fat-soluble vitamins, B vitamins also have potent effects on sperm development. Folic acid or Vitamin B9 is important for DNA and protein synthesis throughout multiple cell types; however, it is hypothesized to also have vital effects on spermatogenesis.[9] 16-week treatment of folic acid (5 mg) showed an increase in sperm concentration in the small study of 21 patients.[13]

Microminerals

Like vitamins, microminerals, such as selenium and zinc, also improve sperm processing. Selenium is known to maintain sperm structure and functions synergistically with Vitamin E, much like Vitamin C. 25 crossbred rams were treated with 1 mg of selenium daily and/or gossypol, a toxic agent to the reproductive agent.[14] Four groups were created as the following: Group 1 (control), Group 2 (9 mg/kg gossypol), Group 3 (14 mg/kg gossypol), and Group 4 (9 mg/kg gossypol and 1 mg of selenium).[14] In this study, selenium improved libido, sperm motility, and sperm output regardless of gossypol levels.[14] Reduction of oxidative stress can be achieved by zinc as well. Zinc maintains sperm structure, and supplementation with 220 mg of zinc daily can decrease abnormalities in chromatin integrity of sperm.[14]

AMINO ACIDS AND DERIVATIVES

In 2015 study of 47 patients with oligoasthenozoospermia, supplementation therapy included L-Arginine, along with pycnogenol, a nitric oxide synthase activator and synergist of L-Arginine.[15] In this study, the combination therapy statistically improved sperm volume, concentration, and motility showing that amino acids can have a role in antioxidant management.[15] Methionine, a precursor amino acid for glutathione, has been shown to prevent ROS and can improve antioxidant defense system. Three groups of male Wistar albino rats were treated with placebo, reproductively toxic anti-tuberculosis drugs, and a combination of anti-tuberculosis drugs and methionine, respectively. Shayakhmetova *et al.* found that sperm count was significantly increased with the supplementation of methionine regardless of the presence of anti-tuberculosis drugs.[16] Another precursor of glutathione, N-acetylcysteine can also increase glutathione and contribute to more effective antioxidative defense.[17] Finally, L-carnitine, an amino acid derivative, protects sperm DNA and prevents ROS-induced apoptosis.[17]

Table 2: Antioxidant supplementation and its impact

Compound	Effect	Study treatment	Study population	Outcome measures	Results
ALA	Potent antioxidant in its reduced form Can reduce ROS, prevent lipid peroxidation, and chelate transition metals	12-week supplementation of ALA (600 mg) or placebo	Forty-four infertile men with idiopathic asthenozoospermia	Total sperm count Sperm concentration Sperm motility Seminal levels of total antioxidant capacity Seminal malondialdehyde concentration	Improved, $P<0.001$ Improved, $P<0.001$ Improved, $P<0.001$ Improved, $P=0.001$ Improved, $P=0.002$
Astaxanthin, ubidecarenone, L-carnitine, zinc, lycopene tablet[18]	Algae-derived carotenoid extract Potent antioxidant	3-month supplementation with Astaxanthin, ubidecarenone, L-carnitine, zinc, and lycopene	Forty patients with either oligozoospermia and/or asthenozoospermia	Sperm count Sperm motility MDA PC GSH	Improved, $P<0.05$ Improved, $P<0.05$ Improved, $P=0.002$ $P=0.584$ Improved, $P=0.000$
Clomiphene citrate[11]	Synthetic steroid that works primarily as an antiestrogen	6-month supplementation with either Vitamin E, clomiphene citrate, or both	Group 1: Vitamin E (400 mg/day) in patients with oligoasthenozoospermia Group 2: Clomiphene citrate (25 mg/day) in patients with oligoasthenozoospermia Group 3: Combination therapy in patients with oligoasthenozoospermia	Mean sperm concentration Total sperm motility	Group 1: $P>0.05$ Group 2: Improved, $P<0.05$ Group 3: Improved, $P=0.001$ Group 1: Improved, $P=0.000$ Group 2: Improved, $P=0.003$ Group 3: Improved, $P=0.000$
Jurenia dolmaiaea (JDEE)[26]	A perennial herb that has antioxidant properties	Eighteen Sprague-Dawley male rats Group 1 (control) Group 2 (vehicle) Group 3 (CCl4) Group 4 (CCl4 + silymarin) Group 5/6 (CCl4 + JDEE) Group 7 (JDEE)	Group 1 (control) Group 2 (vehicle) Group 3 (CCl4) Group 4 (CCl4 + silymarin) Group 5/6 (CCl4 + JDEE) Group 7 (JDEE)	Activity level of antioxidant enzymes	Decreased, $P<0.05$ Increased, but P=NS
L-Arginine[15] Pycongenol	Acts to increase NO production Japanese pine bark extract that activates endothelial NO synthases and is a potent antioxidant and inhibitor of inducible NO synthase Works synergistically with L-arginine	4th-month cosupplementation with L-arginine and Pycnogenol	Forty-seven patients with oligoasthenozoospermia and mild erectile dysfunction	Sperm volume Sperm concentration Sperm motility	$P=0.09$ Improved, $P=0.01$ $P=0.08$

(Contd...)

Table 2: *(Continued)*

Compound	Effect	Study treatment	Study population	Outcome measures	Results
Lycopene[19]	Can function synergistically with Vitamin E and Se	12-week supplementation with tomato juice	Control group (n=12) Tomato juice group (n=17)	Seminal plasma WBCs Sperm motility Seminal plasma lycopene level	P=0.039 P=0.019 P=0.023
	May have an effect on AA/DHA acid ratios. High AA/DHA ratios in blood and sperm were found in infertile men than in fertile normozoospermic males (Safarinejad – 5 – Filipcikova)	3-month treatment with lycopene capsule* (10 mg of lycopene twice daily) *Capsules contained 5.98 micromols of Vitamin E as a stabilizer	Control group (n=13) Lycopene group (n=44)	Seminal plasma AA level Seminal plasma DHA level Seminal AA/DHA ratio	Decreased, P<0.05 Increased, P<0.05 Decreased, P<0.05
Methionine[16]	Precursor amino acid for glutathione Prevents oxidative damage and can function as part of the antioxidant defense system	Male Wistar albino rats were treated with: Group 1 (control) Group 2 (anti-tuberculosis drugs) Group 3 (anti- tuberculosis drugs + methionine)	Group 1 (n=8) Group 2 (n=8) Group 3 (n=8)	Sperm count	Increased, P<0.05
Myo-inositol (MI)[31]	Sugar-like molecule that is utilized in key signaling pathways Can have implications in metabolic syndrome (MS) and associated asthenospermia	3-month supplementation with 1g MI, 30 mg L-carnitine, 30 mg L-arginine, 30 mg vitamin E, 55 microg selenium, and 200 microg folic acid (andrositol)	Forty-five men with asthenospermia and MS	Sperm concentration Sperm motility Sperm morphology	Improved, P<0.001 Improved, P<0.001 Improved, P<0.001
PU[32]	Antioxidant found in pomegranate juice	Adult *Mus musculus* mice Group 1 (control) Group 2 (PU 9 mg/kg/day) for 4 weeks Group 3 (Lead acetate 100 mg/kg) for 4 weeks Group 4 (PU + Lead acetate for 4 weeks)	Group 1 (n=8) Group 2 (n=8) Group 3 (n=8) Group 4 (n=8)	Lipid peroxidation	Increased, P<0.05

(Contd...)

Table 2: *(Continued)*

Compound	Effect	Study treatment	Study population	Outcome measures	Results
			Group 3 (*n*=8) Group 4 (*n*=8)	Glutathione level	Increased, *P*<0.05
Resveratrol[24]	Phytochemical with antioxidative properties	Male albino mice were divided into 5 groups (*n*=6) each Group 4 (cisplatin 7.5 mg/kg b. wt./week for 4 weeks) Group 5 (resveratrol + cisplatin)	Group 1 (control) Group 4 Group 5	Sperm motility	Improved, *P*<0.001
Retinol[10]	A major component of Vitamin A helps with growth and differentiation of cells, especially gonadal cells	N/A; serum levels of lycopene, beta-carotene, and retinol were measured	Control group of normospermic men (*n*=71) Men with idiopathic infertility (*n*=61)	Sperm DNA fragmentation rate	Increased, *P*<0.001
			Control group of normospermic men (*n*=71) Men with idiopathic infertility (*n*=61) Control group of normospermic men (*n*=71) Men with idiopathic infertility (*n*=61)	Serum MDA level Seminal MDA level	*P*=NS Increased, *P*<0.001
			Control group of normospermic men (*n*=71) Men with idiopathic infertility (*n*=61)	Lycopene, beta-carotene, and Vitamin A levels	Decreased, *P*<0.05

(Contd...)

Table 2: *(Continued)*

Compound	Effect	Study treatment	Study population	Outcome measures	Results
Royal Jelly (RJ)[27]	A honeybee product that has anti-hypercholesterolemic, antioxidant, and hypoglycemia properties	Twenty-eight male Wistar rats Group 1 (1 ml distilled water for 6 weeks) Group 2 (RJ 100 mg/kg for 6 weeks orally) Group 3 (Diabetic rats + 1 ml distilled water for 6 weeks) Group 4 (RJ-treated diabetic group for 6 weeks)	Group 3 (n=8) Group 4 (n=8)	Catalase activity	Increased, P=0.001
Selenium (Se)[14]	Maintains sperm structure Can function synergistically with Vitamin E	Treatment with 1 mg selenium daily and/or gossypol (reproductively toxic agent)	Twenty-five crossbred rams Group 1 (control) Group 2 (9 mg/kg gossypol) Group 3 (14 mg/kg gossypol) Group 4 (9 mg/kg gossypol + 1 mg selenium) Group 5 (14 mg/kg gossypol + 1 mg selenium)	Libido Percentage of forward motility Total sperm output Total functional sperm fraction	Improved with selenium regardless of gossypol levels P<0.001 P=0.019 P<0.001 P<0.001
Tamoxifen[30]	A selective estrogen receptor modulator that is commonly used for idiopathic male infertility	3-month supplementation with: Group 1: oral TAM 10 mg, bid Group 2: oral indomethacin 25 mg, bid	Group 1 (n=55) Group 2 (n=41)	Total sperm count Increased sperm SDH activity Sperm MMP ATP contents	Increased, P<0.001 Increased, P<0.01 P<0.001 P<0.001
Ubiquinol (reduced form of Coenzyme Q10)[9,22]	Important in sperm energy production Improves sperm motility and count Antioxidant properties against ROS	6-month Ubiquinol (150 mg/day) supplementation of oligospermic patients Study parameters were measured before, under (after every 2 months), and after supplementation	Experimental group (n=60)	Testosterone level Total sperm count Total sperm motility	No change 53%, P<0.05 36%, P<0.05
		3-month supplementation with 200 mg/day	60 men with idiopathic oligoasthenoteratozoospermia Control group (n=30) Experimental group (n=30)	Sperm forward and total motility Sperm concentration Sperm morphology	Increased, P<0.05 P=NS P=NS

(Contd...)

Table 2: *(Continued)*

Compound	Effect	Study treatment	Study population	Outcome measures	Results
		26-week supplementation with Ubiquinol (200 mg) daily	Control group (n=114) Experimental group (n=114)	Sperm motility	Increased, P=0.008
		12-month supplementation with Coenzyme Q10 (300 mg orally twice daily)	Experimental group of infertile men with idiopathic olgioasthenoteratozoospermia	Mean sperm concentration Sperm progressive motility Sperm with normal morphology	Improved, P<0.05 Improved, P<0.05 Improved, P<0.05
Vitamin B9[13]	Important for DNA and protein synthesis and may be essential for spermatogenesis	16-week treatment with two capsules daily: Group 1 (placebo/placebo) Group 2 (folic acid 5 mg/placebo)	Group 1 (n=18) Group 2 (n=21)	Sperm concentration	Increased, P=0.05
Vitamin C[8,12,17]	Protects against oxidative DNA damage Role in proper sperm morphology Can function synergistically with Vitamin E	3-month supplementation of Vitamin C (1000 mg/day) for 5 consecutive days in a week	Control group (n=120) Lead-exposed experimental group (n=120)	Sperm motility Sperm total count Abnormal sperm morphology	Improved, P<0.001 Improved, P<0.001 Improved, P<0.001
		6-month supplementation of 1000 mg Vitamin C every other day	Control group (n=50) Vitamin C group (n=100)	Sperm volume Sperm motility Sperm morphology	P=NS Improved, P<0.05 P=NS
Vitamin E[11,17]	Prevents lipid peroxidation of sperm membranes and ROS-induced damage Increases sperm motility	6-month supplementation with either Vitamin E, clomiphene citrate, or both	Group 1: Vitamin E (400 mg/day) in 30 patients with oligoasthenozoospermia Group 2: Clomiphene citrate (25 mg/day) in 30 patients with oligoasthenozoospermia Group 3: Combination therapy in 30 patients with oligoasthenozoospermia	Mean sperm concentration Total sperm motility	Group 1: Decreased, P>0.05 Group 2: Improved, P<0.05 Group 3: Improved, P=0.001 Group 1: Improved, P=0.000 Group 2: Improved, P=0.003 Group 3: Improved, P=0.000

(Contd...)

Table 2: *(Continued)*

Compound	Effect	Study treatment	Study population	Outcome measures	Results
WZYZP[28]	Comprised five medicinal plants that are used in kidney dysfunction and impotence, sterility, spermatorrhea, premature ejaculation, and lumbago	Adult male Kumming mice irradiated to cause testicular dysfunction and 3-week treatment with WZYZP Group 1 (no irradiation, treated with distilled water) Group 2 (treated with 0.25g/kg of WZYZP) Group 3 (treated with 1.0g/kg of WZYZP)	Group 1 (n=12) Group 2 (n=12) Group 3 (n=12)	Sperm count	Increased in WZYZP groups, P<0.05, P<0.01
Zinc[13,17]	Protects and maintains sperm structure Reduces OS	Treatment with two capsules daily: Group 1 (placebo/placebo) Group 2 (zinc sulphate 220 mg/placebo)	Group 1 (n=18) Group 2 (n=24)	Sperm chromatin integrity	Decrease in abnormalities, P<0.05
Zingiber officinale (Ginger)[25]	Antitumorgenic, antioxidant, and anti-inflammatory properties	3-month oral treatment (capsules of 250 mg of ginger powder twice a day)	Control group (n=50) Experimental group (n=50)	DNA fragmentation	Decreased, P<0.001

ALA: Alpha-lipoic acid, WZYZP: Wuzi Yanzong pill, MDA: Malondialdehyde, *Z. officinale: Zingiber officinale*

CAROTENOIDS

Carotenoids are organic colored pigments that are derived from plants, algae, bacteria, and fungi. In these organisms, they function by absorbing light energy and simultaneously protect chlorophyll structure from photodamage caused by ROS. This functionality can be applied to protecting sperm from ROS-damage. Commonly studied carotenoids include astaxanthin, lycopene, and ubidecarenone (or ubiquinol). Astaxanthin, an algae-derived extract, was utilized in a combination antioxidant regimen for patients with oligozoospermia and/or asthenozoospermia.[18] Along with astaxanthin, patients were given ubidecarenone, L-carnitine, zinc, and lycopene for 3 months. Although the effectiveness of astaxanthin itself cannot be interpreted from these results, the combination therapy of three carotenoids, 1 amino acid, and 1 micromineral offered improvements to sperm count and motility and reduction of malondialdehyde (a ROS by-product).[18]

As a synergist with Vitamin E and selenium, lycopene, a common carotenoid found in tomatoes, improved sperm motility and reduced seminal leukocytosis in a tomato juice supplementation study.[19] Lycopene may also affect fatty acid profiles in the sperm membrane bi-layer. The main components affected include arachidonic acid (AA) and docosahexaenoic acid (DHA). Historically, high AA/DHA ratios in blood and sperm were associated with infertility.[20,21] After 3-month supplementation with 10 mg of lycopene twice a day, 44 patients had a decrease in seminal AA/DHA ratios.[20]

Finally, ubidecarenone has been one of the most commonly studied carotenoids. It is suggested to be increase sperm motility and count.[9] Thakur *et al.* studied the effect of ubiquinol (150 mg/day) on testosterone level, sperm count, and motility in oligospermic patients.[22] Although there was no change in testosterone level, total sperm count and motility were 53% and 35% improved from baseline in these 60 patients.[22] Similar improvement in motility secondary to 200 mg daily ubiquinol was confirmed in a larger study of 114 patients.[21]

FATTY ACIDS AND PHENOLS

Fatty acids are carboxylic acid components of fats and lipids and are important parts of the membrane bi-layers of cells. Fatty acid supplementation with alpha-lipoic acid (ALA) has also been seen to reduce ROS and chelate harmful transitional metals that can increase ROS. Haghighian *et al.* discovered a statistically significant improvement in multiple sperm characteristics, including sperm count, concentration, and motility, and seminal antioxidant balance with a 12-week ALA program for 44 asthenozoopermic patients.[23] In the seminal fluid, there was not only an increase in total antioxidant capacity but also a decrease in malondialdehyde ($P = 0.001$ and $P = 0.002$, respectively).[23]

Like fatty acids, phenols have beneficial effects. They possess antioxidant properties, showing success in research studies. Resveratrol, a phytochemical found in the wine, skin of grapes and other fruits, has been shown to boost sperm motility in male albino mice that were treated with resveratrol 1 mg/kg for 28 days.[24] While resveratrol in wine offers these benefits, punicalagin (PU) in pomegranate juice has shown promise. It caused a rise in the levels of glutathione, a major component of the antioxidant defense system, in adult mice treated with lead and those treated with lead and PU.[24] While the lead caused reproductive damage through ROS, PU use was shown to improve antioxidant balance.[24]

COMMERCIAL ANTIOXIDANT PRODUCTS

With the success of antioxidant therapy in studies, the market for antioxidant supplements has increased dramatically. Formulations of multiple ROS-fighting substances have been compounded to create daily antioxidant supplements. Such therapies include *Zingiber officinale* (ginger) tablets, *Jurinea dolomiaea*, Royal Jelly™, Shengling capsule, and Wuzi Yanzong pill (WZYZP). Many of these homeopathic medications are derived from Eastern medicine practices and have shown success in research studies.

Z. officinale (ginger) has antioxidant and anti-inflammatory properties.[25] Within 3 months of daily 500 mg of ginger powder use, DNA fragmentation, a key cause of sperm dysfunction, was decreased ($P < 0.001$).[25] A perennial herb, *J. dolamaiaea* also has similar functioning. Although antioxidant levels in the treated rat were increased, these findings were not significant in male rats.[26] More commercialized products, such as Royal Jelly™, Shengling capsule, and WZYZP showed some results in improving catalase activity and sperm parameters in mouse and rat models, but there is limited randomized control trial data in humans for Chinese herbal medications.[27,28] Yao *et al.* summarized existing human data on these two therapies, the Shengling capsule and WZYZP.[29] The Shengling (decoction for generating sperm) capsule improved sperm concentration, motility, and reduced antisperm antibodies.[29] This formulation was found to be more effective than WZYZPs (pills for reproduction) in terms of improving sperm parameters.[29] No studies on the effect of WZYZPs on antisperm antibodies were discussed.[29] Although these medications appeared effective, there is no regulating body for drug manufacturing, making standardized testing for these supplements difficult.

Finally, FDA-approved selective estrogen receptor modulators (SERM), such as clomiphene citrate (CC) and tamoxifen, had some improvement in sperm health. CC is an antiestrogen steroid that is indicated in the treatment of polycystic ovarian disease and subsequent anovulatory infertility. Patients with oligoasthenozoospermia were treated with 6-month supplementation with either Vitamin E, CC, or both.[11] Outcome measures of mean sperm concentration and total sperm motility were analyzed, showing that CC alone and CC with Vitamin E therapy offered more benefits than Vitamin E therapy alone.[11] Another SERM, tamoxifen, is currently used in the US for idiopathic male infertility. Guo *et al.* showed improvement in total sperm count and antioxidant enzyme activity with daily 20 mg tamoxifen use in 41 men.[30] Due to the availability of these drugs on the US market, these medications can easily be utilized to improve infertility.

CONCLUSION

As a better understanding of the pathogenesis of idiopathic male infertility emerges, treatments targeted for ROS reduction appear to have success in improving sperm stability. Although some amount of ROS is needed for proper functioning, excessive levels can easily accumulate due to certain pathologies and extrinsic factors that hasten the production of ROS through ineffective oxidative metabolism. In sperm, the accumulation of harmful ROS causes devastating damage to sperm structure. It is hypothesized that ROS targets cell membranes, DNA, and tissue structure, rendering germ cells incapable of normal function. The findings in the current literature suggest that vitamins, certain micro-molecules, herbal supplements, and medications can offer some therapeutic options. Although the data on the efficacy of these treatments are limited, strides in this field of research have validated the usefulness of some of these substances. These results can help augment existing treatment methods of weight loss, diet modification, and smoking cessation to better address the growing problem of male infertility.

AUTHOR'S CONTRIBUTION

Author, Annika Sinha, completed the literature review and the manuscript. Author, Sajal Gupta, MD, served as the advising primary investigator of this work.

REFERENCES

1. Imamovic Kumalic S, Pinter B. Review of clinical trials on effects of oral antioxidants on basic semen and other parameters in idiopathic oligoasthenoteratozoospermia. Biomed Res Int 2014;2014:426951.
2. Agarwal A, Tvrda E, Sharma R. Relationship amongst teratozoospermia, seminal oxidative stress and male infertility. Reprod Biol Endocrinol 2014;12:45.
3. Sinha A, Gupta S. Lipid peroxidation and its impact on fertility. Women's Health and Gynecology 2018;4:82-92.
4. Jung JH, Kim MH, Kim J, Baik SK, Koh SB, Park HJ, *et al.* Treatment of leukocytospermia in male infertility: A Systematic review. World J Mens Health 2016;34:165-72.
5. Asadi N, Bahmani M, Kheradmand A, Rafieian-Kopaei M. The impact of oxidative stress on testicular function and the role of antioxidants in improving it: A Review. J Clin Diagn Res 2017;11:IE01-IE05.
6. El SA, Balbaa BM, Hassan IA. N-nitrosamines induced infertility and hepatotoxicity in male rabbits. Environ Toxicol 2017;32:2212-20.
7. Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi MR, Baghestani AR, Hekmatdoost A. Dietary fatty acid intakes and asthenozoospermia: A case-control study. Fertil Steril 2015;103:190-8.
8. Rafiee B, Morowvat MH, Rahimi-Ghalati N. Comparing the effectiveness of dietary vitamin C and exercise interventions on fertility parameters in normal obese men. Urol J 2016;13:2635-9.
9. Majzoub A, Agarwal A. Antioxidant therapy in idiopathic oligoasthenoteratozoospermia. Indian J Urol 2017;33:207-14.
10. Ghyasvand T, Goodarzi MT, Amiri I, Karimi J, Ghorbani M. Serum levels of lycopene, beta-carotene, and retinol and their correlation with sperm DNA damage in normospermic and infertile men. Iran J Reprod Med 2015;13:787-92.
11. ElSheikh MG, Hosny MB, Elshenoufy A, Elghamrawi H, Fayad A, Abdelrahman S, *et al.* Combination of vitamin E and clomiphene citrate in treating patients with idiopathic oligoasthenozoospermia: A prospective, randomized trial. Andrology 2015;3:864-7.
12. Men LI. Clinical relevance of vitamin C among lead-exposed infertile men. Genet Test Mol Biomarkers 2012;16:1001-6.
13. Raigani M, Yaghmaei B, Amirjannti N, Lakpour N, Akhondi MM, Zeraati H, *et al.* The micronutrient supplements, zinc sulphate and folic acid, did not ameliorate sperm functional parameters in oligoasthenoteratozoospermic men. Andrologia 2014;46:956-62.
14. El-Mokadem MY, Taha TA, Samak MA, Yassen AM. Alleviation of reproductive toxicity of gossypol using selenium supplementation in rams. J Anim Sci 2012;90:3274-85.
15. Kobori Y, Ota S, Sato R, Yagi H, Soh S, Arai G, *et al.* Antioxidant cosupplementation therapy with vitamin C, vitamin E, and coenzyme Q10 in patients with oligoasthenozoospermia. Arch Ital Urol Androl 2014;86:1-4.
16. Shayakhmetova GM, Bondarenko LB, Voronina AK, Kovalenko VM. Comparative investigation of methionine and novel formulation metovitan protective effects in wistar rats with testicular and epididymal toxicity induced by anti-tuberculosis drugs co-administration. Food Chem Toxicol 2017;99:222-30.
17. Mora-esteves C, Shin D. Nutrient supplementation: Improving male fertility fourfold. Semin Reprod Med 2013;31:293-300.
18. Singh A, Jahan N, Radhakrishnan G, Banerjee BD. To evaluate the efficacy of combination antioxidant therapy on oxidative stress parameters in seminal plasma in the male infertility. J Clin Diagn Res 2016;10:QC14-7.
19. Yamamoto Y, Aizawa K, Mieno M, Karamatsu M, Hirano Y, Furui K, *et al.* The effects of tomato juice on male infertility. Asia Pac J Clin Nutr 2017;26:65-71.
20. Filipcikova R, Oborna I, Brezinova J, Novotny J, Wojewodka G, De Sanctis JB, *et al.* Lycopene improves the distorted ratio

between AA/DHA in the seminal plasma of infertile males and increases the likelihood of successful pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159:77-82.
21. Safarinejad MR, Hosseini SY, Dadkhah F, Asgari MA. Relationship of omega-3 and omega-6 fatty acids with semen characteristics, and anti-oxidant status of seminal plasma: A comparison between fertile and infertile men. Clin Nutr 2010;29:100-5.
22. Thakur AS, Littarru GP, Funahashi I, Painkara US. Effect of ubiquinol therapy on sperm parameters and serum testosterone levels in oligoasthenozoospermic infertile men. J Clin Diagn Res 2015;9:BC01-3.
23. Haghighian HK, Haidari, F, Mohammadi-asl, J, Dadfar, M. Re: Randomized, triple-blind, placebo-controlled clinical trial examining the effects of alpha-lipoic acid supplement on the spermatogram and seminal oxidative stress in infertile men re: Epididymitis: Ascending infection restricted by segmental boundaries re: Sperm telomere length is positively associated with the quality of early embryonic development. J Urol 2015;195:1076.
24. Singh I, Goyal Y, Ranawat P. Potential chemoprotective role of resveratrol against cisplatin induced testicular damage in mice. Chem Biol Interact 2017;273:200-11.
25. Hosseini J, Mardi Mamaghani A, Hosseinifar H, Sadighi Gilani MA, Dadkhah F, Sepidarkish M, *et al.* The influence of ginger (*Zingiber officinale*) on human sperm quality and DNA fragmentation: A double-blind randomized clinical trial. Int J Reprod Biomed (Yazd) 2016;14:533-40.
26. Shah NA, Khan MR. Increase of glutathione, testosterone and antioxidant effects of jurenia dolomiaea on CCl_4 induced testicular toxicity in rat. BMC Complement Altern Med 2017;17:206.
27. Ghanbari E, Nejati V, Khazaei M. Antioxidant and protective effects of royal jelly on histopathological changes in testis of diabetic rats. Int J Reprod Biomed (Yazd) 2016;14:519-26.
28. Ji H, Wang DM, Wu YP, Niu YY, Jia LL, Liu BW, *et al.* Wuzi yanzong pill, a Chinese polyherbal formula, alleviates testicular damage in mice induced by ionizing radiation. BMC Complement Altern Med 2016;16:509.
29. Yao DF, Mills JN. Male infertility: Lifestyle factors and holistic, complementary, and alternative therapies. Asian J Androl 2016;18:410-8.
30. Guo L, Jing J, Feng YM, Yao B. Tamoxifen is a potent antioxidant modulator for sperm quality in patients with idiopathic oligoasthenospermia. Int Urol Nephrol 2015;47:1463-9.
31. Montanino Oliva M, Minutolo E, Lippa A, Iaconianni P, Vaiarelli A. Effect of myoinositol and antioxidants on sperm quality in men with metabolic syndrome. Int J Endocrinol 2016;2016:1674950.
32. Rao F, Zhai Y, Sun F. Punicalagin mollifies lead acetate-induced oxidative imbalance in male reproductive system. Int J Mol Sci 2016;17:pii: E1269.

How to cite this article: Sinha A, Gupta S. The Role of Antioxidant Supplementation in Male Infertility. Clin Res Obstetr Gynecol 2018;1(1):1-12.