Nutritional Supplementation for the Treatment of Male Infertility

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11.1 INTRODUCTION

11.1.1 MALE INFERTILITY

Infertility is a common healthcare problem affecting nearly 15% of couples. Although previous studies have focused on female factors as the primary cause, current research indicates that about 25% of cases are exclusively caused by a male factor, and nearly 30–40% of all infertility cases have direct contributions from male factor insufficiency [1]. Several research groups have also noted a steady decrease in sperm quality over the past 50 years, further contributing to male factor infertility [2,3].
11.1.2 Reactive Oxygen Species and Male Infertility

The etiology of male infertility is often varied and may include environmental, endocrine, and genetic factors. One significant cause of male factor deficiency is the generation of reactive oxygen species (ROS), which can damage sperm DNA, membranes, and proteins. If not properly neutralized, ROS can lead to impaired motility, cytoskeleton damage, disruption of membrane fluidity, and even sperm apoptosis [4]. ROS include oxygen-containing compounds that have one or more unpaired electrons (free radicals) as well as non-radical oxygen compounds. The most frequently produced free radical is the superoxide radical \( \text{O}_2^- \), but other common free radicals include \( \text{HClO}^- \) and \( \text{OH}^- \). Ozone and hydrogen peroxide (\( \text{H}_2\text{O}_2 \)) are examples of non-radical ROS [5].

Numerous sources of ROS exist. The two most prevalent sources are leukocytes and abnormal sperm [6,7]. Leukocytes (particularly macrophages and neutrophils) produce ROS such as \( \text{O}_2^- \) and \( \text{H}_2\text{O}_2 \) as part of the natural host immune defense against pathogens. Neutrophils also produce \( \text{HOCl}^- \) through the action of oxygen-dependent myeloperoxidase. Abnormal sperm may retain more cytoplasm than developmentally normal ones, leading to increased ROS production [5]. NADPH oxidase in the sperm membrane produces ROS, and the concentration of this enzyme may increase with abnormal cytoplasmic retention [6]. Along with this, diaphorase (a mitochondrial NADH-dependent oxidoreductase) may also increase sperm ROS production [8]. Lastly, \( \text{H}_2\text{O}_2 \) generated by superoxide dismutase (SOD) may temporarily inactivate glucose-6-phosphate dehydrogenase, which decreases the amount of NADPH available to neutralize ROS [5].

Under normal physiological conditions, the amount of ROS produced does not exceed the rate at which the sperm are able to neutralize these compounds. The production of ROS is imperative for cellular functions in a limited capacity. \( \text{O}_2^- \) may serve as a metabolite for signal transduction within the sperm [9,10]. A natural overproduction of ROS also occurs during sperm hyperactivation, capacitation, and fertilization [6,9,11,12]. Significantly elevated levels of ROS, however, may cause 30–80% of all male infertility cases [10]. Specific risk factors for the development of ROS

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**FIGURE 11.1** Causes, mechanisms, and effects of oxidative stress on male infertility.
Nutritional Supplementation for the Treatment of Male Infertility

are diverse, and common examples include lifestyle (obesity, stress, alcohol, tobacco), environment (heat, pollution), infection (acute, chronic), and inflammation [13]. Figure 11.1 illustrates the effect of oxidative stress on male fertility.

11.1.3 Oxidative Stress

When the generation of ROS surpasses the sperm capacity to eliminate the free radicals and reactive metabolites that are generated, oxidative stress (OS) occurs. Figure 11.1 illustrates the mechanism of oxidative stress. OS can lead to a decrease in semen quality, resulting in a pathological decline in several sperm parameters as a result of free radical damage. For example, it may lead to a decrease in sperm motility as a result of reduced ATP production or damaged axonemal proteins [14,15]. The ability of sperm to undergo capacitation and induce fertilization may also decrease owing to reduced membrane fluidity, increased membrane peroxidation, and loss of membrane ATP [16]. OS can also lead to a loss of membrane integrity as well as DNA damage and apoptosis [4,7,17].

The functional morphology of sperm increases its susceptibility to OS and subsequent oxidative damage. Sperm are vulnerable to oxidative damage owing to their abundance of polyunsaturated fatty acids (PUFAs), which are at a high risk for lipid peroxidation. In addition, sperm maturation leads to a reduction in cytoplasmic content, limiting the amount of enzymes and antioxidants available to counter ROS production and repair ROS-induced nuclear and mitochondrial DNA damage [5].

11.2 Antioxidants

Semen naturally contains antioxidants to counter ROS. Antioxidants are molecules that scavenge free radicals and prevent deleterious cell damage due to chain reactions involving unpaired electrons. Sperm contain two broad categories of antioxidants: enzymatic antioxidants, including SOD, catalase, and glutathione peroxidase [18–20], and nonenzymatic antioxidants including vitamin C, vitamin E, glutathione, amino acids, albumin, carnitines, carotenoids, flavonoids, and prostasomes [13]. The nonenzymatic antioxidants can be further divided into synthetic and dietary antioxidants.

Dietary antioxidants can be found in natural foods. These foods often contain multiple antioxidants and other enzymatic cofactors that may act synergistically within the body to eliminate ROS. In contrast, synthetic antioxidants are manufactured dietary supplements. For this reason, isolated supplementation with a synthetic antioxidant may limit the synergistic effect commonly observed with dietary antioxidants, and therefore, these compounds may offer suboptimal protection against ROS in certain cases [21,22]. The effective use of synthetic antioxidants may require combination supplementation to achieve a significant ROS-scavenging ability [23].

Because of the prominent role OS plays in male infertility and the promising ability of dietary and synthetic antioxidants to neutralize ROS, significant research has been performed to assess their efficacy. A substantial number of these studies have reported diminished ROS levels on supplementation and improved semen parameters. However, other trials have found that many of the same antioxidants had little or no effect on ROS and/or semen quality.

Sections 11.2.1–11.2.10 review the most common antioxidants, together with their recommended dosing and possible value in improving sperm function and male fertility potential. Table 11.1 shows the effects of antioxidants on male fertility.

11.2.1 Vitamins A, C, and E

Vitamins are metabolic cofactors needed in a variety of biochemical processes for synthesis of essential nutrients. Vitamins A, C, and E have been heavily researched in the last two decades and possess antioxidant activities. Vitamin A is lipid soluble and necessary for visual acuity, and it may also act as a growth factor [24]. Vitamin A also helps maintain the mucous membranes of the genitourinary tract, gastrointestinal tract, eye, and skin [25]. The mechanism of action as an
<table>
<thead>
<tr>
<th>Study</th>
<th>Antioxidant</th>
<th>Effects on Semen Quality</th>
<th>Reproductive Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al. [26]</td>
<td>Vitamin A (with selenium, vitamins C and E)</td>
<td>Increased motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Ehrenkranz [27]</td>
<td>Vitamin C (with vitamin E)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Palamando and Kehrer [28]</td>
<td>Vitamin C (with vitamin E)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Kessopoulou et al. [29]</td>
<td>Vitamin C</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Thiele et al. [30]</td>
<td>Vitamin C</td>
<td>Increased normal morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Baker et al. [31]</td>
<td>Vitamin C (with vitamin E)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Rolf et al. [32]</td>
<td>Vitamin C (with vitamin E)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Kessopoulou et al. [29]</td>
<td>Vitamin E</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Suleiman et al. [33]</td>
<td>Vitamin E</td>
<td>Decreased MDA, increased motility</td>
<td>Improved pregnancy rate</td>
</tr>
<tr>
<td>Geva et al. [34]</td>
<td>Vitamin E</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Keskes-Ammar et al. [35]</td>
<td>Vitamin E</td>
<td>Increased motility</td>
<td>No change</td>
</tr>
<tr>
<td>Menchini-Fabris et al. [36]</td>
<td>Carnitine</td>
<td>Increased motility with increased supplementation</td>
<td>N/A</td>
</tr>
<tr>
<td>Bornman et al. [37]</td>
<td>Carnitine</td>
<td>Increased motility with increased supplementation</td>
<td>N/A</td>
</tr>
<tr>
<td>Moncada et al. [38]</td>
<td>Carnitine</td>
<td>Increased progressive motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Costa et al. [39]</td>
<td>Carnitine</td>
<td>Improved count, motility, and morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Vitali et al. [40]</td>
<td>Carnitine</td>
<td>Increased motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Lenzi [41]</td>
<td>Carnitine</td>
<td>Increased concentration and motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Cavallini et al. [42]</td>
<td>Carnitine</td>
<td>Increased concentration, motility, and morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>De Rosa et al. [43]</td>
<td>Carnitine</td>
<td>Increased motility, count, and membrane integrity</td>
<td>Increased cervical mucus penetration</td>
</tr>
<tr>
<td>Balercia et al. [44]</td>
<td>Carnitine</td>
<td>Increased motility velocity</td>
<td>No change</td>
</tr>
<tr>
<td>Sigman et al. [45]</td>
<td>Carnitine</td>
<td>No change</td>
<td>N/A</td>
</tr>
<tr>
<td>Zhou et al. [46]</td>
<td>Carnitine</td>
<td>Increased motility</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Balercia et al. [47]</td>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>Increased motility</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Balercia et al. [48]</td>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>Increased motility</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Mancini et al. [49]</td>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Author and Year</td>
<td>Supplementation</td>
<td>Effect of Supplementation</td>
<td>Additional Effects</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>Lewin and Lavon [50]</td>
<td>CoQ10</td>
<td>No change</td>
<td>Increased IVF/ICSI success rates</td>
</tr>
<tr>
<td>Safarinejad [51]</td>
<td>CoQ10</td>
<td>Increased concentration, morphology, and motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Safarinejad et al. [52]</td>
<td>CoQ10</td>
<td>Increased count, motility, morphology, acrosome reaction efficiency. Increased inhibin B and FSH</td>
<td>N/A</td>
</tr>
<tr>
<td>Nadjarzadeh et al. [53]</td>
<td>CoQ10</td>
<td>Increased morphology, concentration, and activity of catalase and SOD</td>
<td>N/A</td>
</tr>
<tr>
<td>Gupta and Kumar [54]</td>
<td>Lycopene</td>
<td>Increased motility, morphology, and concentration</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Mendiola et al. [55]</td>
<td>Lycopene</td>
<td>Decreased semen quality with decreased supplementation</td>
<td>N/A</td>
</tr>
<tr>
<td>Vicari et al. [56]</td>
<td>NSAIDs</td>
<td>Increased motility and viability, decreased ROS</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Cavallini et al. [42]</td>
<td>NSAIDs</td>
<td>Increased concentration, motility, and morphology</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Srivastava and Agarwal [57]</td>
<td>Arginine</td>
<td>Improved motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Landau et al. [58]</td>
<td>Folic acid</td>
<td>No effect</td>
<td>N/A</td>
</tr>
<tr>
<td>Wong et al. [59]</td>
<td>Folic acid</td>
<td>Improved sperm concentration, no improvement in sperm motility or morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Ebisch et al. [60]</td>
<td>Folic acid</td>
<td>Decrease in folic acid in seminal plasma caused by increase in DNA fragility and sperm DNA damage</td>
<td>N/A</td>
</tr>
<tr>
<td>Tremellen et al. [61]</td>
<td>Folic acid</td>
<td>N/A</td>
<td>Improved pregnancy rate</td>
</tr>
<tr>
<td>Imhof et al. [62]</td>
<td>Folic acid</td>
<td>No effect</td>
<td>N/A</td>
</tr>
<tr>
<td>Lenz et al. [63–65]</td>
<td>GSH</td>
<td>Increased sperm motility and morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Kodama et al. [12]</td>
<td>GSH</td>
<td>Increased sperm concentration</td>
<td>N/A</td>
</tr>
<tr>
<td>Atig et al. [66]</td>
<td>GSH</td>
<td>Maintained good sperm quality and motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Oeda et al. [67]</td>
<td>NAC</td>
<td>Preserved sperm motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Erkkila et al. [68]</td>
<td>NAC</td>
<td>Improved germ cell survival</td>
<td>N/A</td>
</tr>
<tr>
<td>Comhaire et al. [24]</td>
<td>NAC</td>
<td>Decreased ROS. No effect on semen motility and morphology</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*(Continued)*
<table>
<thead>
<tr>
<th>Study</th>
<th>Antioxidant</th>
<th>Effects on Semen Quality</th>
<th>Reproductive Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciftci et al. [69]</td>
<td>NAC</td>
<td>Increased sperm volume, concentration, motility and viscosity</td>
<td>N/A</td>
</tr>
<tr>
<td>Safarinejad and Safarinejad [70]</td>
<td>NAC</td>
<td>Improved sperm motility and morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Noack-Fuller et al. [71]</td>
<td>Selenium</td>
<td>Preserved normal sperm morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Scott et al. [26]</td>
<td>Selenium</td>
<td>Sperm concentration unchanged, increased sperm motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Tremellen et al. [61]</td>
<td>Selenium</td>
<td>N/A</td>
<td>Improved pregnancy rates</td>
</tr>
<tr>
<td>Safarinejad and Safarinejad [70]</td>
<td>Selenium</td>
<td>Improved sperm motility and morphology</td>
<td>N/A</td>
</tr>
<tr>
<td>Wong et al. [59]</td>
<td>Zinc</td>
<td>Improved concentration and sperm count</td>
<td>N/A</td>
</tr>
<tr>
<td>Colagar et al. [72]</td>
<td>Zinc</td>
<td>Improved sperm parameters, increased seminal antioxidant capacity, and reduced oxidative stress</td>
<td>N/A</td>
</tr>
<tr>
<td>Atig et al. [66]</td>
<td>Zinc</td>
<td>Fertile men have greater concentration of zinc than infertile men. Decreased amount of zinc correlated with poor sperm production, concentration, and motility</td>
<td>N/A</td>
</tr>
<tr>
<td>Tremellen et al. [61]</td>
<td>Menevit</td>
<td>No effect</td>
<td>Increased pregnancy rates</td>
</tr>
<tr>
<td>Tunc and Tremellen [73]</td>
<td>Menevit</td>
<td>No change in concentration, motility, or morphology. Increased DNA integrity and protamine packaging</td>
<td>N/A</td>
</tr>
<tr>
<td>Omu et al. [74]</td>
<td>Vitamin E, zinc</td>
<td>Increased motility</td>
<td>Increased fertilization capabilities</td>
</tr>
</tbody>
</table>

**Note:** CoQ₁₀, coenzyme Q₁₀; FSH, follicle-stimulating hormone; GSH, glutathione; IVF/ICSI, in vitro fertilization/intracytoplasmic sperm injection; MDA, malondialdehyde; NAC, N-acetylcysteine; NSAIDs, nonsteroidal anti-inflammatory drugs; ROS, reactive oxygen species; SOD, superoxide dismutase.
antioxidant is not yet well understood, but studies have shown that it can reduce ROS levels and improve semen parameters [24,26]. Studies on vitamin A as a monotherapy have yet to be performed, and therefore, its efficacy as a sole agent remains unknown [25].

Vitamin A has been studied in combination with other antioxidants including zinc, N-acetylcysteine (NAC), selenium, and vitamins C and E. Scott et al. reported a 30% increase in motility after a 3-month regimen of vitamin A supplementation combined with vitamins C and E and selenium [26]. Galatioto et al. found seminal fluid analysis showed that the median value of sperm count was 14.42 (11.75–15.45) millions/mL before treatment and 32.58 (18.75–35.25) millions/mL after antioxidant treatment ($P = 0.009$) [75]. Over-supplementation (above 10,000 IU/day) is associated with decreased visual acuity, skin dryness, hepatotoxicity, gastrointestinal (GI) distress, and other side effects [76]. Vitamin A is found in many foods including meat, dairy products, eggs, fish, fruits, and vegetables such as carrots and leafy greens [25].

Vitamin C is a water-soluble antioxidant that is available in semen at a concentration 10 times higher than that in in serum [77]. It functions in the generation of biomolecules such as collagen, proteoglycans, and other essential intercellular proteins [69]. Vitamin C also prevents peroxy attack by lipoproteins, sustains vitamin E in its reduced form, and defends against oxidative DNA damage [77,78]. Many studies have been performed to assess the efficacy of vitamin C as a supplement and its ability to combat ROS. A study of 42 patients by Thiele et al. showed that vitamin C levels were positively correlated with the number of morphologically normal sperm in a specimen [30]. Most studies combined vitamin C with vitamin E and various other antioxidants [79,80]. Although some studies have reported a possible synergistic effect when vitamins C and E are used together [31], most have shown no efficacy. For instance, a randomized, placebo-controlled, double-blind study in which subjects received 1000 mg of vitamin C and 800 mg of vitamin E for 56 days showed that the regimen had no effect on sperm parameters or pregnancy rates [32]. Studies assessing vitamin E as a monotherapy also found that it had no significant effects [27–29,32]. Over-supplementation with vitamin C has been associated with ROS generation and kidney stones [81,82]. The most common sources of vitamin C are fruits and vegetables [25].

Vitamin E is the most studied vitamin antioxidant. This lipid-soluble vitamin directly blocks lipid peroxidation in the sperm membrane by neutralizing ROS-generated free radicals. Vitamin E may also block ROS formation by diminishing leukocyte attraction via its anti-inflammatory actions [83]. Lastly, vitamin E is similarly thought to reduce ROS by aiding the activity of other important antioxidants in the body [27,28]. Studies contain conflicting data on the efficacy of oral vitamin E supplementation in reducing ROS levels in semen. However, two randomized controlled studies showed that it improved semen parameters. Suleiman et al. reported an increase in sperm motility and a 21% increase in pregnancy rates and decreased malondialdehyde (MDA) levels in asthenozoospermic men after supplementation with vitamin E [33]. In another double-blind randomized, placebo, crossover controlled trial by Kessopoulou et al., a 3-month vitamin E supplementation regimen increased the efficiency of sperm zona binding [29]. In addition to these studies, Geva et al. also showed decreased MDA levels and increased fertilization rates in a prospective study analyzing the effects of a 3-month, 200 mg/day supplementation regimen [34].

The current allowable intake of vitamin E for men is 15 mg/day, with possible side effects beginning at 400 IU [82]. Common sources of vitamin E include fruits, vegetables and vegetable oil, eggs, meat, poultry, grains, and wheat germ [25]. Because it can inhibit platelet aggregation, it is contraindicated in patients with hemorrhagic illnesses or those currently taking anticoagulants [84]. Side effects associated with supplementation include GI distress, rashes, blurry vision, headache, fatigue, and muscle weakness [85].

### 11.2.2 Carnitines

Carnitines, which include both l-carnitine and l-acetyl carnitine, are important water-soluble antioxidants that generate metabolic energy by shuttling long-chain fatty acids across mitochondrial
membranes to initiate β-oxidation. This process generates reducing equivalents in the form of NADH and FADH$_2$ as well as the two-carbon molecule acetyl-CoA which can then be further oxidized in the tricarboxylic acid (TCA) cycle to generate cellular energy. Carnitines provide the principle energy source necessary for sperm motility [86]. They also play a role in protecting the phospholipids of the mitochondrial membrane by preventing the oxidation of fatty acids located within it [41,87]. Carnitines are synthesized in the liver, transported to the epididymal epithelium, and carried into the lumen of the epididymis, which is an important site of sperm development [88]. As antioxidants, they play a role in preventing membrane and DNA damage from free radicals and subsequent apoptosis of the cells [41,42,63,89]. Supplementation with carnitines has also been shown to increase both sperm concentration and motility [36,37]. The effects of carnitines on sperm parameters are thought to occur in the epididymis after the sperm have left the testes [41,63].

For L-carnitine or combined carnitine supplementation, many studies have reported increased motility and/or concentration with supplementation [38–43,46,47]. For example, Vitali et al. studied subjects on a 3-month, 3 g/day supplementation with L-carnitine and found that it increased motility in 78% of patients along with sperm density [40]. Other studies, however, indicated no improvement in semen parameters with L-carnitine supplementation [39,45].

The most prominent sources of carnitines are red meat, but they also may be found in poultry, fish, dairy products, fruits, and vegetables [90]. Supplementation above 4 g/day is associated with GI distress, foul-smelling body odor, and possibly seizures [85].

### 11.2.3 Coenzyme Q$_{10}$

Coenzyme Q$_{10}$ (CoQ$_{10}$) is an antioxidant involved in many biochemical reactions but most commonly in those related to metabolism and the electron transport chain (ETC). Within the ETC, this lipid-soluble molecule transfers electrons from complexes I and II to complex III. Because of the role it plays in mitochondria, it is located primarily in the midpiece of the sperm. As an antioxidant, the active form, ubiquinol, acts as a free radical scavenger for lipoproteins and membrane lipids [83]. This antioxidant may have a natural protective function because its concentration increases with ROS sperm damage [49].

A study by Safarinejad et al. analyzed supplementation with CoQ$_{10}$ in 228 men with idiopathic infertility by dividing them equally into two groups: one received 200 mg of ubiquinol/day and the other received a placebo. This study reported a significant increase in sperm count (9.8%), motility (4.5%), and morphology (1.8%) and an improvement in the efficiency of the acrosome reaction. The authors also reported a significant increase in levels of inhibin B and follicle-stimulating hormone (FSH), indicating that CoQ$_{10}$ had a positive effect on both semen and Sertoli cells [51]. Most recently, Nadjarzadeh et al. showed that supplementation with CoQ$_{10}$ increased catalase and SOD activity and improved sperm concentration and morphology [53]. Several other studies have reported similar positive effects on motility, count, morphology, and pregnancy rates, but whether these improvements are clinically significant remains to be established [44,47,48,50,70]. Mancini et al. found that CoQ$_{10}$ supplementation did little to improve sperm motility and quality in subfertile men with varicocele [91].

Although no Recommended Daily Allowance (RDA) has been established, the optimal dose is thought to be 200–300 mg/day [25]. Common sources of CoQ$_{10}$ include fish, organ meats (heart, kidney, and liver), nuts, soybeans, grains, and vegetables [85]. Over-supplementation has been associated with skin rashes, decreased appetite headache, and GI distress [25].

### 11.2.4 Lycopene

Lycopene is a natural antioxidant that is part of the carotenoid family. This compound scavenges free radicals and prevents cellular membrane and protein damage. It plays a role in immune reactions,
signaling in gap junctions, modulation of cell growth, and regulation of gene expression [92]. Of interest is the fact that lycopene is thought to have the greatest ROS-quenching rate of all the antioxidants [93]. Lycopene levels are high in semen and the testes. Infertile men are noted to have lower levels than fertile men [54].

Several studies have been performed to assess the efficacy of lycopene on semen quality. Gupta and Kumar found that lycopene significantly increased sperm count, motility, and normal morphology. In addition, in the patients who had a sperm count of at least 5 million/mL, supplementation also increased conception rates [54]. A study by Mendiola et al. compared the dietary intake of 30 men with poor semen quality to that of 31 normozoospermic men. In this study, semen quality improved with lycopene supplementation [55].

Lycopene is found in fruits (tomatoes, grapefruits, and watermelons) and vegetables [54]. As of yet, there are only very mild observed side effects (GI distress and skin color change) with gross over-supplementation [25].

### 11.2.5 Arginine

Arginine is a semi-essential amino acid that is a precursor to nitric oxide and spermine. It is necessary for spermatogenesis and sperm motility and plays a crucial role in cell division, wound healing, immune function, and hormone production [94]. Men who have arginine-deficient diets may suffer from low sperm count and have increased levels of nonmotile sperm. In a recent study by Srivastava and Agarwal, arginine improved motility and metabolism in sperm through the nitric oxide pathway [57]. However, the lack of a large number of randomized controlled studies exploring the efficacy of arginine makes it difficult to gauge its effect on male fertility [95,96].

Owing to lack of human data, there is no current RDA for arginine. Sources of arginine include animal and plant products such as dairy, turkey, beef, pork, seeds, soybeans, and nuts [96]. Commonly observed side effects associated with supplementation with arginine are GI distress, renal insufficiency, electrolyte imbalance, hypotension, and increased bleeding risk [95].

### 11.2.6 Folic Acid

Folic acid is a derivative of the water-soluble vitamin B\textsubscript{9} and is essential for the synthesis of purines and thymidine. It also plays a role in many other important cellular functions such as the transfer of one-carbon molecules and promoting proper spermatogenesis, although the underlying mechanism for this process is currently unknown [59,62]. Folic acid also acts as a free radical scavenger to prevent damage to lipids and proteins [86]. Infertile men may have lower concentrations of folic acid than fertile men [97].

Several studies have noted that folic acid supplementation improves sperm quality. A study by Wong et al. showed an increase in sperm concentration despite a lack of improvement in sperm motility or morphology [59]. Ebisch et al. showed that a decrease in folic acid concentration in seminal plasma correlated with an increase in sperm DNA damage [60]. These findings underscore the role folic acid plays in DNA synthesis and protein methylation reactions [98]. Despite these positive results, several other studies have reported that folic acid supplementation is ineffective in improving sperm quality. Originally, a study by Landau et al. reported that folic acid alone failed to improve sperm concentration in subfertile men [58]. A more recent study by Imhof et al. showed that supplementation with folic acid in fertile and subfertile men did not improve sperm parameters [62].

Sources of folic acid include green, leafy vegetables, beans, citrus fruits, and avocados. Over-supplementation with folic acid is associated with GI distress, rash, sleep disturbances, confusion, increase in seizure frequency, allergic reaction, and increased risk for myocardial infarction [99–101].
11.2.7 Glutathione

Glutathione (GSH) is an essential antioxidant that is synthesized in the liver and transported into the epididymis. It alleviates OS and helps maintain exogenous antioxidants in their active state. It is the most abundant reducing agent in the body, making it vital to the intracellular defense against ROS [86]. Its sulfhydryl group directly neutralizes superoxide anions and other free radicals and therefore protects proteins and nucleic acids against oxidative damage [26,86]. Many studies have shown that GSH supplementation has a positive effect on semen parameters. Others have found that it increases sperm motility, morphology, counts, and forward progression as well as prevents DNA fragmentation [63–65,102]. Recently, Atig et al. studied the altered antioxidant status of the seminal plasma in infertile men and found that GSH helps maintain good sperm quality and motility. These authors showed that infertile men may have lower GSH levels than fertile men and that insufficient amounts of GSH can lead to abnormal sperm motility. In addition, their results suggested that GSH may enhance fertility by reducing lipid peroxidation [66].

GSH is found in fresh meat, fruits, and vegetables. The maximum RDA is 3 g/day [86], and a deficiency of GSH results in an unstable sperm midpiece, leading to defective morphology and motility [103].

11.2.8 N-AcetylcySteine

N-Acetylcysteine (NAC) is a nontoxic derivative of l-cysteine. It is a precursor of GSH and promotes its production to assist in neutralizing ROS [104,105]. It can also interact directly with oxidants, thiols, and hydroxyl radicals to remove free radicals and reduce oxidative stress in seminal plasma [69]. Many studies have shown that it has a beneficial effect on semen parameters. An in vitro study by Erkkila et al. showed that NAC improved germ cell survival [68]. Several studies have reported increased sperm motility, concentration, volume, and viscosity. Additional improvements included decreased ROS levels, increased efficiency of the acrosome reaction, and reduced oxidation of the sperm DNA [24,67,69,75]. In contrast, another study found that NAC supplementation did not improve semen parameters even though its seminal plasma concentration increased [51].

Sources of NAC include poultry, yogurt, egg yolks, oats, onions, and other vegetables. The limited side effects associated with supplementation are GI distress, rash, fever, headache, drowsiness, hypotension, and hepatic toxicity [106].

11.2.9 Selenium

Selenium is an essential micronutrient necessary for normal male reproductive function, testicular development, spermatogenesis, and spermatozoa motility and function [107]. It is a required cofactor for the reduction of antioxidant enzymes. It maintains sperm structural integrity by protecting against oxidative DNA damage. However, the exact mechanism of its action remains unknown [5,86]. Many studies have shown a positive correlation between increased selenium levels and increased sperm concentration, motility, and normal morphology [26,70,71,108].

Selenium is commonly found in soil, plants, and meat. The current recommended daily dose of selenium is 55–400 mcg [86]. A selenium deficiency is linked to decreased motility, breakage at the midpiece, and sperm head morphologic abnormalities. On the other hand, over-supplementation is associated with GI distress, nail changes, fatigue, and irritability [109]. Excessive intake has also been linked to serious side effects such as liver cirrhosis, pulmonary edema, and even death [83].

11.2.10 Zinc

Zinc is an essential micromineral that is an important cofactor for metalloenzymes, and it plays a role in DNA transcription and protein synthesis [86]. Zinc SOD is involved in DNA repair [96]
and also helps increase the concentration of GSH, both of which limit the damaging effects of ROS [86]. Many studies have reported that zinc supplementation improves sperm parameters such as concentration, progressive motility, and sperm integrity as well as pregnancy rates. In an in vivo study, men treated with 66 mg of zinc daily for 6 months experienced improved sperm concentration and count [59]. Omu et al. conducted a prospective study that showed zinc therapy increased sperm parameters and antioxidant capacity and reduced sperm DNA fragmentation and apoptotic markers. Omu’s study also showed that fertile men have a greater concentration of zinc than infertile men and that a decrease in zinc concentration leads to an increase in OS and loss of sperm integrity [74]. A study by Colagar et al. showed improved sperm parameters, an increase in seminal antioxidant capacity, and a reduction in oxidative stress with zinc supplementation [72]. These results suggest that zinc may be useful in reducing OS and thus helping prevent sperm membrane and DNA damage [86].

A study by Atig et al. showed that fertile men have a greater concentration of zinc in their seminal plasma than infertile men. The researchers also found that the infertile men had an increased ROS level, which is associated with increased abnormal sperm parameters. They reported a positive correlation between decreased zinc levels and poor sperm production and concentration as well as motility [66]. Zinc supplementation has been shown to improve sperm parameters such as concentration, progressive motility, sperm integrity, and pregnancy rates.

Zinc is found naturally in soil, plants (such as wheat and seeds), beef products, oysters, and liver. Zinc deficiency has been associated with abnormal flagella and deformed midpiece [86]. The limited amount of experimental data for humans prevents the establishment of an RDA [110]. Side effects that may be a consequence of zinc supplementation above 200 mg/day include GI distress, rash, headache, loss of appetite, and dehydration [85]. More severe side effects such as anemia, low copper levels, impaired iron function, reduced immune function, and decreased high-density lipoprotein (HDL) levels are associated with supplementation above 450 mg/day [111].

### 11.2.11 Combination Antioxidant Therapy

Many research studies have focused on the use of combination therapy to determine whether there is a beneficial synergism between individual components. Vitamin E has been studied in several other combinations with different antioxidants. Keskes-Ammar conducted an in vivo study in which men were given a mixture of vitamin E and selenium daily for 6 months. Sperm motility was the only sperm parameter that improved [35]. A study by Omu et al. showed that combination supplementation with vitamins C and E and zinc improved motility and fertilizing capacity [74]. Wong et al. showed that combined supplementation with zinc and folic acid improved sperm concentration and sperm count [59]. Other examples include combination therapies with selenium and vitamins A, C, and E [26]; NAC with vitamins [75]; as well as nonsteroidal anti-inflammatory drugs (NSAIDs) combined with carnitines [42,56] as discussed previously in this chapter. One study showed that the combination of NAC and selenium improved sperm count, motility, and morphology [70].

One important emerging combination supplement is Menevit, which is a synthetic compound composed of several common antioxidants. It includes vitamin C, vitamin E, zinc, folic acid, lycopene, garlic oil, and selenium. This supplement was designed so that the different components would perform specific functions to reduce ROS levels synergistically and increase semen parameters and sperm quality. To date, two studies have been performed to analyze the efficacy of Menevit. In the first one, Tremellen et al. studied 60 couples with known male factor infertility. They found that Menevit supplementation increased in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) pregnancy rates better than placebo [61]. In the second study, Tunc et al. assessed the antioxidant therapy in 50 infertile male patients for 3 months. In that study, Menevit reduced ROS levels and apoptosis in sperm cells while improving DNA integrity and protamine packaging [73]. Neither of these studies found any improvements in sperm count, motility, or morphology [61,73].
11.3 HERBAL THERAPY FOR MALE INFERTILITY

Herbal therapy, along with other complementary and alternative therapies, is used for medicinal purposes in the treatment of infertility in up to 18% of cases in the United States [112]. It has been known to regulate systemic dysfunctions naturally and may affect levels of luteinizing hormone (LH), FSH, and testosterone in humans. In an in vivo animal study by Abdillahi and Van Staden, aqueous stem extracts of Bulbine natalensis were shown to increase blood testosterone concentrations in animals, thereby modifying their sexual function and behavior (especially effective for rats that have hypotestosteronemia) [113]. In a rodent study by Wang et al., 8 weeks of supplementation with the Wuziyanzong herbal pill lead to improvements in sperm quality. These improvements included such parameters as sperm density and viability and mitochondria in rodents with oligoasthenozoospermia [114]. In the in vitro study of Peng et al., human spermatozoa were incubated with Tu Si Zi, which enhanced spermatic motility [115]. In another in vitro study, the combination of six herbal extracts incubated with infertile male semen resulted in an increase in viability, number of progressive motile sperm, curvilinear velocity, average path velocity, and lateral head displacement [116].

Clinical observations of married couples showed that the herb Sheng Jing Zhongzi Tang improved spermatic density, motility, percentage of normal spermatid morphology, and pregnancy rates [117]. This herb was also associated with a decrease in the amount of antisperm antibodies in the semen [118]. In an investigation of Withania somnifera effects on semen, the herb effectively reduced various oxidants, decreased OS, and increased antioxidant levels. This herbal treatment also returned levels of testosterone, LH, FSH, and prolactin back to normal in infertile men [119]. In another study, 219 men with varicocele-associated infertility were treated for 2 months with a daily dose of 60 mg of Escin, an extract of Aesculus hippocastanum seed. The herb was shown to target OS, resulting in an increase in sperm motility, density, and normal sperm morphology. In addition, Escin significantly improved the severity of varicocele [120]. These results were similar to those of another study in which infertile men treated with Bu-Zhong-yi-qi-tang for 3 months experienced an increase in sperm concentration and motility [121]. Another herb, Rou Cong Rong, was shown to promote the sperm generating functions of the testes as well as improve the microenvironment of epididymis.

### TABLE 11.2

<table>
<thead>
<tr>
<th>Study</th>
<th>Compound</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peng et al. [115]</td>
<td>Tu Si Zi</td>
<td>Improved sperm motility</td>
</tr>
<tr>
<td>Liu et al. [116]</td>
<td>Mixed herbal (6 components)</td>
<td>Increased viability, number of motile and progressive sperm, curvilinear velocity, average path velocity, and lateral head displacement</td>
</tr>
<tr>
<td>Furuya et al. [121]</td>
<td>Bu-Zhong-yi-qi-tang</td>
<td>Increased concentration and motility</td>
</tr>
<tr>
<td>Sun and Bao [122]</td>
<td>Yikang Tang</td>
<td>Improved sperm parameters and pregnancy rates</td>
</tr>
<tr>
<td>Tijani et al. [123]</td>
<td>Manix</td>
<td>Improved sperm quality</td>
</tr>
<tr>
<td>Ahmad et al. [119]</td>
<td>Withania somnifera</td>
<td>Decreased oxidative stress and increased levels of antioxidants</td>
</tr>
<tr>
<td>Fang et al. [120]</td>
<td>Escin</td>
<td>Increased sperm motility, sperm density, and normal sperm morphology</td>
</tr>
<tr>
<td>Yang et al. [109]</td>
<td>Sheng Jing Zhongzi Tang</td>
<td>Improved spermatic density, motility, percentage of normal spermatid morphology, and pregnancy rates</td>
</tr>
<tr>
<td>Yang et al. [109]</td>
<td>Rou Cong Rong</td>
<td>Increased sperm generation in testes</td>
</tr>
<tr>
<td>Abdillahi and van Staden [113]</td>
<td>Mixed herbal</td>
<td>Increased serum testosterone levels</td>
</tr>
<tr>
<td>Wang et al. [114]</td>
<td>Wuziyanzong herbal pill</td>
<td>Increased sperm density and improved sperm viability</td>
</tr>
</tbody>
</table>
In a 6-month study, men with idiopathic oligozoospermia treated with Manix, a combination of 11 herbs with honey and sugar, experienced a significant improvement in sperm count, motility and density, and serum testosterone levels. The only sperm parameter that did not improve was semen volume [123]. Another study conducted on 100 infertile men utilized an herbal combination called Yikang Tang. The therapy increased sperm parameters and pregnancy rates while decreasing the sperm agglutination rate [122]. Other combinations of herbs taken by infertile men have also been shown to significantly reduce sperm disomy [124].

In vitro studies and clinical trials have continuously found that the use of herbal treatment can improve OS-induced male infertility [113]. Herbal treatments may become a more important factor in treating male infertility in the future, and they have been shown to significantly increase sperm density and sperm viability [114]. Most research indicates that these supplements have little effect on vital signs, blood counts, and liver and kidney function [120], which may make them a safer option than some currently prescribed medications [125]. Herbal treatments may also offer a better and safer method to restore sex hormones in infertile men [119]. Unfortunately, owing to a lack of studies, the data surrounding their efficacy is very limited. More research on herbal treatments should be explored to further evaluate their effects and possible clinical applications and their potential side effects. Table 11.2 shows herbal therapy for male infertility.

11.4  THE ROLE OF NUTRITIONAL SUPPLEMENTATION IN THE TREATMENT OF CHRONIC PROSTATITIS

Chronic prostatitis is just one of the many causes of OS-induced male infertility. We have included it in this chapter because it is a rising problem. It affects up to 14% of men of reproductive age and is difficult to treat. This condition, defined as inflammation of the prostate gland with genitourinary pain but without the presence of bacteria, is associated with increased ROS levels and sperm damage [126]. Kullisaar et al. reported a positive correlation between chronic prostatitis and seminal OS [127]. The most common symptoms involve the lower urinary tract and often include genitourinary pain, dysuria, and altered frequency, although a host of other symptoms have also been linked to this condition [128]. The National Institutes of Health (NIH) International Prostatitis Collaborative Network divides prostatitis into four categories: (1) acute bacterial prostatitis, (2) chronic bacterial prostatitis, (3) chronic prostatitis or chronic pelvic pain syndrome (CPPS), and (4) asymptomatic prostatitis [129]. Of particular importance is category III (genitourinary pain without bacteria present), which is the most prevalent among the four categories [129,130]. The causes of CPPS may be such conditions as an unidentified bacterial infection (Ureaplasma and Mycoplasma), autoimmune or inflammatory reactions (including ROS, inflammatory cytokines, and white blood cells), and other causes such as pelvic muscle spasms and anti-inflammatory drug supplementation [131–133].

Much of the current therapy for chronic prostatitis involves a multidisciplinary approach involving dietary supplementation, acupuncture, and physical therapy. Several antioxidants have been investigated as possible treatments, but few have been researched in great detail. In one study, a 3-week regimen of lycopene decreased prostate-specific antigen (PSA) levels [134]. Lycopene supplementation has also been associated with decreased interleukin-6 (IL-6) production and therefore decreased inflammation [135]. This anti-inflammatory effect may act synergistically with other agents such as zinc, selenium, ellagic acid (EA), and epigallocatechin-3-gallate (EGCG) [116,136]. Vicari et al. described carnitines as a possible therapy for chronic prostatitis owing to their ability to reduce ROS and oxidative damage and improve semen parameters [56].

In addition to the aforementioned dietary supplements, several compounds have also been investigated as possible treatments for chronic prostatitis. One study examined supplementation with pollen extract (Cernilton) in patients with CPPS. Supplementation increased the patient-reported quality of life, decreased pain, and generally improved patients’ overall well-being [128]. The use of quercetin, a flavinoid, has also been explored. Shoskes conducted a preliminary prospective,
double-blind, placebo-controlled trial in which men with CPPS received 500 mg of quercetin twice daily for 1 month. Mean NIH chronic prostatitis symptom scores decreased (from 21 to 13), and 67% of the patients experienced an improvement in symptoms [137]. Another study by Shoskes et al. showed that 84% of patients with chronic prostatitis experienced an improvement in their symptoms after supplementation with quercetin for 26 weeks [139].

Another common nutritional supplement is saw palmetto. Kaplan et al. indicated that supplementation with saw palmetto did not have any long-term efficacy in relieving the symptoms of chronic prostatitis [138]. Another researched nutritional supplement is profluss. Morgia et al. showed that treatment with profluss (composed of *Stylidium repens*, selenium, and lycopene) effectively improved symptoms associated with CPPS [126]. Although some trials showed improvements with supplemental treatment, more studies with larger, more defined cohorts are needed to draw meaningful conclusions and to determine the clinical efficacy of these supplements in the management of chronic prostatitis. Table 11.3 shows nutritional supplements for the treatment of chronic prostatitis.

### TABLE 11.3
**Nutritional Supplements for the Treatment of Chronic Prostatitis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Supplement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoskes et al. [137]</td>
<td>Quercetin</td>
<td>Improved NIH symptom score</td>
</tr>
<tr>
<td>Kaplan et al. [138]</td>
<td>Saw Palmetto</td>
<td>No long-term improvement in prostate parameters</td>
</tr>
<tr>
<td>Herzog et al. [135]</td>
<td>Lycopene</td>
<td>Decreased IL-6 and inflammation</td>
</tr>
<tr>
<td>Wagenlehner et al. [128]</td>
<td>Cernilton</td>
<td>Increased quality of life, decreased pain, and improvement of overall condition of chronic prostatitis</td>
</tr>
<tr>
<td>Shoskes et al. [139]</td>
<td>Quercetin</td>
<td>Improved pain, urinary symptoms, and quality of life</td>
</tr>
<tr>
<td>Morgia et al. [126]</td>
<td>Profluss (<em>Stylidium repens</em>, selenium, and lycopene)</td>
<td>Decreased CPPS symptoms</td>
</tr>
<tr>
<td>Lombardo et al. [134]</td>
<td>Lycopene</td>
<td>Decreased PSA</td>
</tr>
</tbody>
</table>

*Note:* CPPS, chronic pelvic pain syndrome; IL-6, interleukin-6; PSA, prostate-specific antigen.

**11.5 CONCLUSION**

Owing to the growing prevalence of infertility around the world, much research is being devoted to understanding its underlying causes and in devising more effective treatments. Many current therapies for treating OS-induced male infertility are not fully reliable and are expensive. Owing to the ever-growing cost of medical care, alternative therapies represent a possible way to minimize costs and improve pregnancy rates. A systematic review of the literature indicates that a wide variety of supplementation is available for the treatment of OS. Theoretically, supplementation with antioxidants should provide a valuable solution to OS-related sperm damage. Although many experiments and trials have been performed, the efficacy of many of these antioxidants has not been proven and, as a result, acceptable daily allowances have yet to be established. Many antioxidants decrease ROS levels and increase sperm motility, morphology, and count with supplementation. An increase in pregnancy rates is also often observed. Many trials, however, report conflicting data for the same antioxidant, indicating that larger trials and more well-defined studies are needed to fully uncover the hidden mechanisms that may be present. Furthermore, even when an antioxidant is positively correlated with sperm quality, it is often difficult to infer with a high degree of confidence whether the effect is clinically relevant. In general, little research has been performed to find alternative,
Nutritional Supplementation for the Treatment of Male Infertility

Nonantioxidant treatments and herbal supplements for the treatment of OS-induced male infertility, as these generally exist outside of current mainstream medical care. Both of these treatment strategies, however, are becoming more prevalent and may one day represent the preferred treatment option. One of the most important and fundamental issues is finding the normalized cutoff values that define OS and subsequent sperm damage. This has yet to be elucidated partially because current methods for measuring ROS are expensive and unreliable.

In conclusion, studies investigating antioxidants and other nutritional supplements often suffer from a lack of standardization, making it difficult to quantify the results of a given study. For the efficacy of these supplements to be determined, larger trials with high-quality controls and randomization must be performed to establish clinically relevant guidelines for supplementation.

11.6 KEY POINTS SUMMARY

1. Infertility affects 15% of couples, with impairment in sperm function being the primary underlying cause in up to 40% of cases.

2. Although the causes for sperm dysfunction in male infertility are many and varied, oxidative stress related damage to sperm appears to be a contributing factor in up to 80% of cases. Oxidative stress occurs when the production of reactive oxygen species (ROS) by leukocytes or sperm themselves exceeds the neutralizing capacity of antioxidants contained in the sperm or seminal plasma, resulting in damage to the sperm. This oxidative damage impairs fertility by reducing sperm motility (direct ROS damage to the sperm tail or mitochondrial energy source for sperm propulsion), by damaging the sperm acrosomal membrane leading to impaired fertilization capacity, or by initiating paternal DNA fragmentation.

3. The use of nutrition supplements with antioxidant capacity to prevent ROS-mediated damage to sperm function holds promise as an effective treatment of male infertility for several reasons. First, nutrients such as minerals (zinc, selenium), vitamins (vitamin C, folate), and phytochemicals (lycopene), all with powerful antioxidant capacity, have been reported to be present in lower concentrations in the serum or seminal plasma of men experiencing infertility. Therefore, supplements of these nutrients may reverse these relative deficiencies, bolstering natural antioxidant defenses and in turn improve sperm quality. Second, several studies have shown that antioxidants such as vitamin C, vitamin E, and selenium do have the capacity to reduce oxidative damage to the sperm membrane and DNA, which theoretically should improve sperm functionality.

4. Although the theoretical basis for antioxidant supplementation to boost sperm function and assist male fertility is strong, the quality of studies proving this point is poor for several reasons. First, the majority of studies are not placebo controlled, making firm therapeutic conclusions impossible. Second, very few studies have fertility (live birth) as the primary outcome, with the majority reporting only changes in sperm parameters. Although an antioxidant nutritional supplement may produce a statistically significant improvement in sperm concentration or motility, it is not always possible to extrapolate that this will translate into improvements in natural fertility given the limited diagnostic sensitivity of routine semen analysis for natural fertility. Finally, although dozens of studies have been conducted examining the effects of antioxidant herbal or nutritional supplements on sperm quality or fertility, each has tended to use a different combination of antioxidants at various dosages, making firm conclusions by comparison of studies impossible.

5. No universally accepted antioxidant nutritional supplement for the treatment of male infertility has been agreed on. However, scientific principles would suggest that a combinational approach using antioxidants with different modes of action would have the best chances of success. For example, the use of a combination of vitamin C and vitamin E is likely to be useful, as vitamin C potentiates the antioxidant effect of vitamin E by keeping it in its active form.
reduced form. The nutrients zinc and selenium are likely to be useful for their direct antioxidant effect and because they play an important role in protamine packaging of sperm DNA, protecting it from ROS-mediated attack. Carnitine and coenzyme Q$_{10}$ both play important roles in sperm mitochondrial energy production, above and beyond their antioxidant effects. Therefore, these two agents are likely to boost sperm motility and fertility potential. Finally, the group B vitamin folate has been shown to boost sperm quality, possibly due to its antioxidant effects and its important role in DNA synthesis. Although the results of clinical studies are conflicting, all of the above nutrients have been shown to boost sperm quality, as have nutrients such as lycopene, glutathione, N-acetylcysteine, and antioxidant herbs such as *Withania somnifera* and *Aesculus hippocastanum*.

6. Future placebo-controlled studies with clinically important end points (sperm DNA damage, live birth) will need to be conducted before firm conclusions can be drawn on the benefits of antioxidant nutritional supplements for the treatment of male fertility. However, as antioxidants are generally inexpensive and carry minimal side effects, a combination antioxidant therapy appears to be a reasonable treatment for optimizing male fertility potential.

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