Nutritional Pathways to Protect Male Reproductive Health

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Key Points

- Oxidative damage is associated with alterations in spermatogenesis and subfertility.
- Several nutrients – including arginine, zinc, selenium, vitamin C, vitamin E, and carnitine – have been identified as antioxidant compounds and implicated in male reproductive health.
- In some studies, these antioxidant compounds have been shown to improve semen parameters and fertility outcomes.
- It is unclear what role antioxidant supplementation plays on male reproductive health and fertility outcomes.
- Obesity and alcohol intake have been found to have variable effects on semen parameters and remain the subject of active investigation.

42.1 Introduction

Nutrition is an essential component of one's overall health. Many common disease processes can be alleviated or prevented by a healthy diet. First reports of antioxidant deficiency and decreased male fertility can be traced back to over 50 years ago [1]. With the understanding of oxidative damage to spermatogenesis, most of the nutritional research has focused on the role of antioxidants in improving male fertility. However, there are not any randomized controlled trials studying whole food diet in infertile male patients. Patients are often counseled based on data extrapolated from antioxidant supplement studies. This chapter is intended to give an overview of contemporary research on nutrient and male reproductive health with guidance to natural food sources that contain high levels of antioxidants.

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42.2 Nutrients and Male Reproductive Health

42.2.1 Arginine

Arginine is a semi-essential amino acid because it can be synthesized by the human body from glutamine, glutamate, and proline. It plays an important role in cell division, wound healing, immune function, hormone production, and ammonia metabolism. Arginine also serves as a precursor for nitric oxide synthesis and, therefore, has significant effects on endothelial function. It is involved in the pathophysiology of many vascular disorders including vasogenic erectile dysfunction [2].

Arginine is required for normal spermatogenesis. Researchers have found that adult men on an arginine-deficient diet have decreased sperm counts and an increased percentage of nonmotile sperm [1]. Oral administration of arginine to infertile men for 6–8 weeks has shown improvement in sperm counts, motility, and conception rates [3–6]. However, similar benefits were not observed in patients with baseline sperm concentrations of less than 10 million/mL [7]. Interestingly, in animal models, higher doses of L-arginine supplementation actually inhibit fertility compared to controls, suggesting that further research is needed to establish the optimal dose needed for enhanced fertility outcomes [8].

Since de novo biosynthesis does not produce sufficient arginine to meet bodily needs, dietary intake remains the primary determinant of plasma arginine levels. It is considered

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an essential nutrient for human children but not adults by the US Department of Agriculture [9]. Currently, there is not a consensus on the daily recommended intake of arginine; studied doses range from 1 to 15 g/day. Although no significant adverse effects have been observed in studied doses, patients with impaired renal or hepatic dysfunction might not be able to metabolize arginine properly. The effect of arginine on the airway is also unclear, and caution should be taken in asthmatic patients. Animal sources of arginine include dairy products, turkey, pork, and beef. Vegetable sources include seeds, soybeans, and nuts.

42.2.2 Zinc

Zinc is an essential micromineral. There are 2–4 g of zinc throughout the human body with the highest concentrations found in the prostate and parts of the eye [10]. It serves as a metalloprotein cofactor for DNA binding and, as part of the enzyme copper/zinc superoxide dismutase, is involved in the repair of damaged DNA. It also has an important role in testis development and sperm function. Consequently, zinc deficiency is associated with hypogonadism, testicular/seminiferous tubular atrophy, and inadequate development of secondary sexual characteristics [11].

Semen analyses of fertile and infertile men have shown a positive correlation between low zinc levels and poor sperm quality [12]. Specifically, higher levels of zinc in seminal fluid have been found to be associated with increased sperm count and normal sperm morphology [12]. Treating men with asthenozoospermia with zinc for 3 months also demonstrated an improvement in semen parameters, an increase in seminal antioxidant capacity, and a reduction of oxidative status [13]. Researchers postulate that poor zinc nutrition can impair antioxidant defenses, be a risk factor in oxidant release, and compromise the mechanism of DNA repair, making the sperm cells highly susceptible to oxidative damage [12, 13]. In order to combat this oxidative damage, there is an increasing concentration of extracellular zinc throughout the length of the reproductive tract. While the seminiferous tubules have a zinc concentration similar to that of nonreproductive organs (i.e., liver, kidney), the epididymis, vas deferens, and seminal vesicles all have a progressively greater concentration of zinc. Ultimately, the spermatozoa are ejaculated in the seminal plasma, which has a zinc concentration nearly 100 times greater than blood [14]. This increase in zinc concentration is largely secondary to the expression of zinc transporters throughout the reproductive tract. Recent studies have begun to elucidate these pathways involved in zinc transport. For example, we now know that the epithelial cells of the testis and epididymis appear to be programmed to supply zinc, while the spermatozoa are designed to rapidly take it up. This suggests that zinc trafficking may play a role in the process of sperm maturation and sperm quality [14].

Currently, there is limited data available in humans to establish a dietary dosage of zinc necessary to achieve optimal seminal plasma levels. The daily recommended dietary allowance of zinc is 8 mg/day for women and 11 mg/day for men [9]. Excess zinc absorption (>15 mg/day) can interfere with copper and iron absorption, disrupt cholesterol metabolism, and cause anosmia. Animal sources of zinc include red meat, oysters, and liver. Vegetable sources include seeds, nuts, and whole grains.

42.2.3 Selenium

Similar to zinc, selenium is an essential micronutrient. It functions as a cofactor for antioxidant enzymes, such as glutathione peroxidase. Although rare in a healthy, well-nourished adult, selenium deficiency is associated with reduced or impaired reproduction [15]. A sperm-specific selenoprotein has been identified and is suspected to play a key role in selenium deficiency-induced subfertility [16]. In fact, a number of selenoproteins have been found to protect against oxidative damage during sperm maturation, as well as act as structural components of mature spermatozoa [17]. Specifically, x-ray fluorescence microscopy has shown that selenium is concentrated within the sperm head and midpiece structures [18]. Selenoproteins are also critical for transporting this selenium from the blood to the testis, condensing chromatin during sperm maturation, and ensuring normal sperm morphology [17].

Despite selenium's many roles on the cellular level, population studies on the effect of selenium in subfertile men have yielded conflicting results [19, 20]. In a randomized, double-blinded study, treating subfertile men with selenium once a day showed no influence on sperm count but did demonstrate an improvement in sperm motility compared to placebo [21]. Ultimately, more research is needed to fully understand the impact of selenium on semen parameters.

The recommended daily allowance for selenium is 55 μg/day for men [22]. Selenosis can occur when intake reaches the level greater than 400 μg, and may result in cirrhosis, pulmonary edema, and death. In Europe there has been a documented decline in the mean intake from 60 μg/day in the 1970s to 30 μg/day in the 1990s due to a change in the source of cereals for bread making; it is unclear what impact this decline has had on male reproductive health [23]. In addition to wheat/cereals, other vegetable sources include Brazil nuts and soy products. Animal sources of selenium include meat, fish, and eggs.

42.2.4 Vitamin C

Ascorbic acid is an essential nutrient for humans and other animal species. It has been associated with fertility for many years; however, the precise mechanism of action has not been elucidated. Most consider the effect of vitamin C on fertility to be related to these three principal functions: promotion of collagen synthesis, role in hormone production, and protection or prevention against oxidation.

Early reports on the effects of vitamin C on male fertility were based on animal studies. Ascorbate deficiency was associated with poor breeding performance and degeneration of the testicular germinal epithelium [24, 25]. The gonadal growth-enhancing effects of gonadotropins were enhanced by simultaneous treatment with ascorbic acid [26]. As one recent animal model demonstrated, oral vitamin C administration was associated with a dose-dependent increase in serum FSH level and serum testosterone, as well as sperm motility and normal sperm morphology [27]. In human studies, low ascorbate level has been associated with low sperm counts, increased number of abnormal sperm, reduced motility, and agglutination [28]. Dietary treatment with vitamin C has yielded mixed data on improvement of sperm parameters [29]. In one recent randomized trial, men treated with 1000 mg of vitamin C every other day for 6 months were found to have a significant increase in sperm concentration and motility [30]. However, additional trials are needed to reproduce this improvement in the semen parameters and assess the pregnancy rates of healthy infertile men who take oral vitamin C supplements.

The recommended daily allowance of vitamin C is 90 mg/day for adult male and 75 mg/day for adult female [9]. Dietary intake should not exceed 2300 mg/day since intoxication can lead to gastrointestinal disturbances, iron poisoning, and even hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency. A well-balanced diet without supplementation is generally sufficient to meet the daily requirement for vitamin C, except those who are pregnant or smoke tobacco. The highest natural sources are fruits and vegetables, particularly black currant, red pepper, and guava.

42.2.5 Vitamin E

Vitamin E is a lipid-soluble antioxidant. It protects cell membranes from oxidation by reacting with the free radicals generated during lipid peroxidation. Various forms of vitamin E have been identified, but the exact role and importance of these isoforms remains unclear. It is known, however, that the motility of spermatozoa depends on the integrity of the mitochondrial sheath, which is composed of phospholipids and can be damaged by lipid peroxidation [31]. Therefore, vitamin E has been hypothesized to be an important factor for mitigating damage to this phospholipid-rich mitochondrial sheath structure and maintaining overall health of sperm.

Specifically, men with asthenozoospermia have been found to have an increased concentration of the peroxidation by-product malondialdehyde (MDA) in their seminal fluid. Treating these patients with vitamin E in a randomized, double-blinded fashion showed improvement in sperm motility and decreased MDA concentration, as well as resulted in successful pregnancies for 11 of the 52 (21%) patients [32]. However, these improvements in semen parameters were not seen in other randomized controlled trials [33, 34].

Additionally, studies of vitamin E supplementation in combination with other micronutrients have shown mixed results. For example, one randomized trial comparing daily supplementation with both vitamin E and selenium versus controls demonstrated a significant decrease in MDA concentration and improvement in sperm motility among patients in the treatment group [35]. Other studies examining the effect of both vitamin C and vitamin E supplementation, however, failed to show any improvement in semen parameters [36, 37]. Ultimately, few studies have demonstrated any significant effect on semen parameters using vitamin E as either a single treatment or in combination with other antioxidants [38].

The recommended daily intake of vitamin E is 15 mg (30 IU) per day for adults [9]. A dose greater than 1000 mg (1500 IU) per day is associated with an increased risk of hemorrhage and death. The best sources of vitamin E are nuts, seeds, and vegetable oils, along with green leafy vegetables and fortified cereals.

42.2.6 L-Carnitine

Carnitine is a semi-essential nutrient that can be biosynthesized from lysine and methionine by the liver and kidneys. Two stereoisoforms exist, with L-carnitine as the bioactive form. It is involved in the metabolism of long-chain fatty acids and serves as an antioxidant by removing acetyl-CoA, which is responsible for mitochondrial lipid peroxidation [39]. This antioxidant effect is so significant that, in animal models, L-carnitine supplementation has been shown to protect against gamma-irradiation-induced testicular injuries [40]. The highest concentration of carnitine occurs in the epididymis, with epididymal concentrations being 2000-fold higher than plasma [41].

Low seminal levels of L-carnitine have been associated with subfertility. In one single-center study of 61 men all azoospermic, asthenospermic, and oligoasthenoteratospermic men were found to have significantly lower levels of seminal free L-carnitine compared to fertile controls, with a lowest value of seminal free L-carnitine being found in the azoospermic group [42]. Given these findings, it has been hypothesized that L-carnitine supplementation may improve semen parameters. A multicenter, uncontrolled trial showed that oral administration of L-carnitine (3 g/day) for 4 months in asthenozoospermic patients resulted in an improvement in sperm motility, linearity index, rapid linear progression, and mean velocity [43]. In a randomized, double-blinded, placebo-controlled trial, L-carnitine therapy (2 g/day) for 4 months in infertile men showed improvements in sperm concentration and motility [44]. However, L-carnitine monotherapy may not be as beneficial as combination therapy. In one prospective, nonrandomized study of men with at least 1 year of subfertility and one abnormal semen analysis, participants were treated with either 3 months of L-carnitine or with a combined compound which included L-carnitine as well as several other micronutrients. While all semen parameters (volume, density, overall progressive motility, percent normal morphology) improved significantly from baseline in both groups, the relative change in sperm density and overall progressive motility was greater for the combined micronutrient treatment group compared to the L-carnitine monotherapy group [45]. Despite the observed improvement of semen parameters with carnitine supplementation in these studies, other randomized controlled studies have not been able to replicate similar results [46].

Seventy-five percent of the carnitine that is present in humans is derived from diet [47]. Currently, there is not a recommended daily allowance of carnitine intake or any detrimental reports of carnitine overdose. Oral intake greater than 1 g/day did not show any advantage, since absorption studies indicate saturation at this level. The highest concentration of carnitine is found in red meat and dairy products. Vegetable sources include nuts, seeds, and asparagus.

42.3 Factors Contributing to Subfertility

42.3.1 Obesity

Multiple population-based studies suggest an increased risk of subfertility among obese couples [48]. In women, there has been extensive research on the effects of body composition on altered menstrual function and fertility [49]. Epidemiologic studies have also observed a higher incidence of male factor infertility in obese males [50, 51]. Obese men often exhibit an altered reproductive hormone profile, including decreased androgen levels, decreased sex hormone-binding globulin (SHBG) levels, and decreased inhibin B levels along with elevated estrogen levels [52, 53]. Obesity has also been associated with sexual dysfunction, which may in turn affect fertility.

Currently, there is limited data on the reversibility of obesity-associated male infertility with weight loss. One small, randomized controlled trial demonstrated an increase in SHBG and testosterone after 10 weeks of a very low-energy diet and behavior modification program [54]. Other studies on the effect of weight loss - including both surgical and diet/lifestyle modification programs - have shown mixed improvements in hormonal profile and sperm parameters [48].

There is also a growing body of literature to suggest that bariatric surgery and subsequent rapid weight loss may negatively impact semen parameters. In several case studies, male patients who underwent bariatric surgery were found to have decreased sperm concentrations, sperm motility, and normal sperm morphology [55, 56]. Even more dramatically, in one case series, six previously fertile men were found to be azoospermic with complete spermatogenic arrest after undergoing a Roux-en-Y gastric bypass [57]. As the rates of bariatric surgery continue to increase, additional research is needed to fully understand the impact of this procedure on male fertility outcomes.

42.3.2 Alcohol

Alcohol abuse has been shown to cause impaired testosterone production and testicular atrophy resulting in impotence, infertility, and reduced secondary sexual characteristics [58]. It has been shown to have a deleterious effect on all levels of the male reproductive system, including: the hypothalamic–pituitary–gonadal axis, Leydig and Sertoli cell function, and spermatogenesis, even leading to spermatogenic arrest and Sertoli cell-only syndrome in advanced cases [59, 60]. In an uncontrolled study, alcohol users were found to have decreased sperm count, normal morphology, and motility. This association was most significant with alcohol consumption of greater than 40 g/day [58]. In contrast, there are reports of alcohol consumption having beneficial effects on fertility, since some drinks (such as red wine) may exert a protective antioxidant effect [61]. In one recent prospective cohort study from Italy, moderate alcohol intake was positively associated with semen quality, compared to high- or low-intake groups [62]. Currently, the dose-dependent effects of alcohol on male factor infertility are not well understood, and remain a subject of investigation.

42.4 Conclusion

Dietary modification and nutritional supplementation are popular areas of concern for the infertile patient. Altering one's nutritional habits is usually easily done at little to no cost and empowers the patient to feel as though they are actively modifying their condition. From our survey of the literature, it appears that several antioxidant compounds have demonstrated a positive effect on semen parameters; however, no consensus exists regarding the best pathway to maximize fertility. Moreover, basic science research does not always translate into clinical success – especially in the field of infertility – and many of the findings from animal studies may not be readily applicable to humans. However, avoidance of toxicants, proper nutrition, and stress reduction are general guidelines that all men should follow, regardless of their fertility status. For infertile men, these lifestyle modifications will not only improve their general well-being but may also positively impact their semen parameters and fertility outcomes. Further research is needed to more fully understand the biochemical mechanisms behind these behavioral modifications and establish more specific recommendations for infertile patients.

42.5 Review Criteria

An extensive search of studies examining the relationship between nutrients, obesity, and alcohol intake on male reproductive health was performed using search engines such as ScienceDirect, OVID, Google Scholar, PubMed, and MEDLINE. The start and end dates for these searches were August 2018 and May 2019, respectively. The overall strategy for study identification and data extraction were based on the following keywords: "nutrition," "oxidative stress," "male infertility," "nutritional supplements," "arginine," "zinc," "selenium," "vitamin C," "vitamin E," "carnitine," "obesity," "alcohol," and "semen parameters." Articles published in languages other than English were also considered. Websites and book-chapter citations provide conceptual content only.

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