Beneficial Effects of Antioxidants in Male Infertility Management

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Infertility, defined as the failure to conceive after one year of regular, unprotected intercourse, affects 50–80 million people worldwide. In the etiology of male infertility, the association between poor semen quality and oxidative stress (OS) is well known. In men showing low-quality semen, diet supplementation with antioxidants may improve the sperm quality by alleviating OS-induced sperm damage and enhancing hormone synthesis and spermatozoa concentration, motility, and morphology.

antioxidant male infertility reactive oxygen species oxidative stress sperm

1. Introduction

Infertility, a male or female reproductive system disease, is defined by the failure to conceive within one year of regular, unprotected sexual intercourse [1]. Male infertility is commonly caused by alterations in semen ejection, absence or low levels of sperm, or sperm morphology and motility alterations [2].

Spermatogenesis represents the process by which spermatozoa production occurs. It is composed of spermatocytogenesis (mitosis where stem-cell spermatogonia produce primary spermatocytes), meiosis (composed by an exchange of genetic material between homologous chromosomes of primary spermatocytes and a reduction division producing haploid spermatids), and spermiogenesis (the final process where spherical spermatids differentiate into mature spermatids, which are released in seminiferous tubules as spermatozoa with fertilization capacity) [3]. The whole process is under the control of the testes' Sertoli cells that facilitate the progression of germ cells to spermatozoa via direct contact [4].

Once produced, spermatozoa are released by the ejaculation process, leading to spermatozoa-oocyte interaction. In the process, called capacitation [5], sperm become motile, are attracted towards the oocyte, bind to it, undergo the acrosome reaction, and finally fuse with the oocyte plasma membrane to create a zygote [6].

One of the most relevant factors in fertility is gamete quality. It is defined as the ability of spermatozoa and oocyte to interact in order to develop a normal embryo [7]. The spermatozoa quality is normally assessed by a spermiogram [8].

In the heterogeneous etiology of male infertility, the association between poor semen quality and oxidative stress (OS) is well known. OS is defined as the result of an imbalance between reactive oxygen species (ROS) and

antioxidant defenses [9].

ROS are highly reactive oxygen-containing molecules, including hydroxyl (HO^-) and superoxide (O_2^-) free radicals and non-radical molecules, such as hydrogen peroxide (H_2O_2). ROS are mainly produced via the mitochondrial electron transport chain and by enzymatic reactions involving cyclooxygenases, NADPH oxidases (NOXs), xanthine oxidases, and lipoxygenases, and through the iron-catalyzed Fenton reaction. Finally, ROS are generated after exposure to physical agents, such as ultraviolet rays and heat [10].

Eukaryotic cells benefit from antioxidants, as they tightly regulate ROS levels. Indeed, even though moderate ROS levels are needed during sperm capacitation and fertilization, high ROS levels could lead to spermatozoa damage [11]. Therefore, antioxidants represent a defense mechanism against OS by reacting with and quenching ROS [12]. Based on their activity, antioxidants are classified in two main groups: enzymatic and non-enzymatic antioxidants.

In sperm cells, due to the high concentration of plasma membrane polyunsaturated fatty acids and the lack of cytoplasmic defense mechanisms [13], high levels of ROS can increase OS by triggering the oxidation of sperm cell DNA, proteins, and lipids, and modifying sperm vitality, motility, and morphology [14].

Sperm DNA integrity and chromatin condensation are pivotal for fertilization. Any form of sperm chromatin alteration or DNA damage results in male infertility [15]. Testicular (defective maturation and abortive apoptosis) and post-testicular (OS) modifications are involved in the sperm-DNA-fragmentation etiology.

DNA packaging alterations could affect sperm chromatin decondensation, which would be detrimental to fertility. The chromatin condensation could be modified by several factors, such as zinc deficiency and alterations of protamines, proteins replacing histones during spermatozoa maturation [16].

Commonly, DNA fragmentation is a result of ROS-mediated damage. Direct or indirect ROS-mediated damage results in single- or double-strand fragments and abnormal apoptosis. Sperm DNA fragmentation is caused by extrinsic factors (e.g., smoking, heat exposure, chemotherapeutics, and environmental pollutants) and intrinsic factors (e.g., abortive apoptosis, defective germ cell maturation, and OS) [17].

Caspase activation, phosphatidyl serine externalization, mitochondrial membrane potential change, and DNA fragmentation are apoptosis markers detectable in human ejaculated sperm [18]. ROS impact multiple signaling pathways involved in the activation of extrinsic and intrinsic pathways of apoptosis. However, compelling evidence suggests that in the majority of cases ROS apoptosis induction depends on intrinsic pathway activation, which affects the integrity of the mitochondrial permeability transition pores. ROS also trigger apoptosis by inactivating or increasing Bcl-2 anti-apoptotic protein ubiquitination.

Currently, the association of several natural antioxidants, such as inositol, alpha-lipoic acid, zinc, folate, coenzyme Q10, selenium, and vitamins, with sperm quality improvement by acting as a defense mechanism against OS is well documented.

3. Inositols

In nature, the most abundant form of inositol is myoinositol (myo-Ins). Serum myo-Ins cannot cross the tight junctions at the testicular level and is therefore transported into cells by a sodium/myo-Ins cotransport protein, whose expression is sensitive to osmolar changes [19].

In spermatozoa, the main site of action of myo-Ins is the mitochondria, where, by controlling the intracellular Ca^{2+} levels, it regulates mitochondrial oxidative metabolism and ATP production. Consequently, myo-Ins improves sperm mitochondrial function, enhancing many processes, such as capacitation, acrosome reaction, and regulation of sperm motility [20]. This leads to an improvement of sperm motility in patients with altered sperm parameters [21]. Accordingly, Governini et al., have demonstrated that treatment with myo-Ins results in a significant increase in sperm motility [13].

4. Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) acts as the coenzyme for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase in the mitochondria, contributing to ATP production, which is necessary for sperm viability [22]. Inside cells and tissues, ALA is reduced to dihydrolipoic acid (DHLA), which has a higher antioxidant capacity [23]. ALA and DHLA chelate ROS and transition metals to prevent membrane lipid peroxidation and protein damage [24].

ALA was also tested as cryoprotection agent during the freezing–thawing process that occurs in assisted reproductive techniques (ART). During cryopreservation, sperm is exposed to different changes that may result in incremental OS and may induce some adverse effects due to cryodamage. Asa et al., have demonstrated that an optimal concentration of ALA protects against ROS production and cryodamage. This is reflected in the improvement of sperm motility and viability and by a decrease in DNA damage, and, consequently, apoptosis [25].

5. Zinc

Zinc is the most abundant element in human semen, where its concentration is significantly higher than that found in the blood. Seminal plasma zinc originates from the prostate gland and reflects the prostatic secretory function [26]. Zinc affects essential physiological processes, such as cellular responses to OS, DNA repair, cell cycle, and apoptosis [27].

Zinc is necessary for testicular development and normal spermatogenesis. It is involved in antioxidant defense, production, storage, secretion, and function of several enzymes which play important roles in meiosis during spermatogenesis and other gametogenesis stages [28]. It affects the stability of sperm chromatin and biological membranes in general, as it influences the fluidity of lipids [29].

Normozoospermics show high zinc levels in seminal plasma, followed by asthenoteratozoospermics, oligoasthenoteratozoospermics, and azoospermics [30].

6. Coenzyme Q10

Coenzyme Q10 (CoQ10) is an essential cofactor for energy production and has high antioxidant properties [31]. It is a component of the mitochondrial respiratory chain that regulates ROS production, thereby protecting the cell membrane against lipid peroxidation-induced damage [32]. For adequate motility, the sperm cells require high energy viability, which is produced in mitochondria via oxidative phosphorylation. In the mitochondria, CoQ10 neutralizes free radicals produced during the electron transport chain [33]. However, subfertile men show low CoQ10 concentration levels [31].

Low seminal plasma concentrations of CoQ10 have been correlated with impaired sperm parameters, such as motility. Accordingly, evidence revealed that CoQ10 improves sperm count and motility in infertile men [34][35].

7. Selenium

Selenium (Se) is incorporated in a large number of proteins, named selenoproteins, involved in several metabolic pathways related to antioxidant defense, redox state regulation, and cancer prevention [36].

During normal spermatogenesis, mitochondrial activity, and capacitation, Se is involved as a cofactor of antioxidative enzymes responsible for the neutralization and prevention of the synthesis of ROS [37]. Among all selenoproteins involved in male reproduction, glutathione peroxidase plays a critical role in many redox reactions. In spermatozoa, it is incorporated into the mitochondrial membrane, counterbalancing the ROS production occurring in the motility process [38].

8. Vitamins

8.1. Vitamin E

Vitamin E is the primary antioxidant component of spermatozoa and protects the cell membrane from ROS [39]. Rengaraj and Hong showed that vitamin E deficiency causes abnormal spermatogenesis [40].

Vitamin E has positive effects on testis and sperm functions, but supplemental prescriptions containing vitamin E have done little to improve overall sperm quality [39].

8.2. Vitamin C

Similar to vitamin E, vitamin C has a potential role as a membrane protector against ROS. In Cyrus et al., vitamin C supplementation did not improve sperm count, but had some beneficial effects on sperm motility and morphology [41].

8.3. Vitamin B12

Vitamin B12, or cobalamin, is a cofactor in DNA synthesis and in both fatty acid and amino acid metabolism [42]. Vitamin B12 positively influences semen quality by increasing sperm count and sperm motility and by reducing sperm DNA damage [43].

9. About the Combination of Antioxidants

According to Bish et al., a combination of antioxidants could be useful in order to exploit their functions in ROS-inactivation and decreasing ROS production due to enzymatic activities. Thus, the authors recommend a diet containing a mix of antioxidants, especially zinc and selenium [44].

Santoro et al., assessed the in vitro and in vivo effects of supplementation with a mixture of antioxidants containing mainly myo-Ins. Antioxidant preparations could have a beneficial role in semen preparation for in vitro fertilization procedures. Moreover, oral supplementation with the nutraceutical mix improves the performance of OAT sperm, without any risks or side effects [45]. Accordingly, Scaruffi et al., showed an increase in fertilization rates by administering a mix of antioxidants to men before semen deposition [46]. However, both studies agree on the need of further studies to enhance the understanding of the effects.

One of the natural sources of a combination of antioxidants is vegetables. Dietary modifications showed potential benefits in improving sperm quality, and the recommendation is to adhere to a healthy dietary pattern rich in plant-based foods, such as a vegetarian diet, the Dietary Approach to Stop Hypertension (DASH) diet, or the Mediterranean diet, alone or in association with antioxidant supplementations [47][48].

Taken together, the peculiar effect of the combination of antioxidants has not yet been clarified. This is due to the poor populations involved in clinical studies and the lack of randomized, placebo-controlled, double-blind clinical trials. Indeed, a retrospective study noted that the antioxidant therapies available currently may not improve sperm function, and the high cost of treatment could lead to poor patient compliance [49].

10. Conclusions

The etiology of several diseases, including male infertility, is strictly dependent on OS [50]. Consequently, normal spermatozoa production, function, and vitality require a balance between ROS and antioxidants.

In men presenting low-quality semen, diet supplementation with antioxidants showed a potential role in improving the overall sperm quality by alleviating OS-induced sperm damage and enhancing hormone synthesis, spermatozoa concentration, motility, and morphology. Future clinical trials should focus on the association of several antioxidants to take advantage of their combined mechanisms of action.

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