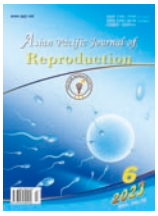

Review Article

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/2305-0500.390299

Oxidative stress in male infertility and therapeutic approach: A mini-review

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ABSTRACT

Growing evidence suggests that oxidative stress is a major cause of male infertility. Spermatozoa are highly sensitive cells due to the vulnerability of their membrane fatty acids and the diminished antioxidant defense. Reactive oxygen species (ROS) impact multiple signaling pathways involved in mitochondrial dysfunction, hormonal unbalance and semen quality decline. The origin of ROS is diverse, including generated normal cellular metabolism, environmental exposure, advanced paternal age and inflammation. Research has indicated that antioxidant supplementation can improve oxidative stress and reduce the risk of chronic diseases. Moreover, it is widely known that antioxidant supplementation can enhance sperm quality and increase the pregnancy rate in couples undergoing fertility treatments. The current study highlights the deleterious effect of ROS and its impact on semen function. In addition, it contributes to the development of a clinical approach for the use of antioxidants in the management of male infertility.

KEYWORDS: Oxidative stress; Reactive oxygen species; Mitochondria; Antioxidant supplementation; Spermatozoa

1. Introduction

Recently, accumulating evidence reported that oxidative stress plays a key role in semen quality decline and it has been detected in 30%-80% of infertility cases[1]. During both physiological and pathological conditions, the significant source of reactive oxygen species (ROS) production within cells is mitochondria. Furthermore, small level of ROS is required to maintain a normal spermatogenesis including various sperm function like capacitation, acrosome reaction and hyperactivation[2-4]. When the production of the free radicals increases to the normal threshold value and exceeds the cell's ability to detoxify them (the disparity between free radicals and weak endogenous defense), a variety of cellular changes and damage can occur[5,6], including alterations to mitochondrial function[7]. Mitochondria are organelles within cells responsible for energy production through the process of cellular respiration. Oxidative stress can lead to mitochondrial dysfunction, characterized by impaired energy production, altered calcium homeostasis, and increased cell death[8,9]. Overall, oxidative stress and its effects on mitochondrial function are implicated in a variety of diseases, including infertility, cancer and cardiovascular disease[6].

Therefore, the clinicians recommended the use of oral antioxidant (mono or poly formulation involving some medicinal plants) as a therapy to reduce ROS damage in male infertility[10,11]. Several trials testing numerous micronutrient combinations have been published and explained the target effects of certain antioxidants. For example, Coenzyme Q10 (CoQ10) is a cofactor and antioxidant that is essential for the function of the electron transport chain in the mitochondria. CoQ10 is involved in the transfer of electrons between complexes Ⅰ, Ⅱ, and Ⅲ of the electron transport chain, which is responsible for generating adenosine triphosphate (ATP), the main energy currency of the cell. It also has antioxidant properties and can protect mitochondria from oxidative damage and also improve some sperm parameters like sperm motility, morphology, and testosterone level[7,12]. A study involving 50 patients diagnosed with idiopathic oligoasthenospermia found that coenzyme therapy

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How to cite this article: Lahimer M, Mustapha H, Bach V, Khorsi-Cauet H, Benkhalifa M, Ajina M, et al. Oxidative stress in male infertility and therapeutic approach: A mini-review. *Asian Pac J Reprod* 2023; 12(6): 249-255.

Article history: Received: 19 May 2023; Revision: 20 July 2023; Accepted: 21 August 2023; Available online: 5 December 2023

led to an improvement in sperm motility[13]. It is widely known that supplementation based on *L*-carnitine significantly improves the sperm parameters as well as the DNA damage and testosterone and luteinizing hormone (LH) level[12,14–17]. Nateghian *et al* assessed the effect of *L*-carnitine and pentoxifylline supplementation on 26 samples. The study result showed a significant improvement in sperm motility and sperm vitality[17]. Zinc is crucial for the proper functioning of several enzymes involved in energy metabolism, including pyruvate dehydrogenase and carbonic anhydrase. These enzymes play roles in glucose metabolism and carbon dioxide removal, respectively. Moreover, zinc has been shown to significantly increase semen count[18–20]. Ascorbic acid (vitamin C), α-tocopherol (vitamin E), and selenium act as antioxidants protect mitochondria from damage caused by free radicals generated during energy production[21]. Ziamajidi *et al* reported that the combination treatment of zinc, vitamins A, C, and E reduces the oxidative markers in rat[20]. In addition, the studies of Jannatifar demonstrated that following *N*-acetyl-cysteine treatment, there were notable improvements in certain sperm characteristics, including increased sperm count and motility, alongside significant decreases in abnormal morphology and DNA integrity issues, including DNA fragmentation and protamine deficiency[22,23]. However, protection against the overproduction of free radicals is accomplished through a range of endogenous mechanisms, including enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)[14,24].

Therefore, the current mini-review aims to raise awareness about the factors contributing to male infertility, including the impact of oxidative stress on sperm quality and function. Additionally, it suggests preventive strategies, such as maintaining a healthy lifestyle, reducing exposure to environmental toxins, managing stress, limiting alcohol consumption, and considering antioxidant supplementation as potential ways to mitigate the effects of oxidative stress.

2. Oxidative stress and the genesis of ROS

Oxidative stress is an imbalance between the production of ROS and the antioxidant defense system of cells. ROS are produced as a natural byproduct of cellular metabolism and can cause damage to cellular components such as proteins, lipids, and DNA[2]. The antioxidant defense system of cells includes enzymes such as SOD, catalase, and GPx, which neutralize ROS and prevent oxidative damage. When the production of ROS exceeds the capacity of the antioxidant defense system to neutralize them, oxidative stress can occur[1].

Oxidative stress has been implicated in a variety of disease processes, including neurodegenerative diseases, cardiovascular disease[25], and cancer[26]. It can also contribute to aging and age-related diseases by promoting cellular damage and dysfunction[8,27,28]. In addition to ROS, other factors such as inflammation[29], radiation exposure, environmental toxins[30] and advanced paternal age[31,32] can contribute to male infertility[33–40]. Within semen, there are two principal sources of ROS synthesis. The exogenous sources include ionizing and UV radiation, smoking, drugs, advanced age, and xenobiotics such as pesticides. The endogenous source includes leukocytes, including neutrophils[41,42], mitochondria[43], NADPH oxidase 1, amino acid oxidase[44], pathology as varicocele[45], autoimmune disease[46] and even the immature spermatozoon itself can be a source of ROS[2,47]. However, low levels of ROS are involved in normal cellular signaling processes, such as regulating gene expression and cell proliferation. The balance between ROS production and antioxidant defense systems is important for maintaining cellular homeostasis and preventing oxidative stress. Excessive levels of ROS can lead to oxidative damage.

3. Impact of oxidative stress on male infertility

Oxidative stress can indeed have negative effects on male reproductive function and potentially contribute to infertility[24]. ROS are highly reactive molecules that can cause damage to cells and tissues if their levels become excessive. Oxidative stress can affect male fertility through various mechanisms including sperm damage[48], hormonal imbalance[49], testicular dysfunction[50,51] and inflammation[52,53].

3.1. Oxidative stress and hormonal disorder

Oxidative stress can adversely affect male reproductive function and may contribute directly or indirectly to infertility by affecting the hypothalamic-pituitary-gonadal (HPG) axis and/or its crosstalk with other hormonal axes that can affect sperm production and maturation[54]. Consequently, testosterone production may decline, and the process of spermatogenesis could be compromised[55]. In the context of male reproductive function, the HPG axis involves a complex interplay between the hypothalamus, pituitary gland and testes. The hypothalamus produces gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to release LH and follicle-stimulating hormone (FSH). LH and FSH then circulate in the bloodstream to reach the testes, where they promote testosterone production and support the process of sperm production and maturation[56].

Furthermore, oxidative stress can directly affect the Leydig cells in the testes, which are responsible for testosterone production[53,57]. These cells are highly susceptible to ROS-induced damage, leading to decreased testosterone synthesis. The hormonal imbalances caused by oxidative stress can have detrimental effects on sperm production, maturation, and overall reproductive function. Reduced levels of LH, FSH, and testosterone can result in impaired sperm development and reduced sperm quality[2,51].

3.2. Oxidative stress is associated with mitochondria signaling dysfunction

Mitochondria is a cellular organelle. It is often called the powerhouses due to their role in producing ATP. The generation of

ATP within mitochondria takes place through a complex biochemical process known as cellular respiration[58]. There are three main stages of cellular respiration, including the glycolysis, which is the breakdown of glucose into two molecules of pyruvate[58], citric acid cycle (also known as the Krebs cycle) which is the breakdown of pyruvate into carbon dioxide and water. This process takes place within the mitochondria's matrix[59]. Then, the electron transport chain (ETC) is the transfer of electrons through a series of proteins and enzymes embedded in the inner mitochondrial membrane[60–62].

It is well known that oxidative stress is significantly associated with mitochondrial dysfunction. There is a growing body of evidence suggesting that mitochondrial DNA (mtDNA) is more susceptible to oxidative damage than nuclear DNA[63]. One of the common types of oxidative damage is the formation of 8-oxo-2'-deoxyguanosine (8-oxo-dG), which is considered a biomarker of oxidative stress. Many studies have reported that the level of 8-oxo-dG is higher in mtDNA compared to nuclear DNA in both human and animal cells[8,64].

There are several reasons why mtDNA may be more vulnerable to oxidative damage. First, mitochondria are the primary site of ROS production in the cell. Second, mtDNA lacks protective histones, which act as a shield for nuclear DNA against oxidative damage. Third, mtDNA repair mechanisms are less efficient in comparison to nuclear DNA repair mechanisms, potentially resulting in the gradual accumulation of oxidative damage in mtDNA over time[65,66].

Morphological changes in mitochondria, such as swelling and fragmentation, are also observed in cases of mitochondrial dysfunction. Mitochondrial fission increases under pathologic conditions, resulting in the formation of smaller, fragmented mitochondria. This process can impair mitochondrial function and contribute to cell death[67].

Disruption of the mitochondrial membrane potential (MMP) is a hallmark of mitochondrial dysfunction. The MMP is critical for maintaining mitochondrial function, as it drives ATP synthesis and regulates the flow of ions across the mitochondrial membrane. When the MMP is disrupted, there is a decrease in metabolic oxygen consumption, ATP depletion, and low energy metabolism[28,62,68].

Mitochondrial dysfunction can also trigger programmed cell death, or apoptosis. This process is regulated by the mitochondrial apoptotic pathway, which involves the release of cytochrome c from the mitochondria to the cytoplasm. This, in turn, activates pro-apoptotic caspases and triggers cell death. The opening of the mitochondrial permeability transition pore is a critical step in this process[69].

Disruptions in calcium homeostasis can likewise induce mitochondrial dysfunction. Calcium plays a pivotal role in the regulation of mitochondrial function and ATP generation. An imbalance in calcium levels can impair mitochondrial function and lead to cell death[70]. Additionally, genetic mutations in mtDNA can also lead to mitochondrial dysfunction[66].

3.3. Oxidative stress induces damages to spermatozoa

Spermatozoa are particularly vulnerable to oxidative stress due to their high content of polyunsaturated fatty acids (PUFA) in their plasma membrane, which makes them more susceptible to ROS attack[71]. Moreover, spermatozoa has limited antioxidant defenses and poor DNA repair mechanisms, making them more vulnerable to oxidative stress-induced damage. The oxidative damage to sperm cells is a major contributing factor to male infertility. Lipid peroxidation of the sperm plasma membrane is one of the earliest and most significant oxidative damage events observed in infertile men[72]. Lipid peroxidation can lead to the production of toxic products that can damage cell membranes and other cellular structures[36]. This oxidative damage can lead to diminished motility, reduced viability, and abnormal morphology[73,74]. Therefore, it is essential to minimize exposure to the factors inducing oxidative stress and increase antioxidant defenses to maintain optimal sperm health. Oxidative stress can lead to protein oxidation, which can alter protein structure and function including cleavage of peptide bonds, oxidation of amino acid residues, and aggregation between proteins[75]. Several diseases have been linked to the presence of oxidized proteins, such as Alzheimer’s disease, rheumatoid arthritis *etc*[76]. This can lead to the generation of abnormal proteins, which can accumulate and cause damage to the cell. Additionally, DNA and RNA can be oxidized by ROS, resulting in potential damage to the genetic material. ROS can react with nitrogenous bases and deoxyribose, leading to a variety of oxidative reactions that can result in DNA mutations, carcinogenesis, apoptosis, necrosis, and hereditary diseases. When DNA is damaged by ROS, the nucleosomes, which are the basic units of chromatin organization, can be disrupted, leading to DNA fragmentation and compaction defects. This can have serious consequences for the cell, as it can disrupt normal cellular processes and lead to genetic instability[46]. The DNA damage caused by ROS can result in the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is a common biomarker of oxidative stress and can be used as an indicator of DNA damage[77]. It has been shown that ROS increase the levels of 8-OHdG in various tissues. The production of 8-OHdG due to oxidative stress may be more prominent in genome regions that are less protected by protamines, which are positively charged proteins that replace histones in the later stages of spermatogenesis, leading to the compaction of DNA into the highly condensed chromatin structure found in mature sperm[78,36].

4. Oral antioxidant therapy in oxidative stress

Antioxidants are molecules that neutralize or eliminate harmful ROS in the body. It plays a crucial role in reproduction by protecting reproductive cells and tissues from oxidative stress. It contributes to maintaining hormonal balance, protecting sperm DNA integrity and maintaining overall sperm health which are essential for successful fertilization.

There are two main types of antioxidants: enzymatic and non-enzymatic.

4.1. Enzymatic antioxidants (EAs)

The EAs are naturally produced by the body and include enzymes such as SOD, catalase, and glutathione (GSH). These enzymes collaborate to convert ROS into less harmful substances that can be safely eliminated from the body.

SOD is a metalloenzyme present in both eukaryotic and select prokaryotic organisms. It is distributed within various cellular compartments, including the cytosol and the intermediate mitochondrial membrane, mitochondrial matrix and inner membrane and extracellular compartment[79].

The glutathione family of enzymes includes the GPx, the glutathione S-transferase (GST), and GSH reductase. In cells, GSH plays multiple roles, including maintaining cells in a reduced state and forming conjugates with several dangerous endogenous and exogenous compounds[80].

The catalase is an oxidoreductase enzyme that plays a crucial role in quenching the ROS, specially the hydrogen peroxide, often produced as a by-product of aerobic respiration to a water and oxygen[81].

4.2. The non–enzymatic antioxidants (NEAs)

NEAs are obtained from the diet or through supplements. These include vitamins like vitamin C, vitamin E, and beta-carotene, as well as minerals such as selenium and zinc. NEAs work by donating electrons to neutralize free radicals and prevent oxidative damage to cells and tissues. Several micronutrients play a crucial roles in spermatozoa function maintaining[82]. Vitamin B is beneficial for the synthesis of enzymes involved in energy metabolism[83]. Ascorbic acid (vitamin C) and α-tocopherol (vitamin E) are antioxidants that protect mitochondria from damage caused by ROS generated during energy production[20]. Zinc is also a cofactor implicated in several enzymes of energy metabolism[19]. CoQ10 is a cofactor and an antioxidant that plays a key role in the electron transport chain. It is responsible for generating ATP in the mitochondria[12]. Carnitine is involved in transporting fatty acids into the mitochondria for energy production[82]. Several studies reported that *L*-carnitine improves sperm count, sperm morphology, and sperm motility, while also enhancing testosterone and LH levels[12,15,17].

It is well known that spermatogenesis and sperm DNA integrity can be affected by unsuitable vitamins intake[84]. Several studies reported that micronutrient treatment based on co-enzyme10 and zinc and vitamin C have a positive effect on semen parameters, DNA integrity, assisted reproductive technology outcomes and live birth rates. Saya in 2019 involved a total of 175 males aged between 19 and 44 years old with idiopathic oligoasthenozoospermia who failed to conceive for 12 months. The result of the study revealed that after a 3-month Proxeed Plus treatment, there were improvements in sperm parameters such as the volume, the progressive motility and vitality, along with a significant reduction in the DNA fragmentation index[85]. The combination of micronutrient containing sufficient amounts of antioxidants and vitamins A, B, C, and E can protect cell from oxidation and damage and improve sperm quality, DNA integrity and *in vitro* fertilization outcome[86,87]. Scaruffi *et al* suggested that administering antioxidant treatment to men who had experienced low fertilization rates in previous intracytoplasmic sperm injection (ICSI) cycles could potentially enhance the reproductive potential of their sperm[86]. A network meta-analysis of randomized controlled trials (RCTs) analyzed a total of 23 RCTs involving 1917 patients and 10 different types of antioxidants. The results of the study revealed that *L*-carnitine has a significant positive effect on improving sperm motility and morphology, while Omega-3 fatty acids ranked highest in enhancing the sperm count[87].

5. Conclusions

Male infertility is acknowledged as a substantial public health issue. Several contributing factors are under consideration, including oxidative stress. It has gained attention due to its adverse effects on male fertility, resulting in a sperm quality decline and sperm DNA integrity disruption. Many preventive strategies could be considered, reducing or mitigating exposure to environmental toxins, and considering antioxidant supplementation. As with any supplement, it is crucial to consult with a healthcare provider before starting antioxidant supplementation.

Conflict of interest statement

The authors declare no conflicts of interest to disclose.

Funding

The study received no extramural funding.

Acknowledgements

We thank the editors for their positive feedback and hope that the revisions prompted by their comments have improved the manuscript.

Authors' contributions

Marwa Lahimer was in charge of writing the original draft; Henda Mustapha was responsible for visualization; Véronique Bach was in charge of visualization; Hafida Khorsi-Cauet, Moncef Benkhalifa, and Mounir Ajina were responsible for writing, review, editing, and supervision; Habib Ben Ali was in charge of writing, review, editing, and supervision.

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