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The Impact of Oxidative Stress in Male Infertility

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ABSTRACT
Oxidative stress has emerged as a significant factor contributing to male infertility, impacting the quality and functionality of sperm. This phenomenon, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms, has garnered increasing attention in the realm of reproductive health research. Understanding the mechanisms through which oxidative stress affects male fertility is crucial for developing effective diagnostic tools and treatment strategies.
KEYWORDS:ROS (reactive oxygen species), oxidative stress, male infertility, spermatozoaand the parameters of sperm.

I. INTRODUCTION

In recent decades, a widespread decline in reproductive health has been observed, mainly due to increased exposure to environmental toxicants, stress, and unhealthy lifestyles. There is increasing evidence suggesting that reactive oxygen species and/or oxidative stress play an important role in the etiology of male infertility, which affects a significant number of couples wishing to start a family but are unable to conceive. Infertility affects about 15% of the couples and a male factor is the main responsible in 50% of the cases, due to the decrease of testicular sperm and semen quality. The World Health Organization defined infertility as: "the inability of a couple to achieve conception or to bring a pregnancy to term after 12 months of regular unprotected sexual intercourse". In about 50% of the cases, and in about 80% of them, infertility is the result of sustained and irreversible sperm impairments**[1,2]**.

Despite the increasing number of studies devoted to infertility, exact data are still missing for male factor infertility, since human males are capable of releasing about 40 million sperm/h; at the same time, a decreased production of sperm is related to social effects (smoking, alcohol, etc.) and/or occupational hazards (pesticides, additives, etc.). The effectiveness of semen depends on the number of sperm, sperm motility, sperm morphology, and sperm concentration; an abnormality in one of these parameters impairs the "sperm quality", decreasing male fertility. Several studies carried out to isolate the reasons of male infertility revealed that genetic, hormonal, physical, psychological, and environmental factors are responsible for changing the comfort area of human reproduction. Furthermore, sperm contain several proteins in addition to lipids, DNA, and RNA. Some of these proteins involve cellular processes, such as metabolism, movement, signaling, cell cycle regulation, or apoptosis, while the majority of them are involved in the protection of the cell, including antioxidant enzymes and/or chaperon proteins**[1,2,3,4]**.

OVERVIEW OF MALE INFERTILITY

Male infertility is a multifactorial biological condition that occurs when a male exhibits low fertility for an extended period. Several factors cause male infertility, such as cryptorchidism, varicocele, sperm abnormalities, restricted seminal plasma protein, and serum concentrations. ROS are involved in various physiological processes as signaling and regulatory molecules. However, when overproduced, ROS overreact with other moieties, causing oxidative damage to lipids, proteins, and DNA. Experimental evidence presents an association between oxidative stress and male reproductive diseases. The anatomy, histology, and physiology of the male and female reproductive systems present distinct differences, suggesting different ROS profiles between both biological sexes**[9,10,11]**.

The gender gap, which is the phenomenon that the male reproductive system is less studied and characterized in comparison with the female reproductive system, contributes to the unclear roles of ROS in variations of male reproductive diseases. Hence, feedback regarding the ROS profiles in the male reproductive system and their complex interactions, which shape male reproductive diseases, remains incomplete. Nevertheless, recent studies employed state-of-the-art techniques to identify proteins that are present

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in the relative absence of proteomic studies of the male reproductive system. The same proteins are likely performing ROS-scavenging functions, corroborating the observed lower susceptibility of females to reproductive diseases**[1,2,5]**.

OXIDATIVE STRESS

Since oxygen has both beneficial and detrimental effects on biological systems, it plays a crucial role in life. The fundamental oxygen contribution is in adenosine-5-triphosphate (ATP) age through mitochondrial oxidative phosphorylation, a response likewise embroiled in ROS and RNS creation**[6,7]**. Several intracellular signaling pathways, immune and mitogen responses, and cellular homeostasis are all regulated by ROS/RNS at moderate levels. On the other hand, higher levels of ROS can cause oxidative damage to proteins, lipids, and nucleic acids (DNA, RNA), which has negative effects on the cell. Notwithstanding, a mind-boggling arrangement of cell reinforcement particles has been developed to keep a redox balance and keep away from organic framework injury**[8,9]**. A few circumstances (as natural variables, exorbitant actual activity, lacks in cell reinforcements, resistant framework dysfunctions, persistent issues) may modify oxidant/cell reinforcement balance, prompting oxidative pressure. Tissue injury and cell death are mediated by oxidative stress, which plays a pathological role in a number of diseases like inflammation and aging, cardiovascular and neurodegenerative diseases, autoimmune disorders, cancer, and changes in the reproductive system**[6,8,9,10]**.

THEPHYSIOLOGICALROLEOFROSIN SPERMATOZOA

Physiologically, ROS are thought to control a number of intracellular pathways by changing how different transcription factors are activated**[6]**. ROS animate cyclic adenosine monophosphate (cAMP) in sperms, advancing tyrosine phosphorylation by tyrosine phosphatase restraint. Several transcription factors involved in intracellular signaling cascades for sperm physiology are activated as a result of this molecular mechanism. To be sure, a few examinations showed that higher ROS levels animate sperm capacitation and hyperactivation, acrosome response, motility and chemotaxis and chromatin compaction in developing spermatozoa. Additionally, ROS may increase the sperm's ability to bind to the zona pellucida, resulting in sperm-oocyte fusion. Coincidentally, cell reinforcement atoms might adjust spermatozoa development, slowing down physiological sperm capability. Especially, it was showed that catalase or superoxide dismutase (Turf) repress sperm capacitation or acrosome response, supporting the proof of the focal contribution of ROS in spermatozoa working**[11,12]**.

THEPATHOLOGICALROLEOFROSIN SPERMATOZOA

Other than to the physiological job of ROS, extreme ROS age and oxidative pressure appear to be related with destructive impacts on spermatozoa, bringing about morphological and dynamic cell properties modifications lastly in lower treatment capacity**[13,14].** A growing body of research in recent years has demonstrated that an altered redox balance in the seminal fluid may have negative effects on sperm homeostasis, resulting in male infertility. Infertile men have been found to have altered blood and plasma redox status. A recent study found that oligoasthenozoospermic men had lower plasma total antioxidant capacity (TAC), increased plasma lipid peroxidation (LPO), and higher blood leukocyte ROS production than healthy men. In line with this, a number of studies have shown that ROS-mediated sperm oxidation may cause cell dysfunctions that affect the concentration, total number, and motility of spermatozoa**[15,16,17]**. Due to the presence of docosahexaenoic acid, a polyunsaturated fatty acid with six double bonds per molecule, in their plasma membrane, spermatozoa are particularly susceptible to ROS-induced oxidation. Without a doubt, ROS intercede the hydrogen deliberation from the hydrocarbon side-chain of an unsaturated fat, respecting a carbon- centered lipid radical (L), whose interaction with oxygen results in the formation of a lipid peroxyl radical (LOO), which is capable of combining with nearby unsaturated fat proliferating the interaction. Following inner sub-atomic revisions formed dienes and hydroperoxides are produced**[18,19].**

MAINSOURCESOFROS

It is to a great extent acknowledged that few exogenous variables might add to irritation and redox status modifications, advancing male barrenness. Active factors include smoking, drinking alcohol, obesity, varicocele, bacterial/viral infections, microorganism mutations, and sexually transmitted diseases. However, immature spermatozoa and leukocytes, which produce 1,000 times more ROS than normal spermatozoa, are primarily responsible for oxidative stress in the

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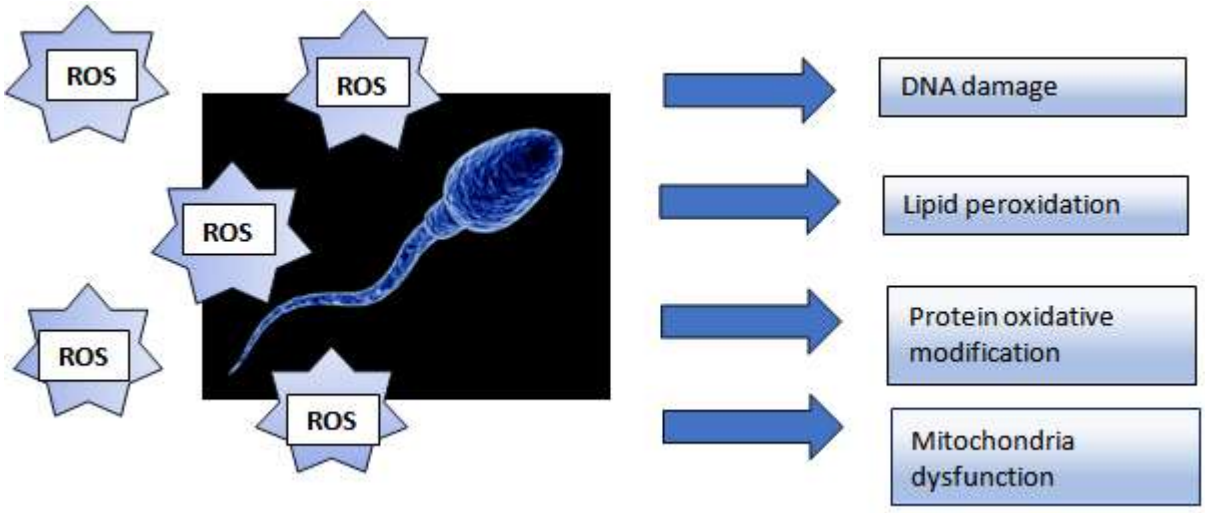
seminal fluid**[20]**. Leukocytospermia. Leukocytospermia, which is defined as a concentration of peroxidase-positive leukocytes greater than 1106 per mL of sperm, has been found in approximately 10–20% of men who are unable to conceive. New findings suggested that seminal WBC could directly or through the release of soluble products into the sperm microenvironment enhance the sperm's capacity to generate ROS. However, the role of leukocytospermia in sperm quality and its clinical significance are still up for debate. Higher original WBC levels were seen in barren men contrasted with sound controls and leukocytospermia was essentially related with changes in sperm number, motility and morphology**[13,19,20]**. In accordance with this proof, further examinations upheld WBC as a trigger variable for spermatozoa ROS age, prompting diminished sperm quality and sperm DNA harm**[22,23]**. Spermatozoa at various stages of maturation are characterized by variations in ROS levels, membrane lipid content, chromatin compaction, morphology, and motility. Leukocytospermia was associated with alterations in sperm concentration, motility, and morphology in leukocytospermic patients in comparison to nonleukocytospermic patients or healthy subjects. Immature spermatozoa inducing oxidation in mature sperm cells during sperm migration from the seminiferous tubules to the epididymis may be a significant contributor to male infertility due to their higher ROS generation and DNA damage**[3]**. Another potential ROS source in spermatozoa is addressed by mitochondria. Indeed, the electron transport chain on the mitochondrial membrane can be altered by a variety of factors, including electromagnetic radiation, polyunsaturated fatty acids, and apoptotic factors. Sperm mitochondrial dysfunctions improve ROS creation and are related with sperm quality debilitation and loss of treatment potential**[19,21,24]**.



Oxidative stress negatively affects sperm cells causing mitochondrial injury and alterations in lipids, nucleic acids and proteins

OXIDATIVESTRESSEFFECTSONSEMEN PARAMETERS

During these years, the likely relationship between's spermatozoa ROS creation and semen boundaries has been generally explored. Oxidative stress mainly leads to decrease in the concentration, count,motility,vitality and DNA fragmentation in the sperms**[2]**.The inconvenient impacts of ROS on sperm motility and morphology has been over and again announced**[15,25-29]**. In vitro tries exhibited that lipid aldheydes dependence on spermatozoa advanced misfortune motility in human sperm cells. As a result, astheno- and oligo-teratospermic men's sperm motility, morphology, and count were significantly correlated with LPO and TAC levels in the seminal fluid**[30,31]**. The beneficial effects of therapeutic antioxidant supplementation on the quality of sperm in infertile men support the central role that oxidative stress plays in spermatozoa alterations. In idiopathic male infertility, therapeutic Coenzyme Q10 treatment specifically improved sperm parameters (concentration and motility), redox status, and sperm DNA fragmentation. Intriguingly, a vitamin D-deficient

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infertile male with oligoasthenozoospermia experienced an increase in sperm concentration and motility following vitamin D supplementation**[32,33,34]**. The beneficial outcomes of a cell reinforcement treatment on semen quality has been recommended as a helpful device to further develop fruitful origination rate in patients with oligoasthenozoospermia going through intracytoplasmic sperm infusion (ICSI). On the other hand, other authors found no relationship between ROS levels and sperm motility. This suggests that it is still not clear whether decreased sperm functional performances are the result of fewer sperm or a direct ROS effect**[19,35]**. A new blood diagnostic tool that can evaluate sperm morphological and/or functional abnormalities is becoming increasingly useful in this setting to support the diagnosis and treatment of male infertility. In this respects, blood Grass and GSH levels were found to decidedly correspond with sperm count and motility, while improved MDA levels were related with modified sperm morphology. In accordance with this, signs of oxidative stress were found in the seminal fluid and plasma TAC was reduced in men who were unable to conceive. Especially, plasma TAC fundamentally and decidedly corresponded both with original liquid TAC and with semen boundaries, showing that plasma redox status mirrors the redox status of original liquid microenvironment and sperm quality**[36,37]**. It has been demonstrated that infertile men's plasma and seminal fluid MDA and NO levels were correlated with sperm parameters, supporting the connection between redox status in the blood and sperm parameters. However, there are currently only a few reports that link oxidative stress in the seminal fluid and blood, and disputable, possibly because of various systems and applied strategies**[5]**. In fact, there was no correlation between blood and seminal fluid oxidative status, indicating that seminal fluid redox homeostasis is independent of the systemic microenvironment and other external factors**[38]**.

OXIDATIVE STRESS ASSESSMENT AND CLINICALUSEOFREDOXBIOMARKERS IN MALE INFERTILITY

The investigation of semen boundaries as indicated by the WHO rules addresses, presently, the highest quality level for male fruitlessness finding. However, a number of studies demonstrated that ROS-induced sperm oxidation can alter sperm quality and reduce sperm fertilization potential. New tests aimed at evaluating male fertility by monitoring oxidative stress status are required on the basis of this evidence. Measures for oxidative pressure identification might recommend new biochemical ways to deal with further develop male barrenness analysis and the board, utilizing straightforward, quick and more affordable strategies. Different biological samples, including plasma, serum, urine, and follicular/peritoneal/seminal fluid, can be used to evaluate oxidative stress, providing a precise picture of redox status and eventually allowing for the planning of a therapeutic supplementation with antioxidants when they are required**[19,39,40,41]**. There are a variety of assays for oxidative stress that focus on ROS production, lipid peroxidation products, and total antioxidant capacity. ROS estimation in semen incorporate various strategies as chemiluminescence, nitro blue tetrazolium (NBT) test, cytochrome c decrease test and electron turn reverberation. However, cytometry, which involves incubating cells with the fluorescent probe H2DCF-DA (2.5 M), is widely used to assess intracellular ROS production in blood cells like erythrocytes and leucocytes, spermatozoa, and other cellular categories. Because of its vulnerability to ROS-prompted oxidation by hydrogen peroxide, peroxynitrite, hydroxyl revolutionaries and furthermore by superoxide anions, H2DCF-DA is presently considered among the vital strategies for estimating intracellular ROS levels, detecting redox status varieties and cell oxidative pressure**[42,43]**. Cytofluorimetric investigation can be additionally utilized for the appraisal of layer lipid oxidation, utilizing the fluorescent test BODIPY 581/591 C11. In order to investigate alterations in redox status in the erythrocytes of RVO and SSNHL patients, this method was suggested. Additionally, a novel method for assessing membrane fluidity, fluorescent anisotropy of cellular membranes, may provide a new approach for future research into sperm motility defects**[44,45,46]**. LPO and TAC levels in biological fluids are also evaluated for oxidative stress. LPO levels can be recognized by estimating lipid oxidation finished results as MDA, 4HNE, isoprostanes with spectrofluorimetric or immunochemical examines. Thiobarbituric Corrosive (TBA) Measure or the ALDETECT Examine are the for the most part involved tests for LPO appraisal**[47]**. For low MDA concentrations, highly sensitive high pressure liquid chromatography (HPLC) is advocated, whereas commercial immunoassays or mass spectrometry offer an alternative approach for evaluating lipid peroxidation end products in the form of isoprostanes. In parallel, enhanced

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chemiluminescence or colorimetric methods can be used to measure TAC level. Among chemiluminescent procedures, Oxygen Extremist Absorbance Limit (ORAC) Examine depends on the force fluorescence rot of a fluorescent test, fluorescein, ensuing to its oxidation by free extreme species (particularly the peroxyl radical), which is produced when 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH) azo-compound is thermally broken down. Colorimetric techniques assess samples' antioxidant capacity to repress the oxidation of 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic corrosive) (ABTS) to ABTS + by metmyoglobin**[48,49]**. Several studies emphasized the development of a specific global parameter or index capable of distinguishing fertile men from infertile men better than ROS or TAC alone, based on alterations in infertile men's redox biomarkers. In particular, a novel method for examining redox status in male infertility was proposed as the ROS-TAC score, which is derived from the antioxidant capacity and ROS levels of a specific patient group. Barren men with male component or idiopathic determinations had altogether various ROS-TAC scores than controls. Especially, the likely utilization of ROS-TAC score for anticipating the oxidative harm of semen tests in asthenozoospermic men was proposed. The measurement of oxidation reduction potential (ORP) has also been shown to be a new, quick, simple, and repeatable method for determining oxidative stress in seminal fluid. ORP shows the proportion among oxidant and cell reinforcement particles, assessing the potential for electrons to move from a compound specie to another**[19,53,54]**. The MIOSYS test, which measures electron transfer between antioxidants and oxidants in the presence of a low voltage reducing current, is used to evaluate ORP. The got information address oxidant and cell reinforcement action in an example: especially, high ORP levels demonstrate upgraded oxidant movement and thusly a state of oxidative pressure**[50]**. Some proof reports a decent relationship between ORP level and semen boundaries being found higher ORP levels in fruitless men than in solid controls**[51,52]**. In addition, there is a negative correlation between the ORP value and the parameters of the sperm (such as motility, morphology, and total sperm count) was observed, pointing to ORP as an additional predictor for the diagnosis and treatment of male infertility. In accordance with this, further examinations affirmed the critical relationship of ORP both with semen boundaries and DNA fracture in barren men. Critically, it was likewise shown that ORP is a more precise device for exploring redox status in male fruitlessness than chemiluminescent ROS evaluation**[50,51]**.

TREATMENTOFOXIDATIVESTRESS RELATED MALE INFERTILITY

Due in part to the unidentified etiology of this condition, clear treatment guidelines for oxidative stress-related male infertility are still lacking. Nonetheless, during these years a few clinical preliminaries have been created to research the impacts of cell reinforcement supplementation **(**as Vitamin-A(as beta carotene), Vitamin-C(as ascorbic acid), Vitamin-D3(as cholecalciferol), Vitamin-E, Vitamin-B1, Vitamin-B6(as pyridoxal-5-phosphate), folic acid, Vitamin-B12, Biotin(as d-biotin), Selenium (as selenomethionine), Manganese, Copper(as anhydrous copper sulfate), Zinc(as zinc citrate), Molybdenium(ammonium molybdate), L-Carnitine, L-Tartate, L-Arginine, Lycopene(10%), Grape seed extract, N-Acetyl L-Cysteine, Coenzyme- Q10, Astaxanthin, Ginseng extract**)** on fundamental liquid oxidative pressure and semen boundaries**[40,42,52]**. Antioxidants had promising effects on sperm concentration, motility, morphology, and DNA fragmentation, according to many of them and so it is considered to be the first line treatment**[1]**. Twenty clinical trials on the effects of antioxidant therapy on early oxidative stress were looked at. The sperm redox status and parameters of 19 of them improved, and there was a strong correlation with the outcome of the pregnancy**[53]**. However, it is still up for debate whether antioxidant therapy contributes to male infertility. In a randomized clinical trial, it was demonstrated that a three-month antioxidant treatment for infertile men did not improve DNA fragmentation**[4]** and sperm parameters, nor did it increase the likelihood of pregnancy or live birth**[54,55]**. These perceptions show that proof to help the utilization of cell reinforcements in male barrenness are as yet unsure. However, Both oxidative stress assessment and traditional semen analysis have the potential to accurately evaluate infertile patients**[17,56]**.

II. CONCLUSION

A novel pathological mechanism of male infertility is oxidative stress, which plays a central role in sperm dysfunctions. New methods and diagnostic approaches for male reproductive disorders are required based on previously reported investigations and results. Along with fundamental liquid oxidative pressure appraisal, blood redox

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status checking and leukocytes ROS levels, could address another potential and less intrusive practice for clinicians to assess sperm cells quality and preparation capacity. In order to reduce systemic oxidative stress in infertile men, improve male infertility diagnosis and management, and increase the success rate of ART, taken into consideration redox parameters may be useful in the development of new antioxidant-based therapeutic strategies**[13,16,57]**.

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